Secondary Hypertension

Screening, Diagnosis and Treatment

Nanfang Li
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Foreword

Hypertension is the most important risk factor for cardiovascular diseases. It remains one of the greatest threats to human health nowadays. Hypertension can be divided into essential hypertension and secondary hypertension. A large number of studies on differential diagnosis have shown an increase in the number of secondary hypertension, and the prevalence of secondary hypertension has increased to over 10–15% among the hypertensive population.

However, secondary hypertension is not easy to be diagnosed because of its insidious and complicated causes. Its detrimental effects include not only the final occurrence of cardiovascular and cerebrovascular diseases but also the accompanying damage of target organs caused by hypokalemia, hyperaldosterone, increased cortisol, high renin, and high catecholamine.

The etiology of secondary hypertension includes cardiovascular diseases, endocrine diseases, kidney diseases, sleep medicine, autoimmune diseases, and mental and psychological diseases. Therefore, the screening, diagnosis, and treatment are also a complicated process. Clinicians are required to do careful physical as well as detailed laboratory examinations to finally identify the causes of hypertension and carryout individualized treatment.

The Center of Hypertension of the People's Hospital of Xinjiang Uygur Autonomous has been engaged in hypertension clinical work and scientific research for more than 20 years and has a lot of clinical experience on secondary hypertension diagnosis and treatment. The authors completed the book *Secondary Hypertension: Screening, Diagnosis and Treatment* by consulting a large amount of research material combining with the clinical practice and research experiences of the Center. This book is a systematic comprehensive reference book about screening, diagnosis, and treatment of secondary hypertension. It includes the description of the occurrence mechanism, clinical manifestations, diagnosis, and treatment of secondary hypertension, which is helpful for the early diagnosis and treatment of secondary hypertension, and it is a valuable reference book for clinicians, especially professional physicians and researchers who are studying and treating hypertension.

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Contents

Introduction

The high prevalence of hypertension is closely related to cardiovascular and cerebrovascular diseases, which has caused great harm to human health. We know that hypertension can be divided into primary hypertension with unknown causes and unclear pathogenesis and secondary hypertension with clear etiology. Traditionally, secondary hypertension accounts for only 5–10%. However, with the in-depth study of the etiology of hypertension and the improvement of the clinical diagnostic techniques, the detection rate of secondary hypertension has far exceeded our expectations, for example, obstructive sleep apnea syndrome (OSAS) is one of the most important secondary hypertension, accounting for at least 30% of adults with hypertension. Only a part of primary aldosteronism is combined with hypokalemia, accounting for 5–15% of patients with hypertension. It could be said that all hypertension has certain causes. As for the so-called essential hypertension, it is not known by us or we are unable to understand the cause. Hypertension is a common clinical manifestation of many disorders and intermediate link in their pathophysiological process. Different hypertension individuals or populations may have different mechanisms, hypertension mechanisms, and the same individual may have multiple blood pressure elevated mechanisms at the same time.

The etiology of secondary hypertension is often hidden and complex, involving cardiovascular diseases, endocrine diseases, kidney diseases, sleep medicine, mental illness, and other disciplines, and at the edge of above disciplines. Due to the intensive clinical division, the number of cases of secondary hypertension that has been reported is much incompatible with the actual prevalence. While the etiological detection and treatment of the secondary hypertension can not only benefit blood pressure control and target organ damage reduction, but also cure hypertension and greatly reduce the patients' medical burden through long-term treatment. We can imagine that the individualized treatment of hypertension, including etiological treatment, is the higher field of hypertension treatment.

Therefore, we (Hypertension Center of the People's Hospital of Xinjiang Uygur Autonomous Region) have been engaged in the diagnosis and differentiation of secondary hypertension for a long time and successfully screened lots of secondary hypertension. We have also consulted a large number of data and documents, gained our own clinical experience and understanding, based on the above, we write this book—secondary hypertension. It focuses on renal parenchymal hypertension, renal vascular hypertension, hypertension caused by other renal diseases, endocrine

hypertension, hypertension caused by neurogenic and psychiatric disorders, as well as cardiovascular diseases, obstructive sleep apnea syndrome, drug-induced and exogenous hypertension, secondary hypertension induced by connective tissue diseases, blood system diseases, pregnancy-induced hypertension, and nearly hundreds of diseases. Each disease is described from general level to details, especially the mechanism of hypertension, standardized diagnosis, and treatment process.

Although all of our compilers have made great efforts on this issue, secondary hypertension is really a very broad field, which makes us feel our understanding is very superficial and knowledge is limited towards secondary hypertension.

Taking this opportunity, I would like to express my sincere gratitude to those who have cared, supported, encouraged, and helped me and my team for a long time. I would like to express my sincere respect to my colleagues who have worked hard, shared the joys and sorrows with me for a long time, and who have also made great efforts in compiling this book.

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Part I

General Theory of Secondary Hypertension

Summary of Secondary Hypertension

1

Nanfang Li, Menghui Wang, and Mei Cao

1.1 Screening for Secondary Hypertension

Nanfang Li

Hypertension can be classified into essential hypertension and secondary hypertension based on the etiology whether it is clear or not. Previously, we think that the proportion of secondary hypertension was much lower than essential hypertension. However, with the deep understanding of the etiology of hypertension and the improvement of clinical diagnostic techniques, the proportion of secondary hypertension has far exceeded expectation. For example, Obstructive Sleep Apnea Syndrome (OSAS) is the most common type of secondary hypertension, which may account for more than 30% of adults hypertension, and primary aldosteronism accounts for more than 10%. In addition to cardiovascular damage caused by hypertension itself, secondary hypertension can also lead to cardiovascular damage independent of hypertension, which is more harmful than primary hypertension, such as hypokalemia, hyperrenin, hyperaldosterone, hypercortisol, hypercatecholamine, and hypoxia [1–11]. Early detection and treatment of secondary hypertension is of important clinical significance.

The etiology of secondary hypertension is complex, involving cardiovascular diseases, endocrine diseases, kidney diseases, sleep medicine, mental illness and other disciplines, and therefore it is an interdisciplinary science. If there is no systematic understanding and standardized screening process, missed diagnosis and misdiagnosis can easily occur. Blindly screening of secondary hypertension not only causes missed diagnosis and misdiagnosis, but also causes huge waste of medical resources, and brings unnecessary economic burden to patients and society.

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1.1.1 Prevalence of Secondary Hypertension

At present, there is no epidemiological data on secondary hypertension in general hypertension population. Previously, the prevalence of secondary hypertension was 4.7–10.5% [12–14] in hypertensive population. In recent years, studies have shown that the prevalence of secondary hypertension among adults in Grade III Level A hospitals in China has increased from 14.0% [15, 16] in 2005 to 39.3% in 2008 [17], while it increases to 44.3% in hypertension patients when making screening purposely and it reaches to 65.6% [2] in refractory hypertension. Previously, renal hypertension was considered as the most common type of secondary hypertension, accounting for 5–10% of hypertension patients. Renovascular hypertension accounts for 1–5% [18, 19] of the hypertension population, 80% of which are young and middle-aged people, often with multiple arteritis or fibromyogenic stenosis of renal artery intima. Renal artery stenosis in men over 50 years old, smokers, and diabetic patients is mostly caused by renal atherosclerosis [20, 21]. There are also data showing that 30% of patients with coronary heart disease have renal artery stenosis caused by atherosclerosis, and 50% of patients with diffuse atherosclerosis have renal artery stenosis [22].

In recent years, OSAS has been found to be the most common cause of secondary hypertension, which accounts for 37–56% [23, 24] of patients with hypertension and 64–83% [25, 26] of patients with resistant hypertension. In patients with hypertension and snoring, 83.3% of them were diagnosed as OSAS, in which 55.0% were moderate and severe OSAS patients, and the ratio of male to female was 4.4:1. The number of male severe OSAS patients was larger than that of female and most of the female were mild OSAS patients. The detection rate of OSAS in hypertensive patients with obesity was 89.2%, and with the increase of weight, the severity of OSAS gets increased [27–29].

Primary aldosteronism (PA) has been considered as a rare disease in the past, and the prevalence of which is less than 1%. With the in-depth knowing and the application of screening-confirmation-typing system, the detection rate of PA has increased 5–15 times [30], becoming the most common type of endocrine hypertension. Due to the differences of region, case selection criteria, aldosterone-renin ratio (ARR) diagnostic cut-off points (20–50), and diagnostic test methods, the prevalence of PA in hypertensive patients reported by various countries ranged from 5 to 20% [31]. There are also some studies found that the prevalence of PA was 1.50%, 1.99%, 8.02%, and 13.2% in patients with normal blood pressure and grade 1, 2, and 3 hypertension, respectively, and the total prevalence was 6.10% [32]. Among resistant hypertension, the prevalence of PA was as high as 17–23% [33, 34], and 16.48% of OSAS patients complicated with PA [35].

The prevalence of hypertension complicated with anxiety ranges from 11.6 to 38.5% [36–39]. The prevalence of anxiety in community hypertension patients is 23.3 and 38.5% in outpatient hypertension patients and rate is high in female [40]. The prevalence of thyroid dysfunction was 1–2% in patients with hypertension, and the prevalence of hypertension caused by Cushing's syndrome, pheochromocytoma, and arterial coarctation was lower, even in resistant hypertension <1% [41].

The detection rate of hypertension in iatrogenic Cushing's syndrome patients was 20% [42], while that in subclinical syndrome patients was 60% [43, 44], and that in hypothyroidism patients was 20–40% [45].

Studies have shown that secondary hypertension is more common in young adults; the detection rate of OSAS and renal hypertension in young and middle-aged patients is significantly higher than that in the elderly. PA was more common in young people, but there was no significant difference in the distribution of anxiety disorder, pheochromocytoma, Cushing's syndrome, thyroid disease, and arterial coarctation among different age groups [16]. A growing number of studies have shown that obstructive sleep apnea syndrome, primary aldosteronism, renal parenchymal hypertension and renal vascular diseases, mental and psychological disorders (such as anxiety disorders, panic attacks, depression, and anxiety) are common causes of secondary hypertension in clinic.

1.1.2 Preliminary Screening of Secondary Hypertension

Preliminary screening is the first step of diagnosis and treatment of secondary hypertension, that is, to search for suspicious "clues" of secondary hypertension through medical history, physical examination, and routine laboratory examination (including blood and urine routine, blood lipid, glucose, electrolyte, liver and kidney function, double-kidney B-mode ultrasound, ambulatory blood pressure monitoring, etc.) [46–48]. The following questions should be paid attention to in medical history inquiry and physical examination:

1. Symptom: (1) Snoring, especially repeated apnea and dreaminess during sleeping, headache in the morning, and daytime sleepiness. (2) Lumbago, foam urine, gross or microscopic hematuria. (3) Weakness, muscle weakness, increased nocturia, periodic paralysis. (4) Paroxysmal hypertension with headache, palpitation, and sweating. (5) Psychological and physical disorders such as insomnia, irritability, irritability, and depression. (6) Obviously afraid of heat, sweating, and emaciation. (7) Weight gain, menstrual disorders, sexual dysfunction, etc. [49].
2. Sign: (1) Abnormal weight gain or decrease. (2) Skin pale, moist, sweaty, rash, reticular macules. (3) Sanguineous appearance, cyanosis of lip nail bed, large tongue with dental marks, narrow pharyngeal cavity. (4) Rough vascular murmurs can be heard in the neck or abdomen. (5) Decreased tendon reflex. (6) Secondary sexual abnormality. (7) The blood pressure between two upper limbs differ by >20 mmHg (1 mmHg = 0.133 kPa), lower extremity blood pressure was significantly lower than that of upper extremity. (8) Asymmetry of limb pulse, weakening or disappearing of arterial pulse, etc.

General laboratory examinations including blood routine, urine routine, blood lipid, blood sugar, electrolyte, liver and kidney function, erythrocyte sedimentation rate, C-reactive protein, oxygen saturation monitoring, and electrocardiogram, color echocardiography, double-kidney B-mode ultrasound, fundus photography,

and ambulatory blood pressure monitoring can provide important clues for secondary hypertension. The main analysis and discrimination are as follows: (1) Blood routine: increased red blood cells, hemoglobin, and hematocrit may indicate polycythemia vera or secondary hypertension caused by OSAS [50]. The decrease of erythrocyte and hemoglobin may suggest renal parenchymal hypertension or secondary hypertension caused by hypothyroidism and autoimmune diseases. Increased leukocytosis can be seen in the increased excitability of Sympathetic Nervous System (SNS), and systemic vasculitis should be vigilant if accompanied by increased neutrophils and acidic granulocytes. (2) Urinary routine: Proteinuria or increased urinary sediment may occur in the early stage of renal lesions, which has clinical significance in differentiating renal parenchymal hypertension [51]. Hypertensive kidney damage can lead to changes in urinary specific gravity. Renal tubular acid-base and electrolyte imbalance may be associated with secondary hypertension, such as PA and Liddle syndrome [52, 53]. (3) Glucose and lipid: Hypertension and hyperglycemia have a common pathogenesis, namely insulin resistance. As hyperglycemia and hyperlipidemia are important risk factors for atherosclerosis, atherosclerosis involving the renal artery may cause renal vascular hypertension. In addition, renal damage in diabetic patients may lead to renal parenchymal hypertension [51, 54]. OSAS-related hypertension is more likely to be associated with glucose and lipid metabolic disorders. (4) Renal function and electrolyte: Renal dysfunction needs to be combined with patient's age, course of hypertension, past history of urinary system, and urine analysis in order to identify renal hypertension. Hypertension with hypokalemia (hyperkalemia) is closely related to secondary hypertension and PA; glomerular disease or tubular disease should be considered [53, 55]. (5) Oxygen saturation: Hypoxemia of non-chronic obstructive cardiopulmonary disease during night sleep, combined with history of snoring, sleepiness, and nighttime choking, suggesting OSAS [50]. (6) Bilateral renal and renal blood flow ultrasound: Ultrasonography can test the length of long axis of both kidneys, medulla structure of bilateral renal cortex, blood flow velocity of bilateral renal artery, and can further differentiate renal hypertension, renal vascular hypertension, polycystic kidney, hydronephrosis, and other renal hypertension [56]. (7) Fundus photography: It is an intuitive marker of vascular damage and one of the important bases of renal hypertension [56]. (8) 24-h ambulatory blood pressure monitoring: 24-h ambulatory blood pressure monitoring is not only an important means of hypertension diagnosis and evaluation of antihypertensive efficacy, but also can be used to diagnose pseudohypertension, white coat hypertension, and drug-related hypertension [57, 58]. Studies confirmed that 24-h ambulatory blood pressure monitoring can monitor blood pressure in different time periods and postures, as well as the rhythm and variation of blood pressure, which have special significance in the diagnosis of secondary hypertension [11, 59, 60]. Renal hypertension and PA [9, 11, 59–61] should be considered when blood pressure continues to rise and rhythm changes are not closely related to factors such as

daytime and posture. Pheochromocytoma [62] should be considered, and mental factors such as excitement, fear, and anxiety should be excluded when obvious blood pressure variability and major fluctuation occur with paroxysmal elevation and/or with orthostatic hypotension.

24-h ambulatory blood pressure monitoring procedure for screening secondary hypertension is shown in Fig. 1.1.

These clinical features provide important clues for secondary hypertension screening: (1) Age of onset is less than 30 years old, blood pressure level is 2 or 3 levels; (2) Patients over 55 years old have normal blood pressure or stable blood pressure control through regular use of antihypertensive drugs, and suddenly appear hypertension or the efficacy of the original antihypertensive drugs decreases; (3) High fluctuation of blood pressure, poor response to drug treatment; (4) Hypertension progresses rapidly, and the severity of target organ damage is

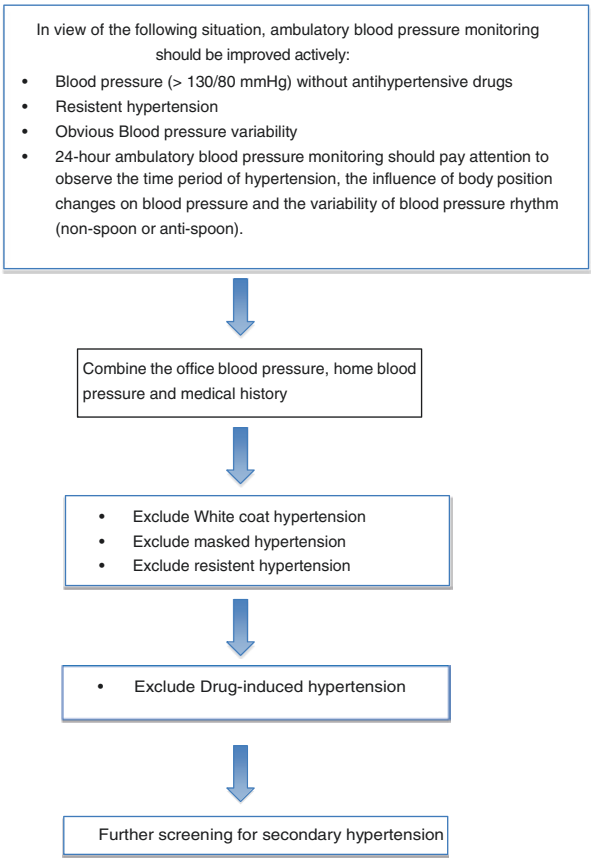

Fig. 1.1 24-h ambulatory blood pressure monitoring

not parallel to the course of hypertension. (5) Hypertensive patients with myasthenia, periodic limb paralysis, or fear of fever, sweating, emaciation, or paroxysmal hypertension accompanied by headache, palpitation, recurrent apnea, or breathing constriction during sleep; (6) Hypertensive patients with unexplained renal dysfunction, abnormal blood routine, electrolyte disturbance, bilateral renal inequality, and adrenal incidental tumors were found by physical examination or clinical examination. According to the above clinical characteristics, it is possible to select relevant specialist examinations to further clarify the etiology of secondary hypertension.

1.1.3 Specialized Examination of Secondary Hypertension

If preliminary screening indicated the possibility of secondary hypertension, further specialist examinations are needed to identify the cause. It should be emphasized that some specialist examinations should be carried out on the basis of the clues of secondary hypertension; some specialist examinations cannot be carried out in primary hospitals, and need to be referred to higher or higher specialist hospitals of hypertension. Specialist examination is recommended in three steps.

Step 1: Primary examination (targeted but relatively universal, noninvasive laboratory examination); (1) Determination of plasma renin and aldosterone: Through this examination, patients can be divided into high renin type, normal renin type, and low renin type secondary hypertension. Primary or secondary aldosteronism can also be screened according to plasma aldosterone/renin activity ratio. This examination has requirements for detection time, body position, and age [63, 64]. (2) Detection of cortisol rhythm and adrenocorticotropic hormone (ACTH): It is mainly used to differentiate hypercortisolism and to preliminarily classify ACTH dependence and non-dependence [65]. (3) Determination of serum catecholamine and its metabolites in urine: It is mainly used to differentiate secondary hypertension with high sympathetic activity. It is also valuable for the differential diagnosis of parasympathetic ganglioma [62, 66]. (4) Thyroid function test: It is used to identify secondary hypertension caused by hyperthyroidism or hypothyroidism [45, 67]. (5) Simple sleep monitor: OSAS and nocturnal hypoxemia were diagnosed, classified, and graded by calculating sleep breathing index, and the degree of secondary hypertension caused by OSAS and its prognosis were preliminarily determined [2, 68].

Step 2: Secondary inspection (tedious, relatively expensive or potentially risky inspection). (1) Saline load test: It is a common method for the diagnosis of PA. Patients whose aldosterone/renin activity value exceeds the cut-off value need to be further tested. It should be noted that patients with cardiac insufficiency or possible risk of cardiac insufficiency, hypokalemia, and adrenal adenoma diameter (>2.5 cm) should not undergo this test [64]. (2) Captopril test: For patients contraindicated by saline load test, captopril test may be considered to diagnose PA [64]. In addition, renal dynamic radionuclide imaging after captopril administration is helpful in differentiating renal vascular hypertension [69, 70]. (3) Dexamethasone inhibition test: Mainly for patients

suspected of hypercortisolism due to elevated basal cortisol level or abnormal rhythm, including overnight, standard low dose, and large amount of dexamethasone inhibition test, it is a qualitative and localized diagnostic test for hypercortisolism [65]. (4) Polysomnometer monitoring: OSAS and nocturnal hypoxemia were diagnosed, classified, and graded by calculating sleep electroencephalogram and respiratory index, and can also determine the degree of secondary hypertension caused by OSAS and its prognosis [2, 68]. (5) Thin-slice CT of adrenal gland: CT is the preferred imaging examination for the diagnosis of adrenal diseases. CT scan can clearly show the morphology of adrenal gland and find its abnormal morphology, which is superior to magnetic resonance and B-mode ultrasonography [64]. (6) Renal artery multi-slice spiral CT three-dimensional angiography (Renal artery CTA): It is noninvasive, safe, convenient, economical, and intuitive. At the same time, it has less radiation and can show the structure of the artery wall and extramural tissue. To some extent, it can replace the digital subtraction angiography (DSA), which used to be as the "golden standard." If renal vascular hypertension is highly suspected, it can be considered. If vascular hypertension is highly suspected, renal artery CTA should be considered. Note that high doses of contrast agents may cause renal damage. (7) Double-kidney radionuclide imaging (double-kidney ECT): It can measure the glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) separately. As it is noninvasive, simple, safe, convenient, economic and can measure the renal function simultaneously, ECT has been widely used in the evaluation of renal function. (8) Radioactive iodine-labeled *m*-iodobenzylguanidine scintigraphy (^{123}I/^{131}I-MIBG scintigraphy) and positron emission computed tomography (PET): It is of great value in the diagnosis of pheochromocytoma, extraadrenal pheocytoma, and metastasis of malignant pheochromocytoma. At present, most scholars believe that they can complement each other in the diagnosis of pheochromocytoma, but PET is expensive.

Step 3: Advanced examinations (expensive, invasive, or invasive examinations with certain risks); these examinations are often traumatic, but they are important for diagnosis, typing, lateralization, and formulation of the next treatment plan. They need to be done after doctors weigh the pros and cons, take full account of the relationship between examinations and treatments, and the possible benefits of treatment. (1) Renal artery angiography combined with renal venous blood sampling to determine renin activity: It is the gold standard for the diagnosis of renal artery stenosis and can provide a reliable basis for the diagnosis and differential diagnosis of renal vascular hypertension [69–71]. (2) Renal puncture and biopsy: Ultrasound guidance combined with automatic biopsy technology can make the difficult renal biopsy technology more perfect, simplified, and safer. It is mainly used to differentiate hypertensive nephropathy from renal parenchymal hypertension. (3) Serum aldosterone levels were measured by bilateral adrenal venous blood sampling. This procedure is conducted in confirmed PA patients, which is the gold standard for diagnosis and classification of PA. (4) Pituitary hormone determination in inferior petrosal sinus venous blood: This examination is used for localization diagnosis of pituitary, adrenal, and ectopic endogenous hypertension.

1.1.4 Screening Process for Secondary Hypertension

The possibility of secondary hypertension should be considered for all new hypertension patients, especially those with resistant hypertension. History inquiry should pay attention to the onset time of hypertension, blood pressure level, type of hypertension (persistent/paroxysmal), whether there are night sleep disorders, snoring, apnea during sleep, daytime sleepiness; whether there is a history of increased nocturia/periodic paralysis, sweating, palpitation, pallor, urinary frequency, urgency, urinary pain and history of hematuria, anemia and edema, and the reaction to antihypertensive drugs. Has a history of licorice preparation, steroid hormones and contraceptives, and menstrual/sexual development, marriage and childbearing. Physical examination should pay attention to blood pressure when laying down, pulse, blood pressure, tendon reflex, body shape, facial color and terminal temperature, skin, hair, capillaries, abdominal and back vascular murmurs, heart rate and heart murmurs, and the development of secondary sexual characteristics on face, eyelid or lower limbs. Attention should be paid to extracting the clinical clues of secondary hypertension from blood routine, erythrocyte sedimentation rate, urine routine, blood electrolyte, blood sugar, blood lipid, renal function, electrocardiogram, color echocardiography, carotid artery ultrasound, double-kidney B-mode ultrasound, adrenal CT, 24-h ambulatory blood pressure monitoring, and fundus examination.

Through analyzing the medical history, clinical symptoms, important positive or negative signs, and the results of general auxiliary examinations, we can find out the clinical clues of secondary hypertension, establish screening objects, and carry out targeted primary examinations. On this basis, we can further carry out corresponding secondary specialist examinations for patients with high probability of secondary hypertension in order to make a definite diagnosis. For patients who have been diagnosed, further typing and positioning are needed so as to establish a treatment plan. For patients who are willing to undergo surgical treatment, and on the basis of taking full account of the benefits of treatment for patients, invasive or invasive high-level specialist examinations of hypertension which are expensive or at certain risk can be carried out.

Detailed screening procedures for secondary hypertension are shown in Fig. 1.2.

As some special examinations of secondary hypertension require high laboratory conditions, highly suspected patients should be transferred to higher qualified hospitals in time to clarify the causes and formulate appropriate treatment plans. Secondary hypertension with clear etiology can be restored to normal level after eliminating the etiology, and some need sustained etiological treatment. Etiology-based treatment can effectively reduce the dosages and types of antihypertensive drugs, effectively improve the hypertension control and cure rate, avoid target organs damages, and improve the patients' life quality.

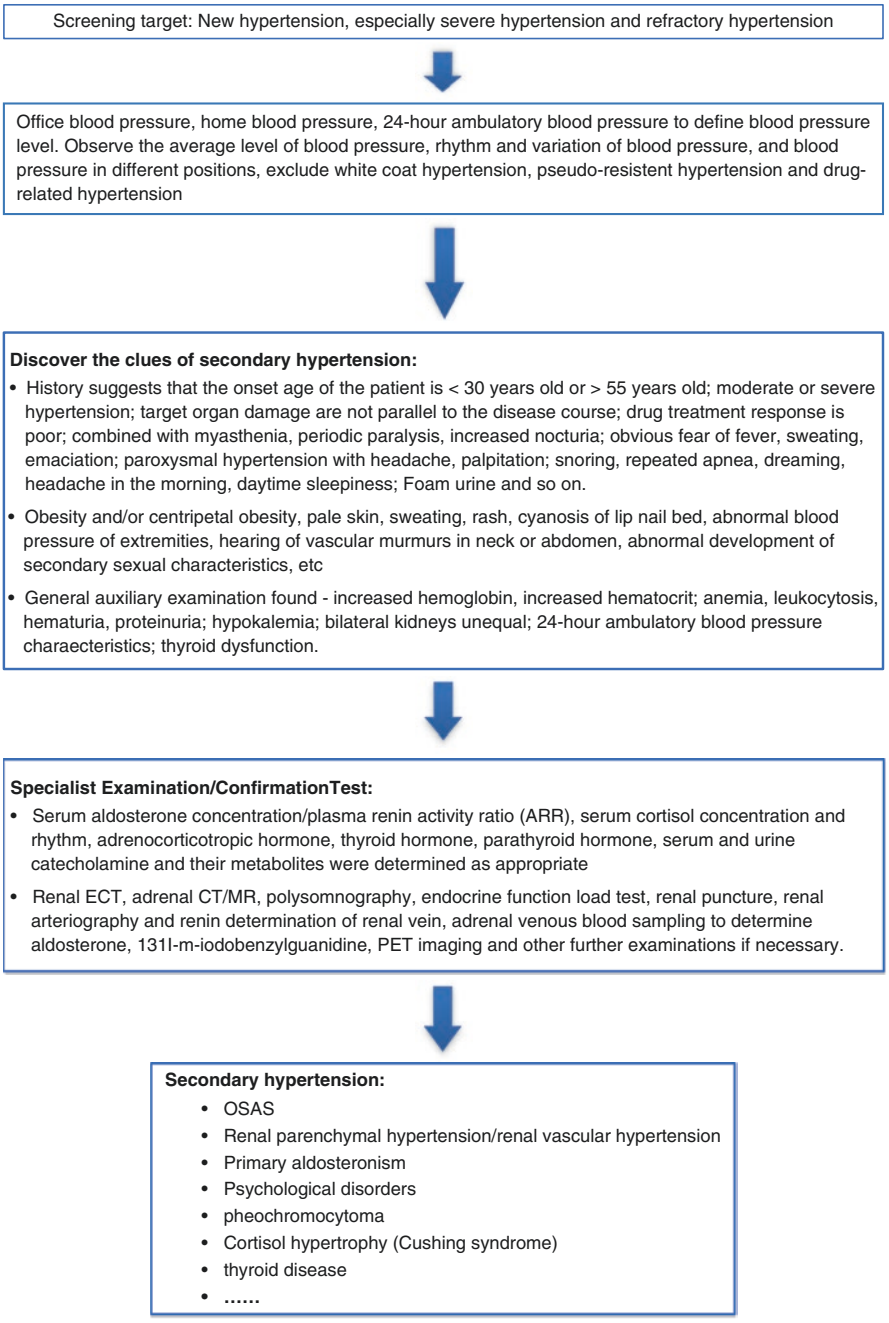

Fig. 1.2 Flowchart of secondary hypertension screening

1.2 Resistant Hypertension

Menghui Wang

Resistant hypertension (RH) is the main screening crowd for secondary hypertension, accounting for about 10% of the population with secondary hypertension. Definition of RH: Blood pressure does not reach the standard after taking three or more antihypertensive drugs including one diuretic in sufficient dose and reasonable combination, or blood pressure can be controlled below 140/90 mmHg after taking four antihypertensive drugs together, which is also known as drug-resistant hypertension [72, 73].

1.2.1 Prevalence and Diagnostic Criteria of RH:

According to the previous health survey results, about 5–40% of patients with hypertension meet the diagnostic criteria of RH. In China, the concept of RH is relatively late, and the prevalence is not exact, estimated as 15–20%. According to the description of relevant hypertension guidelines in different countries, the diagnostic criteria and prevalence of RH are different in different countries, specifically as follows (Table 1.1):

1.2.2 Precautions for the Diagnosis of RH and Pseudo RH

Once diagnosed as RH, it indicates an increase in the prevalence of cardiovascular, cerebral, renal, and vascular diseases and a poor prognosis. Therefore, patients may face great mental pressure, and doctors will spend more energy to investigate the cause of the disease. Therefore, the diagnosis should be made with extra caution. In addition, some patients with RH can achieve satisfactory efficacy after active intervention of some factors, which is also defined as pseudomorphic RH, accounting for about 7% of the RH [82]. The possible factors analyzed are as follows (Table 1.2) [83–86]:

Doctors should pay attention to the following points in the process of diagnosis and treatment: (1) To measure blood pressure correctly, it is better to use long-term home self-measurement or dynamic blood pressure to evaluate the blood pressure after treatment; (2) Actively identify the causes of secondary hypertension; (3) Doctors should repeatedly adjust patients' individualized antihypertensive program to achieve sufficient dose, sufficient course of treatment, and reasonable compatibility; (4) Education and supervision for patients with

Table 1.1 Prevalence and diagnostic criteria of RH in different countries

Time	Nation	Association	Title	Prevalence	Criteria
In 2009 [74]	USA	AHA	Resistant Hypertension: Detection, Evaluation, and Management A Scientific Statement from the American Heart Association	20–30%	140/90 mmg
In 2010 [75]	China	CHL, NCCD	Guidelines for hypertension prevention and treatment in China 2010	15–20%	140/90 mmg
In 2013 [76]	Europe	ESH, ESC	2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension	5–30%	140/90 mmg
In 2016 [77]	France	FSH	Management of resistant hypertension. Expert consensus statement from the French Society of Hypertension, an affiliate of the French Society of Cardiology	27%	1. <80 years old 140/90 mmHg; 2. >80 years old, SBP ≥ 150 mmHg
In 2017 [78]	Canada	CHEP	Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension	10–20% in adult	140/90 mmg
In 2017 [79, 80]	USA	ACC, AHA, AAPA, ABC	Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults	17% in adult	130/80 mmg
In 2018 [81]	USA	AHA	Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. A report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines	9.4–40.4% in adult	No specific standard

Table 1.2 Factors of patients and doctors causing pseudomorphic RH

Patient factors		Physicians factors	
1.	Poor medication adherence	1.	Inaccurate measurement
2.	Agedness	2.	Underdosing
3.	Obesity, physical inactivity	3.	Unreasonable drug combination
4.	Alcohol addiction	4.	Inadequate treatment
5.	High-salt, low-fiber diet	5.	Inadequate treatment period
6.	Another drug interference	6.	Incomplete evaluation
7.	Somnipathy	7.	Unrecognized white coat hypertension
8.	Obstructive sleep apnea syndrome	8.	Limited screening skills for secondary hypertension
9.	Definite etiology of secondary hypertension	9.	Lack comprehensive management

poor medication adherence: the specific method is to increase the appointment rate.

Among them, the lack of adherence to antihypertensive drug treatment is one of the important reasons causing blood pressure to drop difficultly [87]. Simplified treatment regimen is an effective measure to improve medication adherence, the method is as follows: (1) Multiple long-acting antihypertensive drugs should be taken orally only once a day to reduce the medication frequency; (2) It is suggested that patients should be followed up regularly after recording their blood pressure at home; (3) The comprehensive treatment of patients should be guided in collaboration with nursing, pharmacology and nutrition professionals; (4) It is suggested that the patient's family members cooperate with the supervision to take medicine and improve the treatment of life style.

1.2.3 Screening of Secondary Hypertension in Patients with RH:

Most patients with RH can be identified as the cause of secondary hypertension, and the most common ones are obstructive sleep apnea syndrome and primary aldosteronism, accounting for 60–70% and 7–20% of RH, respectively [2, 88]. However, due to the limitations of testing level and diagnosis and treatment technology, many RH is misdiagnosed as primary hypertension. Screening for secondary hypertension requires clinicians to seek and collect clues from medical history, physical examination, and relevant examinations. Combined with clinical experience, the main characteristics of secondary hypertension are summarized as follows (Table 1.3) [89–91]:

1.2.4 Management of RH

The diagnosis and treatment of RH should be based on the screening and treatment of the causes of secondary hypertension, so as to correct the high blood pressure

Table 1.3 Characteristics of several common secondary hypertension in RH

Disease	Clinical clues	The main signs	Screening tests	Confirmatory test
Primary aldosteronism	Hypokalemia, adrenal nodules	No specific	Aldosterone/ renin activity ≥threshold value (different center threshold values)	Inhibition of aldosterone could not be inhibited. Renin stimulation was not activated
Renal parenchyma hypertension	Hematuria, dropsy, lumbago	Puffiness of face	Urine routine examination indicated erythrocyte, renal dysfunction	Pathological examination of renal biopsy
Renal vascular hypertension	Repeated chest tightness, shortness of breath; heart failure	Abdominal bruit	Asymmetric size of both kidneys by ultrasound, and severe unilateral ischemia by ECT	Renal artery stenosis by renal arteriography
Paraganglioma	Palpitations, sweating, headache	Thin, moist skin, fast heart rate	Increased blood/ urine norepinephrine and norepinephrine	Adrenal mass
Cushing's syndrome Cushing's disease	Progressive weight gain	Mood disorders, abdominal striae, hirsutism, dorsal and supraclavicular fat, fragile skin	Cortisol rhythm disorder; cortisol rhythm disorder, and elevated ACTH	Dexamethasone inhibition positive test
Primary hypothyroidism	Dry skin, afraid of cold, constipation; hoarse voice; weight gain	Periorbital edema; rough skin; goiter	Thyroid hypofunction	Decreased iodine uptake in the thyroid
Hyperthyroidism	Sweat; insomnia; angular; diarrhea; proximal muscle weakness	Proptosis; Hands trembling; fast heart rate; goiter	Thyroid hyperfunction	Increased iodine uptake in the thyroid
Hypercalcemia/ primary hyperparathyroidism	No specific	No specific	Elevated serum calcium and urinary calcium	Elevated parathyroid hormone
Aortic disease	Limb weakness, physical weakness; difficulty in breathing	Aortic bruit; abnormal blood pressure distribution in the extremities	Aortic CTA	Aortography

after the internal and external causes of RH, which should be handled according to the following standard operating procedures [81]:

In the first step, an antihypertensive combination of RAS-blocker +CCB+ diuretic can be given after pseudorefractory hypertension has been excluded, and bad lifestyle corrected.

Next step, BP is still not at the target, diuretic can be substituted by the optimally dose thiazide-like diuretic.

Next step, BP is still not at the target, mineralocorticoid receptor antagonists can be added.

Finally, after some factors have been reassessed including adherence, the doses, and duration of antihypertensives, BP is still not at the target, patients should be suggested to see hypertension specialist.

1.2.5 Recommended Hypertension Specialist Visit

If RH patients have possible causes of secondary hypertension and the effect is not good after half a year of treatment with normal antihypertensive regimens, it should be suggested that the patient should be diagnosed and examined in the hypertension specialist for the cause [92–94], which can be effectively controlled and prevent cardiovascular and cerebrovascular diseases [95, 96].

1.2.6 Invasive Interventional Therapy

Because the sympathetic nerve is closely related to hypertension, the current radiofrequency ablation of renal sympathectomy is only effective for some RH patients, but postoperative complications such as gastrointestinal dysfunction, dyspnea, postural hypotension, and erectile dysfunction may be occurred. Whether it can be widely carried out is highly controversial. Therefore, it is necessary to strictly grasp the indications and carry out prudently and orderly according to the operating procedures [97].

In conclusion, the diagnosis and treatment of RH is a great challenge for primary practitioners or hypertension specialists. Patients' age, lifestyle, family inheritance, dependence, economic basis, mental health, pathogenic factors, and other aspects should be considered. Meanwhile, medical behaviors should be reviewed to achieve individualized medication. If necessary, patients can be recommended to visit hypertension specialist.

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2 Clinical Manifestations of Secondary Hypertension: Medical History, Symptom Characteristics, and Signs

Menghui Wang

When diagnosing and differentiating the cause of hypertension, clinicians should be familiar with the main points of medical history collection and the clinical features of secondary hypertension, and look for the diagnostic clues of secondary hypertension from medical history, clinical symptoms, and physical examination to avoid misdiagnosis or missing.

2.1 History Taking

Medical history collection is to understand the process of disease occurrence and development through questions and answers between doctors and patients. Collection history is the initial and core content of screening secondary hypertension and is an important basis for the identification of secondary hypertension. However, all gathering information should revolve around "hypertension," and the details are as follows (Table 2.1) [1]:

2.2 Characteristics of Symptoms

Symptoms are the patient's own experience and feeling of abnormal physiological function after the disease, which is an important part of the medical history. The diagnosis can be made by studying the occurrence, development, and evolution of symptoms in patients with elevated blood pressure. Some patients with hypertension

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Table 2.1 History taking about secondary hypertension

Present illness	1. Duration of hypertension, mode of onset, cute or critical condition 2. Main symptoms, inducement, concomitant symptoms, relationship between symptoms and blood pressure changes, and ways of remission 3. Treatment experience, positive findings, and important negative test results 4. Medication status and efficacy 5. Prognosis and outcome, including diabetes mellitus, cerebral apoplexy, and myocardial infarction 6. Sleep state, mental stress, mood changes
Past history	1. Kidney disease history 2. Other diseases that may lead to hypertension: thyroid disease, adrenal tumors after resection, systemic lupus erythematosus, etc. 3. Long-term medication history: licorice, contraceptives, diet drugs, anti-tuberculosis drugs, steroids, etc. 4. Infectious diseases: hepatitis, tuberculosis, syphilis, etc.
Personal history	1. Endemic disease, epidemic area or plateau dwelling history 2. Duration and frequency of smoking and drinking
Marital history	Male: Sexual dysfunction, childless history Female: 1. Whether the woman of childbearing age can be pregnant normally 2. Relationship between hypertension and pregnant time
Family history	1. Whether a first-degree relative has been definitively diagnosed with secondary hypertension, such as primary aldosteronism or polycystic kidney disease 2. For the immediate family members who have fallen ill or died, the cause of death and age shall be ascertained 3. Whether there is a family history of early onset hypertension or cardiovascular, cerebrovascular, and renal events

Table 2.2 Symptomatology

NO	Pay attention to the time that discovers blood pressure to rise, the level of blood pressure (include at ordinary times blood pressure and the patient's highest and lowest blood pressure level), blood pressure to rise is durative or paroxysmal, whether to have accepted antihypertensive treatment and its curative effect, without medicaments adverse reaction and side effect
YES	1. Symptoms related to high blood pressure: It may be the common symptoms of hypertension patients, such as headache, dizziness, palpitations, and tinnitus, but it is necessary to pay attention to the relationship between these symptoms and elevated blood pressure level, treatment outcome 2. Etiological symptoms: important and critical clues for screening for secondary hypertension, such as recurrent fever and rash; hematuria, foam urine, low back pain, facial edema; soft paralysis, nocturia increase; sudden weight gain or loss; sweating profusely; sleep apnea 3. Accompanying symptom: blood pressure rises abruptly with a headache violently, facial color changes; headache with nausea, vomiting; edema with or without low back pain 4. Symptoms of hypertension target organ damage

have no obvious symptoms, or the description of symptoms is not clear, which is hidden in some meaningless details. Medical history collectors need to carefully appreciate, discard the false and preserve the truth, and skillfully extract the core content. The main points are as follows (Table 2.2) [2, 3]:

Table 2.3 Common characteristics in secondary hypertension

1.	Young patients, or age <40 years old
2.	Increased blood pressure moderately or seriously
3.	Insidious onset, short course, easy to be induced to malignant hypertension, rapid development of the disease
4.	Serious complications did not accord with duration of hypertension
5.	Multiple complications, combination with OSA or DM
6.	High proportion of refractory hypertension
7.	Familial aggregation

2.3 Common Characteristics in Secondary Hypertension

Primary hypertension and all kinds of secondary hypertension can lead to non-specific clinical manifestations such as dizziness, headache, palpitation and chest tightness due to high blood pressure, or harmful manifestations of target organs. Therefore, it is easy to mistake secondary hypertension for primary hypertension when the symptoms of primary disease are few or no obvious. However, if clinicians are familiar with the general characteristics of secondary hypertension, it may improve the identification rate of secondary hypertension (Table 2.3) [4, 5].

2.4 Physical Examination

Physical examination refers to a series of the most basic examination methods for physicians to objectively understand and evaluate patients' physical conditions by using their senses and traditional or simple examination tools, such as thermometer, blood pressure meter, percussion hammer, stethoscope, and ophthalmoscope. Many diseases can be diagnosed clinically by combining physical examination with medical history [2]. The main points of physical examination around hypertension are as follows (Table 2.4):

2.5 Relationship Between Secondary Hypertension and Age

Age is closely related to the etiology of secondary hypertension: the younger the age, the higher the blood pressure and the higher the possibility of secondary hypertension. Infant hypertension is basically secondary hypertension; about 80% of hypertension in children and adolescents is secondary hypertension [6, 7]. Postpubertal hypertension, especially associated with obesity, is more common in primary hypertension [8, 9]. Different age of hypertension onset may lead to different emphasis in screening secondary hypertension, which can be summarized as follows (Table 2.5):

Table 2.4 Physical examination

Vital signs	Correct blood pressure measurement; pay attention to measuring blood pressure of limbs and understand blood flow distribution; postural blood pressure (blood pressure measured in decubitus, sitting, and standing positions in the same limb)
Somatometry	Height and weight were measured and BMI was calculated. Measure waist and hip circumference
Posture and facial features	Anemia, Cushing face, indifferent expression, hyperthyroidism
Skin and mucosa	Note the presence of neurofibroma, rash, edema; cyanosis of the lips and nail bed
Head	Cranial nerve examination
Neck	Goiter and nodules; cervical vascular murmur
Chest	Chest deformity, straight back; thoracic aortic murmur (costal ridge angle on both sides of back); heart murmur, heart rhythm, heart boundary size
Peripheral vessels sign	Limb pulse symmetry, no pulse, peripheral vascular pulse
Abdomen	Abdominal vascular murmur (upper abdomen, both sides of umbilicus, waist, and costal ridge); double kidney size, tapping pain, ureteral tenderness
Genitals	Pseudohermaphroditism; varicocele in male
Nervous system	Consciousness state, muscle strength, muscle tension, physiological reflex, pathological sign

Table 2.5 Different age of hypertension onset may lead to different emphasis in screening secondary hypertension

Starting age	Possibility	Medical history collection highlights of physical examination	Major disease to screen for secondary hypertension
Teenagers	Almost all	Fever, hematuria, physical strength, intelligence and psychology; physical appearance, sex, thyroid, vascular murmur	Arteritis, congenital adrenal disease, dullness, dwarfism, aortic constriction
Young and middle-aged	Main crowd	Comprehensive screening	**Body fat**: Primary aldosteronism, hypercortisolism, hypothyroidism, obstructive sleep apnea syndrome, pituitary disease, depression, etc. **Body thin**: Renal hypertension, hyperthyroidism, anxiety disorders, pheochromocytoma, etc.
Middle-aged and old	Main crowd	Comprehensive screening	No special
Old and the advanced ages	A few	Fatigue, intermittent claudication, exercise tolerance, chest tightness; Limb blood pressure; neck, chest, and abdomen murmur, postural blood pressure measurement	Renal vascular hypertension; aortic constriction, aortic dilatation, postural hypertension

2.6 Characteristics of Different Types of Secondary Hypertension History and Physical Examination

There are many types of secondary hypertension, and the following are the clinical characteristics of common secondary hypertension (Table 2.6) [10, 11]:

In short, clinicians should be familiar with the clinical characteristics of various secondary hypertension; patients with hypertension should be alert to the possibility of secondary hypertension, especially young patients with early onset or newly developed elderly patients. In the process of medical history collection and physical

Table 2.6 Clinical characteristics of common secondary hypertension

Secondary hypertension	History and symptom characteristics	Signs
Sleep apnea hypopnea syndrome	Snoring during sleep, frequent episodes of apnea during sleep, dreaminess, enuresis, night angina; excessive daytime sleepiness, fatigue, memory loss, decreased ability to work, etc.	Obesity, short neck, small jaw deformity, dark skin, cyanosis, fat tongue, etc.
Primary aldosteronism	Muscle weakness, palpitations, abdominal distension, etc.	No special
Renal parenchymal hypertension	Fever, edema, hematuria, foam urine, renal area pain, etc.	Sunken edema of the face or limbs; percussion pain in renal region; bladder percussion area enlargement, etc.
Renal vascular hypertension	Diastolic pressure significantly increased, prone to pulmonary edema, etc.	There are vascular murmurs on both sides of the umbilicus of the upper abdomen or the lumbar ridges
Hypercortisolism	Mood disorders, menstrual irregularities, muscle weakness, etc.	Weight gain, abdominal striae, hirsutism, dorsal and supraclavicular fat, fragile skin, etc.
Pheochromocytoma	Paroxysmal hypertension, palpitations, excessive sweating, severe headache, etc.	Emaciation, rapid heart rate, postural hypotension, moist skin, etc.
Thyroid disease	1. Hyperactivity: Good appetite, palpitations, hyperhidrosis, irritability, etc. 2. Hypoglycemia: dropsy, depression, etc.	1. Convex eyes and flapping pterodactyl tremor of both upper limbs 2. Mucous edema, etc.
Aortic disease	Double lower limb weakness, difficulty in breathing, etc.	Aortic murmur; abnormal blood pressure distribution in the extremities: double upper limb blood pressure, double lower limb blood pressure, etc.
Pituitary adenoma	Gigantism, acromegaly, galactorrhea; headache, nausea, vomiting, double vision, etc.	Abnormal physical appearance; visual field defect, etc.
Hyperparathyroidism	Recurrent urinary stone, bone pain, etc.	No special

examination, clues related to secondary hypertension were carefully collected and analyzed. For suspicious objects with clues, relevant laboratory examinations and clinical experiments were further conducted to identify the cause of secondary hypertension.

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3 Significance of General Laboratory Examination in the Diagnosis of Secondary Hypertension

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Routine biochemical examinations should be carried out for all patients with hypertension, most of which can be completed in clinics of community health service centers and primary medical units. The purpose of routine biochemical examination in patients with hypertension is to combine medical history and physical examination to evaluate patients as follows: first, to identify the etiology of hypertension and to find evidence of secondary hypertension; second, to look for other risk factors related to risk stratification for high blood pressure except blood pressure level, such as diabetes and dyslipidemia, and determine the degree of target organ damage, such as microalbuminuria. The above assessment can provide a basis for the hypertensive etiological diagnosis, disease evaluation and further treatment decision. The examination should be carried out from simple to complex according to the clues provided by the routine examination, to provide direction for the further diagnosis. Screening for partially specific secondary hypertension needs to be transferred to a specialist hospitalization.

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3.1 Routine Laboratory Blood Tests

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3.1.1 Blood Routine

3.1.1.1 Red Blood Cells

Increased erythrocyte can lead to high blood pressure, which is common in secondary hypertension caused by primary erythrocythemia or excessive use of erythropoietin; the increase of erythropoietin due to chronic sleep hypoxia in patients with obstructive sleep apnea hypopnea syndrome, leading to secondary erythrocytosis; at the same time, patients with hypertension may have a relative increase in red blood cells, which can be alleviated by lowering blood pressure. In addition, red blood cells are able to present the basic health status of patients. In the accelerated hypertension, there can be Coombs test negative microangiopathic hemolytic anemia, accompanied by deformed red blood cells. In the case of chronic renal insufficiency also appear anemia, the anemia is positive cell positive pigment anemia. When the serum creatinine exceeds 2 to 3 mg/dl, the hematocrit decreases, and in the end stage renal disease, the hematocrit is 15 to 30%. At this point, anemia only can help assess kidney function, while the causal relationship between hypertension and kidney function needs to be determined by the combination of medical history and other tests.

3.1.1.2 White Blood Cells

The increase of leukocyte count is a predictor of the progression of hypertension, which may be related to insulin resistance and hyperinsulinemia, and the increase of leukocyte count is associated with increased risk of vascular disease, which was found in the Framingham population. In patients with secondary hypertension caused by autoimmune system diseases such as systemic lupus erythematosus and polyarteritis nodosa, as well as in women with preeclampsia, the leukocyte counts also increased with volatility, which is closely related to abnormal activation of the immune system.

3.1.1.3 Platelets

Platelet counts are usually normal, but the concentration of purine dinucleotide vasoconstrictor in platelets in patients with hypertension is higher than in healthy control.

Platelet function activation is prevalent in patients with hypertension (whether primary or secondary), which is more pronounced in some patients with secondary hypertension, such as PIH, obstructive sleep apnea hypopnea syndrome, including high shear force, activation of renin-angiotensin-aldosterone system, endothelial changes, etc.

3.1.2 Serum Potassium

The normal range was 3.5–5.3 mmol/L (flame photometer method).

3.1.2.1 Hypokalemia (K^+ <3.5 mmol/L)

The most common cause of hypertension with hypokalemia is the loss of potassium ions through the kidney (renal potassium loss).

The criteria for renal potassium loss were as follows: when serum potassium was lower than 3.5 mmol/L, 24 h urinary potassium was more than 25 mmol/L; or serum potassium was lower than 3.0 mmol/L, 24 h urinary potassium was more than 20 mmol/L. Renal potassium loss can be divided into hypokalemia with acidosis and hypokalemia without acidosis according to blood gas analysis.

Hypokalemia with acidosis was mainly seen in renal tubular acidosis, and blood gas showed hyperchlorinated metabolic acidosis. At this time, hypokalemia was not related to hypertension. Serum potassium showed a slight decrease, generally not less than 3.0 mmol/L, and urinary titratable acid have great value for the diagnosis.

Hypokalemia without acidosis can be divided into two categories: hypokalemia with hypertension and hypokalemia without hypertension.

1. Hypokalemia with hypertension.
   (a) High renin and high aldosterone.
      - Renin secreting tumors, certain Wilms tumors, kidney cancers, and occasional extra-renal malignancies (lung, liver, pancreas, ovary, bladder, adrenal gland, etc.) are capable of secreting large amounts of renin, causing severe hypertension, high renin, hyperaldosteronism and hypokalemia syndrome, in which case CT or MRI examination can help to confirm the diagnosis.
      - Renal artery stenosis: the decrease of renal artery blood flow caused by renal artery stenosis leading to the secondary increase of aldosterone, resulting in hypertension and hypokalemia, which can be clearly diagnosed by color Doppler ultrasound and angiography of renal artery.
      - Other diseases cause secondary aldosterone increase, such as potassium loss nephropathy and advanced pyelonephritis, also often have hypertension with hypokalemia syndrome, which can be diagnosed according to the characteristics of medical history and related targeted examination.

   (b) Low renin and high aldosterone.

   Primary aldosteronism, adrenocortical secretion of excessive aldosterone, resulting in sodium retention and potassium excretion. The increase of blood volume and the activity of renin-angiotensin system were inhibited, such as hypertension and hypokalemia.

   (c) Low renin and low aldosterone.
      - Liddle syndrome: an autosomal dominant monogenic disorder characterized by hypertension, hypokalemia, low renin activity, and low aldosterone. The mechanism is that the increase of ENaC activity caused by the muta-

tion of (ENaC) gene in epithelial sodium channel increases the reabsorption of sodium in renal tubules, and high volume caused by sodium retention will inhibit the renin-angiotensin-aldosterone system. Only renal tubular sodium ion transport inhibitors—triamterene and amiloride were effective for therapy; spironolactone and dexamethasone were ineffective.

- Congenital adrenal cortical hyperplasia (CAH): It was mainly found in 11-β hydroxylase deficiency and 17-α hydroxylase deficiency, with high volume, hypernatremia, hypokalemia, alkalosis, and inhibition of renin-angiotensin-aldosterone system. However, it often affects the synthesis of androgen in adrenal reticular zone at the same time, so most of these patients have abnormal sexual development. Among them, hypertension and hypokalemia in patients with 11-β hydroxylase deficiency were caused by a large number of deoxycorticosterone, which caused androphany in women and precocious puberty in men. Estrogen, androgen, and cortisol were decreased in patients with 17-α hydroxylase deficiency, and sexual hypoplasia in female patients. The male patient was pseudohermaphroditism.

(d) Normal renin and aldosterone.

Cushing's syndrome, especially adenocarcinoma and ectopic ACTH syndrome can cause hypokalemia. However, its characteristic signs and abnormal cortisol levels and rhythms in blood and urine are helpful for diagnosis.

2. Hypokalemia without hypertension.

The main cause of hypokalemia without hypertension include the use of diuretics, Bartter syndrome and Gitelman syndrome. Bartter syndrome and Gitelman syndrome are autosomal recessive genetic diseases, which lead to sodium reabsorption disorder caused by gene mutation, and then lead to hyper-renin and hyperaldosteronemia, resulting in potassium ion loss through the kidney and caused hypokalemia. Compared with Batter syndrome, Gitelman syndrome is more complicated with hypocalcemia and hypomagnesemia, and needs gene detection for final definition.

3.1.2.2 Hyperkalemia (K^+ >5.3 mmol/L)

After excluding pseudohyperkalemia or potassium redistribution, when serum potassium >5.0 mmol/L, the renal potassium clearance rate decreased. Renal potassium clearance was decreased when renal function was severely impaired (GFR < 20 mL/min) or accompanied by moderate renal insufficiency (GFR, 20–60 mL/min) and collecting tubule function under average. In the latter case, the patient may develop hyperkalemic renal tubular acidosis (HRTA). Hyperkalemia can occur in the progressive stage of renal insufficiency, but due to the strong compensatory ability of the kidney to potassium excretion, hyperkalemia does not occur until GFR < 5–10 mL/min. Long-term use of angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor antagonistic (ARB), and potassium-preserving diuretics (such as spironolactone) should be alert to the possibility of hyperkalemia, especially in hypertensive patients with renal

insufficiency. Gordon syndrome is a special form of low renin hypertension, also known as familial hyperkalemic hypertension or type II pseudoaldosteronism, which is volume-dependent and often presents familial disease. The disease is caused by congenital defects in renal tubular function, characterized by hypertension, hyperkalemia, and normal renal tubular function, often accompanied by hyperchlorinated acidosis, and in severe cases may have muscle weakness, short stature, and mental retardation. Thiazide diuretics for the treatment or low sodium intake are effective.

3.1.3 Blood Glucose

1. Fasting blood glucose 7.0 mmol/L or 2-h postprandial blood glucose 11.1 mmol/L is the threshold for the diagnosis of diabetes mellitus (the above indicators are intravenous plasma glucose). Impaired fasting blood glucose (IFG) and impaired glucose tolerance (IGT) are also known as prediabetes. Diabetes mellitus and prediabetes mellitus are the main risk factors of cardiovascular disease risk stratification in patients with hypertension, and hypertensive patients with glucose metabolism disorder are at high risk. Medication for hypertension and other coexisting risk factors or diseases should be initiated immediately.
2. The diagnostic criteria for diabetes published by WHO and ADA are as follows: Table 3.1

Table 3.1 Comparison of WHO and ADA diagnostic criteria for diabetes mellitus

Diagnosis/method	WHO 2006 [1]/2011 [4]	ADA 2003 [2] and 2012 [3]
Diabetes		
HbA1c	Useable	Recommend
	If measured ≥6.5% (48 mmol/mol)	≥6.5% (48 mmol/mol)
	Recommend	
FPG	≥7.0 mmol/L (126 mg/dL)	≥7.0 mmol/L (126 mg/dL)
	or	or
2hPG	≥11.1 mmol/L (200 mg/dL)	≥11.1 mmol/L (200 mg/dL)
IGT		
FPG	<7.0 mmol/L (126 mg/dL)	<7.0 mmol/L (126 mg/dL)
		Not necessary
2hPG	≥7.8–<11.1 mmol/L	If measured 7.8–11.0 mmol/L
	(≥140–<200 mg/dL)	(140–198 mg/dL)
IFG		
FPG	6.1–6.9 mmol/L	5.6–6.9 mmol/L
	(110–125 mg/dL)	(100–125 mg/dL)
2hPG	If measured	–
	<7.8 mmol/L (140 mg/dL)	

HbA1c glycosylated hemoglobin, FPG fasting plasma blood glucose, IFG impaired fasting blood glucose, IGT reduced glucose tolerance, 2hPG plasma blood glucose 2 h after load

3. The significance of diagnosis of diabetes mellitus in early stage for diabetic hypertension

   Diabetic (DM) patients are prone to hypertension, accompanied by obvious metabolic disorders and more serious target organ damage, therefore, with diabetic hypertension is a special type of hypertension, its etiology and pathogenesis has not been fully elucidated. It is generally believed that the occurrence of hypertension in patients with type 1 diabetes mellitus is related to the occurrence and progression of diabetic nephropathy. Hypertension in patients with type 2 diabetes often occurs before or at the same time, is essential hypertension, can also occur after kidney disease, then blood pressure can be further elevated. The mechanism of type 2 diabetes mellitus complicated with hypertension is more complex, which is related to genetic factors, insulin resistance, environmental factors (obesity, smoking, high salt diet), RAAS activation and high reactivity, atherosclerosis, etc. Hypertension can also accelerate the development of diabetic nephropathy, so that glomerular filtration rate is reduced, and that two form a vicious circle.

   With diabetic hypertension patients, double risk factors significantly increase the risk of large blood vessels and microvascular lesions, accelerate the development of heart disease, stroke, kidney disease, and retinopathy, resulting in a significant increase in mortality and disability rates in patients. Therefore, early and accurate screening of patients with glucose metabolism disorders, in order to actively intervene in clinical blood glucose and blood lipid levels, guide the rational selection of antihypertensive drugs, and to provide a basis for the establishment of antihypertensive aim, achieves the prevention and treatment goal of preventing the target organ damage and cardiovascular events.
4. For hypertensive patients with diabetes mellitus, blood pressure control requirements are as follows:
   (a) The 2018 version of the ADA guidelines requires blood pressure control targets of <140/90 mmHg; patients with younger age, proteinuria, and other cardiovascular risk factors more than hypertension and diabetes can control blood pressure to <130/80 mmHg [5].
   (b) Guidelines for the prevention and treatment of type 2 diabetes mellitus in China (2017 edition) [6], Japan, Taiwan China, International Association of African Hypertension (ISHIB) guidelines set the blood pressure <130/80 mmHg as the blood pressure control target for most patients. Because people in these areas have a higher risk of stroke, more stringent blood pressure control strategies help minimize the risk of stroke.
5. For hypertensive patients with diabetes mellitus, blood glucose control requirements are as follows:

   The 2018 ADA guidelines still use glycosylated hemoglobin as the preferred evaluation indicator [7], HbA1c < 7.0% is the blood glucose control target, while the FGP < 6.7 mmol/L (120 mg/dL) and postprandial blood glucose <9–10 mmol/L (160–180 mg/dL) are presented. However, blood glucose control targets should be individualized and determined according to the patient's specific condition.

   Hypertensive patients are often accompanied by abnormal glucose metabolism, only to check fasting blood sugar will miss a lot of patient with abnormal glucose

tolerance or diabetic patients who mainly increase blood glucose of 2 h after the meal, and oral glucose tolerance test (OGTT) can make up for this deficiency. Metabolic syndrome (MS) is a group of clinical syndromes that seriously affect human health with central obesity or overweight, diabetes or abnormal glucose metabolism, hypertension, and lipid disorders as the main components. MS patients have a high risk of early cardiovascular disease and cerebrovascular disease, which seriously affects people's health. The purpose of diagnosing metabolic syndrome is to make medical staff to fully examine the patient objects that they face, from a holistic, systematic, and organic perspective, to detect possible cardiovascular risk factors in patients, and to intervene earlier and more comprehensive, in order to prevent type 2 diabetes, reduce cardiovascular events, and reduce disability and fatality rates in patients. For this part of the patient, when choosing a drug, try to choose drugs that are beneficial or neutral to glucose metabolism, such as angiotensin converting enzyme inhibitors, angiotensin receptor antagonists or calcium antagonists, and alpha-receptor antagonists, while avoiding the use of high-dose thiazide diuretics and other antihypertensive drugs that have a negative impact on glucose metabolism. In addition, beta blockers can reduce the rapid heartbeat caused by catecholamine release when hypoglycemia, which can mask the adverse effects of hypoglycemia.

The endocrine system diseases such as pheochromocytoma, hyperthyroidism, and cortisol hyperplasia are characterized by the increase of blood glucose hormone secretion which can cause secondary diabetes mellitus at the same time of blood pressure elevating. The patient has the characteristic change of the primary disease except blood glucose and islet B cell autoantibodies, and glucose metabolism disorders will improve with the cure or remission of primary diseases. The obstructive sleep apnea hypopnea syndrome is prevalent in insulin resistance and a series of glucose metabolism disorders caused by insulin resistance, which are related to the activation of sympathetic nervous system, hypoxia, increased secretion of glucocorticoid, obesity, and other factors. Effective ventilator CPAP treatment can significantly improve the body's ability of glucose regulation.

3.1.4 Blood Lipids

Blood lipid is the general name of lipid in serum, and its main components are cholesterol (CH), triglyceride (TG), phospholipid, and free fatty acid. Triglycerides and cholesterol, which are closely related to clinical practice, must bind to apolipoproteins to form lipoproteins in order to dissolve in the blood and be transported to tissues for metabolism.

Lipoprotein is divided into chylous microparticle (CM), very low density lipoprotein (VLDL), intermediate dense lipoprotein (IDL), low density lipoprotein (LDL), and high density lipoprotein (HDL). In addition, there is a lipoprotein called lipoprotein (a) [Lp (a)].

Essential hypertension, as a component of metabolic syndrome, is often accompanied by lipid metabolism disorder. Patients with diabetes mellitus, hypothyroidism, nephrotic syndrome, Cushing syndrome, obstructive sleep apnea hypopnea

syndrome also suffer from high blood pressure and dyslipidemia; in addition, there are still multiple metabolic disorders.

Serum total cholesterol ≥5.7 mmol/L (220 mg/dL) or low density lipoprotein >3.3 mmol/L (130 mg/dL), or high density lipoprotein <1.0 mmol/L (40 mg/dL) is one of the risk factors of cardiovascular disease risk stratification in patients with hypertension. Low density lipoprotein (LDL-C) is the first target of lipid-regulating therapy (Class I recommendation, Class A evidence). Non-high density lipoprotein cholesterol (non-HDL-C) is used as a secondary intervention target for lipid-regulating therapy in the prevention and treatment of ASCVD and its high-risk population (Class IIa recommendation, Class B evidence). Non-HDL-C refers to the sum of cholesterol contained in lipoproteins except HDL, which is calculated as follows: non-HDL-C= TC − HDL-C. It is applicable for individuals whose TG level is 2.3–5.6 mmol/L (200–500 mg/dL) and whose LDL-C is not high or who have achieved the treatment goal. There are international guidelines for blood lipids that recommend non-HDL-C as the primary goal of primary and secondary prevention of ASCVD [8].

1. Definition and clinical classification of dyslipidemia.
   (a) Definition of dyslipidemia

   The reference ranges of normal blood lipid were as follows: (1) TC: 3.1–5.7 mmol/L (120–220 mg/dL), (2) TG: 0.4–1.7 mmol/L (35–150 mg/dL), (3) HDL-C: 1.0–1.6 mmol/L (38.6–61.8 mg/dL); (4) LDL-C: 0–3.4 mmol/L, (0–131.3 mg/dL), in which "dyslipidemia" was diagnosed as long as there was one abnormality.

   (b) Classification of dyslipidemia: It is complex, the simplest is etiological classification and clinical classification, and the most practical is clinical classification [8, 9] (Table 3.2).
2. Overall cardiovascular risks assessment process.

   At present, the core contents of the guidelines for the prevention and treatment of dyslipidemia at domestic and overseas include the assessment method of the overall risk of ASCVD and the criteria of risk stratification. It is the core strategy of prevention and treatment of dyslipidemia to take different intensity intervention measures according to the risk of ASCVD, and the overall cardiovascular risk assessment is the basis of the treatment decision of dyslipidemia. Because the incidence of hypertension in China is much higher than that in Europe and the United States, hypertension is the primary risk factor for cardiovascular and cerebrovascular events in the population of our country, so

Table 3.2 Clinical classification of dyslipidemia

	TC	TG	HDL-C	Be equal to WHO phenotype
High TC emia	Increase			IIa
High TG emia		Increase		IV, I
Mixed hyperlipidemia	Increase	Increase		IIb, III, IV, V
Low HDL-C emia			Decrease	

hypertension is listed separately as the most important risk factor in the risk stratification. At the same time, hypertension was ranked first in the list of risk factors.

3. Core content and update of the 2016 European ESC/EAS guidelines for the management of dyslipidemia [10, 11].
   (a) Reaffirm the significance of overall risk management: the new guidelines of the European Society of Cardiology (ESC) and the European Society of Atherosclerosis (EAS) emphasize that interventions should be based on the overall cardiovascular risk of the individual. For asymptomatic people over 40 years of age without cardiovascular disease, diabetes, chronic kidney disease (CKD), or familial hypercholesterolemia (FH), the application of the system coronary artery risk assessment (SCORE) [12] risk assessment tool is recommended to assess overall future cardiovascular risk. For the younger population, two new indicators, risk age and lifelong risk were added, and the accuracy of risk assessment, prevention, and treatment stratification were improved.
   (b) The classification of very high risk population was expanded: transient ischemic attack (TIA) and atherosclerotic plaques found by coronary angiography or ultrasound were classified as very high risk population.
   (c) It is confirmed that LDL-C is the core target and the target value is refined according to the risk stratification. See Table 3.3 for details.

   The new guidelines recommend stricter LDL-C targets for people at higher risk. For high-risk and very high risk patients, such as low baseline LDL-C level, LDL-C is still required to be reduced by ≥50%, and the basic concept of "lower and better" LDL-C is further emphasized in order to improve the prevention and treatment expectation of ASCVD.
4. Other blood lipid levels.
   (a) Apolipoprotein A1: The level of serum ApoA1 can represent the level of HDL, which is positively correlated with HDL-C, and its clinical significance is similar, but the rise and fall of ApoA1 is not necessarily proportional to the change of HDL-C.
   (b) Apo B: There are two kinds of apolipoprotein B—Apo B48 and Apo B100. The former mainly exists in CM and the latter mainly exists in LDL, except for special explanation, clinical routine testing of Apo B usually appoint the

Table 3.3 2016 LDL-C treatment targets recommended in the ESC/EAS guidelines based on risk stratification

Risk stratification	LDL-C Treatment target value
Very high risk	LDL-C <1.8 mmol/L, LDL-C baseline for 1.8–3.5 mmol/L, at least decrease 50%
High risk	LDL-C <2.6 mmol/L, LDL-C baseline for 2.65–2 mmol/L, at least decrease 50%
Middle-low risk	LDL-C <3.0 mmol/L

WHO World Health Organization

Apo B100. Therefore, serum ApoB mainly represents the level of LDL, which is positively correlated with the level of serum LDL-C, and its clinical significance is similar to that of LDL-C. In rare cases, the measurement of Apo B and LDL-C synchronously is beneficial to the clinical diagnosis of "hyperApo B," that is, the increase of blood Apo B and the low level of LDL-C.

(c) Lipoprotein (a) "Lp (a)": The concentration of serum Lp (a) was mainly related to heredity and was not affected by sex, age, body weight, and most cholesterol-lowering drugs. The risk of coronary heart disease is significantly increased in patients with blood concentration above 300 mg/L level, suggesting that Lp (a) may have atherogenic effect, but there is still a lack of clinical evidence [13]. In addition, the increase of Lp (a) can also be seen in a variety of acute phase response, nephrotic syndrome, diabetic nephropathy, pregnancy, taking growth hormone, etc. Lp (a) is considered to be an independent risk factor for ASCVD excluding all kinds of stress elevation.

3.1.5 Serum Uric Acid

Uric acid is the end product of purine metabolism. The increase of serum uric acid is mainly caused by the increase of nucleic acid metabolism and the decrease of excretion. The former includes intake of high purine foods and high catabolic diseases, such as tumors and leukemia, while the latter includes decreased renal function and the effects of certain drugs. In the population, the level of serum uric acid was higher in men than in women, and the level of uric acid increased in women with age or in menopause. Taking diuretics, exercise also can affect the level of uric acid.

Hyperuricemia (HUA) is a metabolic disease caused by purine metabolic disorder, which is closely related to gout, and is an independent risk factor for diabetes, metabolic syndrome, dyslipidemia, chronic kidney disease, and stroke. About half of the patients with untreated hypertension have hyperuricemia, among which gout takes a large number, insulin resistance is their common pathophysiological basis. A large number of studies have shown that HUA is an independent risk factor for hypertension [14, 15]. Serum uric acid level can predict the incidence, long-term blood pressure changes, and prognosis of hypertension. For every 60 μmol/L increase in serum uric acid level, the risk of hypertension increased by 15% ≤ 23% [16].

Diuretics can promote the reabsorption of uric acid in the proximal tubules of the kidney, lead to the increase of uric acid level and induce the paroxysm of gout; aspirin can competitively inhibit uric acid excretion; renal insufficiency is also often accompanied by increased uric acid. However, if it is accompanied by a significant increase in serum uric acid, it should be further examined to exclude lead poisoning nephropathy. Hyperuricemia in hypertensive pregnant women is an important symptom of preeclampsia. For HUA patients with hypertension, coronary heart disease, or heart failure, if serum uric acid is more than

480 μmol/L, it should be treated with drugs to reduce uric acid, which can effectively prevent and treat cardiovascular diseases and reduce the incidence of cardiovascular events [17, 18].

3.1.6 Hypersensitive C-Reactive Protein (CRP)

In patients with early asymptomatic hypertension, increased CRP levels are associated with coronary events, stroke, and peripheral vascular lesions. When hypersensitive C-reactive protein >2.0 mg/L, it indicates an increased cardiovascular risk, which is helpful for early intervention. But CRP is produced when the body is injured by inflammation and lacks better specificity for cardiovascular disease. As a valuable inflammatory marker, hypersensitive C-reactive protein is closely related to all types of secondary hypertension related to immune activation.

3.1.7 Plasma Insulin Levels

Detection of serum insulin levels and understanding of insulin secretion curves can be used to determine the existence of insulin resistance. Insulin resistance exists in many patients with essential hypertension and secondary hypertension, such as obstructive sleep apnea hypopnea syndrome and Cushing's syndrome. Insulin resistance can also be evaluated by dynamic balance model. The formula is: fasting blood glucose (mmol/L) × fasting insulin (μU/mL)/22.5.

3.1.8 Renal Function

The most commonly used indexes to evaluate renal function in clinical practice are serum creatinine (Cr) and blood urea nitrogen (BUN), which can indirectly estimate glomerular filtration function. If the degree of elevation does not match the course of hypertension, it is highly suspected to be renal hypertension.

Serum creatinine (Cr) is the terminal metabolite of creatine in muscle tissue, and its concentration is relatively constant. It is the main index for the diagnosis of acute or chronic renal failure and chronic renal insufficiency. Blood urea nitrogen (BUN) is the end product of protein metabolism, which can reflect glomerular function and evaluate the overall level of renal function, and is more closely related to uremia. Because the blood BUN is affected by many factors, the high decomposition state in the body caused by any reason, such as infection, high fever, dehydration, gastrointestinal bleeding, and so on, can lead to the increase of blood BUN, so the increase is not necessarily the result of impaired glomerular filtration function. It should be identified in the light of the specific situation. When glomerular filtration function must decrease to more than 1/2, the serum BUN will increase, so neither of these two indexes is a sensitive index to detect the decrease of filtration function and monitor its changes in the early stage.

3.1.9 Homocysteine (Hcy)

Homocysteine, also known as homocysteine, is a sulfur-containing amino acid, which does not belong to 209 amino acids that make up protein. It can't be synthesized in vivo, only come from the catabolism of methionine. Some studies have shown that the increase of Hcy level is closely related to the occurrence and development of hypertension: High Hcy activates angiotensin converting enzyme by inhibiting the production of endogenous hydrogen sulfide in vivo, and produces angiotensin II acting on angiotensin 1 receptor. This leads to a series of pathological processes, such as elevated blood pressure and vascular hyperplasia [19, 20]. The increase of Hcy is an independent risk factor for cardiovascular and cerebrovascular diseases, and the increase of VEGF level can increase the risk of atherosclerotic angiopathy, including stroke, by 2–3 times [21].

One of the most important characteristics of hypertension in China is that about 75% of patients are accompanied by elevated Hcy levels [22]. Hcy was positively correlated with blood pressure, cardiovascular and cerebrovascular events, and significantly affected the efficacy of antihypertensive drugs [23]. In order to emphasize its harmfulness and universality, Chinese scholars put forward the concept of H-type hypertension, that is, hypertension complicated with hyperhomocysteine (Hcy $\geq$ 10 μmol/L) [24]. At the same time, Hcy $\geq$ 10 μmol/L is regarded as an important risk stratification factor of hypertension in the guidelines for the prevention and treatment of hypertension in China, and it is suggested that the Hcy of patients with hypertension should be measured synchronously when diagnosis for hypertension, so as to be targeted for treatment.

3.2 Urine Examination

Yuming Peng

Urine is a terminal metabolite produced by glomerular filtration, renal tubule and collecting tube reabsorption, and excretion of blood, and its compositions and characteristics are closely related to the kidney. The capillary wall of the renal tubular basement membrane allows water, ions, sugar, urea, and small molecular proteins in the blood to pass freely, but most of them are reabsorbed into the blood by the renal tubules. The glomeruli filtered about 180 L of liquid every day, 99% of which were reabsorbed by the glomeruli, so the actual daily urine volume of adults (24 h) was about 1000–2000 mL. The generated urine passes through the renal pelvis, ureter enters the bladder for temporary storage, and finally the urine is excreted through the urethra. The changes of urine composition and its content are not only affected by the urinary system and reproductive system, but also related to the physiological or pathological changes of blood circulation, endocrine, digestion, metabolism, respiration, and other systems. Urine analysis

mainly includes routine examination of urine (physical examination, qualitative or semi-quantitative analysis of common chemical components, microscopic examination of visible components in urinary sediment), regular absolute count of cells and tubes in urine (such as determination of 1-h urinary cell excretion rate), special chemical examination of urine, etc. Therefore, urine examination is of great value in the diagnosis and treatment of renal diseases. Urine examination includes:

1. Physical examination: including urine volume (if necessary), color, transparency, smell, and specific gravity (also known as specific density, SG)
2. General chemical examination: including pH, protein, glucose, ketone body, nitrite, bilirubin, urinary cholinogen, occult blood, white blood cells, specific gravity, a total of 10, clinical often referred to as "urine ten" chemical examination.

3.2.1 Examination of General Traits

3.2.1.1 Urine Volume

Healthy adults have a daily urine volume of about 1000–2000 mL, and children measure about three to four times as much per kilogram of body weight as adults. The ratio of diurnal urine volume was 3:1, and the nocturnal urine volume was not more than 750 mL in general.

1. Polyuria: refers to the urine volume exceeding 2500 mL in 24 h. Pathological polyuria is common in diabetes mellitus, diabetes insipidus, and acute and chronic renal failure.
2. Oliguria: refers to 24-h urine volume less than 400 mL, while 24-h urine volume less than 100 mL is anuria. Oliguria and anuria are divided into three clinical conditions: (a) Prerenal oliguria: common in severe dehydration (severe vomiting, diarrhea, massive sweating, extensive burns, etc.), acute blood loss, chronic congestive heart failure, chronic hepatitis, cirrhosis complicated with liver and kidney syndrome, shock, etc. (b) Post-renal oliguria: common in urinary tract obstruction, such as prostate hypertrophy, diabetes with nerve bladder, etc. (c) Renal oliguria: mainly caused by acute and chronic renal failure with various causes.

3.2.1.2 Color and Transparency

The color of urine depends on urochrome and the pH of urine. The most important abnormalities in urine are hematuria, hemoglobinuria, myoglobin urine, etc. Urinary benzidine test and urinary sediment microscopic examination are helpful to distinguish between hematuria, hemoglobinuria, myoglobin urine, etc. Transparency can be expressed by turbidity, and pathological turbidity is related to the content of cells and bacteria in urine.

3.2.1.3 Foam

Normally fresh urine is transparent. If the protein in the urine increases, fine bubbles can appear on the surface of the excreted urine, and these small bubbles are not easy to disappear (for the meaning of urinary protein, see below).

3.2.1.4 Urine Specific Gravity (SG)

The specific gravity of urine reflects the mass of solute per unit volume of urine. The level of SG is related to the moisture, quantity, and properties of crystalline solute in urine, which can roughly reflect the concentration and dilution function of renal tubules. The 24-h total urine specific gravity for normal is 1.015–1.030. If the urine specific gravity is fixed at about 1.010, it is called isotonic urine, suggesting that the concentration function of renal tubules is very poor. Continuous monitoring of urine SG changes is more significant than a single determination.

1. High specific gravity urine: morning urine SG > 1.020 is common, indicating that the concentration function of renal tubules is good, but also common in a large number of sweating, high fever, and dehydration. Persistent high specific gravity urine is mainly found in cardiac insufficiency, early shock, glycosuria, proteinuria, and injection of dextran, mannitol, etc.
2. Persistent low specific gravity urine: SG ≤ 1.010, which is common in acute and chronic renal insufficiency, especially in renal insufficiency caused by chronic pyelonephritis, diabetes insipidus, etc.
3. The significance of urine specific gravity monitoring in fluid replacement: The examination of urine specific gravity has a good guiding effect on clinical fluid replacement and volume expansion treatment of shock. For example, when the volume of shock is rescued and expanded body fluid volume, if the gravity of urine decreases and blood pressure recovers, illustrate the expansion is effective; if the proportion of urine is still above 1.025, the liquid is insufficient and the volume expansion treatment can continue; if the proportion of urine continues to be on the low side, maintain at about 1.010, suggesting acute renal failure, and should limit the amount of fluid.

3.2.1.5 Urinary PH Value

The normal urine was weakly acidic, and pH was about 6.5. With the change of food, pH could fluctuate from 5.0 to 7.0. Persistent acidic urine or alkaline urine is mostly pathological reason. The common causes of persistent acidic urine were high protein diet, fever, dehydration, drugs (ammonium chloride, vitamin C, and other acidic drugs), acute respiratory acidosis, low potassium, metabolic acidosis, and gout. The common causes of persistent alkaline urine are urinary tract infection, metabolic alkalosis, acute respiratory alkalosis, renal tubular acidosis type1, and drugs. When treating urinary tract infection, urine should remain acidic; when treating urate stones, urine should remain alkaline.

3.2.2 Detection of Urinary Protein and Urinary Microalbumin

Normal glomerular filtration membranes allow only small molecules (20–40 KD) of proteins, such as lysozyme, β 2-microglobulin, and immunoglobulin light chains, while medium-molecular albumin (69 KD) and macromolecules (>90 KD) globulin can hardly pass through. Proximal convoluted renal tubules can reabsorb most of the small molecular proteins in the original urine, so the protein content in normal urine is very small, and half of them are Tamm–Horsfall protein and urethral tissue protein secreted by distal renal tubules and ascending branch epithelial cells of medullary loop.

3.2.2.1 Proteinuria Standards (Table 3.4)

Qualitative test positive or quantitative more than 150 mg/24 h urine is called proteinuria. Proteinuria includes Dominant proteinuria and microalbuminuria (MAU). MAU is a sensitive index for the diagnosis of early or mild renal damage, which means that the content of albumin in urine exceeds the reference range of healthy people (<30 mg/24 h) and is lower than the level of urinary protein detected by conventional detection methods [25]. In addition to renal lesions, high-risk factors of cardiovascular system, such as hypertension and diabetes, are the main causes of MAU.

3.2.2.2 Clinical Significance of Proteinuria

According to the mechanism of proteinuria, it can be divided into physiological proteinuria and pathological proteinuria.

1. Physiological proteinuria: refers to the absence of organic lesions in the urinary system, temporary or transient proteinuria in the urine. It can also be divided into (1) functional proteinuria: transient, trace urinary protein, mostly caused by strenuous exercise, high fever, cold, mental tension, etc. The quantity of proteinuria was generally less than 0.5 g < a 24 h, rarely more than 1 g/24 h, and returned to normal after rest or stimulation disappeared; (2) postural proteinuria (orthostatic proteinuria): renal vein pressure increased due to renal displacement and compression of spinal protrusion during upright position. The proteinuria caused

Table 3.4 Proteinuria standards

	Normal	Microalbuminuria	Proteinuria
24 h urine ALB (mg/day)	<30	30–300	>300
UAE (μg/min)	<20	20–200	>200
Urine ALB/Cr (mg/mmol)	<2.5 (male) <3.5 (female)	10–25	>25

24-h urine ALB 24-hour urinary protein quantification, UAE urinary protein excretion rate, urinary ALB/Cr urinary protein creatinine ratio

by poor protein reabsorption through glomerular filtration is called postural proteinuria, which can disappear after bed rest, most of which are found in skinny teenagers, generally <1 g/24 h.

2. Pathological proteinuria: When proteinuria is not affected by receptors and multiple tests are positive, it is called persistent proteinuria, and persistent proteinuria is pathological. However, it is necessary to exclude pseudoproteinuria caused by mixing blood, pus, mucus, and other components in urine. The common pathological proteinuria characteristics are shown in Table 3.5.

   Clinical presence of proteinuria is more indicative of kidney disease. However, the content of urinary protein is not parallel to the severity and renal function of the disease, but is closely related to the nature and location of the disease. Nephrotic hypertension occurs mostly in young adults, the early stage of the disease can appear urinary protein, and the amount is relatively large, can appear hematuria and granular tubular type, some patients with edema and hypoproteinemia. The incidence of essential hypertension with renal injury is late, more

Table 3.5 Characteristic of pathological proteinuria

Classification	Etiology	Characteristic of proteinuria	Quantification of proteinuria	Common disease
Glomerular proteinuria	Injury of glomerular filtration membrane	High molecular weight proteins such as albumin are dominant	>2 g/24 h	Primary secondary glomerular disease
Tubular proteinuria	Proximal tubular lesions with impaired urinary protein reabsorption	Small molecule proteins are dominant	<1 g/24 h	Interstitial nephritis, tubular acidosis, heavy metal poisoning, drugs, and kidney transplantation
Mixed proteinuria	Glomerular and tubular lesions	Urinary proteins of various molecular weights can occur, mainly small and medium molecular weight proteins		
Overflow proteinuria	Normal function of glomerulus and tubule	Most of them are small molecule proteinuria	Usually not much	Abnormal increase of plasma small and medium molecular weight proteins (hemoglobin, myoglobin, light chain)
Histoproteinuria	Destruction of renal tissue or secretion of proteins from renal tubules	/	Minimal proteinuria	Less frequent

common in the elderly, is often after age of 40, hypertension occurs before urine changes, urine protein volume is less, there are few persistent hematuria and erythrocyte tubular type, and renal tubular function damage is more obvious, cardiac, cerebrovascular and retinal vascular sclerosis changes are often more obvious. Some patient manifestation is concealed, cannot judge the distinction of subsequence between hypertension and renal dysfunction. It is difficult to distinguish the two from the medical history, and the diagnosis depends on renal puncture for pathological biopsy. Antihypertensive drug therapy, especially angiotensin converting enzyme inhibitors, can reduce urinary protein, and its reduction degree is parallel to the degree of blood pressure decline, and has the effect of renal protection independent of antihypertensive effect. For patients with high blood pressure with proteinuria, the target blood pressure is below 130/80 mmHg, if 24 h urine protein >1 g, blood pressure should be controlled to 125/75 mmHg, in order to better protect kidney function and delay the deterioration of renal function.

3. Clinical significance of MAU.

Urinary albumin excretion is usually increased in hypertension and is related to the level of blood pressure, which may be related to the increase of glomerular capillary hydrostatic pressure leading to the increase of glomerular filtration permeability, as well as other factors may be involved. The urinary protein excretion and incidence of hypertension patient vary from the etiology, blood pressure level, severity, and course of disease. Although antihypertensive therapy can reduce albumin excretion, and the degree of reduction is parallel to the decline in blood pressure, antihypertensive therapy cannot reduce the incidence of proteinuria.

MAU not only reflects the damage of glomerular endothelial function, but also an important sign of systemic vascular endothelial injury. Vascular endothelial damage is one of the core mechanisms of atherosclerotic lesions. Therefore, the presence of MAU often suggests that the pathophysiological process of atherosclerotic cardiovascular disease has been initiated. Active monitoring and reasonable intervention of MAU have positive significance in reducing the incidence of heart, kidney, blood vessel, and other complications in patients with hypertension and diabetes [26, 27].

(a) Urinary microalbuminuria is a necessary item for examination in patients with diabetes mellitus and hypertension. The occurrence of microalbuminuria strongly indicates progressive diabetic nephropathy in patients with type 1 and type 2 diabetes mellitus. Therefore, MAU is a sensitive index for early diagnosis of diabetic nephropathy, which is of great significance to its clinical stage and prognosis. When the urine routine test is negative in the early stage of kidney disease, the content of urinary microalbumin can change obviously. Without intervention, 20–40% of patients with microalbuminuria developed proteinuria within 5–10 years. Once proteinuria occurs in patients with type 2 diabetes, the decline in renal function will be irreversible and the patient will progress to end-stage renal disease requiring hemodialysis or renal transplantation.

(b) MAU is also an early indicator of hypertensive renal damage. Urinary microalbumin can be increased in mild glomerular lesions. The incidence of urinary microprotein in patients with essential hypertension varies according to the severity and course of hypertension. The treatment of hypertension must be strengthened in MAU positive patients, and their blood pressure should be controlled below 130/80 mmHg.

(c) MAU has important clinical value in the early diagnosis of primary and other secondary glomerular diseases. The increase of urinary albumin excretion can occur in most glomerular diseases in the early stage. Therefore, the monitoring of urinary microalbumin is an important index to observe the curative effect of subclinical glomerular diseases.

Because hypertension and diabetes are the main causes of MAU, for hypertensive and diabetic patients with MAU, it is necessary to emphasize not only the standard of blood pressure and/or blood glucose, but also the standard of urinary protein excretion, so as to ensure the improvement of cardiovascular prognosis of patients.

3.2.3 Urine Red Blood Cells or Occult Blood

Each liter of urine blood content more than 1 mL can be light red, known as naked eye hematuria; The fresh urine was centrifuged and microscopically examined, each high power field of vision red blood cells ≥ 3 is called microscopic hematuria. There can be a very small number of red blood cells in the urine of normal people, which can occasionally cause weak positive occult blood in urine. Women can be positive for occult blood due to menstrual contamination during menstruation.

Clinical significance: Urinary occult blood positive can be seen in glomerulonephritis, urinary tract infection, stones, tumors, and hemorrhagic diseases. The origin of red blood cells can be further identified by observing the size and morphology of red blood cells by phase contrast microscope. The red blood cells discharged through renal units are deformed red blood cells, and the red blood cells that overflow from vascular rupture and overflow outside renal units are homogeneous red blood cells. Since the urine occult blood detected by the urine analyzer includes red blood cells in the urine and hemoglobin overflowed after the cracking of the red blood cells in the urine, urinary occult blood can also be positive in hemolytic diseases, diffuse intravascular coagulation, paroxysmal nocturnal hemoglobinuria, and other diseases.

3.3 Hemorheology

Yuming Peng

Hemorheology is a science that studies how blood and blood vessels complete functional activity and interact. Many clinical diseases are closely related to hemorheological properties, such as coronary heart disease and hypertension. This kind of

disease will cause the human body blood rheological characteristic to change, thus causing the blood microcirculation disturbance. Insufficient tissue perfusion, ischemia, hypoxia, and metabolic disorders even lead to cardiac and cerebral ischemia in severe cases. Hemorheology can provide predictive information for the occurrence and development of certain diseases, and even as a means of predicting certain diseases when there are no clinical symptoms.

3.3.1 Hemorheology and Hypertension

The level of arterial blood pressure depends on cardiac output and peripheral resistance to blood flow. In the development of hypertension, the increase of cardiac output mainly occurs in the early stage of hypertension, and the maintenance of hypertension is mainly due to the increase of peripheral resistance. The main factors affecting peripheral resistance are arteriole contraction and blood viscosity, and many other hemorheological parameters also change blood pressure directly or indirectly by affecting blood viscosity.

3.3.1.1 Hemorheological Characteristics of Obstructive Sleep Apnea Hypopnea Syndrome (OSAHS)

The hemorheological parameters of OSAHS patients were higher than those of normal controls in many terms, such as whole blood high shear viscosity rate, middle shear viscosity rate, low shear viscosity rate, fibrinogen, hematocrit, and sensitive C-reactive protein. The changes of the above parameters were positively correlated with the severity of OSAHS, The more severe the degree of OSAHA, the more obvious the change in blood rheology parameters. Not only the blood viscosity increased, but also the plasma viscosity increased significantly in moderate and severe patients.

Hypoxemia and hypercapnia in patients with OSAHS stimulate the production and release of erythropoietin (EPO) from cells adjacent to glomeruli, secondary increase in the number of red blood cells in the blood, and decrease or even loss of cell deformability. Finally, the whole blood viscosity increased. Nocturnal hypoxia in OSAHA patients can also stimulate the increase of cardiac sodium secretion, enhance the concentration function of distal renal tubules and collecting tubules, and aggravate blood concentration. At the same time, this nocturnal repeated hypoxia can also increase the nocturnal catecholamine level, cause the increase of platelet aggregation ability, and increase the levels of fibrinogen and sensitive C-reactive protein. The combined effect of the above factors not only affects the blood viscosity, but also damages the vascular endothelium, causes the effective perfusion of microcirculation to decrease, is easy to form microthrombus, and aggravates atherosclerosis, which brings a series of clinical consequences.

Various methods of treatment, including oral orthosis, surgically unobstructed airway and ventilator positive pressure ventilation, can improve hemorheological parameters by correcting hypoxia and hypercapnia in various degrees. And then improve the clinical symptoms and metabolic disorder index, so as to change the prognosis.

3.3.1.2 Hemorheological Characteristics of Pregnancy-Induced Hypertension Syndrome

Pregnancy-induced hypertension (PIH) is a kind of microcirculatory disorder and abnormal hemorheology disease. The severity of PIH is related to the degree of placental ischemia. In addition, fetal hypoxia is caused by secondary polycythemia due to placental insufficiency; hypoxia and acidemia will increase whole blood viscosity, decrease erythrocyte deformability, and enhance aggregation and blood hypercoagulability. For the existing vasospasm and pseudocytopenia, it is easy to make the placental circulating bed of PIH patients form a vicious circle.

The whole blood viscosity of normal pregnant women is lower than non-pregnant women except for term, which is beneficial to the decrease of microcirculation resistance and the increase of placental blood flow, and can provide good conditions for the normal development and growth of fetus. It is the physiological compensatory function of the body.

The main pathological change of PIH patients is systemic arteriolar spasm, and blood concentration is its secondary phenomenon. There is a clear relationship between blood concentration and elevated blood pressure. Blood concentration precedes the increase in blood pressure. In severe cases, hematocrit begins to increase at 28 weeks of gestation, which is of great significance in predicting the occurrence of PIH. The decrease of blood volume in patients with severe PIH is related to placental insufficiency, therefore, blood volume supplementation can still improve placental function.

The whole blood viscosity of patients with mild PIH did not increase significantly, but increased slightly. The whole blood viscosity curve of patients with severe PIH increased at different stages. At 32 weeks of gestation, the whole blood viscosity increased 30%. There was a positive correlation between whole blood viscosity and diastolic blood pressure in patients with pregnancy-induced hypertension. Dynamic monitoring showed that the changes of whole blood viscosity in pregnancy-induced hypertension syndrome preceded clinical symptoms (including elevation of blood pressure). The value of increased fibrinogen concentration in PIH is similar to that of whole blood viscosity.

3.3.1.3 Hemorheological Characteristics of Essential Hypertension

Hypertension and high blood viscosity often co-exist in patients with essential hypertension. The increase of whole blood viscosity is often the earliest basic change in the process of essential hypertension, and the level of blood pressure is positively correlated with blood viscosity. In addition to the rheology of blood, the rheological properties of cells also affect the occurrence and development of hypertension. Existing studies suggest that the increase of erythrocyte hardness may be the starting factor of elevated blood pressure. The decrease of erythrocyte deformability is an important rheological cause of hypertension.

Some abnormal hemorheology in hypertension may be the consequence of hypertension, for example the increase of arterial pressure is the main cause of blood concentration caused by the leakage of plasma fluid into the extracellular space. Changes in catecholamine and other hormones in hypertension can increase

fibrinogen concentration, which in turn increases plasma viscosity and erythrocyte aggregation, and high blood viscosity itself can be the cause and risk factor of hypertension. The increase of blood viscosity increases the peripheral resistance and thus promotes and aggravates arteriolar hypertension. During the development of hypertension, the blood viscosity increases before the blood pressure is completely fixed. The increase of blood viscosity was correlated with systolic blood pressure, diastolic blood pressure, and the severity of hypertension. The exact mechanism by which systolic blood pressure, diastolic blood pressure, pulse pressure, and non-dipper blood pressure increase the risk of cardiovascular disease is unclear, but abnormal blood coagulation or endothelial injury/dysfunction may be associated with this. High blood viscosity is also associated with complications of hypertension or other combined diseases, including left ventricular hypertrophy, stroke, hyperlipidemia, coronary heart disease, and chronic renal failure. Therefore, the increase of blood viscosity in hypertension indicates poor prognosis. Therefore, in the treatment of hypertension, we should not only pay attention to the reduction of blood pressure, but also pay attention to the improvement of hemorheology at the same time.

3.4 Ambulatory Blood Pressure and Exercise Blood Pressure

Mei Cao

3.4.1 Ambulatory Blood Pressure

Twenty-four hours ambulatory blood pressure monitoring (ABPM) has been widely used in the world, and it is an important supplement to blood pressure assessment methods such as dual blood pressure measurement and home self-measurement [28, 29] and has become one of the important means to diagnose and evaluate antihypertensive therapy for clinical hypertension [30–32].

Clinical application of ABPM: (1) Early detection of hypertension; (2) Detection and diagnosis of “white coat” hypertension and refractory hypertension; (3) Guidance and evaluation of antihypertensive therapy: (a) Choosing a treatment plan: according to the peak and low time of 24 h dynamic blood pressure of patients, choosing the drug whose action time is suitable for the increase of blood pressure is beneficial to the development of individualized treatment plan, (b) Control of 24 h blood pressure level: it can observe the treatment effect of drugs on the blood pressure rise in a specific time (such as early morning), help to adjust the treatment plan. (c) Reduce adverse reactions and excessive hypotension. (4) Evaluation target organ damage and prognosis. One of the advantages of ABPM is that it can evaluate the circadian rhythm of blood pressure in patients.

The circadian rhythm of blood pressure in patients with hypertension is roughly divided into four types: (1) Normal circadian rhythm: blood pressure of most

patients with low and moderate risk hypertension decreased significantly during sleep at night, but with age, the amount of day and night fluctuation becomes smaller; (2) Circadian rhythm weakens or disappears: more common in Level 3 (severe) hypertension, or with heart, brain, renal target organ damage or related diseases, as well as certain secondary hypertension and severe sleep disorders; (3) Elevated blood pressure at night: in severe autonomic dysfunction, and some of the elderly with obvious atherosclerosis. It is manifested as low or orthostatic blood pressure in the daytime and continuously elevated blood pressure in the night. (4) Pheochromocytoma type: found in pheochromocytoma, renal vascular hypertension, diabetes mellitus with hypertension and very few patients with primary hypertension, often manifested as paroxysmal blood pressure significantly increased and orthostatic hypotension.

The significance of ABPM in the diagnosis of common secondary hypertension: After ABPM found that essential hypertension and secondary hypertension have different circadian rhythms, essential hypertension is similar to normal people, and 66% of patients with secondary hypertension do not have obvious circadian rhythm changes. The blood pressure of patients with pheochromocytoma increased at night, and the difference between the circadian rhythm and the primary hypertension was the greatest. The circadian rhythms of diabetes, nephropathy, primary aldosteronism, and hypertension after kidney transplantation were also significantly different from those of primary hypertension. ABPM can provide some basis for differential diagnosis of the two [33–36].

3.4.1.1 Application of ABPM in Renal Hypertension

At present, hypertension has been considered as the first independent risk factor for accelerated renal function deterioration. The study showed that renal damage was ABPM with hypertensive patients, and it was found that the SBP, DBP and its pressure load of 24 h were significantly increased. The circadian rhythm of blood pressure disappeared in the renal hypertension group, and the nocturnal decrease of systolic and diastolic blood pressure was significantly lower than that in normal people and patients with essential hypertension, and the nocturnal decrease rate of less than 10% was also significantly higher in renal hypertension than that in normal people. Urinary microalbumin is an early manifestation of impaired renal function, which has a poor correlation with occasional blood pressure measurement but is closely related to dynamic blood pressure monitoring. In particular, increased activity of the renin-angiotensin system (RAS) also affects the progression of kidney disease in addition to hypertension and proteinuria. The excretion rates of urinary microalbumin and urinary albumin in patients with non-arytenoid blood pressure were higher than that of patients with ladle blood pressure.

Therefore, we can evaluate the risk of patients with renal vascular hypertension and renal parenchymal hypertension by analyzing the changes of circadian rhythm in ABMP, so as to delay the development of renal damage. More and more nephrology doctors recognize the prevalence and harmfulness of circadian rhythm disorders in patients with CKD, as well as the importance of repairing circadian rhythms of blood pressure.

3.4.1.2 ABPM and Primary Aldosteronism

Primary aldosteronism (referred to as "PA") is the most common endocrine hypertension and is a clinical syndrome characterized by increased secretion of autonomic aldosterone in the adrenal cortex due to high blood pressure, low plasma renin activity, high aldosterone or not with low blood and potassium. By observing the characteristics of ABPM in patients with primary aldosteronism, the load values of nocturnal SBP and DBP were significantly higher than that of primary hypertension, while the circadian rhythm of 82.5% patients disappeared, and the mean of blood pressure during daytime and nighttime was significantly higher than that of patients with essential hypertension. Patients with primary aldosteronism continuously secrete aldosterone during the day or at night to maintain high blood pressure at 24 h. Compared with primary hypertension, patients with PA have a higher incidence of myocardial infarction, arrhythmia, stroke, proteinuria, and other target organ damage, which is extremely harmful to human health**.**

3.4.1.3 ABPM and Pheochromocytoma

Pheochromocytoma is a tumor originated from the residual pheochromocyte of adrenal medulla or adrenal external ganglion. The tumor cells synthesize and release a large amount of catecholamines, which causes the increase of blood pressure, accompanied by the clinical manifestations of sympathetic nerve excitation, and is a common cause of endocrine hypertension. There are two types of clinical feature, paroxysmal hypertension and sudden rise in sustained hypertension. Studies have shown that 93.5% of patients with pheochromocytoma have hypertension, and 61.3% (38/62) of them show continuous increase of blood pressure. The nocturnal mean SBP and PP of the pheochromocytoma group were significantly higher than those of the primary hypertension group ($P < 0.05$), and the circadian rhythm of dynamic blood pressure disappeared in 79.0% of the patients. Patients with pheochromocytoma often present with marked elevation of episodic blood pressure and orthostatic hypotension. Therefore, the circadian rhythm of blood pressure in patients with pheochromocytoma presents a special pheochromocytoma type. Therefore, 24-h dynamic blood pressure monitoring for patients with pheochromocytoma, especially focusing on the control of blood pressure at night, is of great significance for the assessment of target organ damage and prognosis.

3.4.1.4 ABPM and Sleep apnea syndrome

Sleep apnea syndrome is a group of potentially dangerous sleep-related breathing disorder, is listed as one of the most important secondary hypertension, because of recurrent hypoxemia, hypercapnia, etc., can lead to increased sympathetic excitability, disorders of nervous functions, catecholamine, endothelin and renin-angiotensin system disorders, endocrine disorders and hemodynamic changes, systemic multiple organ system damage. At least 30% of patients with hypertension have OSAS, and 45–48% of patients with OSAS have hypertension. Our study showed that compared with the patients with simple hypertension, the nocturnal blood pressure of OSAS patients with hypertension showed a tendency of increasing instead of decreasing, and the normal arytenoid blood pressure was lost. In addition, it was also found

that patients with this condition had increased blood pressure at night, which would increase the load on the cardiovascular system, thus leading to left ventricular hypertrophy and cardiac dysfunction, and increasing the risk of cardiovascular and cerebrovascular events. Therefore, hypertension patients with OSAS should be monitored at night, and the medication time should be adjusted to accidental occurrence.

Therefore, after dynamic blood pressure monitoring, for patients with no reduction in blood pressure at night, attention should be paid to the elimination of secondary hypertension. The decreased or disappeared circadian rhythm of dynamic blood pressure can be seen in severe hypertension, or accompanied by obvious damage to the heart, brain and kidney organs, severe autonomic dysfunction and some obvious atherosclerosis in the elderly also have the phenomenon of continuous increase in blood pressure at night. All these reveal that the loss of circadian rhythm of nocturnal blood pressure is related to the development stage of hypertension, and it is also one of the important characteristics of renal hypertension, endocrine hypertension, and OSAS.

3.4.1.5 ABPM in the Elderly

There is a high incidence of hypertension in old age, and dynamic blood pressure rhythm changes are closely related to the elderly system organ lesions. As you get older, blood pressure showed an upward trend, that is, SBP and DBP increased slightly or significantly with the increase of age. Therefore, normal blood pressure should be determined by age group. Based on some studies (Wiinbery, O'Brien, Batistella) [38–40], AMBP were done in people with age 60–69 and more than 70, the cutoff value of SBP/DBP is shown in Table 3.6.

ABPM has a closer correlation with the prediction of cardiovascular events in the elderly. In elderly patients with multiple organ decline, ABPM is helpful to comprehensively understand the functional status of target organs in the elderly and to evaluate the prognosis, and has important guiding significance for treatment.

3.4.1.6 ABPM for Adolescents

Adolescent blood pressure changes have their own characteristics, susceptible to nerve, body fluids, activities, drugs, and other factors; volatility in different stages of physiological development of blood pressure is different. Teenagers blood pressure standard has not been unified, usually adopts the percentile method, namely the measurement of three or more blood pressure values on the same height with same gender, age, and youth blood pressure percentile comparison, such as average systolic and diastolic blood pressure less than the same gender, age, and youth blood pressure with height of the 90th percentile for normal blood pressure; if the blood pressure is between the 90th and 95th percentiles, or if the blood pressure is greater than 120/80 mmHg but lower than the 95th percentile, it is prehypertension (high

Table 3.6 Reference values of dynamic blood pressure (mmHg) in normal elderly population

	Age (years)	Male	Female
Wiinberg	60–69	134/85	122/76
Wiinberg	>70	131/79	133/77
O'Brien	60–69	121/75	127/74
Batistella	60–69	137/85	124/80

Table 3.7 Classification of blood pressure levels in adolescent ABPM

Classification	Mean ambulate systolic blood pressure	Clinic systolic pressure	Blood pressure load
Normal blood pressure	<95	<95	<25
White coat hypertension	>95	<95	<25
Recessive hypertension	<95	>95	>25
Prehypertension	>95	<95	25–50
Dynamic hypertension	>95	>95	25–50
Severe dynamic hypertension	>95	>95	>50

normal blood pressure). Hypertension is defined as the 95th percentile or higher than 120/80 mmHg.

The application of ABPM is one of the important advances in the diagnosis and treatment of hypertension in adolescents. It is helpful to identify white coat hypertension, diagnose latent hypertension, predict target organ damage, fully reflect the true level of blood pressure at 24 h, and comprehensively reflect the changes of blood pressure in different environments, which has received more and more attention [41] (Table 3.7).

3.4.2 Exercise Blood Pressure

People's understanding of hypertension is mostly limited to the basic and static observation results. When people measure blood pressure,they are asked to stay rest and quiet state. We can find true hypertension patients, however many patients with good blood pressure control and blood pressure are not very high, the incidence of cardiovascular events is not low, and many diseases related to hypertension occur in the commonly considered "normal blood pressure" of the person. Therefore, the clinical need for early assessment of hypertension and risk of hypertension methods and indicators [37, 42].

Athletic hypertension refers to a phenomenon in which the blood pressure exceeds the physiological range of normal people's increased reactivity under a certain exercise load during or just after exercise.

The current studies suggest that it is related to the following two aspects: (1) Sports hypertension is related to vascular endothelial function, atherosclerosis, hypercholesterolemia, and abnormal glucose metabolism. (2) Exercise-induced hypertension is related to the high excitability of sympathetic nerves and the increased secretion of pressurized substances during exercise [43, 44].

The clinical significance of exercise blood pressure: Previous studies have shown that high blood pressure response during exercise can predict the occurrence of hypertension in normal people. Systolic blood pressure during exercise is an independent risk factor for mortality, and the higher the systolic blood pressure during exercise, the higher the mortality of cardiovascular disease. Therefore, exercise blood pressure can early detect hypertension in normal people and evaluate the risk

of hypertension. Excessive increase of blood pressure during exercise indicates poor arterial compliance, which may be caused by atherosclerosis or changes in vascular structure [45–47]. Therefore, the steepness of blood pressure during exercise can be used as a marker of arterial disease to evaluate or predict hypertension, and reducing hypertension during exercise is an effective measure to reduce cardiovascular and cerebrovascular accidents in patients with hypertension. The patients with hypertension have a long asymptomatic period before the increase of blood pressure stability, so early diagnosis and prevention are particularly important. Exercise hypertension is conducive to the screening of key objects for the prevention and treatment of hypertension, which can be used as a supplement to the occasional blood pressure measurement and dynamic blood pressure, applied to the early diagnosis of clinical hypertension and the assessment of the risk of hypertension.

From the correlation between exercise hypertension and diseases, it can be seen that the emergence of exercise hypertension means that the body has been in a sub-healthy state, which should be paid attention to. Current research shows that the intervention of motor hypertension focuses on the improvement of life pattern and regular aerobic exercise, which needs long-term persistence to effectively reduce exercise hypertension. Aerobic exercise is an economic and effective control method.

Since maximal exercise has no physiological similarities with daily activities, exercise blood pressure monitoring which could reflect the blood pressure level in maximal and submaximal exercise and ABPM with routine activity can complement each other, attaches great importance to the patients with obvious high blood pressure in exercise blood pressure monitoring, lowers high blood pressure in exercise and recovery blood pressure circadian rhythm, which has important significance in reducing the morbidity and mortality of cardiovascular disease [48, 49].

3.5 Fundus Examination

Xin Zhao

The central retinal artery is the only artery in the body that can be directly observed in vivo. Therefore, observing the fundus condition of patients with hypertension often helps to understand the degree of damage to the heart, kidney, brain, and other organs of patients, which is of great significance for the diagnosis and prognosis of hypertension.

Hypertensive retinopathy can be divided into two types: progressive (benign) and progressive (malignant)

1. Progressive benign hypertensive retinopathy

   The characteristic of retinal artery in early stage is spasmodic, curving, narrow state and have enhanced reflection of tube wall ,like copper or silver. Retinal vein dilatation can be observed, arteriovenous diameter ratio decreased form normal 3:2 to 1:2, even smaller. Further development may result in retinal edema, hemorrhage, and exudation. Clinical hypertension fundus changes have many

classification methods. At present, Keith-Wagnar classification is still widely used in the world.

Grade I: functional retinal artery stenosis or mild sclerosis, mainly in the second branch and below.

Grade ii: retinal arteriosclerosis degree is more obvious than grade I, arterial stenosis is uneven, and there is arteriovenous cross pressure trace.

Grade iii: in addition to retinal artery stenosis and sclerosis, there are retinal edema, cotton-like spots, hard white spots, bleeding spots, and other retinal diseases.

Stage 4 except stage 3 change, and have visual papilledema.

2. Progressive malignant hypertensive retinopathy

Blood pressure in a short period of sudden and sharp rise, causing retinal and choroidal vascular compensation disorders. Malignant hypertension is often accompanied by fundus, kidney and brain damage, fundus visible arterial significant stenosis, bleeding, exudation, optic disc and surrounding retinal edema. If there is flamelike hemorrhage in the retinal nerve fiber layer around the optic disc, it should be regarded as one of malignant hypertension. Soft exudation indicates the severity of hypertension, and most of the exudation is located in the posterior pole 1–4 pd from optic disc. Microaneurysm and capillary tortuosity and dilation can still be seen. After edema and bleeding subsided, the hard exudate in the deep retina often presents a star-shaped arrangement in the macular area, and the white exudate point with clear edge and irregular shape can also be seen around the optic disc. Fundus fluorescence angiography showed multiple capillary occlusion areas, telangiectasia and microaneurysm, and obvious optic disc leakage [50]

About 70% of patients with essential hypertension have fundus changes. Fundus changes were related to age, blood pressure, and duration of disease. Generally speaking, the older the age, the longer the course of disease, the higher the incidence of fundus changes. Therefore, the treatment of fundus lesions is mainly changed by active, effective and reasonable control of hypertension. Generally, fundus haemorrhagia and exudation can be controlled or improved if blood pressure level lower to target. The serious impact on the patient's central vision is mainly due to the occurrence of complications of advanced retinal arteriosclerosis [51].

3.6 Electrocardiogram and Echocardiography

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3.6.1 Electrocardiogram

Heart is the main target organ of hypertension. It is mainly due to the increase of pressure load. Neurohumoral factors such as catecholamine and aldosterone can affect the characteristics of ion channels of cardiac myocytes. In a short period of

time, electrical remodeling of cardiac myocytes occurs. The impulses caused by cardiac myocytes are transmitted to the surface of human body through cardiac tissue, and recorded by electrocardiogram scanner to display the electric potential change of the heart. The electrocardiogram of patients with hypertension manifests in many forms. In recent years, accumulating evidence has shown that obstructive sleep apnea (OSA) and primary aldosteronism (PA) are closely related to atrial fibrillation (AF).

3.6.1.1 OSA and AF

Recent studies on arrhythmias in OSA patients have shown that the incidence of arrhythmias is high at night. The incidence of arrhythmias in OSA patients is up to 43.3%. Sinus bradycardia, sinus arrest, premature contraction, AF, and ventricular tachycardia are the most common electrocardiographic manifestations (Dimitri et al. [52]). Electroanatomical mapping revealed significant left atrial remodeling in OSA patients, including atrial enlargement, voltage reduction, conduction disorders, and prolonged sinoatrial node recovery time. The estimated prevalence of sleep apnea in patients with AF has been found to be much higher (18–74%) than in controls without AF (3–49%) [53–56]. Hoyer et al. [57] found that there was a high incidence of OSA in patients with recurrent atrial fibrillation. OSA is associated with intermittent hypoxia, hypercapnia, large swings in intrathoracic pressure, autonomic dysfunction, oxidative stress, and inflammation, which may contribute to the development, recurrence, and progression of AF in OSA patients [58–60].

3.6.1.2 PA and AF

Porodko et al. [61] first reported a case of AF with PA about two decades ago. In 2009 [62], AF occurred despite optimal blood pressure and electrolytes in another six cases of report. In several studies on cardiovascular events in patients with primary aldosteronism, a significantly increased rate of AF was reported in patients with PA as compared to patients with essential hypertension. These studies also reported a striking in the relative risk of AF with OR (7–12.1) [63–65]. A recent Swedish nation-wide study showed [66] a doubled prevalence of primary aldosteronism in a large cohort of patients with atrial fibrillation compared with the general population (0.056% versus 0.024%). Medically or surgically treated PA patients showed a lower atrial fibrillation-free survival than EH patients [67].

Many hypotheses have been proposed to explain the higher frequency of AF in PA patients: low potassium concentration per se, the increase in left atrial volume, the excess LVM secondary to both excess aldosterone and hypertension, myocardial fibrosis or ischemia, magnesium losses, and catecholamine potentiation [68]. Furthermore, the proarrhythmic properties of aldosterone may be mediated by an increase in sympathetic drive, a decrease in heart rate variability, a disturbance of baroreceptor function, blunted myocardial norepinephrine uptake, and changes in electrolyte homeostasis [69].

3.6.2 Echocardiography

Echocardiography can realize early diagnosis and detection in hypertensive heart disease because of its high resolution of human soft tissue. In recent years, there have been many studies on the cardiac structure and function of PA and OSA patients, as detailed below:

3.6.2.1 Echocardiographic Findings in PA

1. Left Ventricular (LV) Dimensions: Patients with PA have a greater LV in terms of end-diastolic diameter compared with patients with EH, while the end-systolic diameter is not significantly different [70–72]. Several studies also evaluated LV volumes, with a finding of greater end-diastolic volumes in PA compared with EH, but quite similar end-systolic volumes [73–76].
2. LVM: LVM was increased in PA patients when compared with patients with EH matched for age, sex, and blood pressure levels [72, 77]. According to the study by Muiesan et al., this increased LVM may have been derived directly from the aldosterone excess, causing LV hypertrophy that is "out of proportion" to the increased volume or pressure overload. In six studies, data on LVM in surgically or medically treated patients were available. All patients with APA showed an important reduction of LVM as soon as 1 year after surgery [76, 78], while patients treated with medical therapy needed more time to reach comparable results.
3. LV Systolic Function: The study by Tarazi et al. [79] observed that PA patients had higher ejection fraction and cardiac index compared with EH patients. Similar conclusions were subsequently reported in two different studies by Rossi et al. [80].
4. Left Atrial Dimensions: Six studies evaluated the left atrium morphology, but all of these focused on the antero-posterior diameter only [70, 71, 81]. This measure was significantly increased in PA when compared with EH in three studies [76, 77, 82], while the other three [10, 23, 24] failed to confirm this finding.

3.6.2.2 Echocardiographic Findings in Patients with OSA

1. Left Chamber Dimensions: Left atrial enlargement is reported in 18% of newly diagnosed OSA patients [83], being more common among subjects with moderate-to-severe OSA (52.1%) than in patients with the apnea-hypopnea index (AHI) <15(31%) [84]. Left atrial diameter is higher in patients with severe OSA than in subjects with mild sleep apnea [85]. Several studies showed that both indexed left atrial volume (LAVI) [86–88] and left atrial area (LAA) [89] increase with OSA severity.
2. Left Ventricular Systolic Function: Literature reports concerning LV ejection fraction (EF) and LV fractional shortening in OSA patients are controversial. Some publications show normal LV-EF among patients with OSA [85, 90], and several studies reported no significant differences between OSA severity and left ventricular EF or fractional shortening [86, 87]. However, a study of 411

men, average age of 71 years old, showed that LV-EF is slightly lower in patients with moderate-to-severe OSA than in subjects with AHI <15 [88], and another recent report found that OSA severity is significantly correlated with a reduction in LV-EF.

3. Left Ventricular Diastolic Dysfunction: Previous experimental reports regarding artificially induced OSA in a canine model [90, 91] have shown that each hypoxic episode affects LV diastolic function by increasing left ventricular afterload and that LV systolic dysfunction develops after only 3 months. In humans, OSA-induced systolic and diastolic dysfunction seems to follow a similar pattern, although it typically evolves in a much longer period of time, as it begins by affecting diastolic function, leading to systolic dysfunction only after extended exposure (>10 years).
4. OSA Impact on Right Chambers: Right ventricular dysfunction is a common finding in patients with OSA, and Sanner et al. showed that right ventricular failure is more frequent in patients with OSA even in the absence of any other respiratory conditions [92]. Recent reports showed that the right atrial volume index (RAVI) is higher in subjects with severe OSA than in patients with mild OSA or controls [88].

3.7 Color Doppler Ultrasonography

Zuoreguli Aibaidula

From a clinical point of view, renal ultrasound could contribute to the better evaluation of a hypertensive patient by identifying common causes of secondary HTN originating from the kidney (specific forms of renal parenchymal disease, renovascular HTN), and more recently by detecting renal injury in severe or long-standing essential HTN.

3.7.1 Renal Ultrasound in the Evaluation of Secondary Hypertension

1. Renal ultrasound is the first imaging modality for the detection of renal parenchymal changes. In the early and middle stages of renal parenchymal diseases, ultrasound may be normal, whereas as diseases progress, changes in echogenicity, size, and echotexture of renal parenchyma usually emerge. The most typical finding of renal parenchymal diseases is a diffuse increase in echogenicity of parenchyma of both kidneys with increased or reduced visibility of renal pyramids. Echogenicity increases when there is an increase in material that reflects sound waves back to the ultrasound probe, such as fibrous tissue, proteinaceous casts, vessel wall calcifications, or stones. Decreased cortical echogenicity is related to the magnitude of edema, which is frequently encountered in acute infarction or pyelonephritis. Renal ultrasound can also help to uncover findings of other types of chronic interstitial damage of the kidney, such as deformation

of the outline or papillary necrosis in analgesic nephropathy, or scars from previous pyelonephritis that could contribute to hypertension.

2. Color Doppler ultrasonography provides a functional evaluation of the kidney vasculature through the RRI, a noninvasive and reproducible measure to investigate renal arterial resistance [93]. It is calculated with the following formula: (peak systolic velocity − end-diastolic velocity)/peak systolic velocity. The mean value of three measurements at each kidney is usually considered. A RRI value 0.6 ± 0.1 (mean ± SD) has usually been considered as normal, with a value of 0.70 being regarded as the upper normal threshold [94, 95]. However, this threshold increases with age and a recent population-based study has established reference values for RRI, according to age and sex [95].
3. Renal ultrasound can identify hydronephrosis, a consequence of obstructive uropathy, which can be a cause of secondary hypertension. The most common causes of obstructive uropathy are benign prostate hyperplasia, ureteral stones, or pyeloureteral junction stenosis. Significantly, there are data showing that even unilateral hydronephrosis appears to be sufficient to cause hypertension [96].
4. Renal tumors such as renal carcinoma can be diagnosed with a simple renal ultrasound (when they exceed 1 cm). Among patients with renal cell carcinoma, 40% experience hypertension as a result of increased renin secretion, ureteral or parenchymal compression, and polycythemia.
5. Vesicoureteral reflux (VUR) is a cause of secondary hypertension that can easily be detected by renal ultrasound [97]. VUR results in reflux nephropathy, an entity characterized by renal scarring. It is one of the most common causes of severe hypertension in children [98].

3.7.2 Renovascular Hypertension

Renovascular hypertension, defined as the rise in arterial pressure attributable to reduced perfusion of the kidney, is one of the most important causes of secondary hypertension. In case of suspected renovascular hypertension, first-line diagnostic evaluation includes renal ultrasound with characteristic findings such as the difference in length of more than 1.5 cm between the two kidneys, suggesting the existence of a kidney with perfusion issues [99, 100]. Renal artery Doppler ultrasound is also a widely available method that reliably defines velocity changes consistent with vascular narrowing. In case of a significant renal artery stenosis, the diastolic blood flow is less affected than the systolic one, which leads to a dampened intrarenal, poststenotic waveform called parvus tardus. Other indirect (intrarenal) criteria are a prolonged acceleration time (i.e., the interval measured in seconds between the onset of the wave and the initial systolic peak) (>0.07 s) and a difference in RRI between the two kidneys of at least 0.05. Among the direct criteria are a peak systolic velocity more than 180 cm/s, a renal artery-aorta velocity ratio more than 3.0, and turbulent flow in poststenotic area. For hemodynamically significant renovascular lesions, meaning the presence of at least 60% occlusion, the peak systolic velocity thresholds are considered at 180–200 cm/s [101].

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Special Laboratory Tests

4

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4.1 Polysomnography and Report Interpretation

Yingchun Wang

Sleep disorders have become a prominent medical and public health problem. Nearly 18 million people in the United States suffer from sleep disorders without effective treatment, accounting for about 6% of the population. Up to 42.7% of China's 1.3 billion people suffer from sleep disorders. Insomnia, sleep respiratory disorders, restless regression syndrome, and excessive daytime sleepiness are the most important sleep problems. They are not only the triggers of many errors and accidents, but also the triggers of cardiovascular and cerebrovascular diseases such as hypertension, diabetes, coronary heart disease, and stroke [1–4]. Polysomnography is the most important method to diagnose and study sleep disorders.

4.1.1 Brief Introduction of Polysomnography (PSG)

4.1.1.1 The Purpose of Polysomnography

1. Analysis of sleep structure and monitoring of abnormal electroencephalogram (EEG):

   Polysomnography is the only objective, scientific examination for recording and analysis of sleep so far. Through the monitoring of EEG, chin electromyogram(EMG), and Eye Movement, we can get information about sleep structure and sleep quality objectively, find epilepsy during sleep, and help to evaluate insomnia, depression with insomnia symptoms, and circadian rhythm disorders etc.

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2. Diagnosis of sleep apnea disorders and treatment evaluation: PSG is the gold standard for diagnosis of OSA [5, 6]. When OSA is clinically suspected, indications of PSG examination are [7]: (1) Patients are clinically suspected of OSA-related hypertension, such as sleep snoring, obesity, daytime sleepiness, and anatomical abnormalities of oral-nasopharynx accompanied by characteristic changes of blood pressure; (2) Other clinical symptoms and signs support OSA, such as night asthma, or neuromuscular diseases, which affect sleep; (3) Unexplained daytime hypoxemia or polycythemia; (4) Night arrhythmia with unknown causes, night angina, and morning hypertension; (5) Monitoring the degree of hypoxia during sleep at night to provide objective basis for oxygen therapy; (6) Evaluating the therapeutic effect of various treatment methods on OSA and titrating pressures of continuous positive airway pressure therapy; (7) Screening other diseases with similar symptoms to sleep apnea syndrome.
3. Diagnosis of other sleep disorders: It includes narcolepsy, periodic limb movements during sleep, restless legs syndrome, and various other sleep disorders, such as noctambulism, night terror, nighttime panic attacks, rough movements accompanied by dreams, etc.
4. Other monitoring during sleep according to the need: Cardiovascular function monitoring, dynamic esophageal pH monitoring, transcutaneous or end-tidal CO_2 monitoring, and penile erection monitoring during sleep can help us to find some causes of insomnia and other diseases at night, determine the nature of impotence and so on.

4.1.1.2 Polysomnography

1. Full-night PSG: PSG is continuously and synchronously recording more than ten leads such as electroencephalogram (EEG), electrooculogram (EOG), chin electromyogram (EMG), oronasal airflow, snoring sound, oxygen saturation, rib cage and abdominal movements, electrocardiogram (ECG), body position, and leg EMG during the whole night sleep. All records were automatically analyzed by the instrument the next day and then scored by epochs manually.
2. Split-night PSG: PSG was performed in the first 2–4 h of the same night and then followed by pressure titration of continuous positive airway pressure (CPAP) treatment. Its advantage is that it can reduce the cost of examination and treatment, but only recommended in the following cases: (1) moderate or severe OSA with repeated long duration of sleep apnea or hypopnea and severe hypoxemia; (2) CPAP pressure titrating time should be more than 3 h due to increased rapid eye movement (REM) sleep in late sleep, (3) when patients are in the supine position, CPAP pressure can completely eliminate all apnea, hypopnea, and snoring during REM and NREM sleep. If the above conditions can't be met, it is suggested to choose another night for pressure titration.
3. Testing with Portable Monitors(PM): PM have been widely used in clinical practice which record airflow, respiratory effort, and blood oxygenation at a minimum. PM can enable sleep monitoring under more natural sleep conditions and greatly reduce the cost of examination. PM may be used as an alternative to PSG for the diagnosis of OSA in patients with a high pretest probability of moderate

to severe OSA and should be performed only in conjunction with a comprehensive sleep evaluation [8]. It can also be used for large-scale epidemiological investigation.

4.1.2 Interpretation of PSG Reports

4.1.2.1 Analysis and Evaluation of Sleep Structure

The earliest sleep stages were proposed by Dement and Kleitman, and then summarized into the R&K sleep stages standard by Allen Rechtschaffen and Anthony Kalea of the University of Chicago still in use up to now. Sleep in healthy adults includes non-REM sleep (NREM) and REM sleep (REM). NREM is the first stage of sleep which accounted for 75–80% total sleep time and divided into N1-4 stages from light to deep sleep. REM accounts for 20–25% total sleep time. NREM and REM sleep alternate for about 90 min during and recur 4–6 times the whole night sleep. NREM sleep is mainly in the first half of the night and the duration of REM sleep gradually prolongs in the second half of the night [9]. N3-4 sleep also known as slow-wave sleep because the degree of sleep is very deep, so it is also called deep sleep. In 2007, the American Sleep Medical Association (AASM) published a manuals for the scoring sleep and associated events in which N3 and N4 were merged into N3 [10]. The proportion of each sleep stage varies with age (Table 4.1).

In the analysis of sleep structure, the first step is to evaluate sleep latency, sleep efficiency, total sleep time and sleep cycle, and then judge whether the proportion of each sleep period is within normal range. Sleep efficiency refers to the percentage of total sleep time to the time in bed at night. In the analysis of sleep structure,

Table 4.1 Differences among sleep stages

Sleep stage	Sleep proportion	EEG	Physiological characteristics
N1	2–5%	SEM, LAMF, Vertex sharp waves	Sleep transitional stage, the duration is short and easy to wake up
N2	45–55%	Sleep spindle, K complex	Muscle relaxation and louder sound to wake up
N3	3–8%	Slow-wave activity 20–50%	Sleep deepens gradually and EMG activity further decreased. Not easy to wake up
N4	10–15%	Slow-wave activity ≧50%	Deep sleep stage and is difficult to wake. Sleepwalking and enuresis may occur
REM	20–25%	LAMF, REMs, sawtooth wave	Significant decrease or even disappearance of EMG activity, but eye muscles are active and the eyeball rotates rapidly. Dreams often occur during this period

Note: LAMF low amplitude, mixed frequency activity; SEM slow eye movements; REM rapid eye movements

the first step is to evaluate sleep latency, sleep efficiency, total sleep time and sleep cycle, and then judge whether the proportion of each sleep period is within normal range. Sleep efficiency refers to the percentage of total sleep time to the time in bed. Normal young people should be about 95% and old people can decline in varying degrees. Sleep latency is the time from turning off the light and get ready for sleep to the onset of any stage of sleep which normally is 10–30 min. More than 30 min indicates difficulty in falling asleep. In addition, the awakening time should be less than 5% during the whole night's sleep. Insomnia patients can show decreased sleep efficiency, prolonged sleep latency, increased waking time after falling asleep, decreased total sleep time, increased stage N1, and decreased slow-wave sleep. Insomnia is a common manifestation of depression though about 20% of these patients are presented as excessive sleep. Depression disorders are characterized by prolonged sleep latency, increased number of awakenings, prolonged awakening time during sleep, early awakening, decreased N3 stage, increased REM stage, especially in early sleep. Anxiety disorders are characterized by difficulty in falling sleep, maintaining sleep, and no sense of sleep recovery [11]. Night panic attacks often occur in NREM phase, especially when N2 phase changes to N3 phase. Insomnia often occurs for fear of sleep.

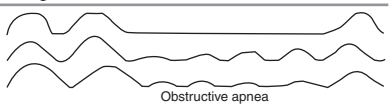
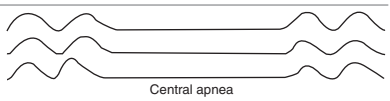
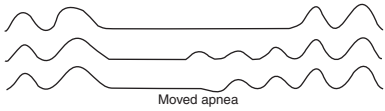
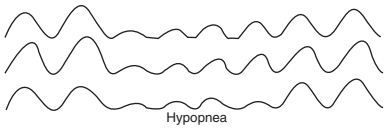
REM sleep is also called contradictory sleep. At this time, except for the diaphragm, the tension of skeletal muscle decreases dramatically, while EEG is in a similar active state of awakening. Dreams often occur during this sleep stage. In the analysis of REM sleep, the main concern is the time from the beginning of sleep to the first appearance of REM sleep, that is, the latency of REM sleep, usually 70–90 min. If it's less than 20 min or REM stage increases, the following factors should be taken into account: (1) severe sleep deprivation before examination; (2) significant delay of bedtime; (3) long-term sleep disorder; (4) abrupt withdrawal drugs which has inhibitory effect on REM sleep, such as antidepressant; (5) Severe OSAHS patients received CPAP treatment for the first time; (6) Night sleep time was shortened. If the above reasons are excluded, screening narcolepsy is needed for shortened REM sleep latency and multiple sleep latency test (MSLT) is helpful to diagnosis.

Arousal is an important parameter in sleep structure assessment. A large number of studies have proved that frequent EEG arousal is closely related to cognitive impairment, sleepiness, and other symptoms of patients [12]. EEG arousal index can be used as an important supplement to the sleep efficiency of patients. In the sleep process of OSA patients, apnea can cause frequent microarousal, also can cause a longer awakening to shorten the total sleep time. Repeated apnea and microarousal, easy to cause night sleep restlessness and sleep fragmentation, leading to increased daytime sleepiness.

4.1.2.2 Analysis and Evaluation of Sleep Respiratory Events

Respiratory events include apnea and hypopnea. Sleep apnea refers to the disappearance or significant decrease of the oronasal airflow during sleep (a decrease of ≥90% compared with pre-event baseline) and a duration of ≥10 s [13]. Apnea is classified as obstructive sleep apnea (OSA), central sleep apnea (CSA), and mixed sleep apnea (MSA). When the sequence of breaths doesn't meet criteria of apnea

Table 4.2 Characteristics of different respiratory events

Respiratory events	Characteristic	Graphic demonstration
OSA	The oronasal airflow is absent and the chest-abdominal breathing still existed	
CSA	The oronasal airflow and the chest-abdominal breathing are absent simultaneously	
MSA	The initial portion of the event is similar to CSA, and the second portion is similar to OSA	
Hypopneas	The oronasal airflow signal amplitude decreased by ≥30% pre-event baseline with oxygen saturation decreased by ≥3% pre-event baseline or associated with an arousal	

and hypopnea, but there is increasing respiratory effort eading to arousal from sleep and lasting ≥10 s, this event is defined as respiratory effort-related arousal (RERA). The commonly used parameters are: (1) apnea hypopnea index (AHI): The total number of apnea and hypopnea divided by the total sleep time. (2) Respiratory disturbance index (RDI): the total number of apnea, hypopnea, and RERA events divided by the total sleep time. (3) Oxygen reduction index: the total number of times of oxygen desaturation divided by the total sleep time (Table 4.2).

Obstructive sleep apnea: Obstructive events are predominant in OSA patients, but there may be a number of central events. Adult obstructive sleep apnea can be diagnosed when the patient has definite clinical symptoms or complications and obstructive events ≥5 times/h or when obstructive events ≥15 times/h. Most respiratory events last 10–30 s, and some events can last up to 1 min or longer. Respiratory events can occur during any sleep period and are more common in N1, N2, and REM than in N3. During respiratory event, oxygen in blood decreases gradually, CO_2 increases gradually, and negative pressure in pharynx increases which cause short-term arousal by stimulating corresponding chemical and baroreceptor, exciting brainstem reticular activation system, then airflow recovers and OSA ends. At present, it is considered that sleep fragmentation caused by arousal is an important reason for excessive daytime sleepiness. In some patients who have daytime sleepiness and snoring and AHI is less than 5 times/h, we can often find frequent EEG arousal which can't be explained by other reasons and signs of increased airway resistance through careful analysis of waveform of airflow and breath movements, snoring and EEG awakening reactions.

Central sleep apnea: In NREM sleep stage I and II, CSA is easy to occur because of shallow sleep and awakening. With the deepening of sleep, the number of awakening decreases, the respiratory regulation tends to be stable, and the number of

CSA decreases when it enters NREM stage III and IV. Respiration relies less on chemical regulation in REM sleep and CSA tends to decrease. The relationship between CSAS and respiratory control dysfunction is clear. Cheyne-Stokes respiration (CSA) and periodic respiration are common types of CSA. Most of them occur in stage I and II of NREM sleep and are found in patients with cardiac insufficiency and newly arrived at high altitude. It is mainly caused by abnormal respiratory regulation which also can been found in cerebrovascular accident, neurodegenerative diseases, encephalitis, etc. When central sleep apnea occurs, and the airflow and the respiratory movement of the chest and abdomen are all disappeared due to the temporary loss of central respiratory drive.

In the analysis of respiratory events, attention should be paid to the influence of body position. According to the relationship between sleep breathing events and sleep posture, OSA patients can be divided into two categories: position-dependent and non-position-dependent. The criteria of position-dependent OSA are as follows: (a) AHI in a supine position is twice or more than that in lateral position; (b) The AHI in lateral position is less than 15 times/h, and the time in lateral position is more than 1 h. Lateral sleeping can sometimes solve the problem in patients with posture-dependent OSA.

4.1.2.3 Analysis and Evaluation of Periodic Limb Movements

The analysis of motor disorders in PSG is mainly the analysis of leg movement. Periodic limb movements of sleep (PLMS) are repetitive and rigid involuntary movements that occur during sleep. Periodic leg movement can occur in the initial stage of N1 sleep, but it is more common in N2, N3, and REM stage. Typical one is characterized by abduction of the thumb of the foot and simple rigid movements accompanied by partial flexion of the ankle and knee joints. Patients often fail to recognize limb movements and sleep not be interrupted. A single movement may last from 0.5 to 10 s. Continuous four or more leg movements, 5–90 s apart can be judged as periodic leg movements. It often occurs intermittently, lasting from several minutes to 1 h. It may involve unilateral lower limbs, typically both sides, but not necessarily in asymmetrical or simultaneous manner. The number of movement divided by total sleep time is called PLMS index (PLMI), that is, the number of periodic limb movements per hour of sleep. When adult PLMI >15 times per hour, attention should be paid to periodic limb movements disorder (PLMD) screening.

AASM scoring manual has clear rules for the analysis of leg movement. It should be pointed out that limb movement events related to sleep disorders are not interpreted as meaningful limb movement events. Therefore, OSA patients need to be treated before PLMS can be identified. PLMS is common in patients with restless legs syndrome (RLS), and in patients with narcolepsy, REM sleep behavior disorders and insomnia. Some PLMS can be associated with autonomic or cortical arousal, which is called periodic limb movement with arousal (PLMA). Current studies have shown that heart rate and blood pressure increase significantly after

PLMS. Sleep fragments induced by PLMS may be associated with hypertension and cardiovascular disease [14, 15].

4.1.2.4 Analysis and Evaluation of ECG

We can observe the changes of heart rate and ECG waveform during sleep and analyze the relationship between arrhythmia and other abnormal waveforms and apnea. Conventional polysomnographic ECG record is a single modified lead II. The most important aspect of ECG analysis is the detection of arrhythmia. During adult sleep, a sustained sinus heart rate of greater than 90 beats per minute is scored sinus tachycardia and less than 40 beats per minute is scored sinus bradycardia. Other common arrhythmias are atrial premature beats, atrial fibrillation, ventricular premature beats, ventricular tachycardia, and atrioventricular block. The waveform of artificial pacemaker also can be recognized.

The autonomic nervous system changes from NREM to REM. During NREM, sympathetic activity decreased to 50% of waking up. With the deepening of sleep, parasympathetic nerve gradually became active, heart rate is slow and regular, blood pressure decreases, and blood flow becomes slow. In REM phase, sympathetic nervous system is over activated and heart rate is rapid and irregular, blood pressure elevated, and oxygen consumption of myocardium increased, which can lead to nocturnal myocardial ischemia, especially in patients with basic heart disease who is prone to angina pectoris and myocardial infarction. The descent or elevation of ST (> 1mm) in myocardial ischemia can be found in PSG, but the sensitivity of single-channel ECG to ischemia assessment is low. If it is not clear, multi-channel ECG should be further evaluated. Sympathetic nervous system is over activated In REM phase, together with the vivid, bizarre, and intense emotional dreams, are prone to ventricular arrhythmia; even induce ventricular fibrillation and myocardial infarction, which lead to serious consequences. OSA patients showed bradycardia during a respiratory event and tachycardia at the end of a respiratory event. Therefore, heart rate fluctuated periodically and heart rate variability increased during sleep in OSA patients.

In addition, pulse transit time (PTT) are used to monitor blood pressure indirectly and continuously by measurement and calculation ECG signal and blood oxygen saturation pulse wave signal, which refers to the time for arterial pressure wave from the aortic valve to the surrounding blood vessels. Before sleep monitoring, PTT is calibrated through matched with brachial artery blood pressure to obtain the fluctuation of blood pressure per stroke at night. In OSA patients, when the obstructive apnea event terminates, significant and transient increases in blood pressure lead to increased vascular tension, stiffness of the arterial wall leads to shortened PTT, whereas when blood pressure decreases, PTT increases. These PTT variation can be calculated and used as indicator for subcortical arousal to assessed changes in nocturnal autonomic nervous system, namely PTT arousal index [16, 17]. Studies have shown that subcortical arousal is associated with over activation of the sympathetic nervous system, which may increase cardiovascular risk and cause daytime sleepiness.

4.2 Venography

Guoliang Wang

Summary: Radiography in a narrow sense refers to angiography: angiography is developed by injecting contrast media through interventional methods [18]. It can be divided into arteriography and venography. The purpose of arteriography is to evaluate the morphological changes of vessels such as stenosis, dilation, occlusion, aneurysm, and dissection. Different from angiography, venography is not usually for diagnosis, but for localization and preparation for subsequent operation, for example, venous blood collection, catheter implantation, electrode placement, and stent implantation. In hypertension-related interventions, these operations involving venography include: renal vein blood collection, adrenal vein blood collection, inferior petrosal sinus vein blood collection, inferior vena cava blood collection, left renal vein stent implantation, etc.

Principle: Venography has its particularity. Unlike anterograde angiography, venography is retrograde angiography because the artery flows to the viscera and the vein flows out of the viscera. Vein pressure is low and arterial pressure is high. High pressure syringe angiography is usually used for arteriography of large vessels. Hand-push angiography is used for small and medium vessels. Hand-push angiography is used for almost all venography, and selective angiography is used instead of non-selective angiography using pigtail catheter.

Approach: The choice of approach is related to the vessel to be reached. When there are many choices, the choice can be made according to the convenience of operation, patient's comfort, the number of complications, the limitation of surgical consumables, and the operation habits. The advantages and disadvantages of various approaches are listed in Table 4.3.

Puncture: The modified Seldinger puncture method is generally used [22], that is, puncture without penetrating the posterior wall, in order to avoid the occurrence of hematoma. The internal jugular vein and femoral vein were punctured blindly except elbow vein. The puncture was performed at an angle of 30–45 parallel to the artery and skin. If you are not sure about blind puncture, ultrasound-guided puncture can be considered, but there is no significant difference between the two [23]. Generally speaking, the technique can be mastered after 50 cases.

Quality assurance of angiography: In retrograde radiography, the intensity is too high and the contrast agent exudates or hematoma appears [20]; the intensity of radiography is too small and the branches or distal ends are not developed; the concentration of contrast agent is too high, the injection is difficult or the patient has irritating pain; the concentration of contrast agent is too low and the development is not clear. The experience of our center is [24]. First, multi-position fluoroscopy is used to coaxialize the catheter and blood vessel as much as possible. Secondly, the contrast agent is concentrated first and then diluted. First, 1 mL of pure contrast agent is slowly injected into the catheter under fluoroscopy, and then 1 mL of diluted contrast agent or heparin water is drawn to connect the catheter. At this time,

Table 4.3 The advantages and disadvantages of various approaches

Approaches	Applicable surgery	Advantages	Disadvantages
Right femoral	Renal vein sampling Adrenal venous sampling Inferior petrosal sinus venous sampling Inferior vena cava sampling Left renal vein stent implantation	High success rate of puncture Two sheaths can be placed at the same time Easy operation Convenient for radiation protection	Postoperative braking and recumbency are needed, and low back pain, urinary retention and lower limb venous thrombosis are prone to occur [19] The puncture site is prone to hemorrhage, hematoma, even arteriovenous fistula or bleeding to the abdominal cavity [20]
Jugular [21]	Nutcracker syndrome	Stent delivery to left renal vein is easier than femoral vein approach	It is sometimes difficult to enter inferior vena cava via superior vena cava Risk of air embolism
Cubital vein [19]	Renal vein and adrenal vein sampling	The operation is minimally invasive, the incidence of puncture point bleeding, hematoma and arteriovenous fistula is low, and there is no need to lie in bed after operation	Respiration has a greater impact on the catheter, and the catheter is prone to prolapse. It is difficult for the left adrenal vein to avoid the inferior phrenic vein
Left femoral vein [20]	As an alternative for right femoral vein puncture: repeated puncture failure of right femoral vein, right femoral vein occlusion, scar infection at puncture site are not suitable for right femoral vein puncture		Less application and low success rate of puncture

the appropriate intensity of the contrast agent is injected, and the adrenal gland or inferior petrosal sinus will be fully developed.

4.2.1 Complications and Prevention

1. *Venous hematoma*: Adrenal vein blood collection, inferior petrosal sinus vein blood collection, need angiographic localization, catheter head or wire pierced the intima of the vascular wall, or the intensity of angiography is too large, may appear adrenal hematoma, inferior vena cava hematoma, internal jugular vein hematoma, etc., the latter two generally have no obvious discomfort, but adrenal hematoma, patients with severe pain, need strong throbbing pain, also have hematoma diameter. Over 4 cm, there was no obvious discomfort in the patients, and the diameter of hematoma was less than 2 cm, which the patients could not tolerate. Because the incidence of adrenal venous blood collection is very low,

according to AVIS (the Adrenal Vein Sampling International Research), the incidence is 0.56% [25], so the cause is unknown, but it is negatively correlated with the number of operations performed by the surgeon. So it's very important to operate softly and carefully and refuse violence. The pain gradually disappeared within 48 h [20], during which analgesics could be used. In order to prevent active hemorrhage or further deterioration, it is recommended to lie still for 5 days and observe the enlargement of hematoma dynamically by ultrasound. Surgery is generally not required.

2. *Mis-penetrating arteries*: Arteries and veins are often parallel; femoral veins and femoral arteries are parallel; basilic veins, median elbow veins, and brachial arteries are parallel; internal jugular veins and common carotid arteries are parallel. When the veins are fully exposed during puncture, special posture can be adopted. The head of the right internal jugular vein is deviated to the left side. The right femoral vein is punctured with 45° of lateral abduction of the right hip joint [26]. The right median elbow vein is punctured with the right elbow joint fully extended and abducted. Distinguishing arteries and veins, arterial blood pressure is big and bright red; venous blood pressure is small and dark; arterial pain is significant and venous pain is weak. If the artery is penetrated by mistake, pull out the needle quickly, remember not to enter the sheath tube, local compression for 5 min can stop bleeding, do not rub the puncture point.
3. *Arteriovenous fistula* [27]: Femoral vein puncture, elbow vein puncture, and internal jugular vein puncture can occur, but the incidence of arteriovenous fistula in the same site of arterial puncture is significantly reduced because the vein is basically blind puncture, except elbow vein. When puncturing, the veins should be fully exposed and the arteries should be avoided. If not skilled, the puncture can be carried out under the guidance of ultrasound. The possibility of arteriovenous fistula should be considered if the bleeding after pulling out the venous sheath is faster, the pressure is higher and the hemostasis is difficult. If the puncture site has large hematoma, hard texture, tremor and systolic murmur during auscultation, the puncture point should be pressed quickly and the ultrasound examination should be performed to make a definite diagnosis. Arteriovenous fistula with less than 3 mm can be closed by compression for 48–72 h. Fistula with more than 3 mm needs surgical suture or ligation of blood vessels.
4. *Hemorrhage at puncture site*: The incidence of bleeding was significantly lower than that of arterial puncture. There was no fatal risk and no pressure bandage was needed. The main cause of bleeding is that the patients do not comply with the doctor's instructions and move in bed or in the ground too early. The risk of hemorrhage at puncture site is very low after 6 h lying on the back, but the bleeding caused by coagulation dysfunction such as thrombocytopenia and abnormal coagulation factors should be fully evaluated and prevented before operation. The hemorrhage manifested as puncture point hemorrhage, subcutaneous hematoma, and subcutaneous congestion. Preventive measures: after operation, pressing the puncture orifice (i.e., the place where the vein enters rather than the skin puncture orifice) for more than

5 min, relieving the compression without bleeding; when coughing or moving the puncture joint may cause the increase of venous pressure, pressing the puncture place should be done; careful observation, once the bleeding is found, pressing treatment in time, whether there is vessel noise in the puncture place, and ultrasound examination should be performed if necessary to exclude arteriovenous fistula.

4.2.1.1 Appendix: Adrenal Venous Sampling

Adrenal Venous Sampling (AVS) is the most commonly used intravenous interventional technique in the specialty of hypertension and the golden standard for the classification and lateral diagnosis of primary aldosteronism [28].

Principle: Intravenous approach, placement of catheter in adrenal vein, venography location, blood determination of cortisol and aldosterone, adrenal/peripheral or adrenal/inferior cortisol ratio to determine whether in place, and bilateral adrenal vein blood aldosterone/cortisol ratio to determine unilateral and bilateral.

Operative classification: AVS stimulated by ACTH and AVS stimulated by non-ACTH were classified according to whether ACTH was applied or not. There are two kinds of stimulation schemes, one is 250 μg intravenous injection, the other is 50 μg/h intravenous injection, and the blood is taken 30 min later. Non-ACTH-stimulated AVS can be divided into synchronous blood collection and non-synchronous blood collection. The 2016 PA Guidelines [28] recommend the preferred ACTH-stimulated AVS. If ACTH-stimulated AVS is not available, synchronous AVS is superior to asynchronous AVS because of the difference of aldosterone and cortisol secretion is caused by pulsed ACTH secretion at different times. Others disagree that although ACTH stimulation is easy to confirm the success of sampling and relieve the fluctuation of aldosterone and cortisol secretion caused by stress, it is laborious and time-consuming and may also reduce the lateralization index, leading to the possibility that some unilateral patients may be misdiagnosed as bilateral.

Suitable patients: Patients with primary aldosteronism (PA) have completed the confirmation test to make a definite diagnosis of proaldehyde. If surgery is feasible and patients agree, AVS is recommended, except for the following cases [29]: (1) age <40 years old and typical PA manifestations, CT scan indicates clear unilateral adrenal adenoma and normal lateral adrenal gland; (2) suspicious adrenal cortical adenocarcinoma; (3) survival; surgical contraindications, such as elderly patients with multiple diseases; and (4) familial hyperaldosteronism I (FH-I) and FH-III (FH-III). The former two can be treated directly by surgical excision of space-occupying lesions or the entire adrenal gland, while the latter two can be treated conservatively without AVS. Expert Consensus 2014 Preoperative Question Flow Chart to determine whether AVS is feasible (Fig. 4.1) [29].

Preoperative preparation: AVS expert consensus in 2014 [29] requires the patient to keep recumbent position for more than one hour before operation. PA diagnosis and treatment guidelines [28] in 2016 require ACTH-stimulated AVS to lie down for more than 1 h before operation, and non-ACTH-stimulated AVS to lie down all night before operation. The standard implemented by our center is that preoperative

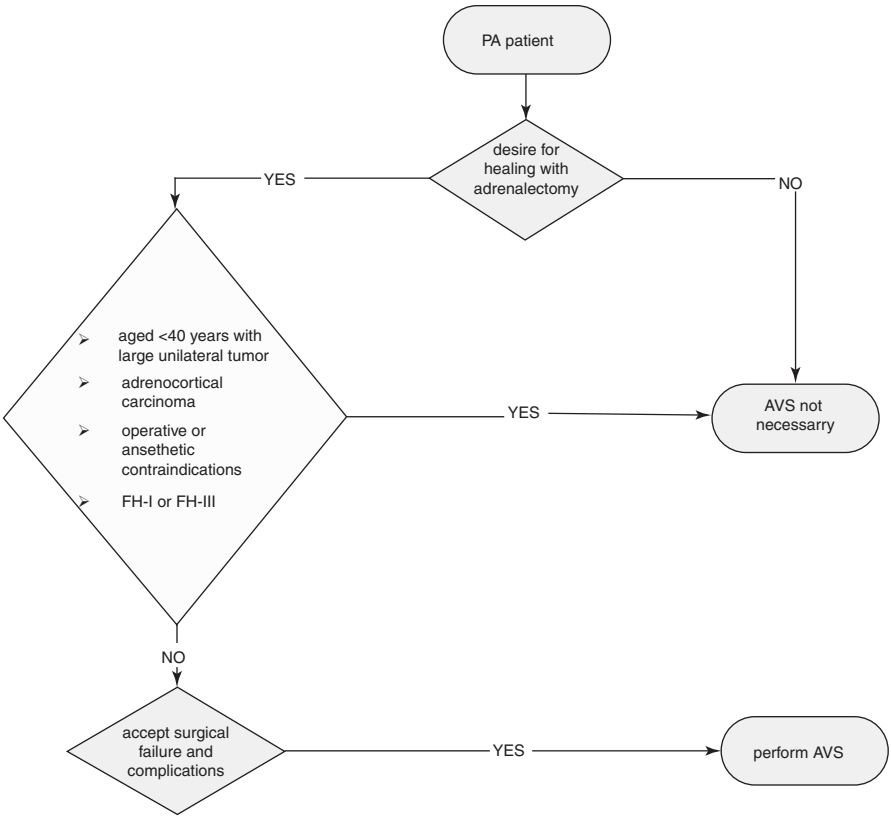


Fig. 4.1 AVS diagnosis and treatment procedures

lie down for no less than 6 h. Surgery is usually performed in the morning to avoid the effect of day-and-night errors in adrenal secretion on measurement. In addition, patients were required to stop taking drugs affecting aldosterone secretion for 4–6 weeks before operation and to supply blood potassium to normal levels.

Surgical approach: As mentioned in the table above, femoral vein and elbow vein approaches can be selected according to the operation habits, each with advantages and disadvantages.

4.2.2 Difficulties and Countermeasures

1. *Right adrenal vein recognition*: It is easy to identify the typical glandular morphology with trunk and vein-like or root-like branches; for the delta, triangle, amorphous/irregular, star/spider, and other atypical morphology, the recognition rate is low. Our experience is that right anterior oblique angiography can make atypical images typical. Intraoperative rapid cortisol determination can also be used to improve the accuracy. Differentiation points with accessory hepatic

veins: the branches of accessory hepatic veins are more abundant, the staining is deeper, the regression is faster, sometimes the lower edge of the liver can be shown, and sometimes the contrast agent can be seen to enter the hepatic vein into the inferior vena cava. There are other interfering vessels, such as renal capsular vein, vertebral vein, and intercostal vein. These vessels basically have no small branches, only the trunk, which is easy to identify.

2. *Location of the right adrenal vein orifice*: The orifice of the right adrenal vein is located in the triangle formed by the lower hepatic boundary, the right spine and the right renal apex, mostly in the inner and upper parts of the triangle. Longitudinally, 82.1% of the cases were at T11-T12 level, 70.5% were at 11 and 12 o'clock, and 70.6% were at the minimum angle and angle of the spine [24].
3. *Selection of right blood catheter*: If femoral vein approach, use 5F Cobra 2 catheter, followed by 5F MIK, 5F Simmons 1, and 5F RH catheter [24]. If the cubital vein approach is adopted, 5F MPA1 catheter is usually used, followed by 5F Cobra 2, 5F VERT, 5F BERN, 5F TIG catheter, etc. [19].
4. Difficulty in drawing blood: The blood vessels are tortuous or not coaxial, which makes it difficult to draw blood. Countermeasure: adjust the catheter to coaxial, draw blood slowly and vigorously, pre-empt part of the air by syringe, tie side holes at the end of the catheter, lower the end of the catheter to make it bleed naturally, combined micro-catheter, combined guide wire, etc. [20, 30].

Result interpretation: Selective index (SI) is the ratio of adrenal/peripheral cortisol or adrenal/inferior cortisol. Lateralization index (LI) is the ratio of aldosterone to cortisol in bilateral adrenal veins. Expert consensus [29] in 2014 considered that SI (>2) of non-ACTH stimulation and SI (>3) of ACTH stimulation were successful blood collection. LI 2.0–4.0 was used as the interception value for non-ACTH excitation, while LI 2.6–4.0 was used as the interception value for ACTH excitation. Because of the difference of measurement in different centers, the intercepted values are different. If the intercepted values are larger than the intercepted values, it can be judged as unilateral or bilateral.

4.3 Imaging and Angiographic Evaluation of Secondary Hypertension

Jina Yili, Keming Zhou

4.3.1 Endocrine Hypertension

Endocrine-related hypertension mainly includes hypertension caused by adrenal, thyroid, pituitary, pancreas, and gonadal lesions, among which the former two are the most common ones, which are the main contents of this chapter. The imaging manifestations of other secretory hypertension are shown in relevant chapters.

4.3.1.1 Adrenal Gland

The adrenal glands are located above the kidneys on both sides, surface of them are brownish yellow. The left adrenal gland is flat and triangular, and the right one is like halfmoon. Normal adrenal gland is about 4 ~ 6 cm long, 2 ~ 3 cm wide and 0.3 ~ 0.6 cm thick.

Adrenal gland examination techniques include ultrasound examination, CT examination, MRI examination, and interventional examination. CT examination is helpful for the detection of small adrenal lesions. MRI examination is often used for the differential diagnosis of adrenal adenoma. Interventional examination, including Adrenal Vein Sampling (AVS), is the most reliable and accurate method for distinguishing between unilateral and bilateral secretions of primary aldosteronism (see this chapter, Sect. 4.2, venous angiography).

The Normal Image

1. Ultrasonic examination: the adrenal glands have weak echo, and it is often difficult to show the glands.
2. CT examination: the normal lateral ramus thickness is less than 10 mm, and the area is less than 150 mm^2. The morphology is different at different levels. The right adrenal gland is usually oblique, The left side is mostly inverted V, inverted Y, or triangle.
3. MRI examination: in cross section, the normal adrenal gland position, shape, edge, and size were the same as those of CT; on the coronal plane, above the upper pole of the kidney, an inverted V or inverted Y shape, the signal intensity varied according to the examination sequence: on T1W1 and T2W1, the adrenal signal intensity was similar to the liver parenchyma, and was significantly lower than the surrounding fat. T1W1 and T2W1 were combined with fat suppression technique, and the signal intensity of adrenal gland was significantly higher than that of surrounding suppressed adipose tissue.

Common Lesions

1. Adrenal hyperplasia

   Adrenal hyperplasia is divided into diffuse hyperplasia nodular hyperplasia, the former is more common, can be unilateral or bilateral hyperplasia, and common in Cushing's syndrome, primary aldosteronism and congenital adrenal cortex hyperplasia.

   Imaging manifestations

   CT: the manifestations were diffuse enlargement of the gland, lateral ramus thickness was greater than 10 mm, and its shape and density were the same as that of normal adrenal gland. Lingam et al. [31] proposed that CT diagnosis of bilateral adrenal hyperplasia, when the average limb width was greater than 5 mm, the specificity was 100%; Nodular hyperplasia is an enlargement of the adrenal margin with one or more nodules at equal densities to the adrenal gland (Fig. 4.2).

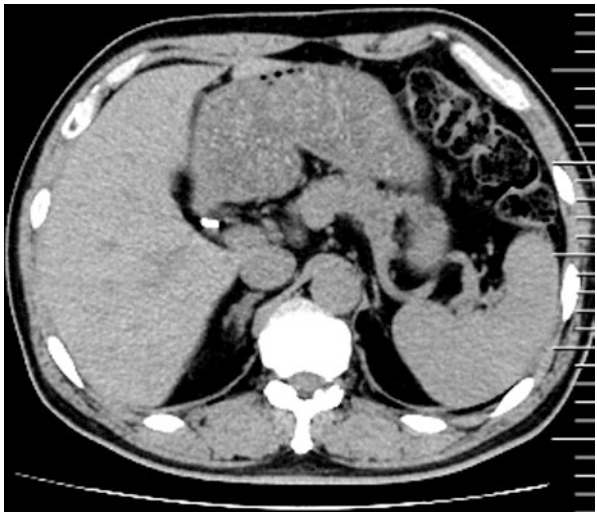


Fig. 4.2 Adrenal cortical hyperplasia

Ultrasound and MRI: bilateral adrenal glands showed diffuse enlargement, with increased adrenal echo or signal intensity similar to normal adrenal glands.

Adrenal vein sampling is the "gold standard" to distinguish primary aldosteronism from unilateral or bilateral hemorrhage [32].

It should be noted that the histological findings of adrenal cortical hyperplasia are not always found on imaging examination. Therefore, the imaging findings of normal adrenal cortical hyperplasia cannot be excluded, and further AVS is required.

2. Adrenal neoplasms: adrenal neoplasms are relatively common and can come from the cortical medulla or interstitial tissue. They can be classified as functional or non-functional, benign, or malignant.
   (a) Adrenal adenoma

   Clinical and pathological: adrenal adenoma is a benign tumor occurring in the adrenal cortex. It may be functional or non-functional. All types of adenomas have complete capsule and are rich in lipids. The functional adenomas were mainly Cushing's adenoma and Conn's adenoma, and the non-functional adenomas had a higher incidence and no symptoms.

   A. Ultrasonography: the appearance of a unilateral adrenal gland like round mass, the border was high echo and clear and neat, internal uniform low or weak echo.
   B. CT: similarities: the common points of all types of adenomas are that they are shown as unilateral adrenal round or oval masses with smooth edges and low density due to rich lipids, which can be similar to water. Enhanced scan showed obvious enhancement and clear edge of the mass (Fig. 4.3).

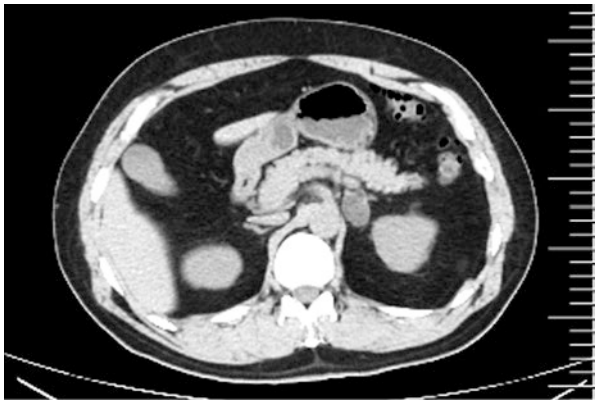


Fig. 4.3 Left adrenal adenoma

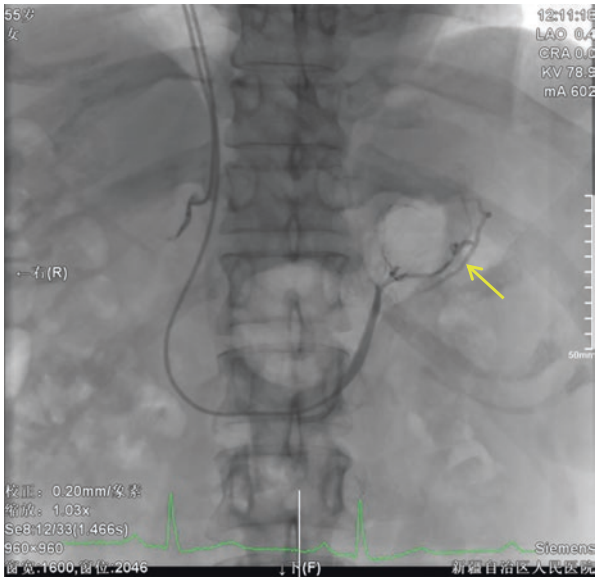


Fig. 4.4 Bulbous changes are seen in the left adrenal gland

Difference: the diameter of Cushing's adenoma is usually 2–3 cm, with ipsilateral residual and contralateral adrenal atrophy. Conn's adenoma diameter was mostly less than 2 cm; Non-functional adenomas are usually 3–5 cm or larger.

C. MRI: it was shown as a round adrenal mass. On T1W1 and T2W1, the signal intensity was similar to or slightly higher than that of liver parenchyma, respectively. Due to the rich lipids, the signal intensity often decreased significantly on the anti-phase.

D. AVS showed Bulbous changes in angiography, and AVS was the standard for distinguishing unilateral and bilateral lesions (Fig. 4.4).

(b) Adrenal pheochromocytoma

Clinical and pathological: Pheochromocytoma and paraganglioma (PPGL) is originated in the adrenal medulla or sympathetic chain. Its main synthesis and secretion of large amounts of catecholamine, such as norepinephrine, adrenalin and dopamine, causing patients with high blood pressure and a series of clinical syndromes, and causing heart, brain, kidney and other serious complications.

Imaging findings: The 2014 guidelines of the American endocrine society recommended the preferred CT for the diagnosis of pheochromocytoma, with a sensitivity between 88 and 100%. CT has good tomography, but like MRI, it lacks specific. (Separate from the last sentence) PET-CT for the preferred location diagnosis of pheochromocytoma outside the adrenal gland, and its diagnostic sensitivity for metastatic PPGLs is 88% [33].

Ultrasound CT and MRI showed that bilateral adrenal masses were unilateral or bilateral, round or oval, usually large, with solid low or moderate echo, and the density was similar to that of the kidney, with low signal on T1W1 and very high signal on T2W1. Large tumors are prone to hemorrhage, necrosis, and cystic degeneration, resulting in uneven echo density and signal intensity. CT and MRI enhancement examinations show no significant difference between the imaging manifestations of malignant pheochromocytoma with obvious enhancement in the solid part of the tumor and non-malignant ones, and sometimes metastatic lesions in liver and lung can be detected.

The above detection methods for heterotopic pheochromocytoma are limited, and segmental inferior caval vein sampling for the location of heterotopic pheochromocytoma is currently considered to be an effective approach. Secondly, the application of M-iodobenzidine whole-body scanning SPECT has important reference value for the location of heterotopic lesions.

(c) Adrenal metastasis tumor

Clinical and pathology: Adrenal metastasis tumors are more common, most of them are lung cancer metastasis, can also be breast cancer, thyroid cancer or kidney cancer metastasis. Adrenal metastasis tumors start in the medulla and then involve the cortex. Adrenal metastasis tumors are usually bilateral, but can also be unilateral. There are often necrosis and hemorrhage within the tumors. The clinical manifestations of adrenal metastasis tumors are mainly derived from the primary tumors and rarely affect adrenal function.

Imaging manifestations: Ultrasonography, CT, and MRI: adrenal metastatic tumors often present as bilateral adrenal masses, occasionally unilateral, oval, or lobulated, varying in size, usually 2–5 cm, or larger masses with uniform or uneven echo density or signal intensity.

Comparison and Optimization of Various Imaging Examinations

CT examination is generally accepted as the best imaging method for adrenal lesions because it shows clear anatomical relationship, high spatial resolution and density

resolution, easy to detect small lesions, especially functional lesions, and can show some tissue characteristics of lesions, such as fat fluid and calcification.

Ultrasound examination as the primary examination method of adrenal lesions should be alert to missed diagnosis, while MRI examination is the complementary examination method after CT and ultrasound, which is helpful for the differential diagnosis of lesions.

Interventional examinations not only provide accurate imaging data, and hormone levels can be analyzed by taking blood samples, which is of decisive significance for the qualitative and localization of the disease. Blood samples were taken through Adrenal Vein Sampling to determine methoxyadrenalin and methoxynorepinephrine in the blood samples, which is of great value for the localization of pheochromocytoma. However, interventional examination is not the first choice due to its high requirements on the medical team and technical level, certain risks and high cost of clinical examination.

4.3.1.2 Thyroid Gland

The thyroid gland is the largest endocrine gland in the human body. The thyroid gland is located between the anterior tracheal cricoid cartilage and suprasternal notch. It is composed of left and right lobes and isthmus and weighs about 12–20 g. The isthmus height and width were about 2 cm and 0.5 cm thick, respectively. The examination techniques included ultrasound, CT, MRI, and thyroid radionuclide imaging.

Normal Image Presentation

1. Ultrasonic examination: the upper and lower diameter of the left and right leaves of the thyroid gland is 50–60 mm, the anterior and posterior diameter is 10–25 mm, and the left and right diameter is 20–30 mm.
2. CT: due to the high iodine content in the thyroid, the density of plain scan was significantly higher than that of muscle tissue, with uniform density and clear boundary, and the enhanced CT scan showed uniform and obvious enhancement of glands.
3. MRI: the thyroid signal on T1W1 and T2W1 was slightly and significantly higher than the muscle signal, respectively.
4. ECT: the thyroid gland has butterfly-shaped double lobes with uniform radioactive distribution inside the lobes. Due to the thin thyroid tissue, the radioactive distribution in the upper pole of the double lobes is somewhat sparse. The isthmus is generally not visualized or its concentration is significantly lower than bilateral thyroid lobes.

Basic Pathological Manifestations

Goiter

1. Clinical and pathology: Goiter is more common in iodine-deficient areas and is commonly seen in women aged 20 to 40. It is caused by an increase in thyrotropic hormone in the pituitary gland due to insufficient synthesis of thyroid

hormone, which in turn stimulates thyroid follicular epithelial hyperplasia. It's usually found by accident, but it can also show up as a lump in front of the neck, Airway compression may occur when the lump turns big.

2. Imaging manifestations:
   (a) Ultrasonography: the manifestations were thyroid enlargement with uneven internal echo, single, or multiple nodules were seen, and the blood flow signals around the nodules were medium and low echo.
   (b) CT: diffuse enlargement of the thyroid gland with low-density nodules, uniform when compared with small, and uneven when compared with large. Nodular goiter is characterized by multiple low-density areas, sometimes with calcification at the margin. Adenomatous hyperplasia nodules may have mild enhancement and generally do not invade adjacent organs or structures.
   (c) MRI: the manifestations were long T1 signals, T1 signal strength was determined according to the protein content in the colloid, and the signal varied from low signal to high signal.
   (d) ECT: diffuse enlargement of the thyroid gland and basically uniform distribution of radionuclides. If nodules are present, they may be hot, warm, or cold.

Thyroid Tumor

1. The clinical and pathological: thyroid tumor (thyroid tumor) is divided into benign and malignant. Benign adenoma accounts for 60% of thyroid diseases. Thyroid cancer is malignant, accounting for 34.2% of head and neck tumors. Papillary cancer is more common in women, and it is common in women aged 20–40 years. It can cause hoarseness and dyspnea, and malignant tumors are prone to lymph node metastasis.
2. Imaging manifestations
   (a) Ultrasonography: the manifestations were thyroid mass. Generally, those with clear boundary, low echo, uniform echo, and lack of blood flow signal are suggested as benign tumor, while those with unclear boundary, uneven echo and rich blood flow signal are suggested as malignant tumor.
   (b) CT: adenoma presents as a circular, quasi-circular, low-density shadow with clear boundary; In contrast, carcinoma presents heterogeneous low-density shadow with irregular shape and unclear boundary, and scattered calcification and necrotic area with lower density can be seen inside. The lesion is not clearly demarcated from surrounding tissues, and cervical lymph node enlargement can be seen. The adenoma is not strengthened or slightly strengthened, and the carcinoma is not uniformly strengthened, and the metastatic lymph nodes are usually annular strengthened.
   (c) MRI: the adenoma on T1W1 presented low, equal, or high signal nodules with clear boundary, and the colloid in follicular adenoma was mostly high signal; adenocarcinoma is an irregular low-to-moderate signal. T1W1 was high signal.

(d) ECT: tumor manifestations can be divided into three categories, namely, hot nodules, warm nodules, and cold nodules. The radioactivity of hot nodules is higher than that of normal thyroid tissues, and radioactive concentration appears at nodules, which is common in autonomic functional thyroid nodules (or adenomas). As a result, the radioactive distribution of nodules is not significantly different from that of the surrounding normal thyroid tissues, which is common in thyroid adenoma. Cold nodules are the radionuclide uptake capacity of the nodules is lower than that of the surrounding normal tissues, and radionuclide distribution is sparse or defect areas. They are common imaging types of thyroid adenoma, and are also found in cystic degeneration, hemorrhage, calcification, thyroid cyst, nodular goiter, thyroiditis, thyroid cancer, and so on.

Comparison and Optimization of Various Imaging Examinations

Ultrasonography is the first choice for thyroid diseases. MRI is increasingly used for imaging in any direction and for its superior soft tissue resolution [34].

4.3.2 Renal Hypertension

Kidney is closely related to hypertension. Hypertension caused by renal lesions is collectively referred to as renal hypertension, including renal substantive hypertension and renal vascular hypertension. This chapter focuses on renal substantive hypertension, which is related to renal vascular hypertension and hypertension caused by arterial disease.

A kidney is located in the posterior peritoneum, divided into the cortex and the medulla. The normal adult male kidney is 11–12 cm long, 5.0–7.5 cm wide, and 2.5–3.0 cm thick. Generally, the left kidney is slender, the right kidney is wide and short, and the male kidney is slightly larger than the female kidney. Its function is to maintain the stability of the internal environment of the body. It excretes metabolic end products, regulates blood volume, maintains electrolyte and acid-base balance, and secretes a variety of active substances to ensure the normal physiological functions of the body.

Examination techniques include ultrasound, X-ray, CT, MRI, and radionuclide imaging. Ultrasonic examination is the most common. X- ray is commonly used in urography, which can show the morphology of calyces, pelvis, ureter, and bladder, and understand the excretory function of both kidneys. CT examination is divided into plain examination and urography (CTU), the latter of which can be used to observe the degree of renal skin and medulla enhancement and the morphology of calyces, pelvis, and ureter. MRI includes routine examination and renal vascular MRA, which can accurately show the aneurysm neck, tumor shape, and size, whether there is thrombosis, and can show the relationship between aneurysm and other local blood vessels. Renal arteries and veins can be displayed simultaneously by dynamically enhanced MRA in different phases, which is of great significance for preoperative evaluation of renal tumor staging and living kidney donors. Renal

radionuclide imaging can provide information of renal perfusion, renal function evaluation and urinary tract patency. It can also be used to determine renal location, natural shape and size, and residual renal function [35].

4.3.2.1 Normal Imaging Findings

1. Ultrasound examination: the normal kidney can be round, oval, or bean-shaped depending on the scanning Angle. The capsule of the kidney is highly echogenic, clear, and smooth. The peripheral renal cortex showed uniform weak echo. The internal renal cone is triangular or circular hypoechoic. The renal sinus is irregular and dense with multiple echoes of the renal pelvis, calyces, blood vessels, and adipose tissue in the sinus. The normal ureter cannot be shown due to intestinal disturbance.
2. X-ray
   (a) Abdominal plain film: renal shadow with slightly higher density can often be shown on the anterograde film, with smooth edge, with a length diameter of 12–13 cm and a width diameter of 5–6 cm.
   (b) Urography: it is mainly used for the observation of calyces, pelvis, and ureter.

   Normal kidneys have 2–4 large calyces and 6–14 small calyces. The morphology of the large and small calyces of the kidney is very different. The small calyces of the kidney have a hollow cup with sharp edges on both sides. The large calyces of the kidney have a smooth and long tubular edge. The upper apex is connected with one or more small calyces, and the lower base is connected with the renal pelvis. The renal pelvis is usually horn shaped, the upper margin is convex, the lower margin is slightly concave, and the margin is smooth.

   The ureter is about 25 cm in length. There are three physiological strictures in the ureter, namely, at the junction with the renal pelvis, through the pelvic margin, and into the bladder.

4.3.2.2 Diagnosis

1. *Diffuse Renal Parenchymal Disease*
   (a) Clinical and pathological: under the induction of external factors, the human body produces different antibodies, which bind into different immune complexes and deposit in different parts of the kidney, forming different types of nephritis and causing extensive pathological damage to the kidney.
   (b) Imaging performance:
   - Ultrasound examination is the preferred examination for renal parenchymal disease, which is mainly used to evaluate renal size, cortical thickness, and cortical echo. (1) normal cortical echo is weaker than liver echo. (2) Cortical echo enhancement ultrasound provides a noninvasive means of monitoring renal size and cortical echo intensity in the follow-up observation of chronic kidney disease. Degree I enhanced renal cortical echo with liver; II degree enhanced renal cortical echo was stronger than hepatic echo but lower than renal sinus echo; III degree enhanced renal echo close to renal sinus fat echo.

- Radionuclide imaging is not specific for renal parenchymal disease, and its advantage is high sensitivity. In the early stage of the disease, renal blood flow changes can be found, and the main lesion site to make a preliminary judgment.
  - Glomerulonephritis glomerulus effective filtration area reduced, lesions can also accumulate renal tubule interstitium and blood vessels, the disease can gradually lead to renal insufficiency. The results of dynamic renal imaging were significantly correlated with the histopathological changes of the kidney and could reflect the progress of pathological injury. The imaging findings were mostly bilateral abnormalities. Early renal structure was normal. Imaging agents were distributed in the renal parenchyma roughly evenly but sparsely within the renal parenchyma, concentrating and releasing into the renal pelvis were slowed down, bladder imaging was delayed, renal function curve amplitude was reduced, descending ramus was decreased slowly, GFR was slightly decreased in quantitative analysis, and ERPF could be normal or slightly increased. With the gradual decline of renal function, the renal shadow decreased, the uptake of imaging agents significantly decreased, and the excretion slowed down, the renal function curve showed a significantly reduced amplitude, a sustained slow increase, a prolonged level, or even a low level of prolonged or descending type, etc. Quantitative analysis showed that both GFR and ERPF decreased, but ERPF decreased later than GFR. Both recovered slowly as the disease improved.
  - Diabetic nephropathy diabetic accompanied by metabolic disorders, kidney high perfusion, high filtration, high pressure, and other renal hemodynamic changes, affecting the glomerular basement membrane and its permeability, and then involved in the glomerular function, eventually lead to glomerular sclerosis. In the early stage of proteinuria, GFR and ERPF were increased, reflecting the high perfusion and filtration status of the kidney. When microalbuminuria occurs, GFR increases while ERPF decreases, and the "separation phenomenon" is an important feature of early diabetic nephropathy. In the later stage of the course, GFR and ERPF showed a progressive decline [36, 37, 38].

2. *Polycystic Kidney*
   (a) Clinical and pathological manifestations: patients with polycystic renal disease, referred to as polycystic kidney, are hereditary lesions with more cases of adult type, and usually complicated with polycystic liver. After middle age, with the increase and enlargement of renal cyst, clinical symptoms appeared, including abdominal mass, hematuria, hypertension. In late stage, both kidneys are full of multiple cysts of different sizes, which may develop into renal failure.
   (b) Imaging performance:
   - Ultrasound showed that the renal volume increased, the surface is not smooth, lobulated. The renal parenchyma has small anechoic foci

resembling honeycomb, and the echo of the collecting system disappears. They are often associated with hepatic, pancreatic, or splenic cysts. Ultrasound can detect 5–10 mm diameter cysts, renal cysts are the preferred means of examination.

- Urography: the bilateral calyces were generally compressed, elongated, deformed, and separated, showing "arachnid"-like changes.
- CT and MRI examination: both kidneys were found to be full of multiple cysts of different sizes, density and signal characteristics similar to simple cysts. Polycystic liver can also be seen. Some complex cysts may have calcification, septa, and mural nodules. Such complex cysts may be benign or malignant and should be evaluated with enhanced CT or magnetic resonance imaging.

3. *Reninoma*

Clinical and pathology: (1) Reninoma is a rare benign renal juxtaglomerular cell tumor (juxtaglomerular cell tumor, JGCT) because it can secrete a large number of renin, cause secondary aldosterone increased, so the clinical main show is serious symptoms such as high blood pressure, hypokalemia [39]. Its pathophysiological features are hyperfunction of renin-angiotensin aldosterone system. Tumors usually have a diameter of about 1 cm and a maximum diameter of 6 cm. Tumors have a complete envelope, including polygonal cells containing cytoplasmic granules, sometimes renal tubular epithelial cells, adrenergic nerve tissue and mast cells.

(2) The findings: There was no obvious enhancement in the arterial phase, and there was mild to moderate enhancement in portal and delayed phase. The CT value of the tumors in the portal phase was higher than that in the early artery phase, and tumors in the portal and delayed phases are more visible. MRI is similar to CT in that it is a well-defined lesion with a lack of specificity. T1-weighted images show equal or low signal areas, while T2-weighted images show high signals. For small tumors, the diagnosis is difficult, so MRI combined with CT is required for diagnosis. Renal venous synchronous blood sampling showed a significant increase in renin on the affected side [40, 41].

4. *Ectopic kidney:* kidney rising insufficiency during embryo development. As a result, it may be lodged in the pelvic cavity (more commonly seen), or it may be located below the diaphragm and in the posterior mediastinum. Excretory urography, CT and MRI enhancement can all reveal this abnormality. The renal image is similar to that of a normal kidney, except in different locations.
5. *Renal agenesis* is also referred to as renal insufficiency. During excretory urography, absent and undeveloped kidneys are present. Ultrasound, CT, and MRI examination showed the absence of renal structure in the absent side, renal bed occupied by intestinal tube and other structures, and compensatory increase in the uninjured side.
6. *Horseshoe kidney*: a fusion of two kidneys at the upper or lower pole, often the lower one, resembling a horseshoe. Urography showed that the two kidneys were in a low position and the lower pole was fused into an isthmus. The pelvis is located on the ventral side with the calyces pointing dorsally, with hydronephrosis and stones (see horseshoe kidney and hypertension).

4.3.2.3 Comparison and Optimization of Various Imaging Examinations

1. Radionuclide dynamic imaging is one of the clinical standard methods for the evaluation of renal function.
2. Images of the kidney in cross-sectional, coronal, and sagittal sections can be obtained without moving the patient, and information on renal function, chemical composition, and blood flow velocity can be obtained through diffusion-weighted magnetic resonance imaging (DWI) and spectral analysis. It can provide better soft tissue contrast than CT and ultrasound, so that it is easier to detect and identify various renal lesions.
3. MRI angiography is performed without contrast media. If needed, MRI contrast agent has no obvious renal toxicity, and the dose is lower than that of CT and intravenous urography in adults. It is especially suitable for patients with renal insufficiency, especially those with renal failure. At the same time, magnetic resonance has no ionizing radiation, no biological damage to the subject, so it can be repeated many times, especially suitable for the fetus, children, young people, and pregnant women follow-up.

4.3.3 Hypertension Caused by Arterial Disease

Renal artery stenosis: RAS is an important cause of hypertension and/or renal insufficiency [42].

1. Ultrasonic examination
   (a) Methods: the renal artery openings, the cortical and medullary branches of the distal and upper, middle, and lower renal arteries were routinely scanned in supine position through intercostal, lateral lumbar, or abdominal approaches.
   (b) Judgment: changes in renal arterial blood flow mechanics: >180 cm/s was the peak systolic flow rate in the stenosis, and the ratio of the peak systolic flow rate in the abdominal aorta at the level of renal artery and renal artery was 3.5. After stenosis, the acceleration time of >0.07 s and the early contraction acceleration <300 cm/s, the difference between the renal artery trunk and segment artery resistance index was >0.15. Renal segmental arterial resistance index may have the value of predicting curative effect. When the resistance index before intervention is greater than 0.80, the possibility of postoperative renal function improvement and hypertension control is low. The accuracy of ultrasound was obviously affected by the interference factors such as operation level, obesity, and abdominal distension [43].
2. CT angiography: high-resolution CTA (64 rows or more) is also important in the diagnosis of renal artery stenosis. Through rapid injection of contrast agent (total about 120 mL, with 4 mL/s) injection, injection delay after 20–30 s to 2 mm

thick rapid scanning, the axis of an original image information construction of renal vascular three-dimensional structure can be clearly showed renal artery trunk and a secondary branch pipe cavity, wall, kidney, and renal artery stent, also can show the artery wall calcification, mezzanine, plaques, and bleeding, and according to the developing time and degree of renal parenchyma to general assessment of renal function, renal artery CTA can be used as the gold standard for noninvasive evaluation of RAS, its high sensitivity, specificity, and accuracy. It has the advantage of being safe and noninvasive. The disadvantage is that the use of contrast media is limited in patients with renal insufficiency [43, 44] (Fig. 4.5).

3. MRI examination: magnetic resonance angiography (MRA) was performed in multiple phases after intravenous injection of Gd^{3+}, angiogenic agent to obtain arterial, venous, parenchymal, and excretory images of the kidney. In combination with digital subtraction angiography, magnetic resonance imaging can be used to evaluate the hemodynamics and function of the poststenosis kidney. The dynamic enhanced MRA can accurately show the aneurysm neck, tumor shape and size, whether there is thrombosis, and the relationship between aneurysm and other local blood vessels [44, 45].
4. Interventional examination
   Percutaneous renal arteriography is the gold standard for the diagnosis of renal artery stenosis [46].
   - Methods: the openings of abdominal aorta and renal artery were observed by transdermal femoral artery or radial artery intubation and intravitreal radiography with pigtail catheter. Then the angiographic catheter was inserted into the renal artery to inject contrast agent rapidly and continuously.
   - Renal arteriography was divided into three phases: (1) The autonomous stem to the branch gradually becomes thin, walks naturally, the edge is smooth, does not have the expansion, the narrow and the interrupt. (2) Renal

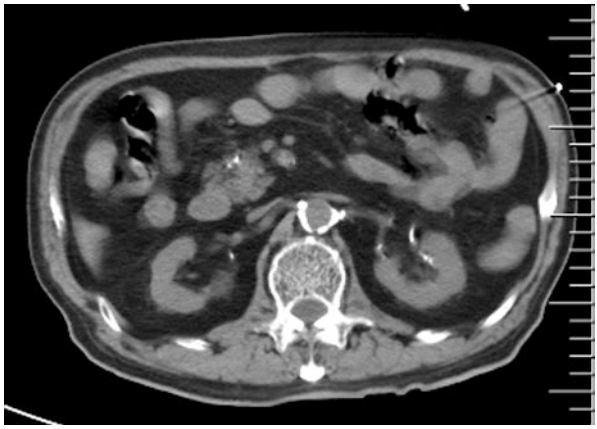


Fig. 4.5 Calcification is seen at the entrance to the renal artery

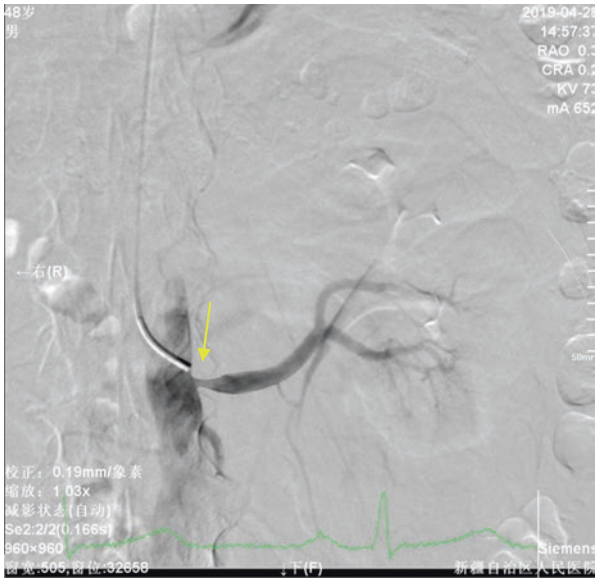


Fig. 4.6 The left renal artery is localized

parenchymal stage diffuse development of the kidney, contour, size, and shape can be clearly distinguished. (3) Renal vein stage renal vein development.

- Judgment: (1) Degree of judgment: Abdominal aortic or renal artery stenosis <50%, the systolic pressure difference of distal and proximal stenosis <20 mmHg, no functional significance. The severity of angiographic stenosis can be simply classified as mild (<50%), moderate (50–70%), and severe (>70%). >60% stenosis in the lumen and >30 mmHg difference between distal and proximal systolic pressure can lead to renal vascular hypertension. (2) Etiology: Atherosclerotic stenosis is common at the opening and proximal segment of the renal artery and presents as an eccentric irregular filling defect (Fig. 4.6). Renal artery stenosis caused by arteritis is mostly bilateral, which is located at the opening and presents as multi-segmental with alternating narrowing and dilatation. The artery wall between the two lesions can be normal, and local stenosis can be complicated with dilatation, aneurysm formation, and calcification. Fibromuscular dysplasia is mainly located in the middle and distal renal artery and typically presents as "beaded" changes [46].

4.3.3.1 Aortic Constriction

1. The X-ray
   (a) Methods: the vertical posterior and anterior position, lateral position, and three congenial radiography of the heart were taken routinely.
   (b) Judgment:

- Direct signs: ascending aorta dilation or (and) narrowing of aortic node. The shadow of "double arch" or "3" on the lower margin of the aortic arch, where the incisions are narrowed.
- Indirect signs: left superior mediastinal shadow widened or pulse enhanced by left subclavian artery dilatation; bilateral symmetrical lateral rib notch can be seen at the posterior costal margin from fourth to eighth, suggesting the establishment of arterial constriction collateral circulation.

2. CT examination

   CTA imaging realized three-dimensional imaging of carotid artery, aorta, iliofemoral artery, renal artery, and pulmonary artery through data collection and three-dimensional reconstruction.

3. MRI

   MRA imaging was performed when the contrast agent first passed through the blood vessel. When the soft tissue and vein were not enhanced, only the artery image was obtained by rapid scanning, and then the three-dimensional image was reconstructed. High resolution, good image quality.

4. Renal arteriography

   Renal arteriography is the gold standard for the diagnosis of aortic constriction.

   Methods: (1) Intubation through the femoral or radial artery.

   (2) Judgment:

   (a) Aortitis: aortic constriction caused by aortitis occurs in the lower segment of descending thoracic main artery and the junction of descending thoracic aorta and abdominal aorta. It is manifested as diffuse, segmental or localized stenosis and obstructive changes, Arterial margin is irregular, can companion limitation narrow throb is abate even disappear.

   (b) Congenital aortic narrowing: more than 90% of the narrowing occurs at the distal end of the left subclavian artery opening and in the area (isthmus) where the arterial catheter ligament is located, most of which are localized stenosis. The disease can be divided into two types. (A) type I typical (simple) narrowing of the aorta is located in the aortic isthmus (near the catheter ligament) at the distal opening of the left subclavian artery. The lesion is limited, the catheter has been closed, and there are no other important cardiovascular malformations. (B) complex type II aortic constriction. There are two subtypes of this type. (1) Type IIa—narrowing is located at the arch of the aorta near the left subclavian artery, or involving the left subclavian artery (open), or involving the distal aorta. (2) Type IIb—major cardiovascular malformations such as aortic constriction combined with patent ductus arteriosus (PDA) and ventricular septal defect (VSD).

4.3.3.2 Nutcracker Syndrome

Nutcracker syndrome mainly refers to the left renal vein compression syndrome, which is a series of clinical syndromes caused by the left renal vein in the abdominal aorta and superior mesenteric artery formed by angle or mechanical compression

between the abdominal aorta and the spine caused by left renal vein backflow obstruction, left kidney, ureter and gonad venous pressure increase.

1. Ultrasound examination: the UK guidelines suggest that the first choice of ultrasound Doppler examination of the left renal vein, with a sensitivity of 69–90% and a specificity of 89–100%. Examination parameters: (1) The internal diameter ratio of the angle between the left renal vein and the renal hilum and the upper mesenteric artery of the abdominal aorta was 3.0–5.0. (2) The ratio of blood flow peak velocity at the angle of left renal vein between the abdominal aorta and superior mesenteric artery and the renal hilum was 2.0–5.0 [47].
2. CT arteriography and MRA: the anatomical structure of the left renal vein can be clearly seen, and the compression and dilation of the left renal vein, as well as perinephric and gonadal varices can be confirmed. Other causes of nutcracker syndrome can be excluded, but the blood flow velocity cannot be determined. CT of nutcracker syndrome showed beak sign (referring to the sharp narrowing of the left renal vein at the compression site, which is recognized as the most specific examination sign), the internal diameter ratio of the left renal vein 4.9, the angle between the superior mesenteric artery and the abdominal aorta less than 41°, and the establishment of collateral circulation near the left renal portal vein [48].
3. Renal venography: the pressure difference between left renal vein and inferior vena cava is greater than 3 mmHg, which can be diagnosed and is the gold standard for defining nutcracker syndrome.

To sum up, medical imaging not only expands the inspection scope of human body and improves the diagnostic level, but also can treat some diseases. Imaging examination plays an important role in the diagnosis and treatment of secondary hypertension, especially CT angiography, interventional examination and treatment, has become an important pillar in medical work.

4.4 Kidney Puncture

Nuerguli Maimaiti

Renal biopsy is an essential method for diagnosing kidney disease, especially glomerular disease. It provides clinicians with a pathological diagnosis basis, which is important for determining diagnosis, guiding treatment, and evaluating prognosis significance. The application of renal biopsy has been used for more than 50 years. The methods include open renal biopsy, transvenous renal biopsy, and percutaneous renal biopsy. Currently, the most commonly used percutaneous biopsy has simple operation and high success rate, and fewer complications [49, 50].

4.4.1 Indications

1. Primary glomerular disease: (1) acute nephritic syndrome with a sharp decline in renal function, suspected acute nephritis or treatment has not been relieved after treatment; (2) primary nephrotic syndrome; (3) asymptomatic hematuria; (4) asymptomatic protein urine, persistent urine protein >1g/day.
2. Secondary kidney disease: clinically suspected but not diagnosed or renal pathological examination for clear pathological diagnosis, guiding treatment, prognosis, such as lupus nephritis, diabetic nephropathy, and renal amyloidosis.
3. Suspected to be hereditary familial glomerular disease (Alport syndrome, thin basement membrane disease, Fabry disease, etc.).
4. Kidney biopsy should be performed early in order to guide treatment if the cause of acute renal failure is unknown or renal function recovery is slow.
5. Slowly progressing renal tubular and renal interstitial diseases.
6. Transplanted kidney disease: (1) primary disease again causes the pathogenesis of transplanted kidney; (2) renal function decline of transplanted kidney; (3) renal allograft rejection; (4) nephrotoxicity caused by anti-rejection drugs such as cyclosporine.

4.4.2 Contraindications

1. Absolute contraindication [51]
   (a) Isolated kidney (Because the newer imaging techniques and renal biopsy techniques have improved the safety of biopsy, isolated kidney has been questioned as an absolute contraindication for biopsy [52].)
   (b) Mental illness, unable to cooperate.
   (c) Those who are unable to control severe hypertension.
   (d) Those who have obvious bleeding tendency.
   (e) Condensed kidney.
2. Relative contraindication
   (a) Urinary tract infections: such as kidney and kidney nephritis, tuberculosis, pyelonephritis, perinephric abscess and so on.
   (b) Kidney malignancy or large aneurysm.
   (c) Polycystic kidney or renal multiple cysts.
   (d) Poor kidney position, nephrospasia.
   (e) Chronic renal failure, although the primary disease is not the same, but the renal pathology is basically the same in the development of renal failure, cannot puncture. For example, in chronic renal failure, the kidney volume is not small, the basic renal function is acceptable, and there is a reversible factor in renal function damage that can be puncture.
   (f) Excessive obesity, massive ascites, pregnancy, etc. should not be puncture.
   (g) Severe heart failure, poor blood, shock, hypovolemia, and elderly people should not puncture.

4.4.3 Puncture Method

1. Manual needle (TruCut disposable puncture needle, Franklin-Silverman, Vim-Silverman) and automatic spring biopsy needle were used. The puncture is performed by one person.
2. Percutaneous renal biopsy is usually performed under local anesthesia and ultrasound guidance to measure the distance from the lower extremity of the right kidney to the skin and renal thickness. Generally, the right lower kidney pole is selected first, which is equivalent to the level of the first lumbar vertebrae, 0.5–2.0 cm below the 12th costal margin, and 6–8 cm from the midline of the spine. Ultrasonic puncture probe was used for real-time positioning, and automatic puncture needle was used to see the puncture tip under direct vision, and accurately positioned at the lower pole of the kidney. The automatic puncture trocar can reach the lower pole of the kidney quickly (within 1 second) and cut the length of the kidney tissue about 1.6–2.0 cm. Its prominent advantages are more accurate positioning, less complications, almost no gross hematuria.
3. The patient takes the prone position, and the corresponding position of the abdomen and kidney area is padded with a 10–16 cm long pad so that the kidney is close to the abdominal wall to avoid sliding displacement during puncture.
4. Conventional disinfection of local skin, the surgeon wears sterile gloves, and a sterile hole towel. Two percent lidocaine is locally infiltrated from the puncture site and directly reaches the renal capsule.
5. The puncture needle penetrates vertically at the puncture point and oscillates with the breath when it reaches the renal capsule fat sac. Let the patient hold his breath at the end of inhalation and immediately puncture the needle into the renal parenchyma about 3 cm to take the tissue and quickly pull it out, and then let the patient breathe normally. The assistant pressurizes the puncture point for more than 5 min. The paralyzed patient was placed in situ for half an hour, then took the free position and stayed in bed for 24 h.
6. Specimen segmentation and processing. Renal pathology should include light microscopy, immunofluorescence, and electron microscopy, with different requirements for specimen segmentation and preservation. Electron microscopy should be cut to 0.5 mm size, fixed with 2–3% glutaraldehyde, stored at 4 °C; immunofluorescence cut to 3–5 mm size, preserved with normal saline, −20 °C; the rest of the specimen is placed in 10. It is used as a light microscope in the % formaldehyde fixative.

4.4.4 Precautions

1. Strictly perform aseptic procedures to prevent infection.
2. Patients should lie supine for 4–6 h after puncture and rest in bed overnight.

To help detect bleeding and other complications, vital signs need to be closely monitored after the biopsy, and urine analysis and a CBC count need to be taken at different points after the biopsy. To minimize the risk of bleeding, ensure that blood pressure is well controlled (target value <140/90 mmHg) [53].

3. Observe postoperative complications: (A) bleeding and hematuria: bleeding is the main complication of renal biopsy. Compared with biopsy at other sites, the risk of bleeding after renal biopsy is the highest (1.2%). The application of desmopressin (dDAVP) before renal biopsy can reduce the risk of bleeding [54, 55]. (B) Waist pain: the pain at the side of puncture disappears in more than 1 week, and renal colic may be caused by blood clots blocking the renal pelvis or ureter. (C) Infection: due to the lax aseptic operation or the spread of infection caused by the original infection lesions after puncture. If the above complications are found, they should be promptly treated.

4.5 Genetic Diagnosis

Ting Wu

4.5.1 Genetic Diagnosis

4.5.1.1 Pandect

Hypertension is the result of the interaction of genetic and environmental factors [56]. Heredity is one of the bases of hypertension. There are two genetic models for hypertension named single-gene inheritance pattern and polygenic inheritance pattern. The polygenic inheritance pattern is the main one, which is mainly found in primary hypertension, while the single-gene inheritance pattern is mainly found in the secondary hypertension that only occurs in a small number of patients with hypertension. The treatment of single-gene inheritance pattern is specific, and most of them are familial, so a clear diagnosis is essential to the patients and their families, which should be paid attention to clinically.

Single-gene hereditary hypertension caused by a gene mutation, which generally conforms to the law of Mendelian inheritance, even though the phenotype is also affected by environmental factors. Monogenous hypertension usually occurs early, mostly in adolescents, with family history, severe hypertension or refractory hypertension, often accompanied by abnormal hormone and biochemical levels.

For adolescents with family history of moderate to severe hypertension, plasma renin-angiotensin-aldosterone, blood electrolyte, cortisol and sex hormone levels should be measured, and the type of single-gene hypertension should be determined according to the history, signs, and test results. Gene diagnosis not only contributes to the early diagnosis and differential diagnosis of patients with monogenic inherited cardiovascular diseases and their relatives, but also plays an important

role in guiding prognostic risk stratification, treatment strategy formulation, genetic screening, and selective fertility.

4.5.1.2 Common Genetic Cause of Secondary Hypertension

Paraganglioma and pheochromocytoma syndrome (PGL/PCC), familial aldosteronism, Gordon syndrome, Liddle syndrome, congenital adrenocortical hyperplasia, apparent mineralocorticoid excess (AME), hypertension with exacerbation in pregnancy and hypertension and brachydactyly syndrome (Table 4.4).

4.5.1.3 Screening and Diagnosis of Pathogenic Genes for Secondary Hypertension

Common Technique of Genetic Diagnosis

Genetic diagnosis is a screening and diagnosis method for single-gene hereditary hypertension. Early diagnosis is helpful for targeted treatment to control blood pressure more effectively. Genetic diagnosis refers to the method and process of using molecular genetics technology to check the defects of gene structure or the analysis of abnormal expression at the level of DNA or RNA, and making diagnosis of human body status and diseases. Compared with the diagnosis of disease phenotype, gene diagnosis has the characteristics of high specificity and high sensitivity. It can not only make a clear diagnosis of patients, but also make the diagnosis and prediction before the onset of disease.

The technical methods of gene diagnosis include: the first-generation sequencing technology, the second-generation sequencing technology, the third-generation sequencing technology, etc. (Table 4.5) [57–59].

For single-gene hereditary hypertension, gene diagnosis is recognized as the most accurate and reliable diagnostic technique and gold standard for the diagnosis of this kind of disease, which can make a clear diagnosis at the molecular level or even in the case of a single base change. Gene diagnosis is the fourth generation of diagnostic technology after morphology, biochemistry, and immunology [60]. It breaks the way of conventional diagnosis and does not take the phenotype of the disease as the main basis, but adopts the techniques and methods of molecular biology to directly detect whether the structure or function of a specific gene is abnormal, so as to make a diagnosis of the disease. Compared with conventional diagnosis, gene diagnosis pays more attention to the individual gene status, which can not only make a judgment on the patient's disease, but also make a prospective diagnosis for carriers with normal phenotypes or those with genetic susceptibility.

4.6 Renal Function Examination

Kaiyang Wang

Hypertensive kidney damage is primary hypertension as the etiology, caused by renal arteriolar sclerosis, nephrotic atrophy and renal function decline, serious renal

Table 4.4 Single-gene inherited hypertension gene

Diseases		Inheritance patterns	Gene	Gene position	Disease characteristics
Paraganglioma and pheochromocytoma syndrome (PGL/PCC)	Paraganglioma	AD	11q23.1	SDHD	
			11q12.2	SDHAF2	Patients with genetic mutations occurs early, and may present as multi-focal bilateral or non-pheochromic tissue metastasis, often with a family history and/or clinical syndrome, such as neurofibromatosis type 1 multiple endocrine adenoma type 2 (MEN2) Von Hippel-Lindau syndrome (VHL)
			1q23.3	SDHC	
			1p36.13	SDHB	
			5p15.33	SDHA	
	Von Hippel-Lindau syndrome	AD	2p25.3	VHL	
	Neurofibromatosis, Type 1	AD	17q11.2	NF1	
	Paraganglioma and pheochromocytoma syndrome (PGL/PCC)	AD	1q43	FH	
			2p21	EPAS1	
			14q23.3	MAX	
			2q11.2	TMEM127	
			19q13.2	EGLN2	
			1q42.2	EGLN1	
Familial aldosteronism	Familial aldosteronism, Type 1	AD	8q24.3	The result of the fusion of the CYP11B2 and CYP11B1 genes	Common clinical manifestations of early-onset hypertension. FHA1 is glucocorticoid-suppressible hyperaldosteronism, so it is also known as glucocorticoid-remediable aldosteronism (GRA). FHA1 and FHA3 are characterized by abnormal adrenal steroid production, including 18-oxocortisol and 18-hydroxycortisol. Glucocorticoid therapy is invalid with FHA2, FHA3, and FHA4 type patients, drug treatment may consider mineralocorticoid receptor antagonist or other antihypertensive drugs
	Familial aldosteronism, Type 2	AD	7p22		
	Familial aldosteronism, Type 3	AD	11q24.3	KCNJ5	
	Familial aldosteronism, Type 4	AD	16p13.3	CACNA1H	

(continued)

Table 4.4 (continued)

Diseases		Inheritance patterns	Gene	Gene position	Disease characteristics
Gordon syndrome (Pseudohypoaldosteronism, type 2)	Pseudohypoaldosteronism, type 2B (PHA2B)	AD	17q21.2	WNK4	Hypertension, hyperkalemia, normal glomerular filtration rate, can also be manifested as reduced renin level, decreased or normal aldosterone level, metabolic acidosis, hyperchloremia, increased urinary calcium level, decreased blood calcium level, short stature, mental retardation, and abnormal tooth enamel development
	Pseudohypoaldosteronism, type 2C (PHA2C)	AD	12p13.33	WNK1	
	Pseudohypoaldosteronism, type 2D (PHA2D)	AD或AR	5q31.2	KLHL3	
	Pseudohypoaldosteronism, type 2E (PHA2E)	AD	2q36.2	CUL3	
Liddle syndrome (Pseudoaldosteronism)	–	AD	16p12.2	SCNN1B	Typical clinical manifestations include early onset of moderate to severe hypertension, low serum potassium, low plasma renin, and low or normal plasma aldosterone levels
	–	AD	16p12.2	SCNN1G	
Congenital adrenal hyperplasia	11-beta-hydroxylase deficiency	AR	8q24.3	CYP11B1	Increased levels of the abnormal adrenal steroids 18-oxocortisol and 18-hydroxycortisol lead to retention of water and sodium, row of potassium, and thus lead to high blood pressure and hypokalemia. Adrenocorticotropic hormone compensatory increase, resulting in adrenocortical hyperplasia, the female patients with excess androgen can lead to male patients
	17-alpha-hydroxylase/17,20-lyase deficiency	AR	10q24.32	CYP17A1	11-deoxycorticosterone and corticosterone secretion increased, resulting in retention of water and sodium, row of potassium, which lead to high blood pressure and hypokalemia, causes the sexual hormone synthesis barrier, puberty delay, the primary amenorrhea and so on
Apparent mineralocorticoid excess	–	AR	16q22.1	HSD11B2	Hypertensive hypokalemia with low plasma renin activity and low aldosteronemia with hematuria hydrocortisone/cortisone metabolic abnormalities
Hypertension with severe exacerbation in pregnancy	–	AD	4q31.23	NR3C2	Hypertension, early onset, with severe exacerbation in pregnancy
Hypertension and brachydactyly syndrome	–	AD	12p12.2	PDE3A	

Table 4.5 Comparison of the characteristics of sequencing technology

	Sequencing methods	Methods/enzyme	Complexity	The length of the sequence (bp0)	Data output per cycle	Time per cycle	Major cause of error	Genome sequencing cost
The first-generation sequencing technology	Sanger	Sanger/DNA polymerase	Difficult	150–1000	56 kb	1.5–3 min	Primers, amplification	3 billion
The second-generation sequencing technology	454-FLX	Pyrosequencing/DNA polymerase	Difficult	240–400	400–600 Mb	10 h	Insertion, loss	1 million
	Solexa	Sequencing by synthesis/DNA polymerase	Difficult	35–75	20.5–25 Gb	9.5 h	Base substitution	60,000
	SOLiD	Ligase sequencing/DNA polymerase	Difficult	35–50	10–15 Gb	6–7 days	Base substitution	60,000
The third-generation sequencing technology	Helicos TSMS	Sequencing by synthesis/DNA polymerase	Easy	30–35	21–28 Gb	8 days	Base substitution	70,000
	PacBio SMRT	Sequencing by synthesis/DNA polymerase	Easy	3000–100,000	10 Mb	/	Unknown	Low
	Nanopore	Electrical signal sequencing/exonuclease	Easy	Infinite	Infinite	/	Unknown	Low

failure. Hypertensive renal damage was found in patients with a history of hypertension of more than 5 years. The damage to the renal tubules was usually earlier than the glomerulus, leading to increased nocturia, decreased urinary concentration function, decreased urinary specific gravity, persistent proteinuria, microscopic hematuria, and tubular type, as well as hypertension and other target organ complications [61]. This section focuses on the laboratory examination of hypertensive renal damage.

4.6.1 Glomerular Function Examination

Glomerular filtration is one of the most important functions of the glomerulus, expressed as Glomerular filtration rate (GFR). It is defined as the amount of plasma fluid per unit time (min) filtered by the glomeruli. Renal plasma clearance rates of various substances were designed to estimate their value. The plasma clearance rate refers to the number of milliliters per minute that the kidney can completely remove a substance contained in the plasma. The number of milliliters per minute of this completely cleared substance is called the plasma clearance rate (mL/min) of that substance.

The calculation formula is: $C = U \times V/P$

The amount of urine excreted per minute/the concentration of a substance in plasma.

"*C*" for plasma clearance (mL/min)

"*U*" for a substance in the urine concentration (mg/mL)

"*V*" for urine volume per minute (mL/min)

"*P*" for a substance in the plasma concentration (mg/mL)

Because GFR cannot be measured directly, it can only be measured by the clearance rate of a marker. Including endogenous and exogenous markers. (1) Endogenous markers: It refers to substances existing in the body, such as creatinine (Cr), urea nitrogen (BUN), and medium and low molecular weight protein (β_2-microglobulin, cystatin C). (2) Exogenous marker: Includes polysaccharides, such as inulin; radioactive nuclide markers, such as ^{99m}Tc-DTPA.

4.6.1.1 Endogenous Creatinine Clearance Rate (Ccr)

Creatinine is a metabolite of creatine in the human body and is non-toxic, and the body generates and releases creatinine at a relatively stable rate, which is circulated to the kidney by the blood and is discharged through the body by urine. The production of creatinine in human blood is endogenous and exogenous, if strict control diet, or under the condition of relatively stable muscle activity, the production of blood creatinine, and the excretion of urine are relatively constant. Most of the creatinine is filtered from the glomeruli, not reabsorbed by the renal tubule and excreted very little. The kidney removes all the creatinine from several milliliters of blood every minute, which is called endogenous creatinine clearance rate (Ccr). The

clinical use of Ccr to represent GFR is the easiest and most reliable way to calculate the rate of glomerular filtration. Methods of determining Ccr have standard 24-h urination, 4-h urine amelioration, and blood creatinine estimation [62, 63].

1. Standard 24-h urination:
   (a) The patient has a 3-day low protein diet, which is less than 40 g/day, and fasting meat (non-creatinine diets), avoiding strenuous exercise;
   (b) The urine was discharged at 8 am on the fourth day, and the urine was collected and recorded at 24 h (the urine must be left at 8 am the next day). Toluene 4–5 mL was added to prevent corrosion. Blood 2–3 mL was taken and examined simultaneously with 24 h urine.
   (c) To determine the concentration of creatinine in urine and blood, the Ccr formula is as follows:
   Ccr (mL/min) = urinary creatinine concentration (μmol/L) × minute urine volume (mL/min) ÷ plasma creatinine concentration (μmol/L).
2. Four-hour urine amelioration:
   It is not convenient to have a 24-h urine, which can cause the sample to be lost and refrigerated, affecting creatinine testing, causing the error. Under strict control conditions, the levels of plasma and urine creatinine in 24 h are constant, which is convenient for the clinical application, and it can be used for 4 h of urine and an empty stomach to test for creatinine, and then calculate the clearance rate by the formula.
3. Blood creatinine estimation:
   The Ccr was estimated based on the serum creatinine value and combined with age, gender, race, height, weight, and other factors to evaluate GFR conveniently and accurately, and to meet the clinical dynamic observation of renal function changes in patients. Cockcroft-Gault formula is commonly used in clinic [63, 64]
   Male Ccr (mL/min) = [140 − age] × weight (kg)/Scr (mg/dL) × 72;
   Female Ccr (mL/min) = [140 − age] × weight (kg)/Scr (mg/dL) × 85.
4. Reference range:
   Adults 80–120 mL/min, older persons grow with age, with natural decline.
5. Clinical significance:
   (a) It is a sensitive indicator of glomerular damage: when GFR is reduced to 50% of normal, the Ccr is low to 50 mL/min, but the Scr and BUN is still in the normal range because the kidney has a strong storage capacity, so Ccr is a sensitive indicator of GFR
   (b) Evaluation of renal injury degree: Ccr is commonly used to replace GFR. According to Ccr, renal function can be generally divided into four stage: Stage 1 (renal failure compensation period) Ccr is 51–80 mL/min. Stage 2 (decompensated stage of renal failure) Ccr is 50–20 mL/min. Stage 3 (renal failure stage) Ccr is 19–10 mL/min. Stage 4 (uremia stage or end-stage renal failure) Ccr < 10 mL/min.

4.6.1.2 Determination of Serum Creatinine (Scr)

Serum creatinine includes endogenous and exogenous creatinine. The body produces 1 mg of creatinine per 20 g of muscle per day. Most of the blood creatinine is excreted from the body through glomerular filtration and is not reabsorbed by the renal tubule, and the renal tubule excretion is very small. In stable exogenous creatinine intake, blood creatinine concentration depends on the glomerular filtration capacity. When renal parenchymal damage and glomerular filtration rate is reduced to one-third of the normal population, blood creatinine increases significantly. Therefore, the measurement of serum creatinine concentration can be used as an indicator of impaired glomerular filtration rate, and the sensitivity is better than urea nitrogen, but it is not an early diagnostic indicator.

Reference range: Serum creatinine, male 53–106 μmol/L, female 44–97 μmol/L.

Clinical significance: Serum creatinine increases in:

(a) Increased serum creatinine is associated with decreased glomerular filtration function due to various causes. Scr increases progressively in acute renal failure, which is an indicator of organic damage and can be accompanied by oliguria. The degree of Scr elevation in chronic renal failure was consistent with the severity of the lesion: renal failure compensatory period, Scr <178 μmol/L; Renal failure decompensation, Scr < 442 μmol/L; Renal failure, Scr < 707 μmol/L; Uremic stage, Scr > 707 μmol/L [65–67].
(b) Differentiate prerenal and renal parenchymal oliguria. Serum creatinine in organic renal failure is often more than 200 μmol/L. The effective blood volume caused by prerenal oliguria (heart failure, dehydration, hepatorenal syndrome, nephrotic syndrome, etc.) decreased, resulting in decreased renal blood flow and increased serum creatinine concentration not exceeding 200 μmol/L.
(c) Serum creatinine may be low in the aged and emaciated persons, so when serum creatinine is elevated, renal function should be alert, and endogenous creatinine clearance should be further tested.
(d) When serum creatinine increased significantly, renal tubular creatinine excretion increased, causing Ccr to exceed true GFR. Cimetidine can be used to inhibit the renal tubule secretion of creatinine.

4.6.1.3 Determination of Blood Urea Nitrogen (BUN)

BUN is the end product of human protein metabolism. Its production depends on dietary protein intake, tissue protein catabolism, and liver function. BUN is mainly filtered through the glomeruli and excreted in urine and is reabsorbed by the renal tubules with only a small amount of excretion. When renal parenchyma is damaged, GFR decreases, resulting in increased blood concentration, so the function of glomerular filtration is roughly estimated by measuring blood urea nitrogen. Urea nitrogen is only elevated when glomerular filtration function drops below 50% normal, so the measurement of blood BUN is not a sensitive indicator of glomerular filtration function. Blood BUN level is greatly affected by factors such as renal blood flow, high-protein diet, gastrointestinal bleeding, fever, infection, extensive

burns, trauma, urinary tract obstruction, and severe edema. Therefore, it is generally impossible to judge GFR by BUN alone.

Reference range: Adults 3.2–7.1 mmol/L, infants and children 1.8–6.5 mmol/L.

Clinical significance: Increased serum BUN in: (a) Increase blood BUN was found to be associated with decreased glomerular filtration. (b) Prerenal oliguria: inadequate blood volume due to severe dehydration, massive ascites, cardiac circulatory failure, and hepatorenal syndrome. At this time, BUN was increased but Cr was not significantly increased, and BUN/Cr (mg/dL) > 10:1 was called prerenal azotoxemia. By expanding the volume of urine increase BUN can be reduced by itself. (c) Excessive protein decomposition or ingestion: such as acute infectious disease, high fever, massive upper gastrointestinal hemorrhage, extensive burns, severe trauma, major postoperative and hyperthyroidism, and high-protein diet, but Scr is generally not elevated. After correction of the above situation, blood BUN can be decreased.

4.6.1.4 Measurement of Glomerular Filtration Rate (GFR)

^{99m}Tc-DTPA was cleared almost completely by glomerular filtration, and its maximum clearance rate was the glomerular filtration rate. SPECT was used to measure the reduction of the two renal radionuclides after pellet intravenous injection, and GFR was calculated automatically according to the formula, which can show bilateral renal GFR, with high sensitivity and accuracy, and can be considered as the "gold standard" for evaluation of GFR in clinical work [68, 69].

Reference range: Total GFR 100 ± 20 mL/min.

Clinical significance: (a) Factors affecting GFR: related to age, sex, weight, so pay attention to these factors. After 30 years of age. Every 10 years GFR decline in 10 mL/min, men than women GFR high about 10 mL/min, GFR increased significantly during pregnancy, 3 months increased by 50%, postpartum dropped to normal; (b) Reduced GFR is common in acute and chronic renal failure, renal arteriosclerosis, pyelonephritis (advanced), diabetic nephropathy and hypertensive nephropathy, hypothyroidism, adrenocortical insufficiency, and glucocorticoid deficiency. (c) GFR increases in: Acromegaly and gigantism, diabetic nephropathy early. (d) It can also be used for observing that position, morphology, and size of the left and right kidney, and can also be used to combine with clinical initial indication that the blood vessel is embolic.

4.6.1.5 Determination of Blood β_2-Microglobulin (β_2-MG)

β_2-MG is a small molecule globulin produced by lymphocytes, platelets, and polymorphonuclear leukocytes. The structure is similar to that of the immunoglobulin stable region. It has a molecular weight of 11,800, consisting of 99 amino acids in a single chain polypeptide. β_2-MG is widely found in plasma, urine, cerebrospinal fluid, saliva, and colostrum. In normal human blood, the concentration of β_2-MG is very low, free to pass through the glomeruli, and then almost all is reabsorbed in the proximal tubule, which is then broken down and destroyed in renal tubular epithelial cells, with only a small amount being excreted from the urine.

Reference range: Adult serum 1–2 mg/L.

Clinical significance: (a) When the glomerular filtration function is impaired, it is stored in the blood. In the evaluation of renal glomerular filtration function, the increase of blood β_2-MG was more sensitive than that of Scr, and it appeared when Ccr was lower than 80 mL/min, while Scr concentration was not significantly changed. If blood and urine β_2-MG were both elevated, and blood β_2-MG < 5 mg/L, both glomeruli and renal tubule function might be impaired. (b) IgG nephropathy, malignant tumors, and a variety of inflammatory diseases such as hepatitis, rheumatoid arthritis can lead to increased production of β_2-MG.

4.6.1.6 Determination of Serum Cystatin C

As there are many problems with using Scr, BUN to evaluate GFR, people are trying to find other endogenous small molecules to replace them. Cystatin C is a low molecular weight basic non-glycosylated protein with a molecular weight of 13 kD and composed of 120 amino acid residues. As a secretory protein, cystatin C is also an endogenous marker with the best correlation with GFR in low molecular protein, even better than Scr, and is not affected by changes in dietary protein intake and inflammation [70]. The production rate of cystatin C in the body is fairly constant and is not affected by inflammation or tumors. It is not affected by muscle mass or gender [71, 72]. Kidney is the only organ for removing cystatin C from the circulation, so its concentration is mainly determined by GFR, which can reflect the decline of GFR more sensitively than Scr and BUN [73–75].

Reference range: Total GFR 100 ± 20 mL/min.

Clinical significance: Serum cystatin C is a more accurate and reliable indicator of glomerular filtration function and has guiding significance for the diagnosis of early renal damage in patients with various kidney diseases.

4.6.2 Renal Tubular Function Examination

When hypertensive renal damage occurs, the damage of renal tubules usually precedes the glomeruli. The mechanism might be hypertension that leads to arteriolosclerosis, lumen stenosis, glomerular ischemia, initiation of renal regulation, and activation of the RAS system. The continuous contraction of the bulbous arteriole causes the ischemia of the capillary network around the renal tubules, resulting in the dysfunction of the renal tubules, the elevated protein associated with the renal tubules in the urine and the dysfunction of urinary concentration-dilution [62, 67].

4.6.2.1 Proximal Renal Tubular Function Test

Proximal tubule is an important part of lifting absorption in renal tubule, mainly reabsorbs inorganic substances such as Na^+, K^+, Cl^-, HCO_3^-, and organic substances such as glucose and amino acids.

Determination of Urinary β_2-Microglobulin (β_2-MG)

β_2-MG is a small molecule globulin produced by lymphocytes, platelets, and polymorphonuclear leukocytes. The structure is similar to that of the immunoglobulin stable region. It has a molecular weight of 11,800, consisting of 99 amino acids in

a single chain polypeptide. β_2-MG is widely found in plasma, urine, cerebrospinal fluid, saliva, and colostrum. Normal people's production of β_2-MG is relatively constant, about 150–200 mg/day. Due to the small molecular weight and non-binding of plasma proteins, it is free to enter the prourine through glomerular filtration. Ninety-nine percent of β_2-MG in prourine is reabsorbed in proximal renal tubules and is broken down and destroyed in renal tubular epithelial cells, only a small amount is discharged from the urine. Because β_2-MG is easily broken down in acidic urine, it should be measured in time after urine collection [76, 77].

Reference range: Adult urine is below 0.3 mg/L or below 0.2 mg/g creatinine corrected.

Clinical significance: According to the excretion process of β_2-MG in the kidney, increased urine β_2-MG can sensitively reflect the damage of proximal renal tubule reabsorption, such as renal tubule-interstitial disease, early renal tubule damage caused by drugs or toxins, and the early stage of acute rejection after renal transplantation, and can be used as a sensitive indicator for early detection of renal function damage caused by drugs.

N Acetyl-β-D-Amino Glycosidase Enzymes (NAG)

NAG is mainly located in the lysosome system of proximal tubules and is mainly involved in the decomposition and metabolism of glycoproteins. As the NAG in serum could not be filtered from the renal glomerulus, the activity of NAG in urine was enhanced, indicating that NAG originated from renal tubules and reflected renal tubular cell damage [78, 79].

Reference range: *P*-nitrophenol colorimetry: Serum NAG: 21.54 ± 6.4 U/L. Urine NAG was normally distributed, with a median of 9.13 U/g Scr and a maximum of 16.10 U/g Scr at the 95th percentile.

Clinical significance: (a) An early sensitive indicator of renal tubular damage that may occur before routine renal function examination and pathological changes. (b) Facilitate early detection of renal diseases and early intervention to prevent further deterioration of renal function. (c) Can be used to test for renal toxicity of drugs.

Determination of α_1-Microglobulin (α_1-MG)

α_1-MG is a glycoprotein produced by hepatocytes and lymphocytes with a molecular weight of only 26,000. In plasma, α_1-MG can be free or bind to proteins, both of which exist. Free α_1-MG can enter the prourine freely through the glomeruli, but about 99% of the α_1-MG in the prourine is reabsorbed and decomposed by proximal convoluted tubule epithelial cells in the manner of pinocytosis, so only a small amount of MG can be excreted from the urine.

Reference range: Adult urine α_1-MG <15 mg/24 h, or <10 mg/g creatinine; serum-free α_1-MG: 10–30 mg/L.

Clinical significance: (a) Suggesting proximal renal tubular dysfunction: Elevated urinary α_1-MG is a specific and sensitive indicator of early proximal renal tubular injury caused by rejection after renal transplantation, and its level can be used to monitor acute renal injury caused by drugs. Compared with β_2-MG, α_1-MG is not affected by malignant tumors, and there is no false negative in acidic urine, so it is

more reliable. (b) Evaluation of glomerular filter function: According to the excretion method of α_1-MG, the increase of serum α_1-MG indicated the blood storage caused by the reduction of GFR, which was more sensitive than the detection of Scr and β_2-MG. At the Ccr < 100 mL/min, the serum α_1-MG is elevated. The increase of α_1-MG in serum and urine indicated that both glomerular filtration function and renal tubular resorption function were impaired. (c) Serum α_1-MG reduction: In the case of severe hepatic lesions, the reduction in production of severe liver disease, like severe hepatitis, liver necrosis, etc.

Urinary Retinol Binding Protein (RBP)

RBP is a low molecular protein with a molecular weight of 21,000. After the transport of retinol to the target cells in the blood, the protein is separated from the binding protein and free to enter the primary urine through glomerular filtration. It is reabsorbed almost completely in the proximal convoluted tubule and quickly decomposed, so the urine content in normal people is extremely small (<0.2 mg/24 h). When renal tubules are damaged, the reabsorption and degradation of RBP is affected, and urinary excretion is increased, so the damage of proximal convoluted tubules can be sensitively reflected. It needs to be pointed out that the output of RBP is relatively constant, which is not subject to the change of urine pH and is not affected by gender, posture, and diurnal differences. Therefore, it is an accurate and reliable indicator for the diagnosis of renal tubular injury and dysfunction [80].

Reference range: Urine RBP: <0.7 mg/L; Serum RBR: 25–70 mg/L.

Clinical significance: Urinary RBP elevation: It is a sensitive marker of renal tubular damage caused by renal diseases, diabetes, drugs, and poisoning. Diuretics can affect RBP output.

4.6.2.2 Distal Renal Tubule Function Test

The main function of the distal tubule is to regulate ion metabolism and maintain the balance of acid base and water. Under the regulation of various nerve and endocrine factors, the quality and quantity of urine is finally determined. In order to maintain the homeostasis of the body, the kidney has a strong ability to regulate water in the body. It can concentrate the daily glomerular filtrate from 180 to 0.4 L, and the urine osmosis is up to 1400 mOsm/(kg·H_2O), playing a role in water preservation. It is also possible to excrete urine of 10–20 L less than 40 mOsm/(kg·H_2O) and excrete excess water in the body.

Urine Osmotic Test

Urine osmosis measurement refers to the total number of all solute particles in urine, such as electrolyte, urea, carbohydrate, and protein. Urine osmotic is a more accurate reflection of renal concentration than urine-specific gravity. Kidney is through the urine concentration or dilution effect to adjust the balance of body fluid osmotic pressure. Urine osmotic pressure reflects the relative excretion rate of the kidney to solute and water, which is not affected by the size and nature of solute particles,

and is only related to the number of solute particles. The so-called concentration or dilution of urine is based on plasma osmosis (285 mOsm/kg·H_2O). If urine osmosis is higher than plasma osmosis, it is hyperosmotic; otherwise, it is low osmotic. If the urine osmotic pressure is always equal to the plasma osmotic pressure, it is called isoosmotic, which reflects that the renal concentration has been seriously damaged.

Reference range: After 8 h of no drinking water, the urine osmosis is 600–1000 mOsm/kg·H_2O. If the urine osmosis can reach 800 mOsm/kg·H_2O, the renal concentration function is good. Normal plasma osmosis was 275–305 mOsm/kg·H_2O.

Clinical significance:

(a) To determine the function of kidney concentration: Urinary osmosis <600 mOsm/kg·H_2O in normal people after 8 h of water restriction, indicating renal concentration dysfunction. It can be seen in chronic pyelonephritis, polycystic kidney, uric acid nephropathy, and chronic interstitial disease. It can also be seen in the late stage of chronic nephritis.
(b) To identify prerenal or renal oliguria: In prerenal oliguria, the renal tubule concentration function is normal, so the urine osmosis is higher, usually greater than 450 mOsm/kg·H_2O. When renal tubular necrosis leads to renal oliguria, urinary osmosis is reduced, always less than 350 mOsm/kg·H_2O.

Urine Concentration Test

After 12 h without drinking water, the urine osmosis should be ≥800 mOsm/kg·H_2O, and the ratio of urine osmosis to plasma osmosis should be greater than 3, which indicates that the kidney has good urine concentration function. When kidney concentration dysfunction is caused by renal tubular diseases, there will be a decrease in urinary osmosis, and the ratio of urinary osmosis to plasma osmosis is significantly reduced.

4.7 Endocrinology Test

Ting Wu

4.7.1 Determination of Plasma Renin Activity (PRA)

Renin mainly produce, storage, and secreted by the renal proximal glomerular cells. The rate of angiotensin-I is known as the plasma renin activity, produced by plasma renin activity catalysis angiotensinogen. Therefore, the increment of angiotensin-I production in 37 °C in unit time of human body is often simulated to indirectly reflect the activity of rennin. The determination of plasma renin activity can provide a basis for the selection of antihypertensive therapy in patients with hypertension, provide a basis for the differential diagnosis of primary and

secondary aldosteronism, and assist clinicians to determine whether there is renal ischemia in patients.

There are many factors affecting the activity of renin, such as physiological factors. There were differences in the activity of renin in different positions. In general, the activity of renin in supine position was 50% of that in erect position, and the activity of renin in sitting position was 75% of that in erect position. In the same state, the secretion of renin was the highest from 2 to 8 o'clock in the morning and the lowest from 12 to 18 o'clock in the afternoon. The activity of renin was the lowest in ovulation period and highest in luteal phase. During pregnancy, plasma renin activity increased and decreased to normal after delivery. Renin activity decreased with age. Some drugs can also change the activity of renin. Contraceptives can increase the activity of renin and return to the original level after withdrawal. Therefore, contraceptives should be stopped for 12 weeks before the experiment. Antihypertensive drugs, such as diuretic, ACEI, calcium antagonist receptor blocker, can increase renin activity, while beta blocker clonidine decreased renin activity. Therefore, it is recommended to discontinue all kinds of antihypertensive drugs for more than 2 weeks before determination if the condition permits.

The laboratory can also use radioimmunoassay or automatic immunoassay to determine the plasma concentration of the renin activity (post-lysis) [81]. The normal range of morning PRA of the sitting position is 1–4 ng/(mL·h), that is, 0.8–3.0 nmol/(L·h) and the corresponding active renin concentration is 8–35 mu/L.

4.7.2 Angiotensin-II

Angiotensin-II is one of the strongest shrinking vascular substances that hydrolysis by angiotensin-I under the angiotensin-converting enzyme. The content of angiotensin-II in plasma can be directly determined by radioimmunoassay, specimen collection also requires an enzyme inhibitor anticoagulant tube to collect blood samples.

4.7.3 Aldosterone

Aldosterone is a kind of halocorticoid synthesized and secreted by adrenal cortical globular zone cells. There are many factors of aldosterone secretion increase, such as primary aldosteronism, pseudo aldosteronism (bilateral adrenal zona hyperplasia), diuretics, heart failure, liver disease, renal failure, and nephrotic syndrome caused by secondary aldosteronism, primary periodic edema, Bartter's syndrome, renal juxtaglomerular apparatus hyperplasia, after surgery, low blood volume, hypokalemia caused by various reasons, malignant hypertension and progressive hypertension, etc. However, adrenal cortical dysfunction, low renin and low aldosterone syndrome, 18-hydroxylase deficiency, diabetes, Turner's syndrome, and acute alcoholism can reduce the level of aldosterone secretion. The plasma aldosterone

concentration and urinary aldosterone excretion effected by position and sodium intake.

In clinical, the determination of plasma aldosterone is an important indicator of aldosteronism. The simultaneous determination of PRA, angiotensin-I, and angiotensin-II is of great value in differentiating primary from secondary aldosteronism, especially in combination with the hydrocordipine inhibition test and the saline load test, which is the "gold index" for the determination of primary aldosteronism. The most popular laboratory methods for aldosterone detection are radioimmunoassay and chemiluminescence [82]. The determination of aldosterone requires the collection of blood serum or plasma. For normal subjects with unrestricted sodium intake, the morning serum (or plasma) aldosterone concentration at sitting position was 5–30 ng/dL (140–830 pmol/L) [83].

The secretion of aldosterone is affected by circadian rhythm and receptor position, the excretion of aldosterone was accurately reflected by 24-h urinary excretion. The aldosterone-18-glucuronic acid can be determined by radioimmunoassay. Its excretion rate is 5–19 g (14–53 nmol) per 24 h. Tetrahydroaldosterone-18-glucuronic acid is a metabolite with a higher content, and its excretion rate is 12–65 g (33–178 nmol) per 24 h.

Guidelines recommend using ARR for early Screening of primary aldosteronism, plasma renin determination can be used to determine the determination of renin activity or direct renin concentration, due to the different laboratory testing method, guide gave no unified ARR tangent point value, but the guidelines mentioned when testing the renin activity and aldosterone concentration unit are respectively ng/mL (h) and ng/dL; currently, the most commonly used ARR tangent point is 30; when the renin concentration and aldosterone concentration were measured in mU/L and ng/dL, respectively, the most commonly used ARR cut point was 3.7 [28]. If active renin concentration (ARC: pg/mL) is used instead of PRA, a PAC/ARC ratio >40 should be used as the criterion [84].

4.7.4 Thyroid Function

There are many methods to determine serum thyroid function, such as immunoassay of enzyme-linked magnetic separation (IEMA), radioimmunoassay (RIA), and automatic chemiluminescence immunoassay (CLIA). For laboratory, radioimmunoassay (RIA) and automatic chemiluminescence immunoassay (CLIA) are sensitively, fastly repeatability to determine of thyroid function, there was no signifcant difference between two methods of test result.

Thyroid function is assessed by one or more of the following tests: serum TSH concentration, total serum T4 concentration, total serum T3 concentration, free serum T4 (or T3) concentration. The range of normal reference values is different in different laboratories, the normal value of TSH used in most laboratories is <4.5–5.0 mu/L, total serum T3: 75–195 ng/dL (1.1–3 nmol/L), total serum T4: 4.6–11.2 g/dL (60–145 nmol/L).

4.7.5 Serum Parathyroid Hormone Assay

The determination of parathyroid hormone in serum is the most reliable direct evidence and sensitive index to determine the parathyroid function. At present, with the development of radioimmunoassay and immunochemiluminescence technology, the determination of serum parathyroid hormone has been widely promoted, and the sensitivity and repeatability of the results are increasingly higher. The patient serum parathyroid hormone of hyperparathyroidism increases, and related to blood calcium concentration and disease severity. Serum parathyroid hormone is decreased or undetectable in patients with parathyroid dysfunction; however, parathyroid hormone levels may be normal or increased in patients with pseudoparathyroidism. At the same time, it should be noted that some physiological factors and drugs have effects on parathyroid hormone levels. In general, serum calcium increases when hyperparathyroidism and decreases when hypoparathyroidism; however, it takes multiple tests to be of diagnostic value. In general, blood phosphorus decreases when hyperparathyroidism, while blood phosphorus increases when hypoparathyroidism, (it is necessary to measure the concentration of blood phosphorus on an empty stomach, and comprehensively evaluate the parathyroid gland function with the results of blood calcium). Urinary calcium levels were increased in patients with primary and pseudo hyperparathyroidism, and normal or low in patients with secondary hyperparathyroidism. Urinary calcium is decreased with hypoparathyroidism. Parathyroid hormone can inhibit the reabsorption of HCO_3– in renal tubule and increase blood chlorine and reduce blood phosphorus. Therefore, measurement of blood chlorine/blood phosphorus ratio can indirectly understand the function of parathyroid gland.

4.7.6 Blood and Urine Catecholamines

Catecholamines (CAs) include epinephrine, norepinephrine, and dopamine, which are secreted by the adrenal medulla and some sympathetic neuronal pheochromocytoma. Epinephrine in blood or urine and the metabolites of norepinephrine—methoxyepinephrine (MN) and methoxynorepinephrine (NMN) are currently recognized as the biomarkers, with >90% of sensitivity and specificity, however, the detection of these biomarkers usually uses high performance liquid chromatography (HPLC), the corresponding equipment is expensive, cumbersome to operate and difficult to popularize. With the development of studies on catecholamines, elisa (EIA) and radioimmunoassay (RIA) has been widely used, especially the determination of plasma MN and NMN. Urinary catecholamine and its metabolites MN and NMN were increased in patients with persistent hypertension. The normal reference value of urine catecholamine was 13–42 g/day, and the normal reference value of urine methoxy metabolite was 1.5–4.6 mol/day. Plasma MN was 60–310 pmol/L (12–61 pg/mL), plasma NMN was 90–570 pmol/L (18–102 pg/mL). The normal

reference value of MN in Xinjiang hypertension diagnosis and treatment research center was <90 ng/L. Plasma samples are usually collected and separated by EDTA anticoagulant tubes.

4.7.7 Urine Vanilla Mandelic Acid

Catecholamines are almost entirely metabolized in the body. There are two metabolic pathways: a small part of CA is activated by monoamine oxidase to generate *p*-dihydroxyamygdalic acid, and most CA is converted into 3-methoxyepinephrine or normethoxyepinephrine after the action of ca-*o*-methyltransferase, and finally becomes VMA, which can be determined by the urine vanilla-amygdalic acid and can supplement the blood catecholamine.

4.7.8 Blood and Urine Cortisol

Cortisol is a glucocorticoid secreted by the cortical fascicles of the human body. It is one of the most important hormones to maintain life activities. It also has anti-inflammatory and anti-toxic effects. The measurement of hormone content by radioimmunoassay (RIA) and chemiluminescence immunoassay are accurate and reliable methods. The blood cortisol secretion presents the circadian rhythm change, the highest from 8 to 9 o'clock in the morning, the lowest at 12 o'clock in the evening. The 24 h urinary-free cortisol excretion can more effectively and accurately reflect the functional status of the adrenal cortex, so the combined determination of the two is of greater diagnostic value. The normal reference value of blood cortisol was 138–635 nmol/L (5–23 μg/dL) at 8 o'clock, 83–441 nmol/L (3–16 μg/dL) at 16 o'clock, and 80–196 nmol/L (1.6–5.4 μg/dL) at 0 o'clock. The normal reference value of urinary free cortisol was 27.6–276 nmol/24 h (10–100 μg/24 h). Serum or plasma was used to measure the blood cortisol, for the determination of urinary cortisol, the urine should be kept for 24 h and embalmed with 5–10 mL hydrochloric acid. The total amount of urine should be recorded and mixed evenly. Twenty milliliters of urine should be sent for examination.

Adrenal glucocorticoid has the effect of inhibiting the secretion of ACTH in pituitary gland, so that the secretion of ACTH is reduced, and the corresponding secretion of adrenal cortisol is also reduced, and the concentration of blood cortisol is reduced. In hypercorticosis, the hypothalamic-pituitary-adrenal axis feedback mechanism is destroyed, so its abnormally elevated cortisol is not inhibited by glucocorticoid. The inhibition experiment of exogenous glucocorticoid dexamethasone with different doses and methods can determine whether the adrenal cortex function of patients is controlled by pituitary ACTH, which can be used for the rough screening of hypercorticosis and the differential diagnosis of etiology (Table 4.6).

Table 4.6 Comparison of dexamethasone inhibition test

	Drug regimen	Analysis of blood cortisol results
Inhibition test of 1 mg dexamethasone	One dose of dexamethasone was taken orally at midnight, and the blood cortisol concentration was measured at 8 am the next morning	The inhibition rate of normal blood cortisol was over 50%, the possibility of Cushing's syndrome was suggested when the control value inhibited to less than 50%. A further 2 mg dexamethasone inhibition test or other examination should be performed to confirm the diagnosis of hypercortisolism
Inhibition test of 2 mg dexamethasone	Oral dexamethasone 0.5 mg each time, 4 times a day (once every 6 h), or 0.75 mg each time, 3 times a day for 2 days, the serum cortisol concentration was measured after taking the drug	Normal person is inhibited rate can exceed 50%, adrenal cortical function is hyperactive person, concentration does not come down, or decrease did not reach the 50% of base value
Inhibition test of large dose dexamethasone (8 mg)	Oral dexamethasone 2 mg each time, 4 times a day (once every 6 h) for two consecutive days, and measure the serum cortisol concentration after taking the drug	Cortisol concentration decreased more than 50% of the base value can be inhibited, suggesting that hypercorticosis is pituitary ACTH-dependent; on the contrary, if the cortisol level does not decrease or the decrease is less than 50% of the base value, it is not inhibited, suggesting that it is ectopic ACTH secretion tumor or adrenal cortisol autonomic secretion tumor
Inhibition test of maximal dose dexamethasone (32 mg)	Blood samples were taken at 8 am on the first day for ACTH and cortisol, 8 mg for dexamethasone at midnight, 8 mg for each at 8 am on the next day, 8 mg at 4 pm and 12 am on the second day, 8 am on the second day for ACTH and cortisol, 7 am on the second day, and 7 am on the third day for free cortisol in urine	This test is also a method for the differential diagnosis of Cushing's syndrome. Because the 8 mg dexamethasone inhibition test for some patients with pituitary Cushing's disease is not inhibited to less than 50% of the base value, the maximum dose (32 mg) dexamethasone inhibition test is designed, and its diagnostic value is better than the 8 mg method

4.7.9 Urine 17-Hydroxycorticosteroid (17-OHCS)

In normal urine, most 17-OHCS are tetrahydro metabolites of cortisol and cortisone (THF and THE), but THS, the tetrahydro metabolite of 11-deoxycortisol, also is present. As a result, 17-OHCS excretion roughly parallels cortisol excretion. Urinary excretion of 17-OHCS in normal adults ranges from 2 to 6.5 mg (5.5–18 mmol)/g of creatinine, independent of body weight. Urine 17-hydroxycorticosteroids can be measured by colorimetry, urinary 17-OHCS excretion is increased in patients with

all forms of Cushing's syndrome and decreased in patients with primary and secondary adrenal insufficiency.

4.7.10 Urine 17-Ketosteroid (17-KS)

Urinary 17-KS are intermediate products of adrenocorticoids. In male, two-thirds from the adrenal gland, one-third from the testicles, while in women, most 17-KS from the adrenal gland. Urinary 17-KS excretion is an indicator of adrenal androgen synthesis. Patients with Cushing's syndrome, testicular tumor (especially mesenchymal cell tumor), precocity, polycystic ovary, acromegaly had significantly increased urinary 17-KS. The use of androgen, corticosteroids, ACTH can also increase the urine 17-KS. Urinary 17-KS can be reduced in adrenocortical hypofunction, adenohypophysis or testicular hypofunction, cirrhosis, diabetes, tuberculosis, and high malnutrition.

4.7.11 Endothelin

Endothelin is a bioactive polypeptide composed of 21 amino acids, which has a strong effect of constricting coronary arteries and renal arterioles, stimulating the release of cardiac natriuretic hormone, increasing systemic blood pressure and inhibiting the release of rennin. Endothelin is a multifunctional physiological regulation hormone, which is involved in the occurrence and development of various diseases such as shock cerebrovascular disease. The normal reference value of endothelin was 50.8 7.58 ng/L (radioimmunoassay). Endothelin elevation is seen in primary hypertension, acute myocardial infarction, angina attack, septic shock, renal disease, uremia, cerebral hemorrhage, cerebral infarction, primary liver cancer, liver cirrhosis, duodenal ulcer, etc.

4.7.12 Atrial Natriuretic Peptide (ANP)

Plasma ANP is an active polypeptide synthesized, stored and secreted by the atrium, which has strong natriuretic, diuretic, vasodilatory, blood pressure lowering, and antagonistic effect on renin-angiotensin system and vasopressin. It is an important index for the differential diagnosis of heart failure. It has many detection methods of ANP. Different detection methods have different reference value. Currently, the commonly used method is radioimmunoassay, and the normal reference value ranges from 50 to 150 pg/mL. The reduction of ANP is common in hyperthyroidism, atrial fibrillation, and post-dialysis uremia. The increase of ANP is found in primary hypertension, renal insufficiency, coronary heart disease, myocardial infarction, heart failure, premature heartbeat, liver cirrhosis, supraventricular tachycardia, cerebral infarction, cerebral hemorrhage, and primary aldosteronism.

4.7.13 5-Hydroxytryptamine

5-Hydroxytryptamine is a transmitter of the central nervous system, and its active part is indoleamine, which is widely found in brain, platelet, stomach, and other tissues, with the largest content in the brain. It is a strong smooth muscle stimulation and vasoconstrictor. The common detection methods of 5-hydroxytryptamine in the laboratory are enzyme-linked immunoassay and radioimmunoassay, and anticoagulant vascularization containing enzyme inhibitor is required for specimen collection to prevent the degradation of 5-hydroxytryptamine. Normal value: 0.22–2.06 mol/L (39–361 ng/mL). 5-hydroxytryptamine increase in carcinoid syndrome, dumping syndrome postoperatively, migraine and low oxygen disease, while decreases in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), mixed connective tissue disease, Parkinson's disease, Huntington's, liver degeneration, schizophrenia, and neurasthenia.

4.7.14 Gonadal and Pituitary Function-Related Hormones

4.7.14.1 Testosterone (T)

Testosterone is mainly produced in the stromal cells of the male testicle, and a small amount in the female blood is a metabolite of dehydroisoandrosterone. The content of testosterone has circadian rhythm changes throughout the day, with the highest content in the morning, and the peak time is from 4 to 9 o'clock in the morning. The best time for blood collection is 6–9 am. Female testosterone is lower than male testosterone and varies with menstrual cycle. After resting and glucose load, testosterone decreased, and increased after active state. When females became masculine, testosterone increased to more than 7.0 nmol/L. Ingestion of human androgen, dexamethasone, digoxin, and ethanol resulted in lower testosterone. Increased testosterone in idiopathic precocious puberty and children of adrenal cortex hyperplasia, part of adrenocortical tumor and the tumor of male gonadotropin secretion, pregnancy chorionic epithelium diseases, testicular feminization, primary hirsutism, sedatives, and taken the barbiturates chlorine meters, gonadotropin, oral contraceptive drugs, decreased testosterone is found in Down syndrome, uremia, myotonic dystrophy, hepatic insufficiency, primary and secondary gonadal insufficiency, and cryptorchidism.

4.7.14.2 Progesterone

The clinical progesterone determination method mostly uses the radioimmunoassay and the chemiluminescence method because of individual physiology period, referenced value range difference is bigger. Elevated serum progesterone was found in hydatidiform mole, mild gestational hypertension syndrome, diabetic pregnant women, multiple pregnancies, secondary hypertension, congenital adrenal hyperplasia, ovarian granulosa cell tumor, and ovarian adipoid tumor. The decrease in progesterone was seen in threatened abortion, luteal dysfunction, fetal growth retardation, stillbirth, and severe gestational hypertension syndrome.

4.7.14.3 Estradiol (E2)

E2 is the most active hormone in estrogen and a marker of gonadal function initiation, changes periodically with the menstrual cycle in adult women and gradually declines at menopause, especially after menopause. E2 mainly comes from the developing follicle or corpus luteum. It is synthesized by follicular membrane cells and granulosa cells under the dual effects of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Male E2 is mainly synthesized and secreted by testicular interstitial cells. The main physiological role of E2 is to promote the development of female reproductive organs and secondary sexual characteristics, regulate the functions of hypothalamus and pituitary through positive and negative feedback, promote the growth of bones, accelerate the fusion of bones, and can affect the metabolism of lipoprotein, water, and salt in the body.

The reference value of E2 varies from reagent provider to reagent provider. The reference value of women varies greatly in different stages and physiological periods. Each laboratory should establish the reference value with its own actual situation. E2 reduction was found in premature ovarian failure, ovarian hypoplasia, or absence of ovary, secondary gonadal insufficiency caused by hypothalamic or pituitary lesions, congenital adrenocortical hyperplasia, and hydatidiform mole, while elevation was found in ovarian tumors with abnormal hormone secretion, pituitary tumor, teratoma, testicular stromal cell tumor, and other diseases. In addition, multiple pregnancies with cirrhosis of the liver are associated with systemic lupus erythematosus (SLE) in men.

4.7.14.4 Follicle-Stimulating Hormone (FSH)

FSH is secreted by basophilic cells in the anterior pituitary and is controlled by luteinizing hormone-releasing factor produced by the hypothalamus. During the menstrual period of women of childbearing age, the level of FSH in blood changes with the level of estradiol and progesterone, and FSH increases obviously and reaches the peak before ovulation. The increase of FSH can be found in primary ovarian failure, postmenopausal women and after gonadectomy, the decrease of FSH indicates abnormal hypothalamic-pituitary axis function, which can be found in amenorrhea caused by pituitary dysfunction, Sheehan syndrome, polycystic ovary syndrome, adrenal tumor, and ovarian tumor.

4.7.14.5 Luteotrophic Hormone (LH)

LH secretion is controlled by hypothalamic luteinizing hormone-releasing hormone (LHRH) and varies with the level of serum estrogen and progesterone. Because postmenopausal women have decreased ovarian function, decreased estrogen secretion and relieved the negative feedback to the hypothalamus, serum LH is increased. LH and FSH are both produced by the anterior pituitary gland and secreted pulsed during the menstrual cycle. Elevated LH is commonly seen in premature ovarian failure, climacteric syndrome, pituitary or hypothalamic tumors, ovarian hypoplasia, Turner's syndrome, and polycystic ovary syndrome. Decreased LH levels are commonly seen in patients with pituitary dysfunction, Sheehan syndrome, pituitary resection, obese genital degeneration syndrome, anorexia nervosa, and estrogen use.

4.7.14.6 Androstenedione

The bioactivity of androstenedione is between testosterone and dehydroandrosterone. In women, 50% of androstenedione comes from the ovaries and 50% from the adrenal glands. Female productivity exceeds 3000 g per day, higher for men. Androstenedione levels were slightly lower in adult men than in women of the same age, and decreased blood circulation in postmenopausal women. Androstenedione can also be measured in female ovaries. Androstenedione level can be increased in females with masculine diseases, and it can be increased in congenital adrenal cortex hyperplasia, and it can be increased in patients with polycystic ovary disease, normal or slightly increased in hypertrichosis.

4.7.14.7 Dehydroepiandrosterone (DHEA)

The majority of DHEA in serum is in the form of sulfuric acid binding compound (DHEA-s), About 90% of the blood circulation of DHEA-s comes from the adrenal gland, and the serum concentration is mostly used to evaluate the situation of suspected adrenal androgen oversecretion. Serum DHEA-s is closely related to the excretion of 17-ketone steroids in urine at 24 h. DHEA-s is increased in adrenal neoplasms and polycystic ovary syndrome, and normal with delayed 21-hydroxylase-deficient adrenal cortical hyperplasia.

4.7.15 Serum Insulin-Like Growth Factor-1 (IGF-1)

IGF-1, as an important bioactive substance, is closely related to the occurrence and development of hypertension. (1) Increased serum IGF-1 level is an independent risk factor for hypertension. The relationship between hypertension and IGF-1 depends on the total concentration of IGF-1 in the serum, and both too low and too high levels will affect the regulation of hypertension. (2) Because IGF-1 and insulin are highly homologous, IGF-1 can increase the sensitivity of glucose to insulin and lead to insulin resistance. (3) During the development of hypertension, continuous oxidative stimulation of blood vessels may up-regulate the expression of IGF-1 and promote the proliferation of vascular smooth muscle cells. (4) IGF-1 can up-regulate endothelin in endothelial cells and reduce nitric oxide. (5) In hypertrophic myocardium of hypertensive patients, IGF-1 synthesis level was significantly higher than that of normal myocardium. (6) The interaction between IGF-l and the renin-angiotensin-aldosterone system is involved in the occurrence and development of hypertension.

In conclusion, endocrine hormone examination and bioactive substance determination are of decisive significance for the diagnosis of secondary hypertension, especially endosecretory hypertension. At the same time, the determination of hormone level can be used to guide the treatment of patients, which is of great clinical significance and cannot be ignored.

4.8 The Biomarkers of Malignant Hypertension Caused by Vasculitis

Ting Wu

4.8.1 Pentraxin 3 (PTX-3)

PTX-3 belonged to a member of the pentraxin family, CRP is a systemic inflammatory marker protein, however, PTX-3, which belongs to the same family as CRP and more specific, and some report suggested that the CRP was in normal range when PTX-3 was higher in some disease [85].

PTX-3 is secreted by macrophages, neutrophils, endothelial cells, epithelial cells, and vascular smooth muscle cells to regulate the immune activity of macrophages [86]. PTX-3 plays a role in regulating the immune activity of the body, participating in the classical activation mode of complement, cell apoptosis, and cell debris clearance, participating in the acute phase of the immune response, and screening of pathogens. PTX-3 is associated with activity in autoimmune diseases such as vasculitis. PTX-3 can be used as a diagnostic marker for malignant hypertension caused by vasculitis, especially when serum c-reactive protein levels are within the normal range.

4.8.2 Lysosomal-Associated Membrane Protein 2 (LAMP-2)

LAMP-2 is a kind of across membrane protein with high glycosylation, which is crucial for maintaining lysosomal membrane integrity and expressing intracellular antigens in autophagy mediated by molecular chaperones. LAMP-2 plays an important role in the pathogenesis of systemic vasculitis and can be detected on the surface of neutrophils and endothelial cells in most AAV patients, as well as circulating human LAMP-2 auto-antibodies (hLAMP-2). Our study showed that LAMP-2 and its antibodies could be used as diagnostic markers for malignant hypertension caused by vasculitis [87].

4.8.3 High Mobility Group Box 1 (HMGB1)

HMGB1 is a group of non-histone nucleoprotein, which is actively secreted by activated immune cells or passively released by injured or dead cells, and reacts with various receptor cells (RAGE, TLR-2, and TLR-9). HMGB1, as a molecular model involved in stimulating the innate and adaptive immune systems, is involved in the

pathogenesis of many autoimmune diseases, including various acute and chronic inflammatory processes followed by aseptic injury or microbial invasion. Recent studies have shown that patients with Kawasaki disease (KD) and antineutrophil antibody-associated vasculitis (AAV) have higher serum HMGB1 levels, especially in granulomas polyvasculitis (GPA). Our study shows that HMGB1 can be used as a diagnostic marker for malignant hypertension caused by vasculitis [88].

4.8.4 Monocyte Chemotactic Protein 1 (MCP-1)

MCP-1 regulates the migration and infiltration of monocyte memory T lymphocytes and natural killer (NK). Stimulated by proinflammatory factors, MCP-1 chemotactic monocytes/macrophages T cells and dendritic cells to the inflammatory site, and in addition to that, it also participated in the process of endothelial cell proliferation and repair. Our study shows that MCP-1 can be used as a diagnostic marker for malignant hypertension caused by vasculitis and related to renal injury [89].

4.8.5 CD146

CD146 is an adhesion factor belonging to the immunoglobulin superfamily. As an important adhesion factor on the surface of vascular endothelial cells, CD146 plays an important role in a variety of autoimmune diseases. CD146 also plays a variety of roles in the evolution of diseases, and CD146 also plays a role in the diagnosis of diseases as a specific surface marker of endothelial cells. Our study shows that CD146 can be used as a diagnostic marker for malignant hypertension caused by vasculitis.

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Part II

Theories of Secondary Hypertension

Renal Parenchymal Hypertension

5

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5.1 Glomerulonephritis and Secondary Hypertension

Nuerguli Maimaiti

5.1.1 Acute Glomerulonephritis

Acute glomerulonephritis includes acute post-infection glomerulonephritis and acute progressive glomerulonephritis, and acute streptococcal glomerulonephritis is the most common disease in children. It is estimated that there are 470,000 new cases of PSGN worldwide each year, 97% of which occur in economically and socially disadvantaged areas with an annual incidence of 9.5–28.5 per 100,000 people. Other bacterial (staphylococci), viral (Epstein–Barr virus, adenovirus), and parasitic infections can also cause these areas [1, 2]. APGN is an immune response induced by streptococcal infection, resulting in deposition of antigen-antibody immune complex in glomeruli and pathogenesis. RPGN is a group of diseases characterized by acute nephritis syndrome, sharp deterioration of renal function, and mostly oliguria acute renal failure in early stage, with the pathological type of crescent glomerulonephritis [3].

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5.1.1.1 Pathogenesis of Hypertension

The mechanism of hypertension in acute glomerulonephritis is mainly related to volume change. In post-streptococcal acute nephritis, hypertension occurs in 50–90% of patients, ranging in severity from mild to severe. Acute diffuse inflammation of renal parenchyma leads to a rapid decline in glomerular filtration rate (GFR), resulting in reduced water and sodium filtration in the body, while renal tubular sodium reabsorption function is still normal, the ball-tube feedback regulation is disordered, and sodium and water retention in the body. Plasma and extracellular fluid volume (FCFV) increased significantly, and volume dilatation led to increased cardiac volume and cardiac output, but peripheral resistance remained normal or only slightly increased, leading to increased blood pressure. However, studies have suggested that hypertension in patients with acute nephritis syndrome is not necessarily associated with a significant decline in GFR, suggesting that other mechanisms are involved in volume change. In acute renal disease, vascular active substances or endocrine hormone effect on high blood pressure still has a lot of controversy; most researchers think the change is due to capacity expansion caused by the secondary change and does not directly affect the factors of high blood pressure, but they may be involved in maintaining hypertension status in different degrees, such as capacity expansion can be secondary RAS inhibition. During the acute phase of the disease, a decrease in plasma renin activity (PRA) and plasma aldosterone levels is often observed, and these changes generally return to normal as patients improve. Although patient PRA was low, it was still high relative to volume expansion [4, 5].

5.1.1.2 Clinical Manifestations and Complication

Clinical manifestations of APGN are mainly acute nephritis syndrome, namely, hematuria, proteinuria, hypertension, edema, oliguria, and azotemia, but most of them have good prognosis. RPGN progresses rapidly and can present oliguria, anemia, and acute renal failure in a short time with poor prognosis [6–8]. Hypertension occurs in 50–90% of patients, ranging in severity from mild to severe. The main causes are salt and fluid retention. Some patients may present with hypertensive encephalopathy or acute pulmonary edema, which is a rare but serious complication, and MRI may show reversible posterior leukoencephalopathy [9]. Severe acute pulmonary edema can cause respiratory distress, and these patients need urgent intervention. Most patients have different degrees of hypertension, which may be related to water and sodium retention and volume overload. The incidence rate is positively correlated with age, and generally presents as a moderate increase in blood pressure parallel to the degree of edema, which gradually returns to normal with the regression of edema, but occasionally occurs severe hypertension or even hypertensive encephalopathy. When blood volume is excessive and blood pressure is elevated, the ventricle secretes n-terminal brain natriuretic peptide BNP (NT-proBNP). Studies have shown that the blood NT-proBNP level of APSGN patients is higher than that of the normal control group, while the blood NT-proBNP level of APSGN patients with left ventricular dysfunction is significantly higher than that of other APSGN patients. Blood NT-proBNP returned to normal after

diuretic therapy. Therefore, NT-proBNP can be used as an index to evaluate the capacity and cardiac function of APSGN patients [10].

5.1.1.3 Treatment

The increase of blood pressure caused by acute renal parenchymal disease will not only further aggravate the original renal damage, such as increasing proteinuria, accelerating renal function decline, but also lead to the damage of other target organs, such as heart failure, pulmonary edema, and acute cerebral apoplexy, so it should be given early active treatment. Glomerulonephritis after acute streptococcal infection is a self-limited disease, and the main treatment principles are to prevent and treat water and sodium retention, control circulating blood volume, prevent fatal complications, and prevent and treat the factors aggravating renal diseases. Specific treatment measures in addition to dietary salt restrictions, the first choice of diuretics, generally with the beginning of the diuretic stage, hypertension will gradually decline, but if the continued more than 2 weeks still no downward trend, often suggest that kidney disease is more serious. Duration of more than 1 month often indicates poor prognosis. For severe hypertension, calcium channel blocker (CCB) can be added. CCB has a rapid antihypertensive effect, which is not affected by salt intake, does not reduce GFR, does not affect electrolytes, uric acid, and various metabolites, and has a good effect of dilating blood vessels and draining sodium. Due to the relative or absolute increase in renin and sympathetic nervous system activity in some patients, can be combined with small dose of renin-angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor antagonist (ARB) and beta blockers, but need to closely monitor patients GFR. If it is still difficult to reduce blood pressure, intravenous infusion of vasodilating drugs such as sodium nitroprusside can be applied. For patients with sharp decline in renal function, hemodialysis treatment should be taken on time.

5.1.2 Chronic Glomerulonephritis

5.1.2.1 Etiology and epidemiology

Chronic glomerular disease is one among a large group of diseases composed of different etiologies and pathological types, including focal segmental glomerular sclerosis, membranous proliferative glomerulonephritis, membranous nephropathy, mesangial proliferative glomerulonephritis, IgA nephropathy, and micropathologic nephropathy. Clinical manifestations are nephritis syndrome and/or nephrotic syndrome, i.e., varying degrees of proteinuria, hematuria, hypertension, and renal impairment. The disease is often characterized by slow progress, treatment is difficult, and prognosis is poor. Among various chronic renal parenchymal diseases, hypertension caused by chronic glomerular disease is the most common [11, 12].

The incidence of hypertension in chronic renal parenchyma disease is significantly correlated with the primary disease, pathological type, and lesion degree. Data show that the incidence of hypertension of chronic glomerulonephritis is

39.9–73.0% [13–15], the incidence of hypertension of simple hematuria patients is lower, and the incidence of hypertension of patients with large amount of proteinuria, and nephrotic syndrome is higher. The incidence of hypertension in patients with mesangial proliferative glomerulonephritis and focal segmental glomerular sclerosis is about 20% [16–19]. Although the incidence of chronic glomerulonephritis and hypertension is high, there are significant differences between different primary diseases and pathological manifestations. In addition, it is related to age, gender, heredity, geographical change, kidney function, and other factors.

5.1.2.2 Pathophysiology

The pathophysiological mechanism of chronic renal essential disease hypertension is the expansion of extracellular fluid volume and the increase of peripheral vascular resistance caused by water and sodium retention. The mechanism may involve the imbalance of sodium balance, the imbalance of vasoactive substances between blood pressure booster and blood pressure depressor, and the increase of sympathetic excitability, which may be the result of the interaction of various factors.

1. Increased volume

   Kidney is the main organ of drainage and sodium; when kidney parenchyma is affected, water-sodium excretion obstacle. water-sodium retention lead to blood capacity and extracellular fluid volume dilate, cardiac beat volume increase, and produce hypertension. With the increase of cardiac output, the blood flowing through various tissues and organs increases. Through the self-regulation mechanism, the systemic arterioles contract, and the resistance of peripheral blood vessels increases, resulting in hypertension. The exact mechanism of its occurrence has not been fully elucidated. In chronic kidney disease, the early increase in blood pressure is due to volume dilation and increased cardiac output. The increase of peripheral vascular resistance is the main reason for the continuous high blood pressure. Volume dilation leads to the release of endogenous digitalis, which inhibit cell Na^+ -k^+ atpase activity, reduces the reabsorption of sodium in the kidney, and increases the excretion of urine sodium, thus contributing to the recovery of blood volume. However, the inhibition of Na^+ -k^+ -atpase activity in vascular smooth muscle cells will lead to relatively enhanced Na^+ -Ca^+ pump activity, increased intracellular calcium ions, and increased vascular stress, leading to increased peripheral vascular resistance and blood pressure. Almost all patients requiring renal replacement therapy have hypertension, which is mainly caused by increased volume. This hypertension is associated with water and sodium retention in the body, and even very small increases in extracellular fluid volume can have a significant effect on blood pressure.
2. Renin-angiotensin-aldosterone system (RAAS) activation

   Studies have shown that renin-angiotensin system (RAS) activity in patients with renal hypertension often increases to varying degrees or relatively, especially the abnormal activation of renal RAS plays an important role in the occurrence and maintenance of renal hypertension. Renin in the blood mainly comes from the glomerular paracycles of the kidney, which accounts for about

10% of the total renin in the body, mainly from the larger arteries, lungs, uterus, and so on. RAS is composed of renin, angiotensin, and its receptor. Chronic kidney disease (CKD) in renal tissue ischemia can activate the RAS, make the body renin, angiotensin II (Ang II), and increased formation of aldosterone. Ang II can be through a series of direct and indirect mechanisms involved in the occurrence of renal hypertension and maintaining. For example, direct effects on renal tubules, stimulation of aldosterone synthesis, and release of hypothalamic vasopressin (AVP) lead to increased sodium reabsorption, enhanced sympathetic nervous system activity, increased myocardial contractility, and increased cardiac output. Ang II combine with angiotensin I receptor (AT1R) on vascular wall, contract blood vessel, causing vascular resistance increases, and increased blood pressure; It can also increase the concentration of calcium ions in vascular smooth muscle cells, increase the release of norepinephrine and enhance the reactivity of blood vessels to vasoactive substances, thereby causing vasoconstriction and increasing peripheral vascular resistance. In addition, Ang II had a greater contractile effect on glomerular inferent arterioles than on the efferent arterioles. Increased pressure and filtration pressure in glomerular capillaries, decreased normal pressure diuretic mechanism, contraction of mesangial cells, decreased filtration area, and ultrafiltration coefficient of glomerular capillaries, all of these effects persist, which can affect renal function and maintain hypertension.

3. Endothelin synthesis increased [20]

   ET is the most powerful vasoconstricting active polypeptide known in vivo and has the longest duration of action. It is known that the heteropeptides ET-1, ET-2, ET-3, and VIC4 are formed in organisms. ET-1 has the strongest biological effect. ET is not only a local or circulating hormone secreted by vascular endothelium, but also a neurotransmitter released by the central and peripheral nervous system. In addition, ET can also play a potential role in reproductive regulatory peptides, hormone regulatory peptides, and intestinal peptides in different parts of the body. Due to its powerful and long-lasting effect of constricting blood vessels, promoting vascular smooth muscle hyperplasia, and increasing intracellular calcium ion concentration, it is believed that it may be involved in the pathophysiological mechanism of hypertension. Kidney blood vessels are more sensitive to ET-1 vasoconstriction than other blood vessels. CKD leads to increased ET-1 synthesis, leading to renal and peripheral vascular contraction and increased vascular resistance. ET not only plays a role in vascular smooth muscle, but also plays a regulatory role in the sympathetic nervous system (SNS). Antagonistic ET receptors are effective in reducing blood pressure and urinary protein in patients with CKD.

4. Sympathetic nervous system activation

   During renal parenchymal disease, sympathetic nerve can be activated by afferent renal reflex, releasing mediators such as norepinephrine. The mediators combine with α-adrenergic receptors on the vascular walls, stimulate the vasoconstriction, increased vascular resistance and can combine with α-adrenergic receptors in the proximal renal tubular epithelial cells, increase of Na^+ absorption, thereby increasing blood volume [21].

5. The production of nitric oxide decreases [20]

   NO is the endothelium-derived relaxing factor (EDRF), can dilate blood vessels, and reduce renal tubular Na+ absorption. When renal parenchyma disease, NO production decreases, which will lead to vasoconstriction and water-sodium retention and resulting in increased blood pressure.

6. Kinin-releasing enzyme—kinin system

   KKS consists of kalitinase, kininogen, and kalitinase. Kinin-releasing enzyme catalyzes the conversion of kininogen to kinins, including bradykinins (BK). BK is produced in tubule cells and ACTS on tubule aggregation, inhibiting sodium reabsorption, reducing water permeability of tubules, and regulating the release of a series of bioactive mediators, such as prostaglandins, nitric oxide, and platelet activation factors, to play a role in dilating blood vessels, regulating blood flow and inhibiting smooth muscle proliferation. The excretion of urinary kinin-releasing enzyme in patients with renal essential hypertension was reduced, and the degree was related to the renal blood flow. However, this abnormality did not recover after blood pressure control was normal, suggesting that kinin changes may be involved in hypertension, but may only play a certain regulatory role [22, 23].

7. Endogenous digitalis Na^+,Ca^{2+},K^+ ions

   EDLS is a circulating hormone secreted by hypothalamus, heart, and other tissues, which can inhibit the activity of Na^+-K^+-atpase of cells, and has the effect of strengthening heart, diuretic and constricting blood vessels. When extracellular volume expansion is caused by renal parenchymal disease, EDLS can be released by the brain tissue of the hypothalamus, inhibiting Na^+-K^+-atpase in the epithelial cells of proximal renal tubules, reducing sodium reabsorption and sodium excretion effect. However, on the other hand, EDLS inhibits Na^+-K^+-atpase in vascular smooth muscle, increases intracellular sodium concentration, reduces transmembrane sodium gradient, reduces Na^+/Ca^{2+} exchange and voltage-dependent Ca^{2+} channel depolarization, so intracytoplasmic Ca^{2+} increases, which promotes the occurrence of resistive hypertension [24].

8. Hyperparathyroidism

   When renal function insufficiency leads to glomerular phosphorus filtration reduce, result in increasing blood phosphorus hyperphosphatemia can stimulate parathyroid hormone secretion, in order to promote phosphorus secretion from renal tubules. When this condition becomes severe, hyperparathyroidism may occur. Parathyroid hormone can cause an increase in the concentration of Ca^{2+} in the cytoplasm of vascular smooth muscle cells, enhancing vasoconstriction and increasing vascular resistance [25].

9. Natriuretic peptide

   The combination of atrial natriuretic peptide and brain natriuretic peptide with their receptors on the kidney can increase the glomerular filtration rate, increase urinary sodium secretion, inhibit the secretion of renin, aldosterone, and antidiuretic hormone (AVP), and directly relax the vascular smooth muscle, thus reducing blood pressure. When the nephrons were destroyed in CKD, the natriuretic peptide effect decreased, and the diuretic and antihypertensive effect decreased.

5.1.2.3 Clinical Manifestations

The clinical manifestations of chronic renal essential hypertension are basically similar to those of essential hypertension. These include symptoms of headaches and other related illnesses. Clinical manifestations are nephritis syndrome and/or nephrotic syndrome: varying degrees of proteinuria, hematuria, hypertension, and renal impairment. Compared with essential hypertension, chronic renal essential hypertension has the following characteristics: (1) The disease course often presents slow progressive progress, difficult treatment, easy to develop into malignant hypertension, IgA nephropathy is particularly prone to secondary malignant hypertension, poor prognosis. (2) The incidence and mortality of cardiovascular complications are high, and hypertensive fundus lesions and renal dysfunction are much more serious. Hypertension in patients usually occurs when GFR is moderately reduced (serum creatinine levels are still normal), and the incidence of hypertension increases successively with the further aggravation of renal impairment, reaching 85–90% by end-stage renal disease. (3) Accelerate the progression of renal parenchyma. Some patients in the original hypertension on the basis of acute hypertension or malignant hypertension, increased hematuria and proteinuria, tubular urine, urine volume, and renal progressive deterioration.

5.1.2.4 Laboratory Inspection

Routine urinalysis showed a decrease in hematuria, proteinuria, tubular urinia, and urine-specific gravity. Blood renal function can be tested with or without increased blood urea nitrogen, creatinine, cystatin C, and renal tubular dysfunction.

5.1.2.5 Imaging Examination

Renal ultrasound can provide information about renal damage from the following three aspects: the size of both kidneys, whether the capsule is smooth, whether the skin and pulp boundaries are clear. Renal CT/MRI can further clarify whether the kidney has tumor, morphological abnormalities, etc. Renal ECT can early reflect the changes of glomerular filtration rate and plasma flow on both sides.

5.1.2.6 Diagnosis

Diagnosis of renal essential hypertension: (1) History of renal substantive disease, albuminuria, hematuria, and renal function abnormality occurs more before hypertension or appear at the same time; blood pressure is higher with diastolic pressure for a characteristic, and the patient is generally younger. (2) On physical examination, there is an anemic appearance and a palpable mass in the renal area. (3) Albuminuria, hematuria, and leukocytosis. Abnormal renal volume and morphology, or mass was found. If necessary, kidney puncture and pathological examination were performed to confirm the diagnosis. Differential diagnosis of hypertensive renal impairment and renal hypertension: Table5.1.

5.1.2.7 Treatment

The principle of treatment of renal essential hypertension: (1) Early treatment. (2) Control blood pressure to reach the target. (3) Limit sodium intake (<2 g/day) and protein intake.

Table 5.1 Differential diagnosis of hypertensive renal impairment and renal hypertension

Key points of differential diagnosis	Hypertensive renal impairment	Renal hypertension
Age	40–60 years old	20–300 years old
Edema	Rare	Common
Urine test	Proteinuria + − + + Hematuria rare	Proteinuria++−+++ Hematuria common
Fundus lesions	More serious than renal function	Less severe than renal function
Left ventricular hypertrophy	Common	Rare
Anemia	Slight	Severe
Uric acid	Increase	Increase with renal insufficiency
Renal pathology	Arteriolosclerosis	Nephritis lesions
The prognosis	Slowly	Rapidly
The cause of death	Cardiovascular and cerebrovascular disease	Uremia

1. Non-drug therapy

   In patients with chronic kidney disease, the renal sodium excretion ability is reduced, which causes the retention of sodium and water in the body, and the increase of blood volume and extracellular fluid volume. For volume-dependent hypertension, attention should be paid to the control of water and salt intake to achieve dry weight (body fluid balance). Dialysis patients need to rely on adequate dialysis ultrafiltration.
2. Drug treatment

   Target value of lowering blood pressure: according to the clinical characteristics and renal function of patients, determine the ideal level of hypertension treatment. The 2018 guidelines [26] recommend that the initial treatment target for all patients with hypertension be <140/90 mmHg, and systolic blood pressure be controlled between 130 and 139 mmHg for patients with CKD.
3. Antihypertensive drug selection
   (a) Renin-angiotensin system inhibitors: because of the important role of RAS in chronic kidney disease, blocking RAS has become the main intervention means to control hypertension and delay renal damage. ACEI and ARB are the main drugs recommended for clinical use. Numerous animal studies and clinical trials have demonstrated that ACEI and ARB are effective in reducing blood pressure, reducing urinary protein excretion, and slowing the progression of chronic kidney disease. ACEI can reduce urinary protein excretion through various mechanisms such as improving intramedullary pressure, high perfusion, high filtration, and improving selective permeability of glomerular filtration membrane. When proteinuria is relatively large, the effect of ACEI on decreasing urinary protein is often more significant, and urinary protein should be reduced to normal or minimum level as far as possible. In

addition to protecting the kidney through the above effects, ACEI can also delay the progress of renal damage by reducing the accumulation of renal extracellular matrix (reducing production and promoting degradation), antagonizing glomerular sclerosis and renal interstitial fibrosis [27, 28]. There is no consensus on whether blood creatinine (Scr) >265 micron/L can still be used for ACEI. It has been reported that at this time, the application of ACEI (especially for those who have already used ACEI) can still effectively delay the progression of renal damage [29]. However, the dosage of ACEI should be reduced accordingly, and hyperkalemia must be highly vigilant. Compared with ACEI, ARB has the following advantages: no irritating dry cough; the effect was not affected by ACE gene polymorphism; not affected by the ACE catalytic angiotensin II generated; the intensity of ARB dilated and scoring arterioles was not as significant as that of ACEI; the effect of potassium storage in ARB kidney is less than that of ACEI.

(b) Calcium channel blocker (CCB):

CCB can increase urinary sodium excretion and produce mild negative salt balance, which is very effective for the control of renal essential hypertension.

It can be used in combination with most antihypertensive drugs, especially ACE1 or ARB, which is the first-line antihypertensive treatment scheme widely used in clinical practice.

There were no significant changes in blood pressure and GFR in CCB patients with normal blood pressure. In hypertensive patients, GFR and renal blood flow increase and renal vascular resistance decreases at the same time as blood pressure decreases. This is most obvious in early hypertension, mainly due to the dilatation of the inferent arterioles. In addition, CCB have many other effects besides reducing blood pressure, such as inhibition of mesangial cell proliferation, inhibit the secretal function of cytokines, inhibiting inflammatory mediators, reduce reactive oxygen species generation, inhibit platelet activation and accumulation, inhibit hypercoagulability, decrease the glomerular capillary permeability, reduce proteinuria, etc. These effects suggest that CCB may have the same renal protective effect as ACEI without relying on lowering blood pressure.

(c) β-blocker: β-blocker mainly block beta receptors to slow down the heart rate of hypertensive patients, reduce myocardial contractility, decrease cardiac output and plasma renin activity, so as to achieve the purpose of lowering blood pressure.

(d) Diuretics: diuretics can reduce blood pressure mainly by removing sodium, reducing extracellular capacity and peripheral vascular resistance. They are divided into thiazides, loop diuretics, and potassium-preserving diuretics, suitable for mild and moderate hypertension. Thiazide diuretics have been used in antihypertensive therapy for more than 40 years, and a series of randomized double-blind clinical trials have confirmed their efficacy and safety. Large doses of thiazide diuretics (such as hydrochlorothiazide >50 mg/day) often have some adverse effects on metabolism. The possible adverse reac-

tions of thiazide diuretics include hypokalemia, hyperlipidemia, increased insulin resistance, gout, and hypercalcemia. Patients with CKD (usually with dilatation even without edema) often need higher doses of diuretics because of reduced kidney function. When GFR < 30 mL/min, the efficacy of thiazide diuretics is reduced [30]. For such patients, loop diuretic is preferred as the initial treatment. The effect duration of torasemil is longer than that of furosamide.

(e) α1-receptor blockers

Selective blocking of alpha 1 receptor after synapses can reduce the resistance of peripheral blood vessels, resulting in antihypertensive effect. The representative agent is prazosin, which has the advantage of lowering blood lipid and good effect on insulin resistance. The side effect is postural hypotension, so the dosage should be increased gradually from small dose.

(f) Combination drugs

Renal disease associated with hypertension often require multiple medications to achieve the target blood pressure. In combination, RAS blockers are preferred because of their specific advantages in renal hemodynamics and proteinuria [31]. Combination drugs are often used with diuretics or CCB. In order to reduce the adverse metabolic effects of diuretics, the dosage should not be too large. Theoretically, ACEI + ARB can block RAS more completely, but in essence, the further decrease of blood pressure is often not very obvious, but some clinical trials have confirmed the increased effect on reducing proteinuria.

Due to the increased risk of serum potassium, special attention should be paid to cases with high serum potassium levels, while serum creatinine levels should be closely monitored and careful use should be made in cases with severe cardiovascular diseases.

ACEI or ARB+ diuretics are commonly used in the prescription of fixed mixture antihypertensive drugs. ACEI or ARB + CCB have proved good efficacy and patient compliance in some clinical applications mainly in the field of cardiovascular diseases. There are no trials and evidences in the field of kidney, and most people believe that ACEI or ARB + CCB can also be used as a reference.

5.1.2.8 Prognosis

Although renal hypertension is caused by renal disease, the increase in blood pressure in turn has adverse effects on the kidneys. But the hypertension that crosses a gender and the hypertension that appears like acute nephritis often have little effect to renal function, and treatment is easier also. Persistent, moderate, and severe hypertension can cause renal arteriole spasm and hardening, accelerate glomerular capillary hardening, and accelerate the destruction of renal units, and renal function showed an obvious deterioration trend. At the same time, the increase of blood pressure will lead to serious cardiovascular and cerebrovascular complications, so the prognosis of chronic nephritis and hypertension is worse than that of the common type. The increase of blood pressure in patients with chronic renal failure is an

important factor for the deterioration of renal function. Therefore, it is very important to actively and effectively control hypertension in patients with kidney disease, and prevention and active treatment of primary renal disease is the key to prevent and treat renal essential hypertension.

5.2 Obesity-Related Glomerulopathy and Hypertension

Lu Wen

The incidence of obesity is increasing. Obesity can lead to a variety of diseases such as hypertension, arteriosclerosis, diabetes, and kidney damage. Kidney disease caused by obesity is called obesity-related glomerulopathy (ORG), including obesity-related glomerular hypertrophy (O-GM) and obesity-related focal segmental glomerulosclerosis (O-FSGS). There is a close relationship between hypertension and kidney. The damage of hypertension is causal and mutually reinforcing, and there is a vicious circle.

5.2.1 Epidemiology

The proportion of ORG increased gradually with the increase of obesity incidence. Kambham et al. [32]showed that the incidence of ORG increased from 0.2% in 1986–1990 to 2.0% in 1996–2000. The ORG ratio of renal biopsy in China was 0.89%, and increased from 0.62 to 1.0% during the 5 years of study observation [33]. About half of the ORG patients have hypertension.

5.2.2 Pathogenesis

The specific pathogenesis associated with obesity-related nephropathy and hypertension is unclear and may be related to the following factors.

1. Hemodynamic change

   Obese patients are often accompanied by metabolic disorders such as hypertension and hyperglycemia. Renal hemodynamic changes occur in the early stage of obesity. Glomerular hypertension promotes capillary wall pressure, leading to basement membrane dilatation, glomerular enlargement, and high filtration [34]. The increase of glomerular filtration rate is mainly attributed to the increase of transcapillary hydraulic pressure difference [35].
2. Insulin resistance and hyperinsulinemia

   Insulin resistance leads to changes in renal hemodynamics, especially glomerular hyperfiltration, hypertension, and excessive sodium absorption. Hyperinsulinemia, secondary to insulin resistance, increases salt retention and causes excessive sodium absorption in distal renal tubules.

3. Renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS)

   Adipose tissue increases substantially, producing angiotensinogen, activating RAAS, releasing angiotensin II and aldosterone, making the contraction of the outgoing arterioles stronger than that of the incoming arterioles, resulting in increased glomerular capillary pressure and glomerular filtration rate [36], while excessive sodium is reabsorbed and blood pressure rises [37], which ultimately leads to kidney injury. Obese patients have obvious sympathetic nervous system activation, which changes the tension of small arterioles, causes glomerular hemodynamic disorders, and aggravates renal damage.
4. Adipocytokines

   Adipocytes can secrete many kinds of peptide and ester active substances called adipocytokines, including leptin, adiponectin, resistin, and tumor necrosis factor-alpha (TNF-alpha), which can promote chronic low-grade inflammation in obese patients. Lipid-mediated inflammation can lead to changes in kidney structure and function [38].
5. Fat metabolism

   Adipose tissue accumulates, compresses the renal parenchyma, increases intrarenal pressure, and causes interstitial vascular compression and interstitial fluid static pressure. Decreased renal medullary blood flow and slowing of renal tubular flow rate directly lead to an increase in sodium reabsorption and an increase in blood pressure, which aggravates kidney damage.
6. Genetic factors

5.2.3 Pathology

The gross specimen of the kidney is an increase in kidney volume and an increase in perirenal fat. However, when hypertension and atherosclerosis were combined, the increase in kidney volume was not significant. Optical microscopy is a key test for the diagnosis of ORG.

5.2.4 Clinical Manifestation

ORG is insidious, occurs in all ages, males are more than females, and the course of disease can be 1–20 years, mainly in the two aspects of obesity and kidney damage, with microalbuminuria or clinical dominant proteinuria as the primary performance, a small number of patients with microscopic hematuria. The blood pressure of ORG patients with hypertension was mainly mild to moderate, and the diastolic blood pressure was increased in clinical practice.

5.2.5 Diagnosis

There is no unified diagnostic criteria for obesity-related nephropathy. For overweight or obese people, routine urine examination has albuminuria, ranging from

microalbuminuria to massive albuminuria (nephrotic syndrome rarely occurs). Glomerular volume increases markedly with or without focal segmental glomerulosclerosis, and other glomerular diseases can be excluded for diagnosis. Early renal biopsy should be performed in patients with high clinical suspicion of the disease.

5.2.6 Treatment

There is no specific treatment for ORG and comprehensive treatment is needed.

1. Weight control: improved eating habits, combined with exercise, can be treated with drugs or surgery in severe cases.
2. Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB): reduces glomerular hyperperfusion and reduces proteinuria, improves insulin resistance without affecting lipid metabolism, delaying progression of renal disease.
3. Improve insulin resistance: hyperinsulinemia can directly or indirectly cause glomerular injury, and improving insulin resistance is an important part of the treatment of ORG.
4. Traditional Chinese medicine: Rhubarb preparation.

5.2.7 Prognosis

ORG interacts with hypertension, and controlling ORG-related hypertension can improve outcomes.

5.3 Lupus Nephritis and Hypertension

Xiufang Li

Lupus nephritis (LN) is an autoimmune disease of systemic lupus erythematosus (SLE) kidney damage; it is the most common and most important renal complications of systemic lupus erythematosus, and its clinical manifestations are diverse, mainly includes asymptomatic hematuria, proteinuria, nephrotic syndrome, acute nephritis and so on [39]. 15–50% LN patients have high blood pressure and are associated with the severity of kidney damage.

5.3.1 Epidemiology

Lupus nephritis is the most common complication of systemic lupus erythematosus; most SLE patients will have clinical evidence of kidney disease at some point in the course of their disease, and eventually about 50% SLE patients will develop clinically significant renal disease [40]. 15–50% LN patients have high blood pressure and are

associated with the severity of kidney damage. The prevalence of lupus nephritis in SLE patients in the United States is higher than in Europe, which may partly reflect racial and ethnic group differences. The incidence of lupus nephritis in blacks (34–51%), Hispanics (31–43%) and Asians (33–55%) is higher than in whites (14–23%) [41]. Most kidney abnormalities occur shortly after the diagnosis of SLE (usually within the first 6 to 36 months). Data from Nephrology Institute of Nanjing General Hospital show that lupus nephritis accounts for about 13.5% of kidney disease, accounting for 54.3% of secondary glomerulonephritis.

5.3.2 Pathogenesis

5.3.2.1 Pathogenesis of Lupus Nephritis

Theory of Immune Complex Deposition

The majority of patients with lupus nephritis are found in the kidneys of immunoglobulin and complement components deposited in the glomerular and renal tubules. It is currently believed that three mechanisms may be involved in the deposition of immune complexes in the kidney. First, the antibody binds directly to the glomerular antigen. Second, the circulating antigen is implanted into the glomerular and then binds to autoantibodies. Third, the circulating immune complexes are deposited in glomerular [42, 43].

Apoptosis Theory

Perfumo F and others believe that the onset of LN is related to the following two points, that is, autoantibodies through nucleosome-mediated binding to the kidney induced inflammatory response, renal tissue apoptosis and proliferation equilibrium state destruction, and the above two pathological states are closely related to the abnormal apoptosis of lymphocytes and renal tissue cells [44]. If the cells are unable to cope with excessive cell apoptosis, the cell clearing disorder will cause a large number of apoptotic cells to lose membrane integrity, secondary necrosis, cell membrane rupture, and release of a large number of unmodified nuclear and cytoplasmic substances and form autoantigen, which lead to inflammation and immune response. Alternatively, the local apoptosis mechanism of glomerular cannot respond with the abnormal proliferation of cells, which leads to insufficient relative apoptosis of glomerular cells. The study also found that the Bax was overexpressed in LN renal tubular cells, and the expression increased with the occurrence and exacerbation of renal tubulointerstitial damage [45]. The apoptosis of renal tubular cells is obviously related to the severity of renal tubular atrophy and interstitial fibrosis, and with the progression of lesions, the excessive loss of tubulointerstitial cells will lead to a series of lesions such as tubular atrophy and interstitial fibrosis.

MiRNA Interference Theory

MiRNA can affect the activation of type I interferon pathway, the methylation of CD4+T cells, the maturation and function of regulatory T cells (Treg), and the

correlation with estrogen, which are closely related to the pathogenesis of lupus erythematosus [46].

5.3.2.2 Mechanisms for Causing Hypertension

Lupus kidney, that is, systemic lupus erythematosus nephritis, the mechanism of hypertension is the same as glomerulonephritis; see renal parenchymal hypertension for details. Studies have shown that kidney lesions are an important cause of hypertension in SLE. In addition, the treatment of SLE-related drugs can cause hypertension, such as high-dose hormone therapy and long course of disease patients prone to hypertension, except hormones, immunosuppressants cyclosporine A, leflunomide, and others can cause hypertension, the removal of B cells anti-CD20 monoclonal antibody rituximab can also cause hypertension; see drug-induced hypertension for details.

5.3.3 Pathology and Pathophysiology

The selection of treatment options for lupus nephritis should be based on the pathological type of renal biopsy. Therefore, kidney biopsy should be actively performed before treatment to identify the type of renal pathology. The pathological criteria for LN were revised by the International Society for Nephrology/Nephrology (ISN/RPS) in 2004, on the basis of which the International Kidney Pathology Working Group drafted a consensus report on the pathological types of lupus nephritis in 2016 [47].

Type I (mesangial slightly diseased LN): This type of lupus nephritis is rarely diagnosed because such patients usually have normal urine analysis results, no or mild proteinuria, and serum creatinine is normal; hypertension is not common. The glomeruli under light microscope are normal, but immunofluorescence and electron microscopy have immunological complex deposition in the mesangial area, which is the earliest and mildest glomerular involvement.

Type II (mesangial proliferative LN): Histological changes of II type lupus nephritis are clinically characterized as hematuria and/or proteinuria under the microscope. Hypertension is not common, and nephrotic syndrome and renal insufficiency have almost never been observed. Any degree of mesangial cell proliferation or mesangial matrix widening with mesangial area immune complex deposition under light microscopy, a small number of isolated subepithelial or subendothelial deposits can be seen under immunofluorescence or electron microscopy.

Type III (focal LN): Patients with type III lupus nephritis usually have hematuria and proteinuria, and some patients may also experience hypertension, decreased glomerular filtration rate and/or nephrotic syndrome. Light microscopy showed <50% of glomeruli with active, focal, segmental or hemispherical, intracapillary, or extra-proliferative nephritis, but immunofluorescence microscopy (for IgG and C3) showed almost all involvement. In particular, focal subendothelial immune complex deposition, with or without mesangial changes. According to the degree of inflammatory activity (A) or chronic degree (C) can be further divided into: type III (A) focal proliferative type LN; type III (A/C) focal proliferative sclerosis type LN; type III (C) focal sclerosis LN.

Type IV (Diffuse LN): IV type lupus nephritis is the most common and most severe lupus nephritis. Hematuria and proteinuria occur in almost all active type IV lupus nephritis, and nephrotic syndrome, hypertension, and decreased glomerular filtration rate are common. Optical microscopy showed that the glomeruli of ≥50% had diffuse activity or inactivity, segmental or globular internal and external hyperplasia of capillaries, especially diffuse subendothelial immune complex deposition or non-mesangial changes. According to activity (A), chronic (C), segmental (S), and globular (G) can be further subdivided into: type IV-S (A), diffuse segmental proliferative LN; IV type-G (A), diffuse spherical proliferative LN; IV-S (A/C), diffuse segmental hyperplasia hardened LN; IV type-G (A/C), diffuse spherical hyperplasia sclerosis LN; IV type-S (C), diffuse segmental sclerosis LN; IV type-G (C), diffuse spherical sclerosis LN (2016 consensus to eliminate the spherical/segmental lesions of IV type LN, with the activity and chronic disease variable scoring system instead of A/C evaluation).

Type V (membranous lupus nephritis): Patients usually show signs of nephrotic syndrome, similar to idiopathic membranous nephropathy, and may also have endoscopic hematuria and hypertension at the time of the visit, and creatinine concentrations are usually normal or only slightly elevated. The morphological changes caused by the deposition or non-mesangial of the spherical or segmental subcutaneous immune complexes under light microscope, immunofluorescence or electron microscopy may be combined with the change of type III or type IV or the sclerosis of the stage.

Type VI (severe hardened LN): Patients usually present with chronic progression renal insufficiency with proteinuria, urinary sediment examination is relatively normal. ≥90% glomeruli have spherical sclerosis and the rest have no active lesions. At the same time, the degree of renal tubular atrophy, interstitial inflammatory reaction, and fibrosis lesions should be briefly described and graded.

Other lupus-related nephropathy: Including lupus-like nephritis limited to kidney, lupus nephritis combined with ANCA-related glomerulonephritis, renal tubular interstitial nephritis, vascular lesions, asymptomatic lupus nephritis, lupus podocyte disease, collapse type glomerular sclerosis, and so on.

Indicators of LN activities and chronic: Activity and chronic degree are important to the severity of lupus nephritis, the reversibility of lesions, and the response to treatment. Bates and other levels of renal tissue biopsy lupus kidney activity and chronic disease score criteria were developed. Among them, the activity indicators include: cell hyperplasia, nuclear fragmentation and necrosis, cell (cell fiber) crescent body, wire ring (platinum ear)/transparent thrombosis, self-cell infiltration, interstitial inflammatory cell infiltration. Chronic indicators include: glomerular sclerosis, renal tubular atrophy, fibrous crescent body, interstitial fibrosis.

5.3.4 Clinical Manifestation

1. Proteinuria: Proteinuria is the most common clinical manifestation of lupus nephritis, with about 25% of patients with nephrotic syndrome.
2. Hematuria: The incidence of gross hematuria was relatively low (6.4%), most of which were microscopic hematuria. Continuous hematuria or a large number of microscopic hematuria, mainly seen in the glomerular capillary loops necrosis,

there are more crescent formation of dangerous cases. The degree of hematuria reflects the activity of kidney lesions to some extent.

3. Cylindruria: One-third of patients with casts in urine, mainly granular casts. Erythrocyte casts can appear when a large amount of hematuria.
4. Hypertension: High blood pressure is present in patients with 15–50% lupus nephritis and is related to the severity of renal damage. In patients with renal vascular lesions, the incidence of hypertension increased significantly, and even malignant hypertension occurred.
5. Acute renal insufficiency: Lupus nephritis complicated with acute renal insufficiency is related to the following factors: (a) glomerular diffuse crescent formation, (b) extensive thrombosis in glomerular capillary loops, (c) Lupus renal angiopathy, such as thrombotic microangiopathy and noninflammatory necrotic angiopathy (d) acute interstitial nephritis, (e) The patients with nephrotic syndrome and positive serum anti phospholipid antibody are prone to thrombosis, which leads to the rapid deterioration of renal function.
6. Chronic renal insufficiency: Active lesions are not effectively controlled; patients can enter the human chronic renal insufficiency. If there are still active lesions in pathology and proper immunosuppressive therapy is given, renal function can be partially restored. 8–15% lupus nephritis can eventually progress to end-stage nephropathy, with the most common type IV, type IV combined V lupus nephritis patients.

5.3.5 Diagnosis of LN

1. Diagnosis of SLE: The sensitivity and specificity of the SLE classification standard are not only related to the design and technical conditions used in setting the standard, but also to the race of the patient and the duration of the disease. In order to explore the development of SLE standards suitable for the clinical and laboratory characteristics of SLE in China and to facilitate early diagnosis, rheumatology experts in Beijing and Shanghai in the 1980s successively formulated the classification criteria for Chinese SLE. In 1982, the Chinese Medical Association Symposium on Rheumatology was held in Beijing to develop the standard for the diagnosis of SLE (Beijing Standard). The 1986 Society of Rheumatology of the Chinese Medical Association intends to revise the above SLE diagnostic criteria and develop 13 SLE diagnostic criteria (Shanghai standard) [48]. (1) Butterfly erythema or discoid erythema, (2) light sensitivity, (3) oral and mucosal ulcer, (4) non-arthritis or polyarticular pain, (5) pleuritis or pericarditis, (6) epilepsy or psychiatric symptoms, (7) proteinuria or tubular urine or hematuria, (8) leukocytes $<4 \times 109$/L or platelets $<100 \times 109$/L or hemolytic anemia, (9) immunofluorescent antinuclear antibody (IFANA) (+), (10) anti-dsDNA antibody(+) or lupus cell phenomenon, (11) anti-Sm (+), (12) complement C3 reduction, (13) skin lupus band test (non-lesion site) (+) or renal biopsy (+). Those who meet any of the 13 items can be diagnosed as SLE. Clinical validation showed that the sensitivity of the Shanghai standard to SLE diagnosis was 95.5% and the specificity was 96.7%

The SLE International Clinical Collaboration Group (SLICC) published a revised version of the ACR SLE Classification Standard at the 2009 American College of Rheumatology (ACR) conference, which includes the following clinical criteria 11 Article [49]. (1)Acute or subacute cutaneous lupus, (2) chronic cutaneous lupus, (3) oral or nasopharyngeal ulcers, (4) non-scarring caused by hair loss, (5) inflammatory synovitis, two or more swollen joints or accompanied by doctors. There is morning stiffness of the tender joint. (6) Serositis, (7) kidney, urine protein/creatinine abnormality (or 24 h urine protein >500 mg), or red blood cell cast, (8) nervous system, seizures, mental disorders, multiple mononeuritis, myelitis, peripheral or encephalopathy and encephalitis (acute insanity), (9) hemolytic anemia, (10) leukopenia ($<4 \times 10^9$/L, at least 1 time) or lymphopenia ($<1 \times 10^9$/L at least 1 time); thrombocytopenia ($<100 \times 10^9$/L, at least 1 time). Immunological criteria include the following six. (1) ANA is higher than the normal reference range of the laboratory; (2) anti-dsDNA antibody is higher than the normal reference value of the laboratory (2 times of ELISA method is higher than the normal reference value of the laboratory); (3) anti-Sm antibody; (4) anti-phospholipid antibody includes false positive for lupus anticoagulant syphilis test, at least two abnormal or medium-high titers of anti-cardiolipin antibodies and anti-β2 GP1 antibody; (5) low complement including low C3, low C4, low CH50; (6) direct Coombs test positive (non-hemolytic anemia state). Determining SLE is consistent with: (1) renal biopsy confirmed as lupus nephritis and ANA positive or anti-dsDNA positive; or (2) meets four criteria, including at least one clinical standard and one immunological standard. Compared with the 11 ACR standards, the 2009 ACR SLE Classification Standard revision has a significantly higher sensitivity (94% vs. 86%), while the specificity is equivalent (92% vs. 93%), and the false-positive rate is significantly reduced ($P = 0.0082$).

2. Diagnosis of LN

On the basis of diagnosis of SLE, if there is persistent proteinuria ≥0.5 g/day or multiple proteinuria ≥2+ or (and) cell tubular type (can be red blood cells, hemoglobin, granules, tubular or mixed tubular type) can be diagnosed. It has been recommended that single urinary protein creatinine ratio>50 mg/mmol can replace 24 h urine protein quantification, “active urinary sediment” (except infection >5 erythrocyte/high power field of vision, >5 white blood cells/high power field of vision) can replace the cellular cast. When not diagnosed as SLE, the kidney as the first symptom is easy to be misdiagnosed as primary glomerular disease, should be carefully examined for the performance of multiple systems, multiple organ involvement, many times as ANA, anti-dsDNA, anti-Sm antibodies, and so on to identify. The best standard for LN is still glomerular nephritis mediated by immune complexes confirmed by renal biopsy.

5.3.6 Treatment of LN

The treatment plan of LN depends on the pathological manifestation and type of kidney, the activity of the disease, other organs involved, comorbidities and other factors causing kidney injury, the response to the initial treatment and the side effects of treatment, etc. [50]. The ultimate goal of clinical treatment is to protect kidney function in the long term, prevent the recurrence of disease, avoid the damage related to treatment, improve the quality of life, and improve the survival rate. Complete remission should be achieved as far as possible, that is, urinary protein creatinine ratio 50 mg/mmol (urinary protein 0.5 g/day), and renal function is normal or close to normal (GFR within the normal range of ±10%). Partial remission is defined as proteinuria lowering ≥50% and renal function normal or near normal. Treatment targets are best reached within 6 months of the start of treatment and cannot exceed 12 months at the latest.

1. Type I and type II LN: Type I and type II LN patients generally do not need immunosuppressants treatment. If there is glomerular hematuria in patients with II LN of urinary protein >1 g/day, it can be used as low-to-medium dose hormone or in combination with Azathioprine (AZA). In addition, in the case of type I LN patients with electro-endoscopic podocyte disease (minor lesions) or interstitial nephritis, it may also be considered to be treated with glucocorticoids alone or in combination with immunosuppressants.
2. Type III and IV LN: It is recommended that the induction remission period of all III and IV LN can be treated with high-dose hormone impact for 3 days, followed by sequential prednisone treatment, gradually reducing to the minimum effective maintenance after a few weeks. The treatment of cyclophosphamide (CTX) or mycophenolate ester (MMF) was also selected for 6 months. After 6 months to evaluate the efficacy, if the condition improves, it can be changed to MMF or AZA maintenance treatment. If the condition does not improve, there is a feasibility of a second round of high-dose hormone shock treatment, reordering and reduction, while CTX and MMF schemes are interchanged for 6 months, and if not, consideration may be given to the application of second-line treatment options such as rituximab (anti-CD20) monoclonal antibody, Bailey monoclonal resistance, or calcium phosphatase inhibitors (such as cyclosporine A or tacrolimus).
3. Type V LN: For the combination of III or IV type of V LN, the treatment recommendation is consistent with the simple III or IV type. For simple V type LN, the first choice for induction relief treatment MMF+ prednisone, 6 months after the improvement is replaced by MMF or AZA maintenance treatment, such as no improvement instead of CTX, calcium phosphatase inhibitors, or rituximab.
4. VI type LN: Based on alternative treatment, it is not recommended to actively apply hormone and immunosuppressant therapy, hormones and immunosuppressants in accordance with the patient's other organ involvement in the use of the situation. Choice of alternative treatment: Patients who are still using immunosuppressants try to avoid peritoneal dialysis in order to avoid increasing the inci-

dence of infection, while for patients with positive anti-phospholipid antibodies, such as hemodialysis should be wary of vascular pathway thrombosis. In addition, if you consider a kidney transplant, you need to choose the patient's lupus activity at a lower level of at least 3–6 months of time.

5. Treatment of antiphospholipid antibody syndrome related nephropathy includes administration of hydroxychloroquine, anticoagulant and antiplatelet. Plasma exchange is the first choice for the treatment of patients with hemorrhagic thrombotic microangiopathy.

   In addition, intravenous immunoglobulin, blood purification, stem cell transplantation, and kidney transplantation can also be used for treatment. Thankfully, there have also been reports of successful treatment of systemic lupus erythematosus by autologous peripheral blood stem cell transplantation in China.

   At the same time, other treatment methods also help to improve the prognosis of LN, such as correction of acid-base disorders, electrolyte disorders, lipid metabolism disorders, protein supplement, dialysis treatment.

5.3.7 Antihypertensive Treatment

Renin-angiotension system inhibition is the first choice for the treatment of LN. The main reason is that the pressor mechanism is the same as that of renal hypertension [51], there is evidence that these drugs have antihypertension, urinary protein, the effect of protecting the kidneys, the dosage should be adjusted on the basis of monitoring blood pressure, blood potassium and glomerular filtration rate level, maximize the effect of reducing urinary protein as much as possible. In addition, consideration may be given to the active application of ARB, CCB, beta receptor blockers, diuretics, and other antihypertensive drugs, and control of blood pressure below 130/80 mmHg. If the pressure relief is difficult, the central antihypertensive drugs or direct vasodilation antihypertensive drugs may be considered. Creatinine levels should be closely monitored and should be reduced or deactivated if the recent increase exceeds 25%, ACEI/ARB. The deterioration of renal function is the key factor for the difficulty of blood pressure reduction. For the treatment of refractory hypertension, dialysis, ultrafiltration and even kidney transplantation can be considered.

5.3.8 Prognosis

Prognostic factors include the control of lupus activity, the irreversible degree of renal parenchymal injury before and after treatment, the quality of blood pressure control, and the recurrence of kidney disease. Hypertension is an important factor in the deterioration of renal function and the loss of renal reserve ability in the inactive period of lupus nephritis. Whether blood pressure can be controlled well is of great significance to prognosis. With the development of medicine and fewer deaths from lupus, cardiovascular and cerebrovascular diseases have become the leading cause

of death in patients with a longer history of systemic lupus erythematosus. Strict control of hypertension and hyperlipidemia is a key factor in the prevention of cardiovascular and cerebrovascular complications.

5.4 Hydronephrosis, Obstructive Nephropathy, and Hypertension

Lei Wang

Hydronephrosis is a dilatation of the renal calices caused by urinary tract obstruction in which urine accumulates in the renal pelvis. Obstructive nephropathy is a disease in which the structure and/or function of the urinary tract are abnormal, leading to obstructed excretion of urine or renal tubule fluid, leading to renal tubular interstitial lesions and renal dysfunction [52].

Chronic obstruction of urinary tract occurs slowly and persists, leading to the destruction of renal structure. When glomerular sclerosis and renal interstitial fibrosis occur and renal insufficiency occurs, the incidence of hypertension increases significantly [53]. It is generally believed that the incidence of hypertension in hydronephrosis caused by unilateral ureteral obstruction is 10–20%. The incidence of hypertension in acute unilateral ureteral obstructive hydronephrosis is relatively high, up to 30%, while the incidence of hydronephrosis caused by chronic unilateral ureteral obstruction is lower than 1.35% [52, 53].

5.4.1 Mechanism of Hypertension

Hydronephrosis and obstructive nephropathy can cause hypertension for two main reasons: One is increased blood pressure due to increased renin secretion, and the other is hypertension due to increased water and sodium retention and volume. The mechanisms vary according to the rate of obstruction, unilateral or bilateral, and complete obstruction.

5.4.1.1 Unilateral Hydronephrosis

After acute unilateral complete obstruction, blood pressure can increase in the short term. Studies have found that when one ureter is obstructed, the pressure of renal tubules increases sharply, and a series of adaptive changes will occur in renal hemodynamics, among which the main one is the contraction of glomerular arterioles and the decrease of renal blood flow. The local renin-angiotensin-aldosterone system is activated, in which angiotensin II (Ang II) is a strong vasoconstrictor substance, which can cause renal vasoconstriction, further reduce the renal blood flow, resulting in impaired renal function and renal atrophy. With further decrease of renal blood flow and GFR, the concentration of sodium ions in the filtrate from glomerular filtration through maculadensa decreased, the reabsorption of sodium ions in renal tubules decreased, the stimulation of renin release increased, and the

activation of circulatory RAS system, resulting in vasoconstriction and increased blood pressure [54, 55].

5.4.1.2 Bilateral Hydronephrosis

Bilateral ureteral obstruction may also result in decreased renal blood flow, but studies have shown that pressure of afferent vessel and renal blood flow are normal, also did not observe renin secretion to increase, which suggests that the increase of the renal vascular resistance is due to renal tubular pressure increasing as a result, rather than relying on pressure of afferent vessel increased, namely, high blood pressure with bilateral hydronephrosis is not caused by the RAS activity increased. Animal experiments and clinical studies have confirmed that bilateral hydronephrosis can lead to renal dysfunction, water and sodium retention, and azotemia, followed by weight gain, congestive heart failure, edema, and a series of pathological and physiological changes [56]. Therefore, the hypertension caused by chronic bilateral hydronephrosis is dependent on capacity. When there is no sodium retention and blood volume increases, hypertension generally can not occur, [57]. Diuretic reaction after the obstruction was relieved and the resulting blood pressure returned to normal, confirmed the opinion on the other hand.

5.4.1.3 Chronic Hydronephrosis

When hydronephrosis and hypertension entered the chronic stage, the activity of peripheral plasma renin activity was no longer increased. In addition to Ang II, other vasoactive substances produced by the kidney on the affected side play a major regulatory role in hypertension at this time increased production of vasopressin, such as thrombopsin A2. The increased release of vasopressin and the decreased synthesis of nitric oxide (NO) can cause the contraction of afferent vessel, decrease glomerular perfusion, and decrease GFR, further aggravating the abnormal activation of renin-angiotensin-aldosterone system (RAS) [58].

5.4.1.4 Other Factors

The ureteral pressure increased after obstruction and the involved renal vascular smooth muscle tension increases correspondingly, which could stimulate mechanicoreceptor, and activate sympathetic nervous system; As well as the macrophages and lymphocytes in the renal tissue after obstruction, producing cytokines to affect renal hemodynamics and may also affect blood pressure [59].

The depressor substance by kidney secretion is decreased: the kidney can produce a variety of depressor substance, such as prostaglandin, kinin (the epithelial cells of the distal renal tubules produce kininase, which converts the plasma kininogen into kininase), nitric oxide (NO). Currently, there are many studies on NO. When renal parenchymal disease occurs, the production of NO is reduced, and the ability to antagonistic vasoconstriction is weakened. In addition, the reduction of NO can also reduce the discharge of sodium from renal tubules and increase the retention of water and sodium. Finally, it can be involved in the occurrence of hypertension from

the two aspects of vasoconstriction and volume [58, 60–62]. However, there is still no conclusive evidence that the above other depressor substance is involved in the occurrence of renal hypertension.

As mentioned above, renin-dependent hypertension is the most common unilateral renal lesion, while volume-dependent hypertension is the most common bilateral lesion.

5.4.2 Clinical Feature

Clinical symptoms of urinary tract obstruction vary according to the location, degree, and duration of obstruction. The clinical manifestation of upper urinary tract obstruction is mechanical obstruction. Lower urinary tract obstruction is manifested as changes in urine volume and acute renal failure or chronic renal failure, mainly including low back pain, hematuria, lumbar and abdominal masses, dysuria, and renal impairment, which may be accompanied by electrolyte and acid-based disturbance [63].

Hypertension is usually ameliorated after obstruction is removed. However, if the lesion time has been relatively long, hypertension can sometimes last for quite a long time, especially for hypertension after obstructive nephropathy accompanied by renal insufficiency, which is often manifested as refractory moderate to severe hypertension.

5.4.3 Laboratory and Auxiliary Examination

1. Urine routine: hematuria, bacteriuria, pyuria, crystallization, and a small proteinuria.
2. Blood examination: obstructive nephropathy is often associated with polycythemia and may be associated with an increase in erythropoietin. The leukocyte count can be increased during the co-infection. Electrolyte disorder including hyperchloremic, hyperkalemia, acidosis; blood urea nitrogen and serum creatinine is increased in patients with renal insufficiency.
3. Ultrasonic examination: it is the most convenient, noninvasive, and sensitive examination to determine the size of the kidney and the presence or absence of urinary obstruction. It can show the degree of dilation of the renal pelvis and ureter and the presence or absence of urinary retention. It is the first choice.
4. Abdominal plain film: it can be used to evaluate the size, shape of the kidney, and the presence or absence of urinary calculi.
5. Intravenous pyelography, CT, and magnetic resonance imaging (MRI): may help to determine the obstruction site, nature, and degree (partial or complete).
6. Radionuclide examination: the uptake of radionuclide-labeled compounds into renal parenchyma and the rate of excretion reflect the function of total and partial kidneys and the effective renal plasma flow.

5.4.4 Diagnosis and Differential Diagnosis

Hydronephrosis and obstructive nephropathy have no specific clinical symptoms and laboratory tests, and the diagnosis of urinary tract obstruction is not difficult. Ultrasound (kidney, ureter, and bladder), intravenous pyelography, and CT/MRI were performed on suspected patients to determine the presence, location, and degree of obstruction. Patients with any acute renal failure or chronic renal failure should be inquired about their medical history and examined carefully to exclude obstructive nephropathy.

5.4.5 Treatment

5.4.5.1 Treatment Objectives

Aim at the etiology, remove the obstruction, improve the renal function, and relieve the symptoms, as far as possible to restore its normal anatomical structure.

5.4.5.2 Removal of Obstruction

The treatment of obstructive nephropathy depends on the location of the obstruction, the cause, and the degree of impairment of renal function. It has been reported that urinary tract reconstruction or nephrectomy can cure hypertension in 67% of patients and significantly improve hypertension in 19% of patients. Another report shows that 70% of the patients have completely normal blood pressure [57, 64].

5.4.5.3 Medical Treatment

Obstructive nephropathy, such as persistent oliguria and anuria, may lead to severe hyperkalemia, acidosis, etc., so the imbalance of water and electrolyte should be corrected actively; dialysis is done if necessary; in the case of co-infection, sensitive antibiotics should be selected to actively control the infection. The treatment of hypertension is fundamental to remove urinary tract obstruction, in the blood pressure control standard (<140/90 mmHg) under the premise, should choose the kidney protection drugs. The mechanism of hypertension after urinary tract obstruction is mainly increased renin activity and water and sodium retention, so RAAS blocker is generally recognized as the first choice [65, 66]:

1. Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin AT1 receptor blocker (ARB): ACEI can reduce Ang II generated, ARB can block Ang II and AT1 receptor, so both can inhibit renin activity, inhibit Ang II pathogenic effect, reduce the secretion of aldosterone, thus reducing the system high blood pressure, reduce the sympathetic nervous activity, expansion of small artery, reduce glomerular high perfusion, high pressure, high filtration, at the same time also can reduce the synthesis of extracellular matrix, protect glomerular podocyte, improve glomerular filtration membrane permeability of choice; it can reduce high blood pressure and delay progression of chronic kidney disease (CKD).
2. Renin inhibitors: It can bind to renin molecules, block the catalytic activity of renin, prevent angiotensin progenitors from being lysed to generate Ang I, and thereby reduce Ang II [67].

3. Calcium channel blocker (CCB): L-type CCB is the most commonly used antihypertensive drug, such as nifedipine, amlodipine, in recent years some new type CCB has come out, such as benidipine, which could block T, L, N type calcium channel at the same time, and are equal to dilatation of afferent arteriole and efferent arteriole, so if blood pressure is not achieved target after using ACEI or (and) ARB, can consider a combination of T type CCB [68].

   Most of the patients with impaired renal function have refractory hypertension, which requires the combination of multiple drugs to reduce blood pressure. ACEI or (and) ARB combined with low-dose diuretics is preferred. Diuretic drugs should not be overdosed. If insufficient blood volume occurs, it will cause an increase in serum creatinine. When the serum creatinine exceeds 30% of the baseline, ACEI or (and) ARB should be reduced or discontinued, and renal function should be closely monitored.
4. Diuretic: patients with renal insufficiency should also refer to the blood creatinine level to choose diuretic drugs: when Scr < 159 μmol/L(1.8 mg/dL), thiazide diuretic drugs can be used; when Scr > 159 μmol/L(1.8 mg/dL), only diuretics can be used, because thiazide diuretics have no efficacy at this time [68, 69].

   If the above combined antihypertensive regimen fails to achieve blood pressure target, beta blockers or a blockers may be added as appropriate.

5.4.6 Prognosis

If the causes of hydronephrosis and obstructive nephropathy can be removed in time, the renal structure and function can be restored to normal, and hypertension can be improved, but if not treated in time, renal function can be irreversibly impaired. Studies have shown that if complete obstruction can be relieved within 1 week, renal function can be completely restored to normal, if complete obstruction can be restored within 4 weeks. Glomerular filtration rate can only be restored to 30%, if complete obstruction can be restored over 6 weeks, it is extremely difficult to restore renal function. Renal function was almost completely lost after 8 weeks [52]. Urinary tract obstruction and hypertension are mostly associated with renal function damage. If malignant hypertension occurs, the risk of cardiovascular and cerebrovascular diseases will be significantly increased, and glomerulosclerosis will be aggravated, forming a vicious cycle.

5.5 Pyelonephritis and Hypertension

Lei Wang

Pyelonephritis is an infection of the upper urinary tract, that is, inflammation of the renal pelvis, mostly caused by bacterial infection, often accompanied by inflammation of the lower urinary tract. Pyelonephritis can be divided into acute and chronic, the former acute onset, good prognosis; chronic pyelonephritis, due to the continuous or repeated inflammation caused by the destruction of the renal interstitium, renal pelvis, calyx, the formation of scar, and even kidney atrophy. Renal

hypertension accounts for about 5–10% of all hypertension, among which pyelonephritis accounts for about 10–30% [52, 53].

5.5.1 Mechanism of Pyelonephritis Causing Hypertension

Pyelonephritis causes hypertension, which is related to the severity of the disease and the state of renal function. Renal parenchymal disease, especially in the case of renal insufficiency, the glomerular filtration rate decreases, and the incipient water and sodium storage increases blood volume. It can also lead to a series of neurohumoral disorders, resulting in vascular resistance or (and) increased blood volume, resulting in hypertension. The essence of chronic pyelonephritis is chronic interstitial nephritis, and the pathogenesis of secondary hypertension mainly involves the following aspects:

1. Volume increase: in chronic renal parenchymal disease, hypertension occurs due to the decrease in the number of renal units, progressive decrease in renal function, decrease in renal excretion of sodium and water, and expansion of extracellular fluid volume [52, 70].
2. Activation of the renin-angiotensin-aldosterone system (RAAS): the primary source of renin in the blood is from the para-glomerular apparatus of the kidney. Ischemia can lead to the activation of RAAS. Angiotensin II (Ang II) can directly stimulate the vasoconstriction, increase sympathetic nervous activity, and the sympathetic nerve endings promote catecholamine release, further shrink blood vessels; causes renin-dependent hypertension. Aldosterone can increase sodium absorption in distal renal tubules and collecting tubules increase water and sodium retention. Therefore, RAAS activation can be involved in both resistance and voluminous hypertension [54, 55].
3. Kidney secretion is decreased: see in 5.4.1.4 [58, 71, 72].

In short, in patients with chronic pyelonephritis complicated with hypertension, simple volume hypertension or simple resistance hypertension are rare, and the vast majority of patients have both pathogenic factors.

5.5.2 Clinical Manifestations

Pyelonephritis can be divided into acute pyelonephritis and chronic pyelonephritis. Acute pyelonephritis is characterized by acute onset and lasts for no more than 6 months. Clinical manifestations include acute onset of chills, fever, low back pain (with obvious percussion pain at the costal ridge angle), often accompanied by nausea, vomiting, painful urination, frequent urination and increased nocturia, and other symptoms of urinary tract stimulation [52].

The onset of chronic pyelonephritis is insidious, and patients are often presented with slow renal insufficiency and hypertension, and their blood pressure is

moderately and severely elevated, which is prone to develop into malignant hypertension. Because the renal interstitium is damaged, when tubular function is severely impaired, urine concentration function decline, which cause polyuria, nocturnal urination, hyponatremia, hypokalemia and metabolic acidosis, even uremia, also appear heart failure because of hypertensive, renal insufficiency, and can be threat to life. Patients have FSGS years after onset, often accompanied by severe proteinuria, with poor prognosis [52].

5.5.3 Laboratory and Auxiliary Examination

1. Urinary sediment: pyuria is a characteristic change, and proteinuria can sometimes be found, which indicates that the lesion has involved the glomeruli, indicating a more serious condition.
2. Urine culture: urine cell culture and colony count are important indicators of diagnosis.
3. Other examination: the urine sediment antibody packages the bacterium examination, cystitis is positive and has the differential diagnosis value.
4. Kidney function: generally no renal dysfunction, when the illness is aggravating, serum creatinine and blood urea nitrogen rise.
5. Imaging examination: X-ray and pyelography can understand the urinary tract system without stones, obstruction, malformation, nephroptosis, and other conditions. Acute pyelonephritis mostly found without positive, chronic pyelonephritis can be seen in the intravenous pyelography of the renal pelvis, calyces deformation, and narrowing; the shape of the kidney is uneven and the size of the two kidneys varies. Ultrasound and CT also showed irregular or even reduced renal shadows.

5.5.4 Diagnosis and Differential Diagnosis

The diagnosis of pyelonephritis is not difficult to decide, based on urinary symptoms, raised urine leukocyte. The diagnosis of chronic pyelonephritis cannot be made solely on the basis of medical history and course of disease. Imaging features need to be incorporated.

The differential diagnosis is mainly differentiated from urinary tuberculosis, lower urinary tract infection, and chronic glomerulonephritis.

5.5.5 Treatment

Actively control infection, remove susceptible factors, and prevent recurrence. To control blood pressure up to standard is helpful to slow down the progress of the disease, especially to delay the occurrence and development of renal insufficiency.

In the treatment of chronic pyelonephritis complicated with hypertension, in addition to following the general principles for the treatment of hypertension,

special attention should be paid to the effective protection of the target organ—kidney, delaying the progression of renal function damage. For patients with chronic renal disease, antihypertensive therapy should be individualized, and the general goal of blood pressure is to control blood pressure below 140/90 mmHg [65, 73, 74].

1. Diuretics: suitable for "volume-dependent" hypertension. When pyelonephritis is associated with hypertension, diuretics should be used in combination with water and sodium retention. It is emphasized that diuresis should not be excessive, so as not to cause insufficient blood volume, leading to the activation of RAAS and adverse blood pressure reduction.
2. Renin-angiotensin inhibitors: angiotensin-converting enzyme inhibitors (ACEI) block angiotensin-converting enzyme (ACE), increase the effect of bradykinin and angiotensin 1–7, more selectively dilate the efferent arteriole and correct high perfusion and high filtration of the glomeruli transmembrane thus reduce the renal vascular resistance, increase the effective renal blood flow. Angiotensin receptor antagonist (ARB) Selectively bind to AT1 receptor, blocking Ang II reaction. After a large number of tests, it has been recognized that ACEI is the most effective drug for the protection of the kidney among all the antihypertensive drugs. It is effective in delaying the progression of renal damage especially diabetic nephropathy with a large amount of proteinuria. Therefore, ACEI should be the first choice for renal disease complicated with hypertension [65, 74].
3. Calcium ion antagonist (CCB): it reduces blood pressure by dilating peripheral resistance vessels, which is especially suitable for elderly patients with hypertension [74].
4. Beta blockers: decrease cardiac output and dilation of blood vessels by blocking-receptors in the heart, kidneys, and centers [75].
5. A blocker: selective blocking of post-synaptic a1 leads to decreased peripheral vascular resistance, resulting in antihypertensive effects.
6. Vasodilators: decrease blood pressure by directly dilating the arterioles and reducing peripheral resistance. It has a good effect on the late stage of pyelonephritis, especially the hypertension caused by chronic renal insufficiency.

In conclusion, in the treatment of renal hypertension, as long as the systemic hypertension is reduced to the target value, the progression of renal function damage can be delayed.

5.5.6 Prognosis

The prognosis of pyelonephritis is different because of different types. And chronic pyelonephritis not only can cause hypertension, but also can cause chronic renal insufficiency. Hypertension in the early stage of chronic pyelonephritis is relatively easy to control, but hypertension in the late stage occurs refractory

hypertension due to renal insufficiency, which forms a vicious circle and makes the insufficiency rapidly. Because the course of chronic pyelonephritis is insidious, clinicians should be vigilant and try to actively treat it to improve the prognosis of patients [52].

5.6 Reflux Nephropathy

Ayinigeer Abulimiti

5.6.1 Introduction

Reflux nephropathy (RN) is one of the most common congenital renal malformations and a frequent cause of hypertension and end-stage renal disease in children and young people, particularly in developing countries [76]. RN is a generic term, first proposed in 1973 by Bayley to describe the evident renal scarring caused by vesicoureteral reflux (VUR) and the urinary tract infections (UTI) associated with it [77]. This definition ranges from cases with minimal kidney scars and self-resolved reflux to those with a severe reduction of the renal parenchyma [77, 78]. The reflux itself may persist in adulthood, heal spontaneously as the patient grows, or be treated employing appropriate surgical or endoscopic interventions [79].

5.6.2 Etiology

VUR is the basis of reflux nephropathy. Normal ureter has the anatomical structure to prevent urine reflux and can effectively prevent urine reflux [79]. VUR can be divided into primary and secondary types according to the etiology. Primary vesicoureteral reflux is a congenital anomaly, which is more common in infants under 5 years old, but also in adult women. Secondary vesicoureteral reflux finger is secondary to lower urinary tract obstruction and bladder injury [80].

There are two main theories that have been put forth to explain how VUR progresses to RN. In the first, RN arises from the reflux of infected urine from the bladder to the kidneys. This leads to a kidney infection which triggers the innate immune response and the influx of inflammatory cells. Others believe that the reflux of even sterile urine can cause an increase in intrarenal pressure that can progress to chronic fibrosis. Finally, others postulate that cases of RN that progress to end-stage renal disease (ESRD) is likely developed in the presence of a congenitally malformed kidney [79].

VUR is graded using a five-point scale as mild (grades I–II), moderate (grade III), or severe (grade IV and V) based on the degree of retrograde filling and the extent of ureteral dilatation observed from the VCUG (voiding cystourethrogram) [81, 82].

5.6.3 Epidemiology

The true extent of RN and its clinical course in different age groups, including adults, is not known. It is primarily a disorder of childhood or early adulthood and is more common in females than males, especially in pregnant females [83, 84]. RN is the fourth most common cause of ESRD in children after focal segmental glomerular sclerosis (FSGS), renal aplasia, hypoplasia or dysplasia, an obstructive uropathy [85].RN accounts for up to 25% of ESRD in children [86], and 7–17% of all cases of ESRD in adults [87]. Based on the North American Pediatric Renal Transplant Cooperative Study annual report for 2008, 3.5% of the 6491 children on dialysis had RN [88].

5.6.4 Complications

The complications of RN are well-known but poorly defined because of their insidious onset and slow progression. These include hypertension, proteinuria, urine concentration defects, hyperkalemia, acidosis, and chronic kidney disease with progressive renal failure, including end-stage renal failure (ESRF) in some patients. Of these, hypertension and proteinuria are the commonest ones that have a significant bearing on long-term renal outcome and both are amenable to medical intervention.

5.6.4.1 Hypertension

The relationship between renal scarring and hypertension was first demonstrated in 1937 when the removal of a small scarred kidney cured hypertension in a 10-year-old female with recurrent UTI and hypertension [89]. Hypertension occurs in 17–30% of pediatric patients [90]and 34–38% of adult patients with renal scarring [91].Confounding factors such as increasing frequency of primary HTN in adults make this interpretation difficult.

According to a study that did survival analysis, it was estimated that 50% of patients with unilateral and bilateral renal damage would have sustained hypertension at about 30 and 22 years of age, respectively [92]. In a follow-up lasting 15 years in pediatric patients with renal scarring, about 13% patients at age 20–31 years became hypertensive, mostly between the ages of 15 and 30 years.

The exact cause for hypertension due to RD is also not known but is believed to be due to segmental ischemia with increased renin secretion [93]. The plasma renin activity (PRA) may increase in some children with renal scars as they grow older, but there is no direct correlation between blood pressure and PRA, plasma creatinine concentration, or degree of scarring [94].

5.6.4.2 Proteinuria

Overt proteinuria, which has been reported in 21% of adult patients with RN [91], is a rare occurrence in pediatric patients. It results from glomerular and/or tubulointerstitial damage caused by immunologic injury, macromolecular trapping and

mesangial dysfunction, hypertension, and glomerular hyperfiltration. Microalbuminuria has been reported in 51% pediatric patients (mean age 9.8 ± 4.2 years) with renal scarring [95]. Microalbuminuria excretion increases with the severity of renal scarring.

5.6.4.3 Focal Segmental Glomerular Sclerosis (FSGS)

RN has also been associated with focal FSGS. In a histological review of 86 pediatric nephrectomy specimens from patients with VUR (with or without apparent obstruction at the vesicoureteral junction), FSGS was found in 18 (21%) patients, 9 of whom were less than 5 years old. FSGS is progressive and can occur in non-scarred parts of the kidney or in the normal contralateral kidney in patients with unilateral RN [79].

5.6.4.4 Renal Failure

RN is responsible for 12–21% of all children with chronic renal failure [96]. According to 2008 North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) report, RN is the fourth commonest cause for chronic kidney disease in 8.4% of the children and is seen in 5.2% of transplanted patients and 3.5% of dialysis patients [88]. In the CKID study that involved a cohort of 586 children aged 1–16 years with an estimated GFR of 30–90 mL/min/1.73 m^2, RN was the underlying cause for CKD in 87 (14.8%) patients. This constituted 19% of the patients with non-glomerular etiology for CKD [97].

5.6.5 Diagnosis

Diagnosis of reflux nephropathy depends on following three items: (1) recurrent urinary tract infection; (2) urination cystourography showed reflux positive; (3) B-ultrasound showed that the renal volume was reduced, the renal pelvis was dilated and deformed, and the echo of renal parenchyma was enhanced. Emission single photon computed tomography (ECT) showed that the shape of the affected kidney was irregular, the volume was reduced, and the local scar formation and local perfusion in the polar area of the kidney could be seen [4].

5.6.6 Management

The purpose of the treatment of RN is to stop vesicoureteral reflux, control infection, and prevent the occurrence of renal scar and renal function injury. The methods of treatment include medical treatment and surgical treatment. Medical treatment mainly uses anti-infection and comprehensive symptomatic treatment measures to delay the loss of renal function. Once uremia occurs, blood purification therapy should be carried out, and kidney transplantation can be performed. Surgical treatment is mainly for a variety of endoscopic injection treatment and anti-reflux ureter replantation [79].

There are no evidence-based guidelines for the management of hypertension, proteinuria, or other complications related to RN. Timely diagnosis and appropriate management of hypertension is essential for preserving renal function. The use of angiotensin-converting enzyme inhibitor (ACEI) and/or an angiotensin receptor blocker (ARB) for proteinuria and/or hypertension is recommended. In patients with poorly functioning unilateral RN, removal of the affected kidney may be considered, keeping in mind that the nephrectomy may not cure hypertension.

5.6.7 Prognosis

Advanced age at presentation and bilateral VUR decreases the probability of resolution. High grade and severity of the VUR have lesser chances of spontaneous resolution. Higher grades of RD were associated with less favorable BP indices. Of note, ambulatory blood pressure monitoring (ABPM) measurements were able to identify additional hypertensive patients who could not be identified with clinical BP measurements. The higher sensitivity of ABPM seems to be important, particularly in patients with RD [93].

Prognosis of RN is closely related to proteinuria, focal segmental glomerulosclerosis and progressive renal dysfunction. The degree of albuminuria was significantly correlated with the presence or absence of glomerular injury and the degree of glomerular injury. Progressive glomerulosclerosis is the most important determinant of chronic renal failure in RN.

5.7 Kidney Tumor and Hypertension

Weijun Tao

Kidney tumor is a common type of disease that seriously threatens human health, and the incidence rate is increasing. The pathogenesis of these diseases is complicated. Different subtypes originate from different parts of the nephron, and all have their own genetic basis and biological basis. It can cause an increase in blood pressure, which is manifested as malignant hypertension. Delayed treatment can lead to serious consequences, which deserves in-depth study and serious treatment.

5.7.1 The Mechanism of Blood Pressure Elevation in Kidney Tumors

The causes of hypertension caused by kidney tumors can be roughly divided into the direct secretion of renin by the tumor, the occupying effect (compressed parenchyma and blood vessels, obstruction of the ureter, etc.), renal failure, etc. The

mechanism is mainly the renin-angiotensin-aldosterone system (RAAS) activation which causes sodium retention or direct sodium retention, and possibly other vasoactive substances involved. After removing the causes, the symptoms can be alleviated or disappeared.

1. Hypertension caused by renin, erythropoietin, and other substances secreted by tumor. Renal tumors that secrete renin include renin-secreting tumor, renal cell carcinoma, and nephroblastoma. The mechanism that causes hypertension is mainly the secretion of excessive renin, which causes RAAS to activate and hypertension. Renin is a proteolytic enzyme that is secreted by cells adjacent to the glomerulus. When the tumor cells synthesize too much renin into the blood circulation, it acts on the angiotensinogen produced by the liver, hydrolyzes the latter into angiotensin I, and then forms angiotensin II by angiotensin-converting enzyme. Angiotensin III, in which angiotensin II causes strong contraction of small arteries and causes hypertension; angiotensin II and angiotensin III also promote aldosterone secretion by stimulating the spheroidal band of the adrenal cortex, causing sodium retention and increased blood volume and increasing blood pressure.

   Some tumor cells have also secretion of erythropoietin, which stimulates bone marrow hematopoiesis, produces red blood cells, and causes an increase in blood volume and blood viscosity, further increases the resistance of small arteries, leading to hypertension. The above factors can be developed from early compensation to decompensation, resulting in continuous increase in blood pressure.
2. Hypertension caused by tumor occupying lesions
   (a) Compression of renal parenchymal

   Renal parenchymal hypertension can occur in patients with severe renal ischemia caused by renal tumor space occupying or tumor squeezing of renal parenchyma. The development of hypertension is related to the extent of the lesion and the degree of renal parenchymal ischemia. The incidence of renal parenchymal hypertension caused by tumors is 1032/100,000. Some believe that its pathogenesis may be related to the role of the RAAS.

   Hypertension caused by other conditions, such as polycystic kidney, solitary renal cyst larger than 5 cm, hydronephrosis, and so on, mainly belongs to renal parenchymal hypertension, while renal cell carcinoma, nephroblastoma, and subglobular tumor also have the characteristics of renal parenchymal hypertension in addition to their own secretion of renin.

   (b) Compression of renal vascular

   Tumor squeezing and blocking renal artery can lead to renal artery stenosis, causing renovascular hypertension, which can also be associated with renal parenchyma hypertension.

   (c) Hypertension caused by renal failure

   The main mechanism is urinary dysfunction, which results in the retention of sodium and water, the expansion of blood volume and the increase of blood pressure.

(d) Tumor crisis

When the condition of some patients with renal tumor worsens, there will be metastatic brain tumor, intracranial hypertension or tumor metabolic disorders, such as hypercalcemia, can also be accompanied by the elevation of blood pressure.

5.7.2 Classification of Renal Tumors

The pathological classification proposed by Barbaric is more practical in clinical practice in 1996 (shown in Table 5.2). Clinical blood pressure is most difficult to control is reninoma and renin-secreting renal tumor, the most resistant hypertension

Table 5.2 Pathological classification of renal tumors

Malignancy	Benign	Inflammatory
Renal cell carcinoma	Solitary cyst	Abscessus
Chromophilic carcinoma	Angiomyolipoma	Focal glomerulonephritis
Chromophobe renal carcinoma	Acidophiloma	Xanthogranulomatous pyelonephritis
Collecting duct carcinoma	Nephradenoma	Infectious renal cyst
Urothelial carcinoma	Metanephric adenoma	Nephrotuberculosis
Transitional cell carcinoma	Cystic nephroma	Rheumatic granulomas
Renal squamous cell carcinoma	Mixed epithelial stromal tumor	
Adenocarcinoma	Reninoma (juxtaglomerular cell tumor)	
Sarcoma	Leiomyoma	
Leiomyosarcoma	Fibroma	
Liposarcoma	Hemangioma	
Hemangiosarcoma	Vascular tumors	
Hemangiopericytoma	Aneurysm of renal artery	
Malignant fibrous histiotoma	Arteriovenous malformation	
Synovial sarcoma	Renal pseudotumor	
Osteosarcoma		
Clear cell sarcoma		
Rhabdomyosarcoma		
Wilms tumor		
Primitive neuroectodermal tumor		
Carcinoid		
Lymphoma		
Leukemia		
Metastatic tumor		
Adjacent tumors invade directly		

is the end-stage of various renal diseases—uremia. The tumors associated with hypertension are described below.

5.7.3 Simple Renal Cyst

Simple renal cyst (SRC) is a unilateral (mostly) or bilateral kidney with one or more circular cysts of different sizes that do not communicate with the outside. Most of the patients were asymptomatic and were found by physical examination and imaging. With the enlargement of cyst, hypertension can be caused.

5.7.3.1 Epidemiology

Simple renal cysts are usually unilateral and single, which may also have bilateral and multiple. The prevalence of SRC in men is twice than that in women and higher in men and the elder [98]. With the increase of age, the prevalence of this disease increased gradually [99]. The prevalence of SRC in hypertensive population was significantly higher than that in the general population [100]. The findings suggest that the bilateral distribution of cysts, the number of cysts ≥2, diameter >1 cm can predict hypertension [101]. In recent years, the more health check-ups include abdominal B-ultrasound examination are, the higher of detection rate of SRC is.

5.7.3.2 Pathogenesis

At present, the pathogenesis is not completely clear, while the SRC is not congenital or hereditary kidney disease, but acquired. Multiple studies have shown that simple renal cysts are an independent risk factor for hypertension [101–103]. The mechanism of hypertension in simple renal cyst may be as follows:

1. Activation of renin-angiotensin system: The increased cysts may result in local renal ischemia or compression of renal parenchyma or renal vessels, decrease in renal blood flow, activation of tractive receptors, and increase in renin release. Thus, activation of renal renin-angiotensin system plays a key role in the pathogenesis of hypertension [104].
2. Renal unit reduction: The renal unit decreased significantly, the load of the remaining renal unit increased, and the proliferation and hypertrophy of renal tubular epithelial cells led to the decrease of renal tubular function, especially the regulation of water and sodium, which in turn led to the increase of blood pressure [98].
3. Renal enzyme secretion reduction: Renal enzymes secreted by the kidney decompose catecholamines (dopamine, epinephrine, norepinephrine) in the circulation, reduce heart rate and regulate myocardial contractility, prevent the increase of peripheral vascular tension reactivity, and thus reduce blood pressure. Therefore, from the point of view of secreting renal enzymes, the existence of simple renal cysts will lead to the decrease of renal enzyme secretion, the degradation of catecholamine, the increase of plasma catecholamine level, and the excessive activation of sympathetic nerve, which will lead to hypertension [105].

4. Postural change: We found that patients with large renal cysts may exhibit high orthostatic blood pressure in our center. Further intravenous pyelography suggests that the position of the kidney moves down in orthostatic position, and renin and aldosterone increase in orthostatic position. It is considered that the increase of blood pressure may be related to the traction of renal artery by postural changes.

5.7.3.3 Clinical Manifestation

Simple renal cysts are generally asymptomatic, but the corresponding manifestations can occur when cyst compression causes vascular occlusion or urinary tract obstruction. Patients with simple renal cysts can show hypertension, most of them may be essential hypertension complicated with renal cysts, and a few may be caused by cyst compression of renal parenchyma or renal blood vessels [106].

5.7.3.4 Diagnosis

The diagnosis of SRC mainly depends on imaging examination, such as B-ultrasound or CT examination. The diagnosis of asymptomatic small cysts is difficult and easy to be ignored. Renal parenchyma cysts need to be differentiated from the following diseases: (1) necrosis and liquefaction of renal solid tumors; (2) carcinogenesis on the basis of renal cysts, which is extremely rare; and (3) autosomal dominant polycystic kidney disease.

5.7.3.5 Treatment

Most of the SRC are asymptomatic and small cysts have little effect on blood pressure. So there is no need for treatment. Patients can be followed up every 6 months to 1 year. If the patient is complicated with hypertension, they can be treated according to the routine treatment of hypertension, and angiotensin-converting enzyme inhibitor or angiotensin receptor antagonist can be selected first [107].

5.7.4 Renal Hamartoma

Renal hamartoma, also known as renal angiomyolipoma (renal angioleiomyolipoma, RAML), is a common benign renal tumor containing mature adipose tissue, fusiform smooth muscle, and abnormal blood vessels, rarely malignant [108]. It is more common in adults, accounting for 0.3–3% of renal solid tumors [109]. It is more common in women, accounting for about 80%. Most of the lesions are asymptomatic after the age of 40, which can be in double kidneys and multiple [106]. Resistant hypertension can often be caused by large tumor compression on the renal parenchyma or renal vessels.

5.7.4.1 Etiology and Pathogenesis

At present, renal hamartoma is considered to be a benign genetic disease. The pathogenesis may be related to the inactivation of X chromosome and mutation or loss of heterozygosity [110]. Since women have a high incidence and are extremely

rare before puberty, it is assumed that their growth is hormone-dependent. Renal hamartoma may be an independent disease or may be accompanied by tuberous sclerosis. Sporadic renal hamartoma usually belongs to a single tumor and is generally small. If renal hamartoma is multiple and bilateral, the size of the tumor is generally large and often accompanied by tuberous sclerosis [111].

5.7.4.2 Clinical Manifestation

The clinical manifestations of the disease are related to the size, location of the tumor, and the presence or absence of ruptured bleeding. Common symptoms and signs include lumbar pain, hematuria, palpable masses, and hypovolemic shock [112]. Some patients may show anemia or high blood pressure. Renal hamartoma leads to hypertension, which is often caused by the compression of renal parenchyma or renal vessels by large lesions. Generally, blood pressure is more resistant, and routine antihypertensive treatment is not easy to reach the standards.

5.7.4.3 Diagnosis and Differential Diagnosis

The vast majority of cases can be diagnosed by specific imaging examinations associated with RAML. The typical ultrasonic feature of RAML is that the boundary is clear, mainly manifested as high echo and strong echo, but cannot be used as a specific diagnosis. When there is acoustic shadow, it is suggested that AML is hypoechoic due to renal cell carcinoma and rarely accompanied by acoustic shadow [113]. CT scanning is the most effective and reliable diagnostic method at present [114], which should be differentiated from the following diseases: (1) Renal carcinoma: When CT scans a very small amount of adipose tissue in renal lesions (CT value is lower than −29HU), the diagnosis of renal cell carcinoma can be ruled out and AML can be considered [115]. (2) Renal lipoma/sarcoma: the incidence of renal lipoma/sarcoma is low, which can be differentiated by special sequence imaging of MRI; (3) Renal hemangioma: Renal hemangioma is mostly hypoechoic and has few blood flow signals, which needs to be differentiated from contrast-enhanced ultrasound or enhanced CT.

5.7.4.4 Treatment

Hypertension caused by renal hamartoma can be treated according to the routine treatment of hypertension, and angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists can be preferred. The occurrence of general hypertension is related to the compression of renal parenchyma or vessels by excessive pathological changes, then the blood pressure can return to normal after operation.

5.7.5 Renin-Secreting Tumors

Renin-secreting tumors include: (1) nephroblastoma (juxtaglomerular cell tumors); (2) renal embryocytoma (Wilms tumor), also known as nephroblastoma, and (3) extrarenal renin-producing tumor.

5.7.5.1 Reninoma

Reninoma, also known as para-glomerular cell tumor (juxtaglomerular cell tumor), is a tumor that autonomously and abnormally secretes renin, leading to high blood pressure. It is rare in clinic, but it is more common in young people. Resistant hypertension is often the first symptom and the blood pressure can be as high as 250/170 mmHg, accompanied by obvious hypokalemia, alkalosis, hyperrenin, and hyperaldosteronemia. The clinical symptoms are similar to primary aldosteronism, which is characterized by high aldosterone and hyporenemia. Reninoma includes tumor of the juxtaglomerular apparatus (JGA tumor), some non-JGA renal tumors (such as Wilms tumor, renal cell carcinoma) and extrarenal ectopic renin-secreting tumor (such as some lung cancer, pancreatic cancer, adrenal tumor) and so on.

Epidemiology

Robertson et al. and Kihara et al. reported the disease in 1967 and 1968, respectively. In the literature, this disease is also known as reninoma and Robertson-Kihara syndrome and so on [116]. In the foreign literature, by the end of 2006, there were about 100 cases of JGA tumor reported abroad, but only 100 cases of JGA were reported in China because the diagnosis of the disease was difficult, so the actual number of cases is far more than the current reported number; however, the incidence of this disease is still very low.

Pathology and Pathophysiology

The tumors were located in the renal cortex, small in size, mostly below 3 cm, and the capsule was intact. Microscopically, the tumor cells were composed of uniform round or polygonal cells with eosinophilic and granular cytoplasm. The nucleus is central, orbicular or ovoid, rarely mitotic. The tumor tissue is organ-like structure, can also be trabecular, glandular tubular, or papillary shape. Immunohistochemistry: vimentin, CD34, CD117, vimentin, smooth muscle actin, Calponin positive are helpful for diagnosis. The stroma is mainly loose connective tissue and abundant capillaries, and the thick-walled vessels with vitreous degeneration could be seen locally, and the rhombic secretory granules in the cytoplasm, that is, immature prorenin granules were found by electron microscope, which had diagnostic value [117].

Clinical Manifestation

In the early stage of the disease, blood pressure fluctuates, then continues to rise, occasionally paroxysmal. The main symptoms were severe headache, thirst, polyuria, limb weakness, hemiplegia, aphasia, cerebrovascular accident, and so on. Patients have hypertension, high plasma renin activity, secondary aldosteronism, and hypokalemia. According to clinical manifestations, the tumor was divided into three types: typical, atypical, and static. The typical cases have hypertension and hypokalemia; the atypical patients were characterized by hypertension and normal serum potassium; the static type was rare and showed normal blood pressure and serum potassium [118].

Diagnosis and Differential Diagnosis

Young patients with hypertension, the clinical manifestations of poor blood pressure control, combined with dry mouth, fatigue, nocturia increased, laboratory examination found that low serum potassium, high urinary potassium, high renin activity, high aldosterone highly suspected of the disease. The tumor can be found by further examination of renal thin layer CT or MRI. The diagnosis can be confirmed by collecting blood from bilateral renal vein. The disease should be distinguished from the following diseases: (1) Renal artery stenosis: renin release increased, but activity did not increase or slightly increased, serum aldosterone increases and serum potassium decreases not significantly, vascular murmur could be heard in abdomen, renal angiography could make a definite diagnosis. (2) Renal carcinoma: some renal cell carcinoma can cause the increase of plasma renin level, but the elevated level is significantly lower than that of renal cell carcinoma. The enhancement of renal cell carcinoma in arterial phase is not obvious during CT enhancement, which is different from the contrast agent "fast in and out" of renal cell carcinoma. (3) Primary aldosteronism: the clinical manifestations were hypertension, hypokalemia, high aldosterone, and low renin. Adrenal space-occupying lesions could be found by B-ultrasound or CT.

Treatment

Surgery is the most effective method for the treatment of reninoma, including nephrectomy, partial nephrectomy and tumor enucleation, and the operative method should be selected according to the size and location of the tumor. Simple tumor enucleation or partial nephrectomy was performed for para-glomerular cell tumors with diameter<3 cm, and nephrectomy was performed for tumors with diameter>3 cm complicated with severe impairment of renal function [119]. However, drugs should be used to control hypertension and correct metabolic disorder before operation.

5.7.5.2 Nephroblastoma (Wilms Tumor)

Nephroblastoma, also known as Wilms tumor, has several names in the literature, such as embryonal nephroma, renal embryonic adenomyosarcoma, carcinosarcoma, and so on. It is the most common renal malignant tumor in children. Seventy-five percent of them occur under 5 years old and the median age is 3.5 years. Ninety-eight percent of them occur under 10 years old, and the incidence of adult is rare [120].

Pathology

Nephroblastoma presents as a solid mass of the kidney. The mass is often large, gray in the section, soft and delicate texture, with bleeding or necrosis and cystic change. Microscopically, tumors are often composed of a variety of components, including renal germ components, epithelial components differentiated into renal units, and mesenchymal tissue differentiated into renal stroma. The worst differentiation was renal germ components, mainly dense small round cells, round or oval nucleus, deep staining, less cytoplasm, but also slightly abundant eosinophils in the

cytoplasm. Immunohistochemistry can prove their multidirectional differentiation characteristics.

Clinical Manifestations

The main clinical manifestations of nephroblastoma are similar to those of renal cell carcinoma. The abdominal masses are often palpable by physical examination or occasionally. When the tumor grows to a certain extent, there will be systemic symptoms, such as emaciation, anemia, fever, hematuria, and so on [121].

Hypertension or erythropoietin can occur if renin or erythropoietin is secreted. In 1937, Pincoffs and Bradley first confirmed that Wilms tumor was complicated with hypertension. In 1958, Lattimer et al. reported that the tumor complicated with hypertension was as high as 60%. Most of the hypertension showed moderate elevation, and occasionally severe or malignant hypertension. In advanced cases, it is found that the tumor itself secretes renin to increase hypertension and the tumor oppresses the adjacent renal parenchyma, resulting in similar renal parenchyma and renovascular hypertension.

Diagnosis and Differential Diagnosis

The diagnosis of nephroblastoma can be seen in the diagnosis of renal cell carcinoma. The imaging findings are similar to those of renal cell carcinoma and cannot be distinguished. The diagnosis is mainly based on clinical information and the age of the general patients is different from that of renal cell carcinoma.

The disease should be differentiated from the following tumors: (1) Clear cell sarcoma: the ratio of male to female is 2:1 and the average age is about 3 years old. Classical clear cell sarcoma cells are arranged in nests and strips, separated by branched small fibrous vessels interspersed with tumor cells. Histology can be divided into sclerosing type, cell type, and epithelioid type, about 3% of which can be anaplastic. Immunohistochemistry: the expression of vimentin, cyclinD1, epithelial markers, WT1, CD99, and other negative. (2) Malignant rhabdomyosarcoma of the kidney: It is more common in children under 2 years old. The tumor cells are diffusely arranged and easy to invade blood vessels, capsule, and renal parenchyma. The nucleus was vesicular, the nucleolus was clear, and the pink stained vitreous inclusion body could be seen in the cytoplasm. Sometimes the cells are small and undifferentiated, similar to renal embryo tissue, but without epithelioid and mesenchymal tissue. The expression of INI1 was negative by immunohistochemistry, and the intermediate filamentous structure could be seen in the cytoplasm under electron microscope, which could be distinguished from Wilms tumor. (3) Renal teratoma: It can occur at all ages and has characteristic components of three embryonic layers, including leaf components and glomerular structure. It is sometimes difficult to distinguish from Wilms tumor, but through careful search. There is no consistent original renal germ composition. There was also a lack of embryonic tubular or glomerular structure, and the expression of WT1 was negative by immunohistochemistry [121].

Treatment

Treatment is often combined with surgery, radiotherapy, and chemotherapy. Comprehensive intervention can reduce blood pressure, but after recurrence of the tumor, blood pressure will rise again. It is reported that the cure rate can reach more than 80% after comprehensive treatment. Therefore, for advanced cases that cannot be operated or recur after operation, radiotherapy and chemotherapy can be chosen. After tumor control remission, hypertension can also be improved accordingly.

5.7.6 Renal Cell Carcinoma

Renal cell carcinoma (RCC) is a malignant tumor of kidney originated from proximal tubule epithelial cells. It is a common and frequent disease in the urinary system. It can occur in any part of the kidney and is most common in the kidney. However, the cause of the disease was unknown. Most of the patients are from 50 to 70 years old and the ratio of male and female was about 2–1. The main clinical manifestations were asymptomatic or hematuria, pain in the waist and abdominal mass. Tumor-associated hypertension can be caused by tumor compression or embedding of renal artery and its branches, as well as tumor internal arteriovenous fistula.

5.7.6.1 Epidemiology

Renal cell carcinoma accounts for about 3.8% of all new cancers [122], the second malignant tumor in the genitourinary system, after bladder cancer. In recent years, the incidence of renal cell carcinoma is increasing year by year, and it is the deadliest tumor in the urinary system. Epidemiological data show that more than 40% of patients with renal cell carcinoma die of the disease. Renal cell carcinoma is rare in children, accounting for only 2.3% of all tumors in children. The average age of onset in children is 8–9 years old. The incidence of renal cell carcinoma is similar to that of men and women. Although Wilms tumors are more common in children, they are as common as renal cell carcinoma at the age of 10 and 20.

5.7.6.2 Etiology

Tobacco and obesity are currently identified as risk factors for renal cell carcinoma. The family history of renal cell carcinoma is also a risk factor. The relative risk of first-degree and second-degree relatives of patients with renal cell carcinoma is 2.9, and the relative risk of patients with hypertension increased 1.4–2 times.

With the significant progress in molecular genetics of renal cell carcinoma, renal cell carcinoma family syndrome and tumor suppressor genes and oncogenes of sporadic and familial renal cell carcinoma have been identified. In epidemiological studies, more than 70% of renal cell carcinoma is clear cell carcinoma, the most common family type of which is von Hippel-Lindau syndrome, referred to as VHL syndrome [123]. This is a relatively rare autosomal dominant genetic disease with

an incidence of 1/36,000. The main manifestations included renal cell carcinoma, pheochromocytoma, central nervous system and retinal hemangioblastoma, endolymphatic sac tumor, renal or pancreatic cyst or tumor, epididymal cystadenoma and other rare diseases [124–126]. Like most tumor suppressor genes, renal cell carcinoma is caused by the inactivation of both alleles of the VHL gene, which is consistent with the theory of "second strike." Other potential genetic components affecting sporadic renal clear cell carcinoma include p53 tumor suppressor gene, PTEN/Akt pathway, and additional loci on the short arm of chromosome 3.

5.7.6.3 Pathology

Renal cell carcinoma is the most common malignant tumor of the kidney, accounting for 90% of all renal malignant tumors. There are many types of pathology; the most common clear cell renal cell carcinoma is followed by papillary renal cell carcinoma, chromophobe renal cell carcinoma, renal collecting carcinoma, renal medullary carcinoma, sarcomatoid carcinoma, and renal cell carcinoma with nephroblastoma. Some of them are familial, accompanied by different clinical syndromes [127]. Most of the tumors are globular in the renal cortex, often protruding the surface of the kidney. The boundary of tumor is clear and it is often a false capsule. The size of the tumor is between 3 and 15 cm, but there are also cases where the tumor is as small as a few millimeters and as large as occupying the entire abdominal cavity. Clear cell carcinoma can be solid, acinar structure, surrounded by thin-walled blood vessels and connective tissue. Eosinophilic fluid can be seen in the central region, forming cysts of different sizes, and occasionally seeing clear powdery structure and pseudopapillary structure. The cytoplasm of tumor cells is rich, transparent, and clear, and sometimes the cytoplasm of tumor cells is eosinophilic around necrosis. The nucleus is round or oval, and the nuclear chromatin is uniform and fine granular.

5.7.6.4 Clinical Manifestation

Renal cell carcinoma cannot have any symptoms in the early stage, more in the physical examination found that some patients only appear general symptoms. For example, fatigue, dyspepsia, low fever, accelerated erythrocyte sedimentation rate, high blood pressure, hypoglycemia, etc. When renal cell carcinoma is further developed, hematuria (70%), lumbar pain (50%), and mass (20–30%) will occur. Known as the "triple sign of renal cell carcinoma," the literature reported that the proportion of the three at the same time is very small, accounting for only 9%. Other systemic symptoms such as emaciation, fever, anemia and so on, of which fever is the most common.

Characteristics of hypertension: about 30% of patients with renal cell carcinoma can develop renal cell carcinoma-associated hypertension, the main reasons of which are tumor direct secretion of excessive renin, tumor compression, or embedding of renal artery and its branches resulting in renal artery stenosis, as well as tumor arteriovenous fistula and so on. The rare causes of hypertension include polycythemia, hypercalcemia, ureteral obstruction, and intracranial hypertension caused by brain metastasis. The characteristics of hypertension are high diastolic blood

pressure, small pulse pressure difference, and small fluctuation of blood pressure. After nephrectomy, the blood pressure of one-third patients returned to normal, but the blood pressure could rise again when there is metastasis of renal cell carcinoma. The most common metastases of renal cell carcinoma were lung (75%), soft tissue (36%), bone (20%), liver (18%), skin (18%), and intracranial (8%). In addition, renal cell carcinoma could secrete ectopic hormones and hormone-like substances, and patients could develop a variety of VHL syndrome.

5.7.6.5 Diagnosis

Regular physical examination are needed when no-cause fever, rapid ESR, anemia should be thought of the possibility of renal cancer. Abdominal (including both kidneys) B-ultrasound, CT, MRI, and intravenous urography can be used.

1. Imaging diagnosis: imaging examination is an important method for the detection and diagnosis of renal cell carcinoma. The examination methods include B-ultrasound, CT, MRI, PET, and intravenous renal angiography, but the diagnostic value of PET in renal cell carcinoma is not clear, the first choice is still CT and B-ultrasound.
2. Imaging findings: most of the tumors showed expansive growth, nodular, lumpy or eroded, destroyed the whole renal structure in the renal parenchyma. The boundary between tumors and renal parenchyma is blurred or unclear. It also has a false capsule and invade the perirenal fat space, renal pelvis. The tumors showed low, equal, or mixed echo and uneven echo on B-ultrasound images. Most of them showed low density or equal density on CT plain scan images and showed low density after enhancement, with obvious enhancement, a few mild or no enhancement. Most of them showed low density or isodensity on MRI plain scan images, and most of them showed low density or isodensity after enhancement. MRI showed isointense or hypointensity on T1W1 images, heterogeneous hyperintensity on T2W1, uneven enhancement of tumors after enhancement, and cystic mass in a few cases, but the cyst wall of the mass was thick and irregular [128]. When the tumor is accompanied by tumor thrombus, there is a filling defect in the renal vein or IVC cavity. Renal cell carcinoma can appear renal hilar and retroperitoneal lymph node metastasis, which can be fused into clusters, wrapped around, compression of renal hilar blood vessels.

The guidelines of the American Urological Association clearly define the indications of renal biopsy, as follows: when renal lesions are suspected to be hematopoietic tumors, or metastatic tumors, or renal tumors with inflammation or necrosis. Renal biopsy was considered [129].

5.7.6.6 Treatment

Renal cell carcinoma is insensitive to chemotherapy and radiotherapy, and surgery is the main treatment for renal cell carcinoma. Surgery can be divided into radical surgery and nephron sparing surgery, as well as recent minimally invasive surgery. Although immunotherapy has a bright future, the overall response rate is still low.

For familial renal cell carcinoma, multiple lesions, severe CKD, and some uniform, well-encapsulated renal tumors, tumor enucleation may be considered to maximize the preservation of renal units; in addition, for advanced age or with significant complications, For patients who are not suitable for traditional surgical treatment and patients with local recurrence after nephron sparing surgery, ablation can also be considered as an alternative treatment for patients with stage cT1a. Both radiofrequency ablation and cryoablation can be used as an option for ablation; some studies have found that small renal tumors grow slowly. Therefore, for solid, imaging examination of enhanced, clear boundary and uniform texture of small renal tumors (diameter less than 3 cm), if the patient is old or the risk of surgery is high, wait for observation to make a safe management strategy.

Treatment of advanced renal cell carcinoma: targeting therapy with tyrosine kinase inhibitor (TKIS) and anti-VEGF antibody has been widely used in routine and second-line therapy. So far, the United States FDA has approved seven drugs for advanced renal cancer: sunitinib, sorafenib, pazopanib, axitinib, and temsirolimus. Treatment of advanced renal cancer, such as everolimus and bevacumab combined with interferon, offers a new treatment option [112].

Renal cell carcinoma is a kind of tumor with strong immunogenicity and is effective in immunotherapy. So vaccine therapy strategy is also a key research direction in biological therapy of renal cell carcinoma in recent years [130].

5.7.6.7 Prognosis

The prognosis of patients with early stage of disease and good differentiation of cells after radical operation is better. In patients with hypertension, blood pressure may decrease after nephrectomy, but if recurrence and metastasis occur, blood pressure may rise again.

5.7.7 Metastatic Tumors

Metastatic tumor is the most common malignant tumor of the kidney, far more than the primary renal tumor. Autopsies showed that 12% of those who died of tumors had renal metastasis, making the kidney one of the most frequently metastatic organs.

The reason is due to the kidney high-speed blood flow and rich blood supply. Almost all renal metastases are caused by blood metastasis. The most common sources of renal metastases include lung, breast, and gastrointestinal cancers, malignant melanoma, and hematological malignancies.

Typical renal metastatic tumors consist of clinically asymptomatic multiple nodules, which in a few cases can also cause hematuria or abdominal pain. CT is the main diagnostic method of renal metastatic tumor. Its typical manifestation is isodensity mass and only moderate enhancement (5–30 hu) is found after injection of contrast medium. Arteriography is usually characterized by low blood supply.

The treatment is mainly to control the primary disease, which may consider according to the clinical condition to carry on the whole body treatment or the palliative treatment, if necessary to carry on the nephrectomy.

Metastatic renal tumors, like other renal tumor lesions, can also lead to hypertension. The treatment is not specific, mainly by conventional antihypertensive drugs.

5.8 Dialytic Hypertension

Wen Jiang

The blood volume of the dialysis patient has significant fluctuations before, during, and after dialysis, resulting in corresponding fluctuations in the measured blood pressure. Dialysis hypertension refers to a mean arterial pressure (MAP) of more than 106 mmHg (1 mmHg = 0.133 kPa) before dialysis, that is, a systolic blood pressure greater than 140 mmHg and a diastolic blood pressure greater than 90 mmHg. Intradialytic hypertension is a special type of dialysis hypertension, It means that the average arterial pressure of dialysis patients during dialysis is increased before dialysis, and this phenomenon cannot be effectively improved with the increase of hemodialysis ultrafiltration. For patients with maintenance hemodialysis (MHD), hypertension, especially dialysis, is one of the common complications and is an important cause of cardiovascular complications and death such as heart failure.

5.8.1 Epidemiology

Different studies have different definitions of dialysis hypertension. The more common one is the concept proposed by Amerling et al., that is, MAP rises more than 15 mmHg before dialysis. At present, it is still unclear when the blood pressure (pre-dialysis, dialysis, and dialysis) can better reflect the actual situation of the patient. Agarwal et al.'s study proves that the blood pressure is measured before, during, and after dialysis. The number can improve the sensitivity and specificity of patients diagnosed with dialysis hypertension.

The currently widely accepted method for measuring hypertension in hemodialysis patients is to be able to include 44 h of ambulatory blood pressure at all time points during the dialysis interval, which is also based on the ability to more accurately predict the occurrence of cardiovascular events, while the blood pressure values routinely measured in the dialysis room. The predictive value of cardiovascular events and risk of death varies. Nowadays, the value of home blood pressure monitoring in the diagnosis and management of patients with hypertension is generally recognized, and blood pressure research in dialysis hypertension has gradually increased and is receiving more attention [131, 132].

Agarwal et al. showed that 86% of patients with MHD had hypertension with a control rate of 30%, which was worse than peritoneal dialysis hypertension. The Chinese People's Liberation Army Special Committee for Kidney Disease investigated 2001 hemodialysis patients in 44 hospitals in 28 provinces, municipalities, and autonomous regions in China. The results showed that the incidence of hypertension was 81.52% and the control rate was 58.98%. Hypertension increases cardiovascular events and death in patients with end-stage renal disease, but the impact on dialysis patients is currently inconclusive. Large-scale observational studies have shown that hypertension and hypotension in dialysis patients are related factors for early death in dialysis patients, presenting the so-called U-shaped relationship, Patients with lower blood pressure were at greater risk of adverse outcomes than those with higher blood pressure. In the study of dialysis patients, the effect of lowering blood pressure on prognosis has not been evaluated [133–137]. In summary, observational data on the relationship between blood pressure and the prognosis of dialysis patients cannot be used to infer dialysis patients' blood pressure goals.

5.8.2 Pathogenesis and Pathophysiology

1. Increased capacity load

   Excessive extracellular fluid volume is the most important cause of hypertension in dialysis patients with end-stage renal failure. Water, sodium retention, increased extracellular fluid volume, vascular tension cannot adjust the increased blood volume, cardiac output and total peripheral vascular resistance, etc., can lead to dialysis hypertension. The study found that patients who are prone to high blood pressure during dialysis often have high blood pressure before and during dialysis, and by long-term dialysis ultrafiltration, the blood pressure of these patients can be reduced to the normal range, and the incidence of hypertension during dialysis. It also dropped significantly. Increased extracellular fluid volume causes vascular reactive contraction to prevent high perfusion of organs, but vasoactive contraction increases blood pressure, while vascular reactive contraction increases vascular tone and shear force, altering endothelin and platelet-derived endothelial cells. The expression of genes such as growth factors and fibroblast growth factors, and the above-mentioned factors secreted by endothelial cells increase, leading to changes in vascular structure and decreased compliance, which further increase blood pressure. The increase of sodium in the body also causes the adrenal gland to secrete endogenous digitalis. The substance, which induces cardiomyocyte hypertrophy, activates the central RAS system and increases blood pressure in MHD patients. Increased volumetric load in patients with MHD also leads to increased sympathetic nervous system activation and release of vasoactive substances such as epinephrine, norepinephrine, and vasoactive peptide Y. Studies by Rajiv Agarwal et al. have confirmed hypervolemia, increased blood pressure, increased mortality in hemodialysis patients, and are independent of traditional or unconventional cardiovascular risk factors.

Therefore, for patients with dialysis, it is our therapeutic goal to control their blood pressure within the normal range.

2. The renin-angiotensin system (RAS) is active

   Although the renal parenchyma has been severely damaged in end-stage renal failure, the RAS system is still be active. Dialysis ultrafiltration can cause a decrease in renal arterial perfusion pressure, stimulate the increase of renin secretion in the para-balloon cells, increase the activity of the RAS system, increase peripheral vascular resistance, and increase vasoconstriction and blood pressure. Therefore, renin-angiotensin blockers provide many benefits for patients with chronic kidney disease. There are significant individual differences in the effects of ultrafiltration on the RAS system. Patients with higher basal renin levels are more likely to be activated, tubulointerstitial. Patients with nephritis and bilateral nephrectomy rarely develop high blood pressure during dialysis.

3. Vascular endothelial dysfunction

   Endothelial dysfunction is also involved in the development of hypertension in patients with MHD. Endothelial cells produce and release vasoactive substances such as nitric oxide (NO) and endothelin (ET). Among them, NO has the function of dilating blood vessels, which is mainly synthesized by L-arginine in the body. Asymmetric dimethylarginine (ADMA) can competitively inhibit the activity of nitric oxide synthase (NOS) and reduce the synthesis of NO. ADMA is mainly cleared by the kidneys in the body. Hemodialysis cannot completely remove ADMA, which causes it to accumulate in MHD patients and inhibit the activity of NOS, reduce the synthesis and release of NO, and restrict vasodilation and cause hypertension. ET has a vasoconstrictor effect and is also involved in the development of hypertension. Landry and other studies have shown that there is no statistically significant difference in plasma catecholamine, renin, and cardiac output between patients prone to hypertension during dialysis, but peripheral vascular resistance after dialysis is significantly increased, plasma endothelin-1 (ET-1). The level increased significantly and the level of NO decreased. Meyer et al.'s study found that hemodialysis can induce endovascular hemolysis and endothelial cell dysfunction in patients with end-stage renal disease, and called it "hemolysis-related endothelial cell dysfunction."

4. Increased sympathetic activity

   Sudden cardiac death in patients with chronic kidney disease (CKD) is mostly attributed to ventricular arrhythmias. The reason is that sympathetic activity is increased in patients with CKD. In patients with renal failure, autonomic neuropathy is mainly characterized by impaired baroreflex receptors, and increased fluid volume load leads to increased sympathetic nervous system activation and release of vasoactive substances such as adrenaline, norepinephrine, and vasoactive peptide Y. Convers et al. found that the release of sympathetic impulses in maintenance hemodialysis patients was 2.5 times higher than that of normal subjects. The norepinephrine secretion in hemodialysis patients with bilateral kidneys was similar to that of normal people, and blood pressure was also significantly decreased. The reduction of plasma volume and the clearance of

serum sodium during dialysis treatment can be transmitted to the hypothalamus and paraventricular nucleus of the central nervous system through pressure reflex receptors and chemical reflex receptors, and the sympathetic nervous system is excited to cause hypertension.

In fact, increased levels of plasma norepinephrine have been a precursor to predicting the incidence of cardiovascular events. Recent studies have confirmed that patients with chronic renal failure and coronary artery disease have an increased risk of sudden cardiac death and are independent of a decrease in glomerular filtration rate. Activation of the sympathetic nervous system has adverse consequences for patients with chronic renal failure.

5. The role of erythropoietin

   Erythropoietin (EPO) is widely used as a drug for the treatment of renal anemia in MHD patients. A large number of studies have confirmed that EPO treatment may be associated with new hypertension or exacerbation of pre-existing hypertension, which is contained in endothelial cells. Nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) promote erythropoietin-induced hypertension. To investigate the mechanism by which erythropoietin induces hypertension, Ioka T et al. collected 56 endothelial progenitor cells from hemodialysis patients (which reflect the functional status of the vascular endothelium). The EPO receptor (EPOR) mRNA gene was found in the cells of these patients, and the signal peptide at the top of EPO receptor, which can be used as dominant negative regulation, was removed, resulting in hypertension. This result is positively correlated with epo-induced increase in blood pressure. Therefore, we can deduce that the detection (evaluation) of EPOR mRNA subtypes in endothelial progenitor cells can predict EPO-induced hypertension. The incidence of elevated blood pressure in uremic patients during EPO treatment was 23–30%.The mechanism by which EPO causes blood pressure to rise is not very clear. It has been thought to be related to the increase in hematocrit, increase in blood volume, increase in blood viscosity, and elimination of anoxic effects of hypoxemia after EPO. Recent studies have shown that genetic recombination erythropoietin (rHuEPO) can affect the level of vasoactive substances in patients with MHD, resulting in decreased serum NO levels, elevated levels of ET-1 and angiotensin II, hypertension caused by rHuEPO and the above substances. The change in concentration is relevant.

6. Effect of dialysate composition on serum electrolytes

   Sodium ion is the main factor determining the osmotic pressure of dialysis liquid crystal. Increasing the sodium concentration of dialysate can maintain the hemodynamic stability of dialysis patients and improve the overall tolerance during dialysis, but also bring thirst, weight gain, water and sodium retention, excessive volume overload, and elevated plasma osmotic pressure, and increase dialysis-related hypertension. In dialysis patients, blood pressure is increased due to an increase in ionic calcium concentration during dialysis, which may result in an increase in myocardial contractility, cardiac output, and peripheral vascular resistance.

7. Dialysis on the removal of antihypertensive drugs
   Many antihypertensive drugs have a certain degree of clearance during dialysis, which is also a cause of high blood pressure during dialysis.

5.8.3 Diagnosis

Dialysis hypertension can be diagnosed based on home self-test blood pressure or ambulatory blood pressure [138]:

Hemodialysis patients: The home self-test blood pressure standard is measured in the morning and evening on non-dialysis days, at least 6 days per week, the average blood pressure measured for two consecutive weeks is ≥135/85 mmHg; the dynamic blood pressure standard is: no more during hemodialysis 24-h monitoring or, if feasible, extended to 44 h, mean blood pressure ≥130/80 mmHg.

Peritoneal dialysis patients: The family self-test blood pressure is measured in the morning and evening, and the average blood pressure is continuously measured for 7 days ≥135/85 mmHg; the dynamic blood pressure standard is, the average blood pressure of blood pressure monitoring over 24 h is ≥130/80 mmHg.

If the dialysis patient can neither perform ambulatory blood pressure measurement nor home blood pressure measurement, the diagnosis can be made based on the blood pressure measurement of the office within 1 day without dialysis during the week: the blood pressure is measured three times in a sitting position, each interval of 1–2 min. High blood pressure can be diagnosed for hemodialysis average office blood pressure ≥140/90 mmHg;

For patients with peritoneal dialysis, hypertension can be diagnosed in the laboratory with BP≥140/90 mmHg.

5.8.4 Treatment

The 2005 K/DOQI (Guidelines for Quality of Life in American Patients with Kidney Diseases) guidelines suggest that blood pressure control targets for dialysis patients are blood pressure<140/90 mmHg before dialysis and blood pressure<130/80 mmHg [139] after dialysis, more observational. The study suggests that hemodialysis patients have a systolic blood pressure of 130–160 mmHg before dialysis, and the patient has the lowest risk of death [140]. In 2015, the International Peritoneal Dialysis Association for Adult Peritoneal Dialysis Patients recommended cardiovascular and metabolic guidelines for peritoneal dialysis patients with blood pressure control below 140/90 mmHg [141].

First, hemodialysis patients [138, 139, 142]:

General treatment

1. Limit sodium: The daily salt intake of dialysis patients with hypertension should be controlled between 3 and 5 g.
2. Water restriction: For patients with oliguria or even no urine, the intake of liquid should be strictly limited.

3. Lifestyle changes: including quitting smoking, exercising properly, maintaining normal weight, etc.
4. Adjustment of dialysis prescription: excessive weight gain during dialysis interval, large amount of ultrafiltration is difficult to reach dry weight, and dialysis hypertension is prone to occur. For this type of patients, the number of dialysis should be increased, the dialysis time should be extended, and the ultrafiltration to the ideal dry weight should be gradually reduced. The sodium ion concentration in the dialysate can be gradually lowered to improve the hypertension, effectively avoiding excessive capacity overload, reducing peripheral sympathetic nerve activity, and reducing super filtration rate, which reduces the occurrence of hypertension during dialysis and the application of antihypertensive drugs.
5. Develop an individualized antihypertensive treatment plan:
   (a) The main capacity load is mainly to control dry weight and strive to achieve dry weight.
   (b) In combination with cardiac insufficiency: α/β blockers are discontinued on the basis of controlled dry weight, patients with acute heart failure stop β blockers, and give cardiac drugs (using digitalis drugs). Attention should be paid to the treatment of hypokalemia during dialysis. Antihypertensive drugs are based on ACEI or ARB drugs.
   (c) Patients with increased heart rate but no heart failure usually have increased sympathetic excitability. On the basis of controlling dry weight, ACEI/ARB and/or α blocker, β blocker or α/β based on receptor blockers, CCB is used when the efficacy is poor.

   In short, the choice of antihypertensive drugs needs to take into account the patient's clinical situation and the individual characteristics of the drug.

Second, peritoneal dialysis patients [138, 141, 142]:

1. Hypertension in peritoneal dialysis patients is also caused by excessive volume. Therefore, as with hemodialysis patients, the patient's volume status should be evaluated and adjusted first. In the absence of mechanical complications and peritoneal ultrafiltration failure, limit salt and water intake; for patients with residual renal function, reduce the volume load by using diuretics.
2. In the formulation of dialysate, increasing the concentration of glucose dialysate can increase ultrafiltration, but at the same time accelerate the loss of peritoneal ultrafiltration capacity. Using icodextrin can increase the amount of ultrafiltration during long-term abdomen. Conducive to the control of blood pressure and volume, it is recommended to use icodextrin dialysate for more than 8 h. However, care should be taken to avoid loss of capacity and to accelerate the loss of residual kidney.
3. Patients with adequate peritoneal dialysis still have poor blood pressure control after reaching the target dry weight, or it is difficult to achieve dry weight, and it is necessary to treat antihypertensive drugs. Compared with hemodialysis patients, the hemodynamics of peritoneal dialysis patients is relatively stable, and the blood pressure fluctuations before and after dialysis are relatively small. Currently, the commonly used antihypertensive drugs in clinical practice can be used for peritoneal dialysis patients. Among them, ACEI or ARB antihyperten-

sive drugs not only have the effects of reversing left ventricular hypertrophy, improving congestive heart failure, reducing sympathetic excitability and oxidative stress, improving endothelial function, but also delaying the loss of residual kidney function and improving prognosis, so it can be used as the first choice.

5.9 Kidney Transplantation and Hypertension

Wen Jiang

Kidney transplantation has now become the treatment of choice for patients with ESRD. Hypertension after renal transplantation is a common complication of renal transplant recipients. The mortality rate of cardiovascular disease associated with hypertension after renal transplantation is 41%. It has become a transplant factor and other transplanted kidney loss and patient death and function. The main cause of kidney transplant death, hypertension is also an independent risk factor for renal failure. Therefore, prevention and treatment of hypertension after renal transplantation is an important measure to improve the long-term survival rate of transplanted kidney and reduce the mortality of functional kidney.

5.9.1 Etiology and Epidemiology

Postoperative renal hypertension is mostly secondary renal hypertension. There are several causes: (1) medical system reasons, including: poor control of hypertension before transplantation; perioperative water and salt metabolism disorder; rejection; transplantation, delayed recovery of renal function; immunosuppressive agents, hormones; (2) early vascular complications after transplantation, including the formation of renal artery or venous thrombosis, late complications mainly include renal artery stenosis, arteriovenous fistula, rare pseudoaneurysm, surgical and vascular factors, including arterial anastomotic stenosis, intubation in the kidney operation, etc., inadvertently damage the intima of the blood vessels, the presence of primary disease or vascular disease in the donor kidney. (3) Recipients' genetic characteristics, body mass index, with diabetes, metabolic syndrome, or hyperlipidemia can cause high blood pressure, high blood pressure, obstructive sleep apnea, and the presence of endocrine tumors (e.g., pheochromocytoma, adrenal adenoma), etc. [143].

Among the above factors, renal artery stenosis is an important cause of hypertension and allogeneic renal transplantation dysfunction. Doppler ultrasound imaging has become the most important imaging mode for postoperative follow-up. Etemadi J Studies by others have shown that the interaction of calcium phosphate deposits, LDL cholesterol, uric acid, and other substances may be a potential risk factor for renal artery stenosis and should be used as an indicator for early detection and prevention. Approximately 72% of patients with chronic rejection are associated with hypertension. Recent studies suggest that, in addition to donor and recipient factors, hypertension after renal transplantation is more associated with immunosuppressive

therapy. Among immunosuppressive agents, hormones, cyclosporine (CsA), and prograf (tacrolimus, FK506) are important predisposing factors for hypertension. Hypertension and renal anemia after kidney transplantation are not only risk factors for renal failure, but also cause left ventricular hypertrophy to become a risk factor for cardiovascular mortality.

The incidence of hypertension after adult kidney transplantation can be as high as 80%, and the prevalence of hypertension after renal transplantation in children is about 58–89%, and more than half of the hypertension requires medical intervention.

5.9.2 Immunostatic Inhibitors Lead to the Pathogenesis of Hypertension After Kidney Transplantation

Corticosteroids cause a 15% incidence of hypertension and are dose related. Hypertension does not occur at doses; CsA is 90%, and FK506-treated patients have a lower incidence of hypertension than CsA. The mechanism by which hormones cause high blood pressure is still unclear. It may be that hormones cause water and sodium retention, increased cardiac output, and increased renal vascular resistance; hormones cause increased sensitivity of endothelin-1 and angiotensin to blood pressure; hormones cause vascular smooth muscle. The density of glucocortic receptors is increased; hormones reduce the production of prostaglandins. CsA can enhance the action of angiotensin II, endothelin, and other vasoconstrictors, enhance the sensitivity to sympathetic stimulation, lead to sodium retention, and thus cause hypertension. Long-term use of CsA can cause damage to systemic endothelial cells, resulting in decreased arteriosclerosis and vascular resistance. CsA can increase plasma renin activity, prevent adrenal spheroid cells from secreting aldosterone when stimulated by angiotensin II, and lower plasma, aldosterone levels; large doses of CsA can also increase the sensitivity of the blood vessels to norepinephrine, causing abnormal function of the renin-angiotensin-aldosterone system (RAS), leaving the body in a state of high renin and low aldosterone. Hypertension caused by CsA is also associated with overexpression of transforming growth factor-β1 (TGF-β1).

CsA and FK506 are the basic immunosuppressive drugs in renal transplant patients, and their mechanism of action plays an important role in immunomodulating by inhibiting calcineurin and blocking the expression of T cell activation genes. Calcineurin is mainly distributed in the kidney, vascular smooth muscle, and nervous system, while they are the target organs or tissues of hypertension. Inhibition of calcineurin in these tissues can lead to sodium retention, vasoconstriction, sympathetic excitation, and activation of the renin-angiotensin system, causing hypertension. In addition, FK506 has a hormone-like effect.

5.9.3 Diagnosis

There is a dispute between the examination method and the diagnostic criteria for the diagnosis of hypertension after renal transplantation. Currently used

examination methods include repeated single blood pressure measurements (including office blood pressure, home self-test blood pressure) and ambulatory blood pressure monitoring (ABPM). Single blood pressure measurement is economical and simple, easy to apply, and popularize, especially the correlation between home self-test blood pressure and ambulatory blood pressure, and dynamic blood pressure monitoring for malignant and atypical, such as refractory hypertension, critical hypertension, and occasional hypertension. The diagnosis of hypertension is more meaningful [144–146]. The incidence of white sputum hypertension in renal transplant patients is between 12 and 32%. Ambulatory blood pressure monitoring can more accurately reflect the patient's blood pressure changes. Another advantage of ambulatory blood pressure monitoring is the ability to screen for abnormal blood pressure fluctuations. There is no consensus on the diagnostic criteria for hypertension after renal transplantation and the target level of blood pressure control, but it is generally believed that antihypertensive therapy should start at systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg for diabetes or transplantation. Antihypertensive therapy in patients with chronic renal disease should begin at a systolic blood pressure of 130 mmHg and/or a diastolic blood pressure of 80 mmHg or lower. The American College of Nephrology recommends a standard blood pressure of 130/80 mmHg [147–149]in renal transplant patients.

5.9.4 Treatment

Hypertension after renal transplantation not only increases cardiovascular complications but also reduces survival after transplantation. Good blood pressure control and immunological surveillance are equally important for patients with kidney transplantation. In order to protect kidney function for a long time, blood pressure must be controlled to an ideal target value. Therefore, once diagnosed as hypertension after renal transplantation, it should be treated promptly. The KDIGO guidelines recommend that kidney transplant recipients control blood pressure ≤130/80 mmHg. Studies from high blood pressure in the general population confirm the benefits of lowering blood pressure for high-risk cardiovascular populations. Controlling blood pressure in CKD population can reduce proteinuria and delay renal function progression [1, 7].

1. First adjust lifestyle, including low-salt diet, avoid weight gain, quit smoking and proper exercise, and maintain mental balance.
2. Antihypertensive drug therapy: Since renal transplant recipients have multiple risk factors for developing hypertension, drug treatment can start at the same time as lifestyle adjustment. Most kidney transplant recipients have only one functional kidney. The use of antihypertensive drugs requires more attention to smooth blood pressure, avoiding insufficient blood volume, and closely monitoring the function of transplanted kidney.
   (a) CCB antihypertensive drugs have good tolerance and antihypertensive effect, which can be used as the first choice.

(b) Diuretic antihypertensive drugs can reduce sodium and water retention, reduce cardiac load, and can be the first choice for patients who need to reduce the capacity overload.
(c) β-blockers can reduce sympathetic excitation, inhibit renin activity, etc., in some patients, as appropriate.
(d) ACEI or ARB antihypertensive drugs are usually preferred in general patients, especially those with proteinuria, diabetes, and chronic kidney disease, but they may cause elevated serum creatinine, hyperkalemia, and glomerular filtration rate. Reducing adverse reactions may interfere with the judgment of acute rejection after renal transplantation, so it is recommended to delay the use of renal function after 4–6 months. Before use, the renal artery stenosis should be excluded, and the small dose should be started. The function of the transplanted kidney should be gradually increased and the dose should be gradually increased. If the creatinine is more than 15% higher than the basal value, it is recommended to suspend use.
(e) Others such as alpha blockers and central antihypertensive drugs should be selected according to the specific circumstances of patients.

3. Therefore, different blood pressure reduction strategies can be formulated according to the characteristics of different periods after kidney transplantation:
(a) Early postoperative renal transplantation (within 3 weeks): At this time, the recipient's hypertension is mainly due to excessive volume overload, use of calcineurin inhibitor (CNI) and hormones, etc., at this time, the blood pressure control target can be appropriately relaxed (<150/90 mmHg), control salt and water intake, diuretics, CCB, β-receptor blockers, etc. can be used. ACEI and ARB may cause adverse reactions such as renal ischemia and hyperkalemia, so they should be used with caution. Transplanted kidney recipients with refractory hypertension should be treated with a view of transplanted renal artery stenosis.
(b) Middle stage after renal transplantation (3 weeks and 3 months): At this time, the patient's condition tends to be stable, the target blood pressure is <140/90 mmHg, CCB can still be used as preferred, and the urazine can be selected for the recipient whose capacity load is still too heavy. Diuretics, recipients of proteinuria may be cautious to use ACEI or ARB depending on the patient's response.
(c) Long-term after kidney transplantation (after 3 months): At this time, the function of transplanted kidney has been stabilized. The focus of blood pressure reduction is to reduce cardiovascular events and protect the function of transplanted kidney. The target of blood pressure control can be lower (<130/80 mmHg). The use of CNI drugs can be reduced under close observation, or changed to other types of immunosuppressive agents. Antihypertensive drugs are preferred for relieving ventricular remodeling and reversing the increase in hemoglobin and the reduction of proteinuria in ACEI or ARB antihypertensive drugs.

(d) Pay attention to the treatment of comorbidities, such as hyperlipidemia, hyperuricemia, obesity, and diabetes. If there is refractory hypertension that is not explained by other reasons, you need to pay attention to screening for secondary hypertension, especially primary aldosteronism, obstructive sleep apnea syndrome, renal artery stenosis, etc. After the diagnosis, the corresponding treatment measures are taken: primary aldosteronism can be based on whether single or bilateral surgery or drug treatment; in the presence of obstructive sleep apnea syndrome, ventilator therapy is started on the basis of active weight control; renal artery stenosis is selected according to the condition of interventional surgery, open surgery to relieve stenosis.

In conclusion, hypertension after renal transplantation is one of the important complications after transplantation, which has a very negative impact on the long-term survival of human/kidney after renal transplantation. Standardized monitoring, timely diagnosis and treatment of postoperative hypertension are of great significance for improving the long-term efficacy of renal transplantation. Hypertension after renal transplantation should be diagnosed in time. On the premise of maintaining sufficient immunosuppressive therapy, immunosuppressive agents and combined use of antihypertensive drugs should be adjusted to provide protection for renal transplantation and cardiovascular system, and to improve the long-term efficacy of renal transplantation.

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Renovascular Hypertension

6

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6.1 General Instructions

Mengru Wang

Renovascular hypertension (RVH) refers to secondary hypertension caused by renal parenchymal ischemia due to stenosis or complete occlusion of unilateral or bilateral renal artery entrances, trunks or their main branches. Renal artery stenosis is a kind of renal vascular disease caused by a variety of causes. It is the anatomical basis of renal vascular hypertension. Generally, renal artery stenosis has hemodynamic significance only when it is more than 50%. Generally, renal artery stenosis more than 50% has hemodynamic significance, and more than 70% can cause renal vascular hypertension. Common diseases include atherosclerotic renal artery stenosis, Takayasu arteritis, and fibromuscular dysplasia. Next were congenital renal artery dysplasia, vasculitis, arterial embolism, renal aneurysm, pheochromocytoma, metastatic aneurysm, renal artery constriction, etc.

6.1.1 Epidemiology

According to the characteristics of different populations, the prevalence of RVH varies from 1% to more than 50%. Overseas reports show that the incidence of renal vascular hypertension in hypertension population is 0.5–5%. Although the proportion of all hypertensive patients is small, it accounts for a high proportion of refractory hypertension. According to the newly published American hypertension guidelines, renal vascular disease accounts for 5–34% of the causes of secondary

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hypertension, which is second only to obstructive sleep apnea. The prevalence rate of hypertension in China is about 1–3%. Atherosclerotic renal artery stenosis (ARAS) is the leading cause of renal artery stenosis in Western countries, accounting for about 90% of all cases of renal artery stenosis [1]. In the past, the incidence of Takayasu arteritis was the highest in China and Asian countries. However, as China enters the aging society, the incidence of atherosclerotic vascular diseases is increasing year by year. At present, atherosclerosis is the most common cause of renal artery stenosis in China, accounting for about 82%, followed by Takayasu arteritis (about 12%), fibromuscular dysplasia (about 5%), and other causes accounting for 1% [1, 2].

6.1.2 Pathology

Pathological changes of renal vascular hypertension include atherosclerosis and non-atherosclerosis. The lesions of different diseases mainly occur in different parts, as shown in Table 6.1, thus forming its specific imaging manifestations. Vascular lesions are common pathological changes of renal vascular hypertension. Thickening of vascular wall and stenosis of lumen lead to renal ischemia, renal infarction, hypertension, and renal failure.

6.1.3 Clinical Characteristics

The patient's medical history and clinical manifestations often indicate the cause and diagnosis of renal vascular hypertension.

6.1.3.1 Medical History

1. Characteristics of hypertension: age, sex, and degree of hypertension. It is generally believed that most patients have significant persistent hypertension. About 60% of the patients had systolic blood pressure higher than 200 mmHg and/or diastolic blood pressure higher than 120 mmHg. It is characterized by a large

Table 6.1 Pathological features and lesion sites of common renal vascular hypertension

Diseases	Pathological characteristics and lesion location
Renal atherosclerosis	Atherosclerotic, renal artery opening or proximal 1/3
Takayasu arteritis	Granulomatous inflammation, aorta and its main branches
Fibromuscular dysplasia of renal artery	Fibromuscular dysplasia, middle and distal renal artery trunk
Congenital anomaly of renal artery	Dysplasia, renal artery trunk or branch
Vasculitis	Arteriovenous and phlebitis of different sizes, renal artery
Renal artery thrombosis	Thrombosis, renal artery trunk or segmental branch

increase in diastolic blood pressure. Generally speaking, young people with newly developed hypertension should be highly suspicious of fibromuscular dysplasia and Takayasu arteritis, while middle-aged and older patients should consider atherosclerotic renal vascular hypertension.
2. Basic diseases: accompanied by other atherosclerotic diseases such as coronary heart disease or peripheral blood vessels.
3. Family history: no family history of hypertension.
4. Others: retinopathy, left ventricular dysfunction, renal failure, pulmonary edema.

6.1.3.2 Medical Examination

Abdominal vascular murmurs: 40% of patients with renal vascular hypertension are 2–3 cm in the mid-upper abdomen or on both sides of the umbilicus, occasionally at the level of the second lumbar spine in the back. Rough and loud systolic murmurs, or continuous murmurs in both systolic and diastolic phases, can be heard.

6.1.4 Laboratory and Auxiliary Examination

6.1.4.1 Noninvasive Examination [3–7]

1. Peripheral plasma renin activity (PRA) determination: only 50–80% of patients with renovascular hypertension peripheral venous PRA increased. PRA is helpful in differentiating primary and secondary aldosterone increase in patients with hypertension and hypokalemia, but its diagnostic value for renal vascular hypertension is limited.
2. Captopril test: The predictive value of PRA can be improved by measuring the increase of PRA after 25–50 mg captopril is given. Compared with normal subjects, PRA increased more strongly in patients with renal artery stenosis.
3. Color Doppler sonography (CDS): It can evaluate the progress of stenosis and its hemodynamic results (such as flow rate and vascular resistance). In addition to the detection of renal artery stenosis at the beginning and main trunk, renal artery resistance index (peak systolic-end diastolic flow rate)/peak systolic flow rate) can be used to effectively predict the recovery of renal function and blood pressure after stenosis relief [8, 9]. Experts in our country agree to diagnose renal artery stenosis by using the peak velocity in the renal artery >180 cm/s and the ratio of the peak velocity in the renal artery to that in the abdominal aorta ≥3.5.
4. Measurement of renin activity in bilateral renal vein plasma: Renin secretion in the stenosis side of the kidney will increase, and there is a significant difference in renin concentration between the two kidneys (unilateral dominant secretion) suggesting that there is a physiological significance of renal artery stenosis. Renin determination can be used to determine which side of the kidney contributes most to hypertension.
5. MR angiography (MRA): Gadolinium-enhanced MRA provides excellent features of renal artery, peripheral blood vessels, renal mass, and even renal excretion function. It tends to overestimate the severity of stenosis, poor visualization of smaller vessels, and the risk of renal systemic fibrosis with gadolinium con-

trast agents. In addition, patients with metal or pacemaker implants or claustrophobia cannot undergo the examination.

6. CT angiography (CTA): It can not only visually and stereoscopically observe the number of renal vessels, their distribution, distortion, stenosis, and variation, but also better display the origin of accessory renal artery. The sensitivity and specificity of CTA in displaying the anatomy and variation of renal vessels are 90–100%. The disadvantage is that the imaging of segmental stenosis and small artery stenosis is poor, and the accuracy of FDM is low; the required radiographic dose is large, and the patient receives a large radiation dose. Clinically, it is necessary to pay attention to the risk of contrast-induced nephropathy (CIN) caused by iodine-containing contrast media. However, with the application of the third generation dual-source CT "double-low" (i.e., low radiation dose and low contrast dose), it is hopeful that CTA will be performed in patients with renal failure [10, 11].
7. Renal radionuclide imaging: It is first used in renal function assessment in the late 1950s and is a functional examination. It is mainly used to determine the relative function of two kidneys, to compare the blood flow and filtration function of two kidneys (including measuring unilateral kidney GFR, ERPF and overall GFR, ERPF). It can objectively and accurately display renal filtration and excretion function. Vascular occlusion of at least 60–75% can limit blood flow and reduce perfusion pressure. However, it cannot provide anatomical information of renal vessels and is still used in patients with renal failure.

6.1.4.2 Invasive Examination: Arteriography

Arteriography or intra-arterial digital subtraction angiography (IADSA): It is the gold standard for diagnosing renal artery stenosis. The main advantage is that the pressure gradient of the lesion can be measured, which is very effective for moderate stenosis. In symptomatic patients, systolic pressure gradient >20 mmHg or distal-proximal pressure ratio <0.90 were considered to be significant stenosis. If it is used only for diagnosis, it has no advantage over CTA. This method is mainly used in patients who plan to undergo renal artery interventions at the same time [12, 13].

6.1.5 Diagnosis and Differential Diagnosis

6.1.5.1 Diagnostic Clues of RVH [14]

1. Onset of hypertension before the age of 30 years
2. Onset of severe hypertension after the age of 55 years, when associated with CKD or heart failure
3. Hypertension and abdominal bruit
4. Rapid and persistent worsening of previously controlled hypertension
5. Resistant hypertension
6. Hypertensive crisis (acute renal failure, acute heart failure, hypertensive encephalopathy, or grade 3–4 retinopathy)
7. New azotemia or worsening of renal function after treatment with RAAS blockers

8. Unexplained atrophic kidney or discrepancy in kidney size, or unexplained renal failure
9. Flash pulmonary edema

6.1.5.2 Diagnostic Methods of Renal Artery Stenosis

Renal artery stenosis refers to unilateral or bilateral renal artery trunk or main branch stenosis of more than 50% the systolic pressure difference between the two ends of the stenosis ≥20 mmHg (1 mmHg = 0.133 kPa), or the mean pressure difference ≥ 10 mmHg. In clinical practice, based on the above clinical diagnostic clues, the patients suspected of renal vascular hypertension were screened and examined, and the final diagnosis was confirmed. Color Doppler ultrasound, CTA, and MRA were first recommended for the diagnosis of renal vascular hypertension. Secondly, DSA could be used as a confirmatory basis in high clinical suspicion and uncertain results of noninvasive examinations cases, instead of renal scintigraphy, plasma renin determination before and after ACEI test, and intravenous renin determination.

6.1.6 Treatment

Treatment of RVH includes drug therapy, interventional therapy (percutaneous transluminal renal angioplasty (PTRA)), stenting Percutaneous transluminal renal artery stenting (PTRAS), and surgical therapy (revascularization, nephrectomy and autologous kidney transplantation).

6.1.6.1 Drug Therapy

Drug hypotension is the basic treatment of renal vascular hypertension. The optional drugs are ACEI/ARB, calcium antagonists, beta-blockers, and so on. Previous studies have shown that calcium antagonists are safe and effective drugs for the treatment of renal vascular hypertension. ACEI/ARB is the most targeted antihypertensive drug. It is recommended for most patients to use [15, 16]. However, these drugs may deteriorate renal function in patients with single-function kidney or bilateral RAS. Therefore, ACEI/ARB is recommended for unilateral RAS, while single-function kidney or bilateral RAS should be used cautiously. Close monitoring of urine volume and renal function is needed when starting to use ACEI/ARB, such as urine volume decreases sharply or serum creatinine rises more than 0.5 mg/dL, which indicates that acute renal insufficiency has occurred. It should be reduced or stopped immediately, and general renal function can be restored. β-blockers can inhibit renin release and have a certain antihypertensive effect, which can be selected. Diuretics activate renin release, which is generally not advocated for renal vascular hypertension, but patients with essential hypertension, pulmonary edema, or heart failure are still available.

6.1.6.2 Interventional Therapy

Interventional therapy includes percutaneous balloon angioplasty and stent implantation. Percutaneous interventional therapy is generally recommended as the preferred method for renal artery revascularization [17, 18]. PTRA is especially suitable for

patients with fibromuscular dysplasia. However, there is no consensus on the extent to which RAS must be revascularized. In recent years, three RCT studies [16, 19] (STAR, ASTRAL, and CORAL studies) have suggested that the revascularization of renal artery stenosis caused by atherosclerosis cannot reduce cardiovascular, cerebrovascular, and renal events, besides lowering blood pressure. Based on this, clinicians should accurately assess the timing and risk of vascular mediator therapy.

6.1.6.3 Surgical Therapy

Surgery can relieve the anatomical abnormalities of renal artery, which is only suitable for some special cases: lesions are not suitable for interventional therapy; abdominal aortic aneurysms near the diseased renal artery need surgical reconstruction, remedial measures for failure of interventional therapy, severe allergies to contrast agents, contraindications for taking antiplatelet drugs, etc.

6.2 Atherosclerotic Renal Artery Stenosis

Keming Zhou and Jina Yili

Atherosclerotic renal artery stenosis is a disease of renal parenchymal ischemia caused by the narrowing or complete obliteration of the ostia, main or main branches of the renal artery in one or both sides caused by renal atherosclerosis. It is a common cause of renal vascular hypertension.

6.2.1 Epidemiology

Atherosclerotic renal stenosis occurs in 5–10% of the general population and is a common cause of renal artery stenosis [20]. A total of 2047 patients with renal artery stenosis from 1999 to 2014 were summarized and analyzed in China Fuwai hospital, 81.5% of whom were caused by atherosclerotic renal artery stenosis [21]. The disease has a higher incidence in high-risk populations, and the main risk factors are the risk factors for atherosclerosis, including: male, elderly, hypertension, smoking, coronary heart disease, aortic-iliac artery occlusion. In the cardiovascular health study, ultrasound found that 9.1% of men and 5.5% of women had renal artery stenosis of at least 60% [22]. In another study, the incidence of renal artery disease was 7.7% in 450 patients who underwent cardiac catheterization, and the incidence of coronary heart disease was positively correlated with the incidence of renal artery disease [23].

6.2.2 Pathophysiology

The pathophysiological mechanisms of atherosclerotic renal artery stenosis include the activation of the renin-angiotensin-aldosterone axis by renal hypoperfusion,

resulting in vasoconstriction, sodium and water retention, aldosterone secretion, sympathetic nervous system activation, and vascular remodeling, which eventually leads to hypertension, or exacerbation of the original hypertension [24]. The decreased filtration function after renal ischemia may be caused by low perfusion or recurrent microthrombus [9].

6.2.3 Clinical Manifestations

Major clinical manifestations include refractory hypertension, unexplained renal failure, and rare pulmonary edema [20]. Clinical features of secondary hypertension caused by atherosclerotic renal artery stenosis include: severe hypertension occurring over 55 years old, characterized by a relatively large increase in diastolic blood pressure, and possible cardiovascular disease or heart failure; hypertension with abdominal vascular murmur; hypertension, which was previously under normal control, rapidly and persistently worsened; refractory hypertension; hypertensive crisis.

6.2.4 Diagnosis

Diagnostic criteria for atherosclerotic renal artery stenosis [25, 26]:

(1) at least one risk factor for atherosclerosis (obesity, diabetes, hyperlipidemia, age > 40, long-term smoking).

(2) at least two imaging manifestations of atherosclerosis (conical stenosis or occlusion of renal arteries, eccentric stenosis, irregular plaques and calcification, mainly involving the proximal segment and opening of renal arteries; atherosclerosis of other abdominal vessels).

6.2.5 Treatment

The etiological treatment of atherosclerotic renal artery stenosis is mainly targeted at risk factors, including smoking cessation, lipid-lowering, blood glucose control, antiplatelet and blood pressure control [27]. The current guidelines for glycemic control target hemoglobin a1c <7%. Patients with diabetic neuropathy should pay special attention to maintain hba1c in the normal range [28]. Long-term use of statins is recommended for lipid-lowering therapy. The lipid-lowering target is LDL-C < 1.8 mmol/L, or if LDL-C is 1.8–3.5 mmol/L before treatment, LDL-C needs to be reduced by 50% [20].

For patients with atherosclerotic renal artery stenosis, it is recommended to strictly control blood pressure, and the antihypertensive target <140/90mmhg is recommended. ACEI/ARB class drugs are recommended for antihypertensive therapy [29, 30]. Elderly and frail patients should consider the tolerance of antihypertensive therapy and avoid postural hypotension.

Because the patients with atherosclerotic renal artery stenosis are often combined with atherosclerosis on the basis of long-term primary hypertension, and then gradually develop into RAS, and renal artery reconstruction can only solve the vascular stenosis, improve renal perfusion, but not change the systemic arteriosclerosis. Therefore, it is often unable to cure high blood pressure, and only makes it lower or easy to control. The guidelines do not recommend routine angioplasty for renal artery stenosis caused by atherosclerosis [20].

Currently, renal artery stenting for the purpose of hypertension control should meet two key points for the selected patients: (1) RAS 70%, and can prove the causal relationship between stenosis and elevated blood pressure. (2) refractory hypertension or hypertension without antihypertensive drugs reaches level III [31].

For the atherosclerotic RAS population, the results are often neutral in randomized clinical studies using renal function changes as the primary endpoint event for drug therapy or vascular remodeling. It is generally believed that the following two conditions should be met if beneficial conclusions are to be reached [32–34]: (1) Most of the glomeruli on the affected side survived (50%) without reversible injury, especially ischemic nephropathy caused by severe renal artery stenosis of bilateral or single-function kidneys (70%). (2) The experienced treatment team engaged in renal artery intervention can effectively prevent the direct damage to the kidney.

Interventional treatments include percutaneous balloon angioplasty and carotid stenting. Guidelines recommend stent implantation for satisfactory vascular remodeling of atherosclerotic RAS and reduction of restenosis [20, 35, 36], but balloon dilatation can be used for a small number of lesions that are not suitable for stent implantation. Drug-coated stents may help reduce the incidence of restenosis [37], which has not been reported in large randomized clinical studies. Studies have shown that about 10–20% of patients will develop stent restenosis after renal artery stenting [38]. For renal artery restenosis, drug-coated stent, drug-coated balloon, and percutaneous short-distance radiotherapy can be considered if the effect of simple balloon expansion is not satisfactory [39–42].

6.3 Fibromuscular Dysplasia

Guoliang Wang

The definition of MeSH (the Medical Subject Headings) of fibromuscular dysplasia (FMD) is a small- and medium-sized vascular stenosis disease caused by congenital non-atherosclerotic vascular smooth muscle disease [43]. However, because the current consensus believes that the disease is a non-inflammatory disease, the qualifier “non-inflammatory” should be added [44], that is, fibromuscular dysplasia is a congenital stage of non-atherosclerotic non-inflammatory vascular smooth muscle disease caused by small- and medium-sized vascular stenosis disease.

6.3.1 Epidemiology

The disease lacks large-scale epidemiological data and the estimated incidence is about 0.4% [45]. It mainly involves the renal artery and the head and carotid artery (also known as the "superior arch artery"), the proportion of which is not very different. In addition, it can also accumulate the superior mesenteric artery, iliac artery, vertebral artery, axillary artery, coronary artery, etc. Sometimes it can also accumulate more than two parts at the same time. Multicenter FMD registration study [46] showed that renal artery involvement was 79.7%, external carotid artery 74.3%, vertebral artery 36.6%, superior mesenteric artery 26.3%, lower limb 60%, upper limb 15.9%, more than two sites 35.3%, aneurysm 21.6%, dissection 22.4%. The ratio of men to women is 1:9. 7.3% of the close relatives of FMD patients had FMD. The etiology is not clear. FMD patients who smoke are more likely to have lower extremity vascular occlusion, aneurysms, coronary heart disease, stroke, and other vascular events. Considering that smoking may aggravate vascular lesions [47].

6.3.2 Pathology

From the naked view, the lesions mainly occur in the middle and distal part of the middle artery or even involved bifurcation. Microscopically, it is now believed that all three layers can involve [48, 49], including 5% of the inner layer, 85% of the middle layer, and 10% of the outer layer. It is not uncommon to accumulate multilayered lesions. Distal ischemia will occur when the diameter of stenosis is reduced by more than 60%. With the progress of the disease, occlusion of blood vessels, aneurysms, dissection of arteries, rupture, and hemorrhage of arteries can occur. Electron microscopy showed that the most important pathological change was the transformation of vascular smooth muscle cells into collagen fibers.

6.3.3 Imageology

The classical FMD with the highest incidence is a lesion involving the middle layer, which is often characterized by a typical "beaded lesion," sometimes referred to as a "multifocal lesion" (as shown in Fig. 6.1). This type is mainly caused by the proliferation of medial fibrous tissue. "Unifocal lesions" often present as single local stenosis (as shown in Fig. 6.2) and long tubular stenosis (as shown in Fig. 6.3), which are common in children. The former may be similar to atherosclerosis, mainly involving the intima, while the latter is similar to vasculitis, mainly involving the adventitia or the lateral mesentery. Because the possibility of obtaining pathological results in vivo is almost zero, and imaging classification is more operable in clinical practice, it can be simply divided into "multi-focus" and "single-focus" [50, 51].

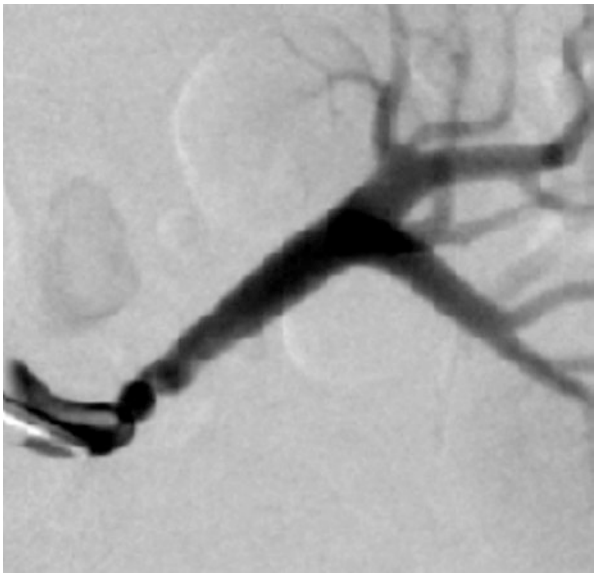

Fig. 6.1 Beaded lesion

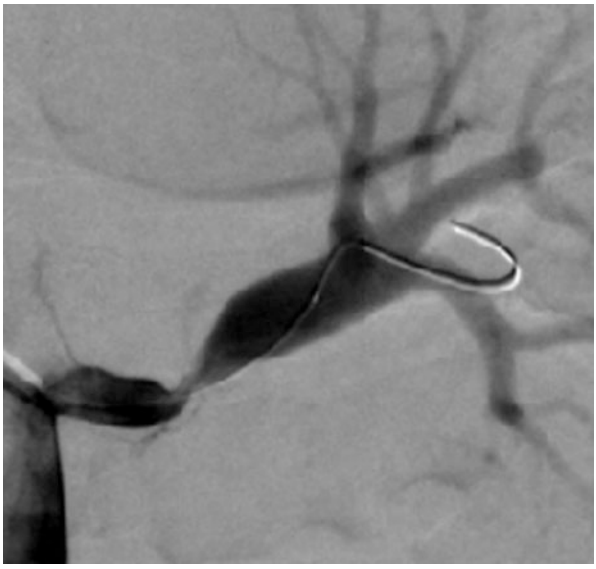

Fig. 6.2 Single-focus

6.3.4 Symptomatology

It is mainly related to the location and degree of stenosis involved in blood vessels. The main manifestations of renal artery involvement are sudden severe hypertension and abdominal vascular murmur. External carotid artery involvement is characterized by migraine and pulsatile tinnitus, limb blood vessels involvement is

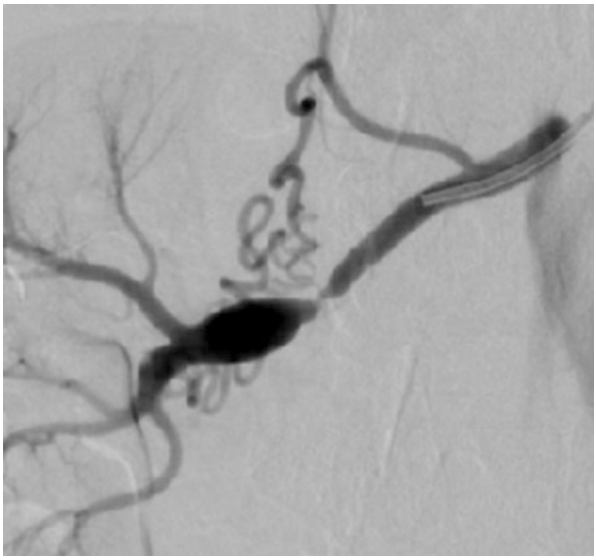

Fig. 6.3 Long tubular stenosis

characterized by ischemic limb weakness, chills, numbness, pain, intermittent rupture, etc., and superior mesenteric artery involvement is characterized by postprandial abdominal pain, diarrhea, and emaciation.

Renovascular hypertension occurs when FMD involves the renal artery. AHA/ACC (American College of Cardiology) suggests that RAS screening for FMD should be performed in people below [52]:

1. Younger than 30 years old, especially female.
2. Blood pressure at grade 3 (>180/110 mmHg), acute or malignant hypertension.
3. Refractory hypertension.
4. Kidney atrophy without urinary diseases.
5. No abdominal murmur with atherosclerosis.
6. Other vessels have been diagnosed with FMD.

6.3.5 Imaging Examination

DSA (Digital subtraction angiography) is the gold standard for the diagnosis of FMD, but noninvasive examinations such as US (Ultrasonography), CTA (computed tomography angiography), and MRA (magnetic resonance angiography) are of great significance in screening and diagnosis. The screening process proposed by the European FMD Consensus [44] is as follows (Fig. 6.4):

It is considered that US is a cheap and convenient method for first-line screening, but sometimes patients are too obese, voice window is poor, patients cannot cooperate, doctors are inexperienced, and so on. CTA/MRA can be considered as a first-line screening method. CTA has higher spatial resolution [53], clearer and higher

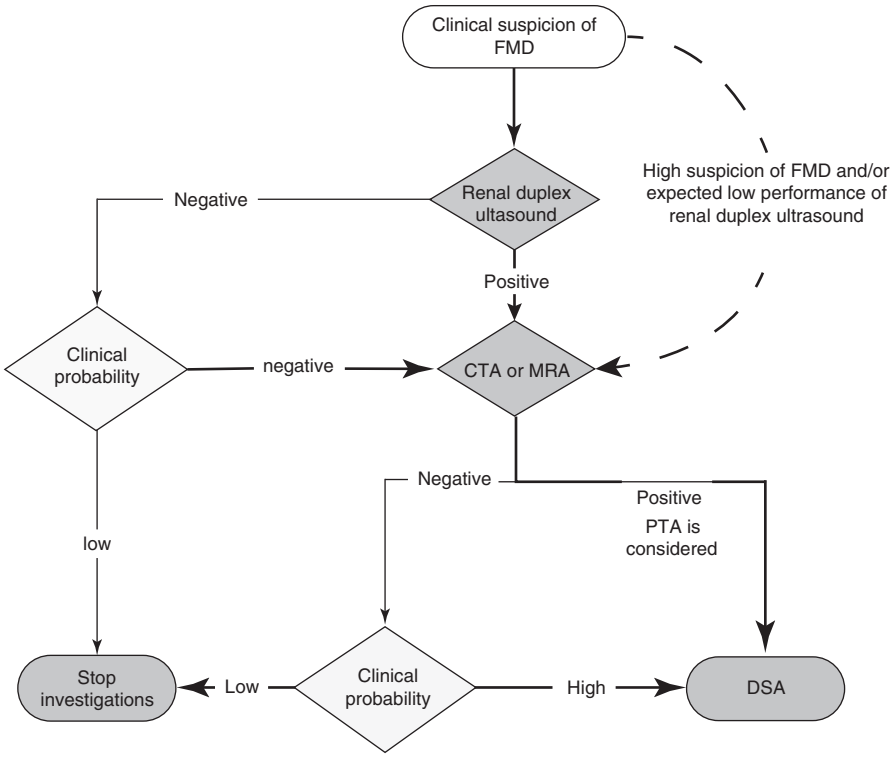

Fig. 6.4 The screening process of FMD

accuracy than MRA, especially for small vessels, but there is a risk of contrast-induced nephropathy and radiation. One of them can be selected according to the situation. With the technological progress of CT and MR, more and more studies have confirmed that the difference of specificity and sensitivity between them and DSA is getting smaller and smaller [54].

DSA can be performed when a definite diagnosis has been made and interventional therapy is considered, or DSA should be performed if a highly suspected but noninvasive examination cannot be confirmed. Whether it is necessary to have a head-to-toe blood vessel examination is still controversial. We believe that it is reasonable to determine the examination site according to the symptoms and signs.

6.3.6 Other Examinations

Renal function, ion, urinary routine, renin activity, aldosterone level, vasculitis-related indicators, ambulatory blood pressure, renal ECT, etc. It is helpful for qualitative diagnosis, differential diagnosis, assessment of severity, and trade-off between advantages and disadvantages of treatment methods.

6.3.7 Diagnostics

The diagnosis is mainly based on imaging examination, and DSA is the gold standard. However, it still needs to be differentiated from other vascular stenosis lesions.

First, atherosclerosis is the most common stenosis of the arteries. However, it is not difficult to differentiate atherosclerosis. The main points are that atherosclerosis occurs late, and there are related risk factors (blood pressure, blood sugar, blood lipid, uric acid, homocysteine abnormality, smoking, drinking, etc.). The lesions are located at the proximal or opening of the blood vessels. The morphology of the lesions is usually eccentric stenosis, often widespread multi-site atherosclerosis or stenosis.

The most difficult to differentiate is nodular polyarteritis, which occurs at similar ages. It can also be seen that "beaded" lesions can also involve multiple organs. There were slight differences between the two groups. Vasculitis was predominant in the middle segment, with relatively few involvement and bifurcation. Serological abnormalities were observed in the active phase. Vascular wall edema was observed on MRI and bubble contrast-enhanced ultrasound. It is difficult to differentiate between quiescent phase and quiescent phase. Fortunately, the treatment of quiescent phase is the same as that of FMD.

Ehlers–Danlos syndrome, also known as congenital connective tissue dysplasia syndrome, is characterized by increased skin elasticity, excessive joint activity, increased skin and vascular fragility, and pseudotumors after trauma. Type IV is varicose veins or aneurysms, mainly with vascular damage. Aneurysmal type has thinning of vascular media and formation of fibrous tissue. If angiographic findings are typical of FMD and multiple aneurysms, Ehlers–Danlos syndrome (type IV) should be suspected. It can be distinguished by the accompanying manifestations of other connective tissue dysplasia.

6.3.8 Therapeutics

At present, due to the lack of results of large multicenter randomized controlled trials [44], it is not clear which is better for medication or surgery, or which is better for PTA (percutaneous transluminal angioplasty) or surgical operation. But for hypertension specialists, more attention is paid to the blood pressure of renal vascular FMD. Even after revascularization, some patients still need antihypertensive drugs, because the antihypertensive effect of simple surgery is negatively correlated with age. Calcium antagonists, diuretics, and beta-blockers are the main antihypertensive drugs. Vascular converting enzyme inhibitors or angiotensin receptor blockers should be used cautiously. Another important goal of vascular reconstruction is to save atrophic kidneys and to protect kidney function as much as possible. The timing of operation can be used for reference of renal artery stenosis caused by atherosclerosis [55]. It is generally believed that the shortening rate of the diameter of the stenosis is greater than 70%, that is, there are indications for operation, and that 50% is more appropriate [56]. It is also suggested that the pressure gradient is

greater than 20 mmHg, and the distal/proximal pressure ratio is less than 0.90. The center considers that it is necessary to combine the patient's gender, age, symptoms and signs, the number and type of drugs taken, the sensitivity of ACEI/ARB antihypertensive drugs, the improvement of renal function, renin activity, ultrasound measurement of kidney size, renal ECT, aneurysm, and so on, to assess the impact of stenosis on blood pressure, to decide whether to revascularize, and to choose vascular surgery or interventional operation.

With the development of precise medical treatment, minimally invasive treatment is the trend. Atherosclerotic renal artery stenosis PTAS (Angioplasty with stent placement) has become the preferred treatment. About 98% of the patients with atherosclerotic renal artery stenosis in the United States have PTA [57]. FMD also often prefers PTA as the first choice [58], but does not recommend patients with third recurrence, complex hemangioma lesions, and multiple or bifurcated lesions, which still require surgical treatment. In addition, cutting balloon is not recommended because it is easy to cause vascular rupture. Normally, stent treatment is not recommended, but stent or covered stent treatment may be considered when interlayer or perforation occurs during operation.

6.3.9 Patient Education

There is a possibility of recurrence of the disease; healthy lifestyle is very important, among which, non-smoking [5], adherence to physical exercise is particularly important. Blood pressure, renal function, ion and urine routine were monitored regularly. Attention should be paid to the following symptoms: low back pain, headache, pulsatile tinnitus, abdominal pain, diarrhea, emaciation, limb weakness, pain, numbness, chills, etc. Once the above symptoms or abnormal examination indicators occur, consult the doctor promptly and inform the doctor of the history of FMD.

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Other Renal Diseases-Related High Blood Pressure

7

Wenli Luo, Junli Hu, and Wen Jiang

7.1 Renal Trauma and Hypertension

Wenli Luo

Renal trauma is a series of pathological changes caused by the structural changes of kidney tissue after the kidney is subjected to violence. Hypertension after renal trauma has long attracted people's attention. Although hypertension is a rare complication of renal trauma, it has a potential negative impact on life expectancy. Therefore, hypertension after renal trauma should be paid attention to by doctors.

7.1.1 Renal Trauma

Trauma is the sixth leading cause of death in the world. About three million trauma patients are hospitalized in the United States every year [1]. Roughly 10% of traumatic injuries involve the genitourinary system (GU) (kidneys, bladder, urethra, etc.). Renal trauma is the second most common urinary tract injury following urinary urethral injury [2]. Among historic series [3–5], up to 3.3% of kidney damage can occur in adult patients after trauma. In developed countries, being blunt was the main cause (>80%) and penetrating (>59%) in developing countries.

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7.1.1.1 Grading of Renal Trauma

Renal trauma is classified into five grades according to the American Association for the Surgery of Trauma system [6].

- Grade I Subcapsular hematoma and/or parenchymal contusion without laceration.
- Grade II Perirenal hematoma confined to Gerota fascia, renal parenchymal laceration ≤1 cm depth without urinary extravasation.
- Grade III Renal parenchymal laceration >1 cm depth without collecting system rupture or urinary extravasation, any injury in the presence of a kidney vascular injury or active bleeding contained within Gerota fascia.
- Grade IV Parenchymal laceration extending into urinary collecting system with urinary extravasation, renal pelvis laceration and/or complete ureteropelvic disruption, segmental renal vein or artery injury, active bleeding beyond Gerota fascia into the retroperitoneum or peritoneum, segmental or complete kidney infarction(s) due to vessel thrombosis without active bleeding.
- Grade V Main renal artery or vein laceration or avulsion of hilum, devascularized kidney with active bleeding, Shattered kidney with loss of identifiable parenchymal renal anatomy.

7.1.1.2 Classification and Manifestation of Renal Trauma

1. Open injury: The injury is connected with the body surface, often combined with other organ damage, accompanied by hemorrhage, shock, and acute renal failure.
2. Closed injury: It is often caused by extrusion, traffic accidents, hitting the waist or falling from a height, and indirect violence, and the kidney itself has certain diseases such as hydronephrosis, cystic lesions, tuberculosis, and other serious infections, due to abdominal force contraction. It can also cause kidney damage, and kidney injury can also be caused by abdominal force contraction. Closed renal injury is the most common type in clinic. According to the degree of injury, it can be divided into the following pathological types (Table 7.1).

Advanced pathological changes include: renal cyst formed by persistent urinary extravasation; tissue fibrosis caused by hematoma and urinary extravasation, resulting in hydronephrosis by compressing the junction of the pelvis and ureter; open renal injury, occasionally occurring arteriovenous fistula or pseudoaneurysm; partial renal parenchymal ischemia or fibrosis around the renal pedicle compressing the renal artery, which can cause renal vascular hypertension.

7.1.1.3 The Clinical Manifestations and Complications of Renal Trauma

The clinical manifestations of kidney trauma are related to the degree of injury and are not exactly the same. Especially when combined with other organ injuries, the symptoms of kidney injury are often neglected or not easily detected. The main symptoms of kidney injury are shock, hematuria, pain, lumbar and abdominal mass, fever, and so on. Common complications included uremia, persistent urinary extravasation, perineal-renal abscess, delayed hemorrhage, and hypertension [7, 8].

Table 7.1 Pathological types of closed renal injury

Type	Injury site	Symptoms and prognosis
Kidney contusion	Limited to part of the renal parenchyma. Forms renal ecchymosis and/or subcapsular hematoma, and the renal capsule and renal pelvis mucosa remain intact	General symptoms are mild and may heal spontaneously. Small amounts of hematuria may occur when the injury involves the renal collecting system
Partial renal injury	Partial laceration of the renal parenchyma, often accompanied by rupture of the renal capsule, can cause perirenal hematoma	If the renal pelvis is ruptured there may be obvious hematuria. It usually heals without surgery
Renal full-thickness laceration	Deep laceration of the renal parenchyma, extending outward to the renal capsule and inward to the mucosa of the renal pelvis and calyces, often leading to extensive perirenal hematoma	Hematuria and urinary extravasation. Some kidney tissue is ischemic and even necrotic, the symptom is obvious, the consequence is serious, all need operation treatment
Renal pedicle injury	Partial or total tearing of the pedicle or segmental vessels of the kidney	Hemorrhage, shock, often too late to treat, leading to death. Sudden deceleration or accelerated movement (such as a car accident, falling from a height) can cause a sharp shift of the kidney, a sudden pulling of the renal artery, resulting in poorly deformed endometrial rupture, thrombosis, and loss of renal function

7.1.1.4 Auxiliary Examination of Renal Trauma

1. Urine routine: Hematuria is an important basis, so urine examination is extremely important. Patients who cannot urinate on their own should undergo catheterization for routine urine examination.
2. X-ray inspection:
   (a) Abdominal plain film: Kidney contusion is generally found without abnormalities. Kidney laceration can be seen as enlarged or blurred kidney shadow, waist muscle shadow disappears, the spine is convex to the healthy side, or there is a fracture. If there is a bullet wound, metal foreign matter can be seen.
   (b) Excretory urography: It should be performed with the permission of injury. Twice or large doses of contrast medium should be used to obtain ideal results. This method can not only understand the condition of injured kidney, but also check the existence and function of contralateral kidney. When the kidney is contused, the pelvis and calyx are normal, and the calyx may be slightly displaced due to subcapsular hematoma. When renal laceration occurs, part of the calyces develops slowly, and the place where the contrast medium overflows is the site of renal parenchymal laceration. When the kidney is comminuted, the pelvis and calyx are often not visualized or there are many spillovers of contrast media.

(c) Retrograde pyelography: This method has diagnostic value for aggregate system trauma, as a supplementary examination. Due to the vulnerability to infection and pain, it has been rarely used clinically.
(d) Radionuclide renal scanning: Renal contusion scan showed normal. Renal laceration shows irregular shape of kidney. Radioactive cold zone was found in the hematoma. It can be used as a supplementary examination.
(e) Ultrasound and CT examination: Both the renal parenchymal condition and the location and extent of the hematoma can be detected.
(f) Renal artery angiography: not as a routine examination, but only when pyelography fails or cannot be clearly diagnosed, especially for the diagnosis of vascular injury.

7.1.1.5 The Treatment of Renal Trauma

The Treatment Principle of Closed Injury

1. Renal contusion and superficial laceration: Non-surgical treatment is generally used, including absolute bed rest for at least 14 days; infusion or blood transfusion when necessary; analgesics and hemostasis drugs; antibiotics to prevent infection; close observation of changes in the condition, vital signs, hemoglobin, hematocrit, urinary blood volume and abdominal mass size changes.
2. Surgical treatment should be taken for severe renal laceration or comminuted injury and aggregation system rupture with large amount of urinary extravasation.

Treatment of Open Injury

After the general condition of the wounded is improved, surgical treatment should be adopted to detect kidney and other organ injuries, and appropriate treatment should be given. The wound should be drained after operation.

Operative Methods

1. Renal laceration repair: Renal laceration can be repaired in patients with limited scope and impaired blood supply of the whole kidney.
2. Partial nephrectomy: It is suitable for patients with severe injury on one side of the kidney, no injury to the rest of the kidney tissue or repairable laceration.
3. Renal vascular repair or revascularization: suitable for patients with renal pedicle vascular tear, rupture, and thrombosis; the proportion of renal vascular injury in patients with renal injury is 2.5–4%.
4. Nephrectomy: It is suitable for the following situations: severe rupture of kidney cannot be repaired; severe pedicle injury cannot be repaired or reconstructed; extensive thrombosis of renal vessels after renal injury; post-traumatic infection, necrosis and secondary massive hemorrhage of kidney. It should be noted that the contralateral kidney has good function before nephrectomy.
5. Renal artery embolization: Selective renal artery embolization has been gradually applied to renal traumatic hemorrhage in recent years, especially in cases of solitary kidney injury which is not suitable for surgical treatment, and has the effect of preserving residual renal function.

7.1.2 Renal Trauma-Induced Hypertension

7.1.2.1 Epidemiology

After Goldblatt [9] et al. reported hypertension in dogs following his "two kidney-one clip" experiment in 1934 and Page [10] et al. reported hypertension following compression of the renal parenchyma with cellophane in 1939, the notion of hypertension following renal trauma has been reported by many. Pooled estimates among all series suggest a prevalence of hypertension following renal trauma to be 0.6–33% over a wide range of time (mean-34 months) [11]. To date, there is not a worldwide consensus on blood pressure monitoring following renal trauma, which leads to inconsistent results of various studies. The European Urologic Association and the American Urological Association both recommend periodic blood pressure monitoring for at least 1 year following injury. One of the largest series was described by Chedid [12] et al. who performed a retrospective review of over 17,000 blunt renal trauma patients and found that only 10 patients developed hypertension. The study was limited by its follow-up time being less than 6 months. Nevertheless, the authors conclude the incidence of hypertension following renal trauma to be 0.57 of 1000. In two reports from large trauma centers [13, 14], estimates of the incidence of new-onset hypertension in patients surviving severe renal trauma were 7/179 (4%) and 4/87 (5%), respectively. These reports gave no details of presentation and subsequent outcome. In a controlled study [15], patients with grade III or above renal injury were treated with stable conservative therapy, over a median follow-up of 4.7 years, significantly more patients who sustained renal trauma were newly diagnosed with hypertension compared with nonrenal, GU trauma patients. After adjusting for cofounders of hypertension in propensity analysis (i.e., age, sex, race or ethnicity, diabetes mellitus, follow-up time, and LOS), the odds of developing hypertension after a high-grade renal trauma was 3.5-fold higher than non-high-grade renal trauma patients. Gerson [16] et al. retrospectively observed 31 patients who sustained high grades renal injury (grades III to V). All the patients were asymptomatic and an average follow-up post-injury of 6.4 years. 24-h ambulatory blood pressure monitoring showed that 9 patients had post-traumatic hypertension. The prevalence of post-traumatic hypertension was 29%. Molly E [17] et al. performed a retrospective review of all pediatric trauma patients at Primary Children's Hospital in Salt Lake City, Utah between 2002 and 2012. A total of 62 children were identified with AAST grade 3–5 renal injuries during our study period. Follow-up blood pressures were recorded in 36 (58%) of these children with a median follow-up of 4.1 years (IQR 2.1–5.1 years) after trauma. Four children (6.5%) were identified to have some degree of hypertension while hospitalized after trauma and started on antihypertensive medication. The children in our study who developed hypertension were identified during their initial trauma hospitalization, and no additional children had elevated blood pressures at follow-up. This finding suggests that if hypertension is going to present after pediatric renal trauma, then it is more likely to occur in an acute fashion. But in one of the pediatric studies that examined renal injury of any grade and the risk of long-term hypertension, the authors reported that none of the children were hypertensive at 3 months post-injury [18].

Hypertension after renal trauma is mostly male. High-grade renal trauma is a risk factor for development of hypertension. Patients with CT findings of medial blood with a mid-pole laceration had increased risks for hypertension development [15].

7.1.2.2 Pathogenesis

The mechanism for hypertension after trauma is not well understood, but many have suggested that it is a result of upregulation of the renin-angiotensin system [19]. Single-center series showed that hypertension following renal trauma was secondary to renal vascular injury (renal artery stenosis or arteriovenous fistula) or external compression (subcapsular hematoma or fibrous capsule). The early stage was due to renal tissue ischemia and excessive renin secretion, while the late stage was mainly due to renal artery stenosis after injury. The pressure of hematoma or scar on renal parenchyma results in insufficient parenchymal blood supply, which can lead to increased renin secretion by proximal glomerular cells and granular plaques and subsequently to hyper-renin hypertension. Most documented cases can be classified into one of three types of renal lesions known to produce renal ischemia with subsequent development of hypertension, namely, renal artery stenosis (Goldblatt mechanism), external renal compression (Page mechanism), and intra-renal arteriovenous fistula. Eric Judd [20] et al. reported a case of renal vascular hypertension caused by pseudohemangioma after renal trauma. The blood pressure returned to normal after stent implantation. Progressive hypertension due to renin dependence may develop into severe or malignant.

7.1.2.3 Treatment

Because renal trauma-induced hypertension is mostly a consequence of hyperreninism which may be abolished by renal resection or revascularization, and may improve after renal scarring, BP outcome is favorable after intervention or medication [17] (the most commonly used drugs are lisinopril, amlodipine, and losartan) and is good. It has been reported that in a patient with unilateral renin oversecretion and contralateral renin suppression, blood pressure spontaneously returned to normal [21]. It has also been reported that malignant hypertension can spontaneously reverse in patients with previous segmental renal infarction with normal blood pressure [22]. Therefore, renal trauma-induced hypertension may be a rare and severe but reversible hypertension.

7.2 Congenital Kidney Disease and Hypertension

Junli Hu

Congenital kidney disease refers to kidney disease that originate from abnormal anatomy or metabolism at birth. Congenital kidney diseases associated with hypertension mainly include abnormal renal position, horseshoe kidney, polycystic kidney disease, and congenital renal vascular dysplasia. The following is the summary of abnormal renal position, horseshoe kidney, polycystic kidney disease, and

hypertension. For details of congenital renal vascular dysplasia, see Chap. 6, Renal Vascular Hypertension.

7.2.1 Abnormalities of renal position and Hypertension

Abnormalities of renal position, including nephroptosis (wandering kidney) and ectopic kidney, are often found in patients with urinary tract infection. Nephroptosis (wandering kidney) is a condition in which the kidneys move out of their normal range with respiratory activity, causing urinary and other symptoms. The occurrence of ectopic kidney is in the process of fetal kidney rising at the fourth to eighth week. Due to factors such as ureteral sprout growth disorder, abnormal blood supply or overgrowth, etc., the kidney rises and stops, overspeed or rises to the opposite side by mistake, resulting in renal ectopic or malrotation, and the kidney cannot reach the normal position in the retroperitoneal renal fossa. Ectopic kidney is usually found in the pelvis, iliac fossa, abdomen, chest, or bilateral cross ectopic kidney. Abnormal renal position can lead to secondary hypertension, especially known as renal position hypertension.

7.2.1.1 Epidemiology

Studies show that about 20% of women develop nephroptosis, compared to just 2% of men. Among them, right nephroptosis accounted for 70%, left nephroptosis accounted for 10%, and two nephroptosis accounted for 20%. But only 20% of patients have clinical symptoms: such as high blood pressure, low back pain, etc., more women than men, commonly seen in thin or pregnant women. More performance is temporary hypertension, often in the upright position, walking, running, jumping, or moderate degree of physical labor when blood pressure suddenly increased; recumbent blood pressure can gradually return to normal; a few cases may present as persistent hypertension [23–26]. The incidence of ectopic kidney is relatively low, with an average of about 1:900. There is no significant difference between the sexes, and it is mostly found due to clinical complications such as hydronephrosis, stones, and renal hypertension [27, 28].

7.2.1.2 Etiology

The position of the kidney may vary slightly with respiration and posture, but the kidney is fixed by strong longitudinal muscles and abdominal organs and is generally not severely displaced. Because of various reasons, the fat around the kidney becomes thin, the renal fossa becomes shallow, then the peritoneal fixation on the kidney is weakened, the kidney is wrapped by the peritoneum and the renal pedicle is loose. Multiple factors interact to cause the kidneys to move in the abdominal cavity and even the pelvic cavity: including increased abdominal pressure (such as chronic cough or constipation) or a sudden decrease in abdominal pressure (such as childbirth), injury (such as a fall from a height or severe shock to the body), and prolonged sitting and standing, etc.

The occurrence of ectopic kidney is in the process of fetal renal uplift at the fourth to eighth week. Due to the growth disorder of ureteral bud, abnormal blood supply, or excessive growth of Wolff tube and other factors, the renal uplift stops, overspeed or mistakenly rises to the opposite side, resulting in renal ectopic or poor rotation.

7.2.1.3 Pathophysiology

When nephroptosis (wandering kidney), abnormally prolonged renal arteries, the distortion of renal arteries, and even the distortion of the kidney itself can lead to decreased renal blood flow, active renin-angiotensin, and increased blood pressure. In addition, long-term position-related nephroptosis pull the renal artery and causes fibromuscular dysplasia, vascular damage. This leads to increased vascular sensitivity to catecholamines and sympathetic activity, leading to activation of the renin-angiotensin system, increased renin levels, and increased aldosterone secretion, resulting in increased blood pressure [26, 29–31]. Other diseases, such as ectopic kidney, can also cause hypertension, but the incidence rate is low, which is related to renal substantive hypertension caused by abnormal kidney development and poor elevation in embryonic period. When the ectopic kidney is combined with the abnormal development of renal blood vessels, it leads to renal vascular hypertension.

7.2.1.4 Clinical Symptoms

Twenty percent of patients with nephroptosis have symptoms as follows:

1. Symptoms in urinary system: The waist pain accounted for 92%. The waist of kidney droping side often appears ache, aggravate after tired, walk, long station. remit or disappear after supine position. More than 50% of patients have symptoms of chronic urinary tract infection, most of which are symptoms of bladder irritation such as frequent and urgent urination, which are related to the distortion of the ureter under the drooping kidney and the occurrence of infection due to blocked urine discharge. About 1/3 of the patients also had a history of low fever or recurrent fever with occasional lower limb edema. In some patients, the kidneys move up and down and vibrate, make kidney blood-vessel gets pull, twist even, cause kidney congested, induce hematuria, and often accompany with urinary calculi, can appear renal colic attack.
2. Digestive system symptoms: As a result of the pull on the abdominal nerve plexus when the kidney is active, the nerve reflex is caused by disorder, which is mostly manifested as abdominal distension, nausea, vomiting, appetite loss, constipation, diarrhea, and so on.
3. Cardiovascular symptoms: Mainly for high blood pressure, may be related to kidney position change after renal blood vessels by force, causing renal ischemia and blood silt up, affect the renin-angiotensin-aldosterone system activation, high catecholamine secretion, increased blood pressure, some patients may be accompanied by obvious heart palpitations, sweating, etc., lay down to rest can alleviate. Hypertension is often manifested as fluctuation, with blood pressure changing with postural changes, postural rise and decubitus decline and even

normal [30, 31]. About 1/5 patients can appear cardiac neurological symptom, often show for anxiety, depression, companion has insomnia, giddy lack of power, memory to drop.

4. Physical examination: In 46% of cases, there was percussion pain in the renal area. About 64% of the right kidney was palpable and 10% of the left kidney was palpable. Due to the anatomically lower position of the right kidney and shallow renal fossa, once impacted by the liver, the right nephroptosis is more than the left one.
5. Most patients with ectopic kidney have no clinical symptoms, and a few of them are found after the occurrence of complications, including renal vascular hypertension, ureteral colic, abdominal mass, urinary tract infection, hydronephrosis and stones, etc., while most patients with thoracic ectopic kidney have no symptoms.

7.2.1.5 Auxiliary Examination

1. Laboratory examination: Most patients had normal renal function, while a small number had renal insufficiency. Red blood cells, white blood cells or proteins can be seen in urine routine.
2. Ultrasonic examination: The activity degree of the kidney can be obtained between the fixed position of the kidney and the position of the kidney after activity by ultrasonic examination half an hour after a position of low head and high foot. Mild: renal activity was 3 cm. Moderate: the range of motion is 3 ~ 6 cm. Severe: renal activity was over 6 cm.
3. X-ray examination: X-ray plain film of the abdomen, excretory urography, and retrograde pyelography: nephroptosis can be diagnosed when the kidney drops by more than 2 lumbar vertebral body height during the examination from the supine position to the upright position. Braasch divided nephroptosis into three levels: Level-I means In supine versus standing position, kidney prolapse one vertebra; Level-II kidney prolapse two vertebra Level-III kidney prolapse three vertebra or more, or with hydronephrosis, ureteral distortion. The ectopic kidney was fixed, the ureter was short, and the renal artery was abnormally located. Most of the ectopic kidneys were located in the pelvic cavity, but less in the chest cavity. Most of the ectopic kidneys were located in the posterior and lower mediastinal spine of the chest, forming smooth soft tissue mass shadows. It can also be a cross ectopia.
4. CT: The ectopic side of the renal fossa was empty and filled with adjacent ectopic liver, pancreas, spleen, intestinal tubes, etc., and there was no normal renal arterial and venous display in the ectopic side. In the posterior thoracic cavity, the anterior spine, pelvic cavity, the kidney density and tissue structure of soft tissue mass shadow are visible, and significantly enhanced; The cross ectopic kidney is usually located on the opposite side.
5. Radionuclide scanning: Reduced glomerular filtration rate and effective plasma flow in the affected kidney [32, 33].
6. Renal angiography in position: In the case of surgical intervention, angiography may help to determine vascular supply.

7. Lower head decubitus test: Patients were instructed to lie in a high decubitus position with head low and foot high for 3 days (the length and diameter of a brick could be raised at the foot of the bed). The urine routine or the excretion rate of blood cells per hour was measured before and after sleep, and the symptoms were observed to alleviate. The diagnosis of nephroptosis may be supported if the blood cells in urine are decreased or even disappeared after sleep and the symptoms are alleviated.
8. Dynamic blood pressure: There is a significant correlation between blood pressure fluctuation and body position. With the change of body position, the difference between systolic blood pressure and diastolic blood pressure can be 20–40mmhg or 10–20mmhg [26].

7.2.1.6 Diagnosis and Differential Diagnosis

For patients with recurrent urinary tract infection and postural-related hypertension, the first consideration should be given to the abnormal position of the kidney, such as nephroptosis and the possibility of ectopic kidney. The symptoms, signs, and auxiliary examinations of patients can be combined to make a diagnosis of the degree of abnormal position of the kidney.

7.2.1.7 Treatment of Nephroptosis

The treatment of nephroptosis can be divided into two categories:

1. Non-surgical treatment, exercise abdominal lumbar muscles, increase abdominal pressure to resist kidney droop. Exercise of abdominal muscles can be done by sit-ups, straight legs, and other training. Kidney brackets and waistbands can also be used.
2. Surgical treatment:
   (a) Injection therapy: injection of quinine, gelatin made of colloidal or spongy preparation into the kidney perirenal adhesion, in order to make the kidney fixed.
   (b) Surgical fixation: open nephropexy, percutaneous nephropexy, and laparoscopic nephropexy.
3. Ectopic kidney: Asymptomatic ectopic kidney can be left free of treatment, and complications can be actively treated [28].
4. Renal positional hypertension: Renal positional hypertension is often associated with increased sensitivity of blood vessels to catecholamine, increased renin levels and sympathetic nerve activity, and a renin-angiotensin system associated with decreased renal blood flow and increased renal vascular resistance. When standing or sitting, the blood flow that circumfluence heart decreases, the heart educts a quantity to reduce, bring about sympathetic nerve overexcitement thereby, systemic small blood vessel, especially small artery is in for a long time systole or spasm condition, cause blood pressure to rise. Antihypertensive drugs should be actively used with calcium antagonists, ACEI/ARB and beta receptor blockers. For refractory hypertension, renal denervation RDN can be selected [34], and renal nephrectomy is necessary [35].

7.2.1.8 The Prognosis

Abnormal renal location—nephroptosis and ectopic kidney. If detected early and treated actively, the prognosis is good. Once renal insufficiency occurs, the progression is rapid and the prognosis is poor. Urinary tract infection and hypertension are often factors leading to the deterioration of the condition and should be treated positively.

7.2.2 Polycystic Kidney Disease

Polycystic kidney disease (PKD) is an inherited kidney disease in which multiple cysts appear in the cortex and medulla of the kidney. In addition to accumulating kidneys, it also causes extrahepatic lesions such as liver and pancreatic cysts, valvular heart disease, colonic diverticulum, and intracranial aneurysms, which ultimately leads to end-stage renal disease (ESRD). It is the most common hereditary kidney disease and the fourth most common cause of global renal failure [36, 37]. There are two types of clinical, autosomal dominant polycystic kidney disease (ADPKD), which is often found in young and middle-aged patients, and can also occur at any age; and autosomal recessive polycystic kidney disease (autosomal recessive polycystic kidney disease ARPKD), the onset of infancy, clinically rare.

7.2.2.1 Autosomal Dominant Polycystic Kidney Disease (ADPKD)

ADPKD is the most common hereditary kidney disease, which can occur in both men and women. There is no obvious gender difference, and the average incidence rate is about 1/400–1000 [38]. As the disease progresses, approximately 45%–70% of patients eventually develop end-stage renal disease at around 65 years [39, 40]. About 5% of patients require dialysis, and 7–11% require renal replacement therapy [41].

Etiology

Three genes have been found to be involved in the pathogenesis of ADPKD. The PKD1 gene is located at 16p13.3 and contains three homologous gene loci (HG-A, HG-B, and HG-C); the PKD2 gene is located at 4q21–23; PKD1 gene mutations account for 80–85% of ADPKD cases, while PKD2 gene mutations account for 15% of cases [39, 42, 43]. Spontaneous mutations are less than 5% of ADPKD [44]. The expression products of ADPKD1 gene and ADPKD2 gene are polycystin 1 (PC1) and polycystin 2 (PC2), respectively. When the above two genes are mutated, it can lead to signal dysregulation and elevated levels of cyclic adenosine monophosphate, and normal tubular morphology cannot be maintained, resulting in cysts [45–47].

Pathophysiology

The mechanism of polycystic kidney causing hypertension is mainly the compression and traction of renal parenchyma by cysts, the decrease of normal nephron, the activation of renin-angiotensin-aldosterone system, the secretion of excessive renin and aldosterone, the retention of water and sodium, the increase of blood volume, and the increase of blood pressure. On the other hand, with the destruction of

medulla and prostaglandin secreting cells, prostaglandin production in vivo decreases, and prostaglandin has a significant vasodilator effect. These two effects cause hypertension. It is generally believed that hypertension occurs in almost all adult polycystic kidney disease.

Pathology

The renal characteristics of ADPKD patients are cysts, which gradually form and grow in number and size. Early kidneys are of normal size and contain a small amount of fluid-filled cysts and a large number of well-preserved substances. At the later stage, the size of the kidney increased and the shape of the kidney was abnormal, but the shape of the kidney remained unchanged. From cortex to medulla, cysts are filled with cysts that are small to invisible to the naked eye, large to centimeters in diameter, and even football-sized. The size of kidney is significantly correlated with renal function and complications. The length of kidney is larger than 15 cm, and it is prone to hematuria and hypertension. The development of pelvis and calyx is normal, but cysts are often compressed, dilated, or deformed.

Clinical Symptoms

ADPKD is a systemic disease that accumulates multiple organs. Its clinical manifestations include renal manifestations, extrarenal manifestations, and complications. There are still many patients who are asymptomatic for life and are finally diagnosed by autopsy.

1. Renal manifestations: Renal manifestations include renal structural and functional abnormalities.
   (a) Abnormal renal structure: The main structural change is the formation of renal cyst. They range in size from cortical to medullary filled with spherical cysts that are invisible to the naked eye, up to several centimeters in diameter, and up to the size of a soccer ball. It increases with the progression of the disease.
   (b) Abdominal mass: When the kidney is increased to a certain extent, it can be found in the abdomen. Both kidneys are about 50–80% accessible and 15–30% are accessible on one side. The palpation kidney has a firm texture, the surface can be nodules, and it moves with the breath. It can be tender after infection.
   (c) Pain: Pain in the back or ribs is one of the common early symptoms, which is common in women. It can be dull pain, pain, tingling, etc. Acute pain often indicates cyst rupture, infection, and blood clots leading to urinary tract obstruction. Chronic pain is mostly caused by enlarged kidney or cyst pulling the kidney capsule and kidney pedicle, and pressing adjacent organs.
   (d) Bleeding: About 30–50% of patients have gross hematuria or microscopic hematuria. Generally, hematuria is self-limiting, mostly spontaneous, and can also occur after trauma. Consider cyst wall rupture, stones, infection, cancer, etc. The frequency of hematuria increases with the severity of hypertension and the increase of cysts, which is directly proportional to the deterioration of renal function.

(e) Infection: Retrograde infection is the main route, and women are more common than men, mainly manifested as cystitis, pyelonephritis, cyst infection, and perirenal abscess.
(f) Stones: 20% of patients with kidney stones, further increase renal insufficiency.
(g) Proteinuria: About 30% of non-uremia patients can be seen. About 80% of patients with renal failure can be seen. Men are more than women, and they are more than 1 g/24 h. Patients with large amounts of proteinuria have larger kidneys, lower creatinine clearance, and faster progression than those without proteinuria or mild proteinuria. Proteinuria is an important risk factor for the progression of renal function and requires active treatment.
(h) Chronic renal failure: It is the main cause of death. Its renal function deteriorates significantly faster than other diseases.

2. Extrarenal manifestations:
(a) Cardiovascular manifestations: Hypertension is one of the most common early manifestations, seen in 30% of children, 60% of patients with renal insufficiency, and up to 80% of end-stage patients. The blood pressure is proportional to the size of the kidney and the number of cysts, and increases with age. Hypertension is one of the risk factors for the deterioration of renal function. The average age of renal decompensation in patients with hypertension was 47 years, while that in patients with normal blood pressure was 66 years. Therefore, the treatment of hypertension is very important to the prognosis. Sometimes the first symptom is left ventricular hypertrophy, mitral valve prolapse, aortic valve insufficiency, intracranial aneurysm, and other diseases.
(b) Anemia: Those with persistent hematuria may present with mild anemia, and 5% of the patients suffer from secondary polycythemia caused by ischemia stimulating the production of erythropoietin by renal interstitial cells. End-stage renal disease can lead to anemia gradually, but it is later and milder than the anemia caused by other causes of renal failure.
(c) Other systems and organs: Digestive system, central nervous system, reproductive system, and other organs can be involved. Most of them are cystic lesions, such as hepatic cysts, pancreatic cysts, and ovarian cysts. About 30% to 40% of patients had hepatic cysts, 10% had pancreatic cysts, and about 5% had splenic cysts. Non-cystic lesions include abnormal heart valves, colonic diverticulum, intracranial aneurysms, etc.

Auxiliary Examination

1. Urinary routine: No abnormalities in the early stage, microscopic hematuria in the middle and late stage, and proteinuria in some patients. Leukocyte and pus cells are present in the presence of stones and infections.
2. Urinary osmotic pressure measurement: When there are only a few cysts in the early stage of the lesion, renal concentration function may be impaired, suggesting that the change is not entirely related to the destruction of renal structure and may be related to the poor response of the kidney to diuretic hormone.

The decrease of renal concentration function preceded the decrease of glomerular filtration rate.

3. Serum creatinine: Progressively increased with the loss of renal compensatory capacity. Creatinine clearance rate is a sensitive index.
4. Abdominal plain film: Plain film shows enlarged kidney shadow, irregular shape, can be lobulated, wavy, and so on. Sometimes cystic wall calcification and kidney stones can be seen.
5. Excretory urography: Showing signs of compression and deformity of the pelvis and calyx. The shape of the pelvis and calyx is peculiar and spider-like. The calyx is flat and wide, and the calyx neck is elongated and thin, often curved.
6. B-ultrasound examination: It is the first choice for polycystic kidney examination. Under ultrasound, the kidney volume is enlarged, and multiple cysts of different sizes can be seen in the kidney.
7. CT: It shows an increase in both kidneys, a lobulated appearance, and a majority of thin-walled cysts filled with fluid. The CT value is between 8 and 20 Hu. The edge of the polycystic kidney is clear, the cysts are different from each other, and the renal pelvis is deformed by compression. Cysts are also seen in the liver and pancreas.
8. MRI: It can be seen that the two kidneys are enlarged, the cyst signals are inconsistent, and smaller cysts can be detected.
9. Radionuclide scanning: eGFR and ERPF decline.
10. Genetic testing: It has been gradually applied to pre-symptomatic and prenatal testing. Genetic imaging is also feasible when imaging results are uncertain. It can also be used to diagnose patients with PKD without family history or with syndrome characteristics.

Diagnosis

There is a clear family history of ADPKD in which the renal cortex and medulla are filled with multiple fluid cysts of varying sizes. It can be diagnosed with liver, pancreas, spleen, accessory cyst, or heart valve abnormality and intracranial aneurysm.

Differential Diagnosis

1. Simple renal cyst: The incidence rate increases with age, but no family history, normal renal volume, typical renal cyst is located in the cortex, single cavity, no small cyst around the distribution, no external renal performance, good prognosis, usually do not need treatment.
2. Medullary cystic disease: The pathogenic gene is MCKD gene, and the autosomal dominant abnormality has a low incidence, which is more than that of adult patients. Renal cysts are confined to the medulla, and the size of the kidney shrinks.

Treatment

At present, there is no effective treatment for ADPKD, and the management measures mainly focus on controlling the complications of the disease.

1. General treatment: First, maintain an optimistic attitude, active exercise, quit smoking, maintain weight < 25 kg/m2; limit salt: 80–100 mmo/day; moderate protein intake: 0.75–1.0 g/kg/day. A low-protein diet (≤0.6 g/kg/day) does not slow the decline in renal function in patients with ADPKD. Caffeine may stimulate the growth of cysts, do not eat chocolate, do not drink coffee, tea, and other caffeinated drinks. Avoid the use of nephrotoxic drugs [48].
2. Symptomatic treatment
   (a) Hypertension: It is one of the most common complications of ADPKD and one of the factors that deteriorate renal function. Active control of blood pressure can delay renal dysfunction. For large amounts of proteinuria (≥25 mg/mmol in males and ≥ 35 mg/mmol in females), the general treatment goal is that blood pressure should be reduced to at least 130/80 mmHg. In patients with ADPKD without proteinuria, blood pressure can be relaxed to 140/90 mmHg [49]. Therapeutic drugs are preferred with ACEI and ARB, supplemented with CCB, beta blockers, and central antihypertensive drugs, and experienced physicians may use diuretics as appropriate [50]. If the blood pressure still fails to meet the standard after the above treatment, the cyst decompression or nephrectomy may be considered.
   (b) Pain: Acute pain is caused by cyst rupture, stones, infection, etc., and is actively treated. Chronic pain can choose painkillers, but avoid long-term use to increase the burden on the kidneys. If the treatment of step analgesia is not effective, surgery can be chosen.
   (c) Cyst hemorrhage and hematuria: A small amount of hemorrhage or hematuria in bed rest, active analgesia symptomatic treatment, serious medical condition, or active intervention.
   (d) Infection: Including urinary tract and cyst infection, is one of the common complications, active anti-infective treatment, mainly lipophilic antibiotics, including compound sulfamethoxazole and fluoroquinolones. If there is still obvious fever after active anti-infective treatment, cyst drainage can be cut open. If the infection occurs repeatedly, beware of complications such as urinary obstruction, perirenal abscess or stones, and actively treat complications.
3. Renal replacement therapy: Mainly for end-stage renal failure, can be active hemodialysis treatment, but also can choose peritoneal dialysis. Conditional renal transplant therapy is available [51].
4. Inhibit the development of cysts:

   Reduce cAMP levels; inhibit cell proliferation; and reduce fluid secretion [52, 53]. Drug classes that have been tested in randomized clinical trials (RCTs) include mTOR inhibitors (sirolimus and everolimus), somatostatin analogues (octreotide, lanreotide), and vasopressin V2 Receptor antagonist (Tolvaptan) [39]. Other drugs under test include bosutinib, CDK roscovitine inhibitors, and triptolide (Triptolide, a traditional Chinese herbal medicine) [54, 55].

Prognosis

There are many factors affecting the prognosis of ADPKD. Controllable factors should be actively prevented and cured. Meanwhile, we should actively improve the life style, prevent and treat various complications, delay the course of disease and improve the prognosis.

7.2.2.2 Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Autosomal recessive polycystic kidney disease (ARPKD) is a rare disease with about one in 20,000 newborns. The incidence rate for men and women is the same, no ethnic differences. The main features are spindle expansion of the renal collecting duct and congenital liver fibrosis. The survival rate in the neonatal period is over 70%, and the survival rate at the age of 10 is over 80% [56, 57]. Hypertension occurs in 90% of children, which may be related to the cystic compression of surrounding tissues, the enlargement of cysts, the reduction of renal vascular bed, and the activation of the renin-angiotensin-aldosterone system.

Etiology and Pathophysiology

Autosomal recessive (infant) polycystic kidney disease (ARPKD/PKHD1), the specific pathogenesis is unknown. The increase in renin secretion due to renal ischemia affects the activation of the renin-angiotensin-aldosterone system and is a major cause of hypertension [58].

Pathology

The severity of kidney disease is inversely proportional to liver pathology, and most patients are mainly nephropathy. The kidneys are enlarged, and the surface of the cortex is distributed with numerous 1–2 mm or smaller cysts, which are characterized by a fusiform or columnar expansion with a radial diameter of 1–8 mm from the medulla to the cortex. The microscope is mainly composed of the cubic epithelium of the collecting tube. The number and shape of the glomeruli are basically normal. The cortex of the kidney is unclear, the renal pyramid is enlarged, and the morphology is abnormal. The renal calices, renal pelvis, and ureter are normal or slightly distorted.

Clinical Symptoms

The clinical manifestations of ARPKD can occur in perinatal, neonatal, infancy, adolescent, and even adulthood.

The clinical manifestations are diverse, and even patients in the same family can show varying degrees of disease severity. Prenatal manifestations of maternal oligohydramnios, fetal kidney enlargement, bladder emptiness; in addition to kidney enlargement in the neonatal period, often with renal failure and lung dysplasia caused by respiratory failure; infant and childhood hypertension is more common, which is characterized by a persistent moderate and severe increase in blood pressure, especially in the first few months after birth, accompanied by myocardial hypertrophy and heart failure, and requires drug treatment. However, kidney function is impaired, often with frequent urination, increased urine output, and

hyponatremia. It is easy to combine urinary tract infections. ARPKD renal failure progresses slowly. About 20 to 45% of children before the age of 15 progress to end-stage renal failure, and 75% of patients before the age of 25 enter end-stage renal disease. With age, liver symptoms and signs gradually become obvious, including portal fibrosis and intrahepatic bile duct dilatation.

Auxiliary Inspection

Ultrasonography is the most commonly used diagnostic method. Most patients have characteristic manifestations in infancy or childhood: the kidney is enlarged, the junction of cortex and medulla is unclear, the collection system is unclear, and the boundary with surrounding tissues is blurred. Kidney volume may shrink in adulthood, but multiple cysts can be seen. Liver ultrasound suggests liver fibrosis.

Diagnosis and Differential Diagnosis

Diagnostic criteria include typical renal manifestations of increased renal volume, congenital liver fibrosis, and genetic history of the intergenerational family. Liver biopsy is sometimes needed to assist with diagnosis. Direct detection of genetic mutations or molecular genetic analysis is a more accurate diagnosis. Need to identify with autosomal dominant polycystic kidney disease: ARPKD is characterized by autosomal recessive inheritance, clinical manifestations of hepatic portal fibrosis, renal ultrasound suggesting an increase in volume, small cysts can be seen, can be distinguished from ADPKD. However, a very small number of adult-onset ARPKD are not easy to distinguish from ADPKD, and feasible genetic diagnosis methods are available.

Treatment

At present, there is no radical treatment, only symptomatic treatment. According to different periods of treatment focus is inconsistent. With the progress of medicine, it is possible to treat the disease by gene targeting. Neonatal patients are more serious, and the focus is to prevent and treat respiratory failure. Treatment in infancy and adolescence is mainly as follows:

1. Hypertension: About 33–75% of patients have hypertension, most of them need medication, which may slow down the progression to end-stage renal disease. In general, ACEI and ARB are often chosen, and calcium antagonists and beta blockers can also be combined. The blood pressure target value is 75% of the normal high blood pressure limit of normal children of the same age [57, 59, 60].
2. Renal failure: With the increase of age, the incidence of renal failure increases year by year. We should consider dialysis or renal transplantation, but be alert to the risk of infection.
3. Edema: The mechanism is not clear, actively limit salt, choose loop diuretics, be alert to hypokalemia and hyponatremia.
4. Urinary tract infection: The incidence is high. Choose liposoluble antibiotics to avoid nephrotoxic drugs and iatrogenic urinary tract infection.

5. Symptoms of hepatobiliary system: Active and effective treatment of portal hypertension, prevention and treatment of complications caused by portal hypertension, such as gastrointestinal bleeding, anemia, and thrombocytopenia.

Prognosis

The prognosis is related to the onset time of ARPKD. The incidence of ARPKD in neonatal period is relatively serious. The mortality rate of infant patients is higher. It is generally better to pass through the infant period. About 50–80% of patients can survive for more than 15 years. There are no long-term survival statistics.

7.2.3 Horseshoe Kidney and Hypertension

Horseshoe kidney is the most common fusion kidney malformation, which is caused by the junction of the lower pole of the two kidneys by the substantive isthmus or fibrous isthmus across the midline. It is characterized by three types of anatomical abnormalities: abnormal kidney position, malrotation, and changes in vascular supply [61–64]. Because most of the patients have no clear understanding of horseshoe kidney and do not pay attention to it, the condition of horseshoe kidney is getting worse and worse, leading to a series of complications, even renal failure. Horseshoe kidney patients often suffer from hypertension through many ways, and hypertension is the main risk factor for deterioration of renal function.

7.2.3.1 Epidemiology

The horseshoe kidney was first described by Berengario Da Carpo in 1552. Morgagni reported the first case of horseshoe nephropathy with complications in 1820. According to statistics, the incidence of horseshoe kidney is very low, and it is common in children at all ages, but it is common in autopsy. About one in 400–500 newborns, mostly male, has a male-to-female ratio of 2:1 [65].

7.2.3.2 Etiology

The causes of horseshoe nephropathy are unclear. At present, three factors are considered: intrauterine environment, genetic/chromosomal susceptibility, and structural factors affecting kidney development and migration.

7.2.3.3 Pathophysiology

More than 95% of the patients' kidneys fused at the lower pole, and a few could fuse at the upper pole. The isthmus is usually connected by blood-supplied renal parenchyma, occasionally by fibrous tissue to connect the two kidneys. Most of them are located at the level of L3 or L4, sometimes even in the pelvic cavity behind the bladder. Some patients may have poor rotation of the kidney, leading to the direction of the calyces forward, but the number is generally normal. The blood supply varies greatly. The lower part of the kidney and its adjacent kidney tissues can accept

branches from the main renal artery or have their own separate blood supply. Because of the variation of kidney position, pressure and traction of blood vessels, some patients activate RAS system, increase renin secretion, and increase excitability of sympathetic nervous system, while the corresponding vasodilators such as prostaglandin and atrial natriuretic hormone decrease. At the same time, due to poor rotation of kidney, it is easy to cause hydronephrosis, repeated inflammation, and infection of kidney, which eventually lead to renal parenchyma damage; in addition, malformed horseshoe kidney can make water-sodium excretion disorder sodium excretion disorder, sodium and water retention, and increased extracellular fluid capacity, thus leading to the occurrence and development of hypertension from a variety of ways.

7.2.3.4 Clinical Manifestations

1. A few patients were asymptomatic and found during physical examination.
2. Renal manifestations, most patients due to nerve plexus, blood circulation or ureter compression and symptoms. There are mainly upper abdominal, umbilical or lumbar pain, chronic constipation and urinary symptoms, such as chronic nephritis, pyelonephritis, hydronephrosis, and stones.
   (a) A mass in the lower abdomen may touch the mass (isthmus) in front of the lower lumbar spine.
   (b) Lumbar or umbilical pain, abdominal distension, constipation, etc., also misdiagnosed as abdominal tumors, appendicitis, pancreatitis, duodenal ulcer, or due to complications.
   (c) Complicated symptoms of urinary system, such as infection, hydrops, and stones. Patients often have frequent urination, pyuria, hematuria, and other symptoms. Due to the high opening of the ureter in the renal pelvis and the limitation of renal fusion, the pelvis cannot rotate normally. The forward displacement of the ureter across the fusion site leads to urinary flow obstruction, which causes hydronephrosis in 80% of cases and also easily leads to infection, stones, tumors, and so on. This is the main clinical feature of the disease.
3. Hypertension mostly occurs before the decline of renal function, which promotes the progression of renal damage. Its occurrence may be related to kidney blood circulation, activation of renin-angiotensin system, and sodium-water retention caused by pressure of ureter and other factors (see pathogenesis). Clinical observation of patients with hypertension is more intractable, and general antihypertensive treatment is not easy to control.

7.2.3.5 Complications

About 1/3 of patients with horseshoe kidney have no clinical symptoms. However, compared with normal people, patients with horseshoe kidney are usually more prone to various complications, such as urinary calculi, infection, obstruction at the junction of pelvis and ureter, renal contusion, hydronephrosis, uremia, and benign and malignant renal tumors.

7.2.3.6 Diagnosis

The diagnosis of horseshoe kidney mainly depends on imaging examination.

1. Ultrasound: Solid hypoechoic areas were seen in the lower pole of the spine in front of the abdominal aorta and the inferior vena cava. The echoes were slightly higher than the homogeneous or central hypoechoic areas, and continued with the renal parenchyma. Color Doppler showed that there were color blood flow signals in the hypoechoic areas. The banded hypoechoic blood flow spectra were consistent with the left and right hypoechoic blood flow spectra. The axis of the kidney changes from the normal "inverted eight-character" shape to the abduction of the upper pole of the kidney. After the adduction of the lower pole of the kidney, the kidney is closer to the column and spine than the normal kidney [66].
2. Abdominal plain film: The isthmus connected by the lower pole of two kidneys overlaps with the spine, the long axis of the shadow of two kidneys becomes straight, and the shadow of the lower pole of the kidney and psoas major muscle disappears or blurs, often accompanied by pelvic calculi [66].
3. Intravenous pyelography: The diagnosis of this disease mainly depends on pyelography. Both sides of the pelvis and calyx have low position, incomplete rotation, the pelvis is forward, the calyx extends inward or backward, and the lower part of the two kidneys is very close to the spine; the shadow of the kidney is inverted octagonal, and the long axis is mostly intersected below the kidney; the two ureters enter the pelvis from the front to the outside, and the renal parenchyma contains iodine contrast agent, resulting in clearer soft tissue in isthmus; hydronephrosis or hydronephrosis with hydroureter. The position of pelvis and calyx moved down [66].
4. Renal radionuclide scanning or nuclear magnetic resonance: Can understand the fusion of the lower pole of the two kidneys, can understand whether there is renal parenchyma tissue in isthmus.
5. CT: It can directly show the fusion part of the lower pole of the two kidneys, i.e., the isthmus crossing the front of the aorta. Because of the poor rotation of the kidney, the calyx is located in front of the kidney, and the ureter crosses the isthmus and descends in front of both sides. However, the location of horseshoe kidney is generally low, and the diagnosis can only be determined by scanning to a lower position.
6. Abdominal aortography: It is very helpful to determine the surgical method.

7.2.3.7 Therapy

Patients without symptoms and complications need not be treated.

Urinary tract obstruction with severe lumbocostal pain and other symptoms, affecting work and life, may consider urological surgical treatment, such as ureterolysis, isthmus amputation and separation of two kidneys and pyeloureteroplasty and fixation. Patients with complications need to be treated according to specific circumstances, such as obstruction of the pyeloureteral junction and pyeloplasty. If there is vesicoureteral reflux, vesicoureteral anastomosis is performed. Special attention should be paid to the fact that the disease has rarely undergone simple

isthmotomy because it has little effect on improving drainage and correcting the location of the kidney and ureter.

In addition to active treatment of primary diseases, patients with horseshoe kidney and hypertension can be treated with hypotension therapy. It is suggested that "angiotensin converting enzyme inhibitor, angiotensin receptor antagonist" be used to delay the occurrence of renal failure, and diuretics can also be considered to combat sodium and water retention. For intractable hypertension, it is generally necessary to use combined drugs. Calcium antagonists have a strong antihypertensive effect and can be used in combination.

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Vascular Disease and Hypertension

8

Bin Zhu and Qing Zhu

Some of the secondary hypertension is caused by different types of vascular diseases. Systemic vasculitis (including Takayasu arteritis (TA), polyarteritis nodosa (PAN), and ANCA-associated vasculitis (AAV)), nutcracker phenomenon, and arteriovenous fistula are more common in clinic. The following is a summary of the above contents in order to improve the understanding of secondary hypertension.

8.1 Macroangiopathy and Hypertension

Bin Zhu

Takayasu arteritis (TA) is a chronic progressive nonspecific inflammatory disease of the aorta and its main branches. Most of the lesions were found in the aortic arch and its branches, followed by descending aorta, abdominal aorta, and renal artery [1]. Because of the concealment of the early onset of TA, nonspecific systemic inflammatory symptoms are the only significant clinical manifestations in the early stage of the disease. Therefore, the early diagnosis of TA is more difficult [2]. TA is closely related to hypertension. More than 60% of TA patients are complicated with hypertension [3, 4]. The most common clinical manifestation is upper limb pulseless caused by brachiocephalic artery involvement. The second is lower extremity pulseless caused by descending aorta and abdominal aorta and renal artery stenosis hypertension caused by renal artery involvement.

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8.1.1 Clinical Manifestations and Complications

8.1.1.1 Systemic Symptoms

Before the occurrence of local symptoms or signs, a few patients may have symptoms such as general discomfort, fatigue, fever, loss of appetite, nausea, sweating, weight loss, myalgia, arthritis, and nodular erythema. They may have acute attacks or conceal onset.

8.1.1.2 Local Symptoms and Signs

Symptoms and signs of local manifestations or organ ischemia caused by arterial stenosis and occlusion or aneurysm formation include headache, dizziness, hypertension, pulse-free blood pressure, asymmetric arterial murmur, limp, abdominal pain, transient ischemic attack, stroke, retinopathy, dyspnea, etc.

8.1.1.3 Characteristics of Hypertension

The most common manifestations are elevated blood pressure in one or both upper limbs, decreased blood pressure in lower limbs, accompanied by decreased or disappeared pulse. When renal artery is involved, there may be refractory hypertension and other renal vascular hypertension manifestations. When multiple sites are involved, most of the clinical manifestations of hypertension and related symptoms have been obvious.

8.1.2 Auxiliary Inspection

1. ESR and CRP are important indicators of disease activity. ESR and CRP can return to normal when the disease is stable.
2. Color Doppler ultrasonography: It can detect the stenosis or occlusion of aorta and its main branches, but it is more difficult to detect the distal branches.
3. Angiography: It can directly show the changes of lumen, diameter, smooth wall, and the range and length of the involved vessels.

8.1.3 Diagnosis and Differential Diagnosis

8.1.3.1 Diagnostic Criteria

The diagnostic criteria of TA are different in different countries. At present, most countries in the world use the diagnostic criteria of TA formulated by the American College of Rheumatology (ACR) in 1990, as shown in Table 8.1.

8.1.3.2 Differential Diagnosis

1. **Congenital coarctation of aorta:** This disease is more common in men, the position of vascular murmur is high, limited to the precardiac area and the back, but not in the abdomen. There is no inflammation in the whole body, and thoracic aortic angiography shows stenosis in specific areas.

Table 8.1 1990 criteria for the classification of Takayasu arteritis [5]

Criterion	Definition
Age at disease onset ≤40 years	Development of symptoms or findings related to Takayasu arteritis at age ≤40 years
Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of I or more extremity while in use, especially the upper extremities
Decreased brachial artery pulse	Decreased pulsation of one or both brachial arteries
Blood pressure difference > 10 mmHg	Difference of >10 mmHg in systolic blood pressure between arms
Bruit over subclavian arteries or aorta	Bruit audible on auscultation over I or both subclavian arteries or abdominal aorta
Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

For purposes of classification, a patient shall be said to have TA if at least 3 of these 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%

2. **Renal artery fibromuscular dysplasia:** This disease is more common in women. Renal arteriography shows distal 2/3 and branch stenosis, showing bead-like changes, most of which are found in the right renal artery, and aorta is rarely involved; vascular murmur can be heard in the upper abdomen of some patients.
3. **PAN:** This disease is more common in men over 40 years old, mainly involving small- and medium-sized visceral arteries; renal artery involvement up to 33% can cause renovascular hypertension.

8.1.4 Treatment

At present, the treatment of TA mainly includes drug therapy and surgical treatment.

8.1.4.1 Drug Treatment

1. **Glucocorticoid:** Hormone is the main drug for the treatment of TA; timely use of drugs can effectively improve symptoms and alleviate the disease. However, attention should be paid to adverse reactions such as infection, hypertension, diabetes, mental symptoms, and so on caused by hormones.
2. **Immunosuppressant**: The curative effect of simple hormone is not good; immunosuppressant combined with glucocorticoid can enhance the curative effect. The commonly used immunosuppressive agents are cyclophosphamide, methotrexate, and azathioprine. In the use of immunosuppressive agents, attention

should be paid to blood, urine routine, liver function, and renal function in order to monitor the occurrence of adverse reactions.

3. **Vasodilators and microcirculation improvement drugs:** The application of vasodilation to improve microcirculation treatment can partly improve the clinical symptoms of patients with obvious vascular stenosis. Tolazoline hydrochloride, phenoxybenzamine hydrochloride, and so on have a certain curative effect.
4. **Antihypertensive drugs:** Patients with secondary hypertension caused by unilateral renal artery stenosis, without bilateral renal artery stenosis or monofunctional kidney, can be treated with ACEI and ARB antihypertensive drugs. For patients with ineffective or failed drug treatment, surgical treatment may be considered if there are surgical indications.

8.1.4.2 Surgical Treatment

1. Arterial endarterectomy plus autogenous venous patch repair
2. Vascular reconstruction and bypass grafting
3. Common carotid artery-subclavian artery anastomosis
4. Autologous renal transplantation and nephrectomy

8.1.5 Prognosis

TA is a chronic progressive vascular disease. The affected arteries are rich in collateral circulation, so the prognosis of most patients is good. The prognosis mainly depends on the degree of hypertension and the blood supply of brain and coronary artery. The complications are cerebral hemorrhage, heart failure, renal failure, myocardial infarction, and so on.

8.2 Moderate Vascular Disease and Hypertension

Qing Zhu

8.2.1 Introduction

Polyarteritis nodosa (PAN) is necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and is not associated with anti-neutrophil cytoplasmic antibody (ANCA) [6]. It often involved the skin (nodules and ulcers), the peripheral nervous system (single or multiple neuritis), and visceral blood vessels (stenosis and microaneurysm) [7], and can cause renal vascular hypertension, and even lead to malignant hypertension [8–10].

8.2.2 Epidemiology, Etiology, and Pathogenesis

In European countries, the incidence of PAN ranges from 0 to 1.6 cases per million, and the prevalence of this disease is approximately 31 cases per million. In the United States, the incidence of PAN is 1.8 per 100,000 [11–13]. Although the incidence and prevalence of PAN were low, hypertension was more common in PAN patients. A study from the French vasculitis research group showed that the prevalence of hypertension in PAN patients was 34.8% [14], significantly higher than the prevalence of hypertension in the general population (27.3%–30%). PAN can occur in patients of every age, with a peak incidence of 40–60 years old, more common in men, and the ratio of males to females is about 1.5:1 [15].

The cause and pathogenesis of PAN were unknown. T-cell-mediated inflammatory responses and immune complex deposition may be involved in the pathogenesis. In addition, although "idiopathic PAN" is not a genetic disease, mutations in specific genes, such as ADA2 (also known as CECR1), and MEFV (related to FMF) mutations may cause necrotizing disease similar to PAN, especially in children [15].

8.2.3 Pathological Mechanism That Causes Hypertension

The pathogenesis of hypertension caused by PAN is multifaceted, mainly involving the renal artery and its main branches, leading to renal ischemia and secondary to renal hypertension.

1. Renin-angiotensin system: Vascular inflammatory lesions involve the main trunk of the renal artery and its main branches, leading to thickening of the intima, strict stenosis, and even severe occlusion of renal artery, resulting in reduced renal blood flow and renal ischemia, thereby activating the RAS system and causing elevated blood pressure.
2. Vasoactive substances: Renal ischemia can stimulate the production and release of endothelin, and endothelin has a strong effect on the renal microvascular bed, causing damage to renal blood vessels and kidney tissues, resulting in hypertension.
3. Immune activation: A number of studies have found that activation of the immune system, especially the activation of T lymphocytes, is involved in the development of PAN, while the immune cells mainly secrete cytokines IL-8, IL-17, IL-6, INF-r, etc., and can directly induce endothelial dysfunction and induce AngII production, leading to hypertension [8–10].

8.2.4 Clinical Manifestations

PAN can affect a single organ and can involve multiple organ systems. The occlusion or rupture of the inflamed arteries may produce tissue ischemia or hemorrhage in a variety of organs and systems. Consequently, PAN may generate a wide constellation

of clinical manifestations. These include nonspecific constitutional manifestations such as malaise, weight loss, fever, arthralgia and myalgia, and symptoms derived from dysfunction or damage of the target organs. The peripheral nervous system and the skin are the most frequently involved territories [7]. Mononeuritis multiplex is the most common neurological manifestation. Cutaneous features include purpura, livedoid lesions, subcutaneous nodules, and necrotic ulcers. If there is no visceral artery damage, it is called "skin type PAN" and its prognosis is better. Gastrointestinal tract and kidneys are frequently involved. Gastrointestinal tract manifestations are among the most serious expressions of PAN; this disease manifests as an acute surgical abdomen. Renal involvement in PAN comprises tissue infarction or hematoma, typically produced from the rupture of renal microaneurysms. PAN does not cause glomerulonephritis, and renal function is usually unaffected, but hypertension and even malignant hypertension are more common. For PAN, cardiac involvement is also one of the leading causes of death. In addition, testis and epididymis can also be affected, with pain as the main feature.

8.2.5 Laboratory Features

At present, there is still a lack of specific laboratory tests for PAN, and some tests have implications for the diagnosis of PAN.

1. Routine test: Erythrocyte sedimentation rate (ESR), C-reactive protein, and other acute phase reactants (leukocytosis) were commonly elevated. Urine tests showed proteinuria, hematuria, and tubular urine. Serum creatinine increased and creatinine clearance decreased.
2. Immunological examination: 7% ~ 36% of the patients were HBsAg positive. ANCA was often negative (Fig. 8.1).

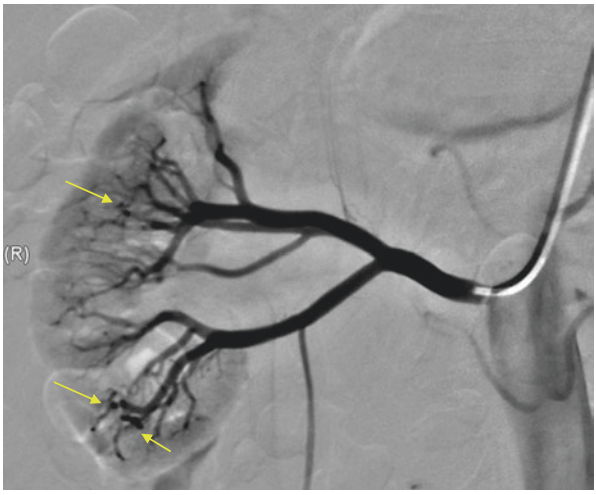

Fig. 8.1 A 50-year-old patient with hypertension for 16 years, renal insufficiency, proteinuria, rash, and weight loss of 4 kg

3. Imaging examination: Selective visceral angiography showed segmental stenosis, occlusion, aneurysm, and hemorrhage in the involved vessels. Aneurysms are most common in the renal, hepatic, and mesenteric arteries.
4. Pathological biopsy: necrotizing vasculitis (inflammatory cell infiltration of vascular wall and surrounding area, fibrinoid necrosis) of small and medium arteries in the affected area, with segment-like distribution of lesions (Fig. 8.2).
5. Other investigators recommend CECR1 screening for asymptomatic siblings of ADAM2 deficiency, cases of familial vasculitis, and case detection of refractory PAN [16].
6. Another researcher suggested to screen CECR1 for the detection of asymptomatic sibling, familial vasculitis, and refractory PAN cases with ADAM2 defects [16].

8.2.6 Diagnosis and Differential Diagnosis

It is currently diagnosed using the classification criteria of the American College of Rheumatology (ACR) in 1990 and the naming and definition of the 2012 CHCC [6]. Because PAN has no specific serum response, it can only be diagnosed according to the pathological changes of typical necrotic arteritis [17], or typical aneurysms displayed during angiography of medium vessels [18]. Because of the focal nature of the lesion, biopsy may sometimes not yield a positive result. When there

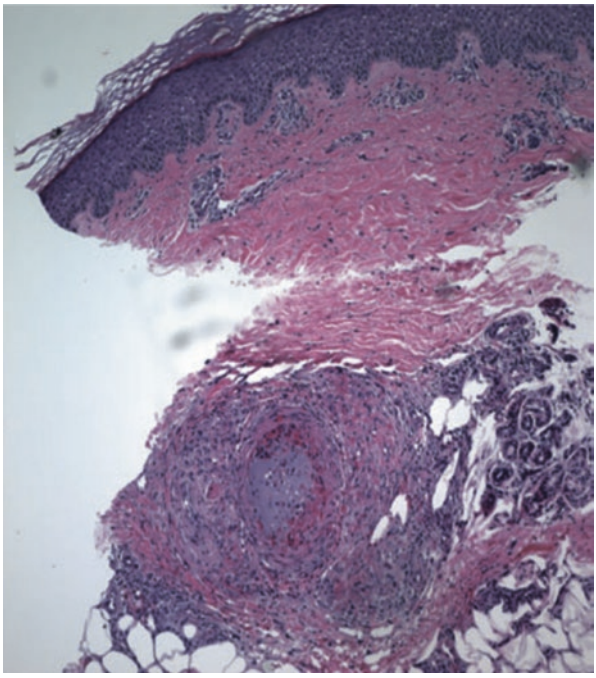

Fig. 8.2 Histologic view of the lesion illustrating vasculitis of a medium-sized artery (hematoxylin-eosin stain, original magnification) [17]

is no affirmative histological evidence, selective angiography shows that the formation of small aneurysms of the kidney, liver, and celiac vascular has diagnostic value for the disease.

8.2.7 Treatment

The level of evidence supporting therapeutic decisions in PAN is low [7]. Treatment of primary disease: The treatment programs should be decided according to the condition. The main drug used in the treatment of this disease is glucocorticoid combined with immunosuppressive agents. (1) Current therapeutic approaches consider treating mild forms of primary PAN (without serious visceral damage) with corticosteroids alone. Prednisone or prednisolone is used at doses of 0.5–1 mg/kg/day with subsequent tapering when remission is achieved. (2) In the presence of critical organ involvement, immunosuppressants are given in addition to prednisone. Combination therapy with cyclophosphamide and glucocorticoids is usually preferred. Cyclophosphamide is used at doses of 2 mg/kg/day orally or as monthly intravenous doses of 0.6 g/m^2 for 6–12 months. Pay attention to adverse drug reactions during medication. It can also be applied to azathioprine, methotrexate, nitrogen mustard, cyclosporine, mycophenolate mofetil, leflunomide, etc. In a few case reports, anti-TNF agents have been examined as treatments for PAN; however, the evidence is inconclusive and it still cannot replace glucocorticoids and cyclophosphamide as the first-line treatment for PAN. (3) In patients with HBV/HCV-associated vasculitis, combination therapy with antiviral therapy (currently lamivudine or adefovir) and short-term glucocorticoid therapy may be effective in controlling disease activity and promoting viral seroconversion. In severe cases, short-term treatment with glucocorticoid and plasma exchange may be beneficial. (4) Because cutaneous PAN does not threaten any major organ function, the general consensus is that treatment does not need to be as intense as that for idiopathic generalized PAN. First-line therapy with salicylates or other non-steroidal anti-inflammatory drugs is widely recommended [19].

8.2.7.1 Blood Pressure Management

1. ACEI/ARB: As the hypertension caused by PAN is mostly secondary to renal artery stenosis, leading to renal ischemia, RAS is activated, so it should be the first choice of angiotensin converting enzyme inhibitor antihypertensive treatment. In addition, ACEI has been shown to protect vascular endothelium. It is speculated from the mechanism of immune activation inducing AngII generation leading to hypertension that ARB can also well control blood pressure. But it need to closely observe the level of urine protein and blood creatinine when using.
2. CCB: The mechanism of hypertension induced by PAN was the same as that of renal vascular hypertension, and CCB had almost no significant effect on GFR, making it a safe and effective drug for the treatment of renal vascular hypertension.
3. β-Receptor blockers: The receptor blockers mainly reduce blood pressure mainly by reducing the plasma renin activity, but the curative effect is limited, and they are often used in combination.

4. Diuretics: Since hypertension was renin-dependent when PAN caused unilateral renal artery stenosis, the use of diuresis will stimulate renin secretion and increased blood pressure. Therefore, diuretics were generally not used for unilateral renal artery stenosis. In the case of bilateral renal artery stenosis, hypertension is associated with water and sodium retention mechanism, and diuretics can reduce blood pressure.

8.2.8 Prognosis

The 5-year survival rate for untreated PAN is 13% [20]. Since the application of hormones and cyclophosphamide to treat PAN, the 5-year survival rate of patients has increased significantly, reaching 80%. The main causes of death include renal failure and mesentery, heart or cerebral infarction.

8.3 Microvascular Disease and Hypertension

Qing Zhu

8.3.1 Introduction

Microvasculitis is divided into ANCA-associated vasculitis and non-ANCA-associated vasculitis. Non-ANCA-associated vasculitis is mostly secondary to malignant tumor, including calla tissue disease, drug-induced vasculitis, and infectious vasculitis [21]. Here, we focus on the relationship between ANCA-associated vasculitis and hypertension.

ANCA-associated vasculitis (AAV) is a group of autoimmune diseases that mainly involve small blood vessels. The pathology is characterized by necrotizing inflammation of the blood vessel wall, with less immune complex deposition. It mainly includes granulomatous vasculitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatous vasculitis (EGPA) [6]. The most commonly affected organs are the lungs and kidneys. Renal involvement often leads to renal parenchymal hypertension [22].

8.3.2 Epidemiology

AAV can occur at any age, but it is more common in patients aged 50–70. The incidence in the United States is about 3.1 cases per million people per year. It is slightly lower, about 1–2 cases per million people per year in Europe. The incidence has increased in recent years. There are slightly more males than females [23]. Studies have shown that the prevalence of hypertension in patients with ANCA-associated vasculitis is 12%, but most of them are characterized by malignant hypertension [24].

8.3.3 Etiology and Pathogenesis

The etiology and pathogenesis of this disease are unknown, and it is currently considered to be the result of a combination of genetic and environmental factors. GPA may be related to bacterial (staphylococcus aureus) infection. Recent studies have shown that the structural specificity of anti-neutrophil cytoplasmic antibodies (ANCA), neutrophil netting (NETs), and complement pathway activation pathway may be involved in the pathogenesis of this disease [25].

The main cause of hypertension caused by ANCA-associated vasculitis is kidney involvement, mainly renal small blood vessels and microvascular lesions, and the mechanism is similar to glomerulonephritis, causing renal hypertension. In the acute active period, due to the acute diffuse inflammation of the renal parenchyma, the glomerular filtration rate is rapidly decreased, resulting in a decrease in water and sodium filtration in the body, while the renal tubular sodium reabsorption function is still normal, and the ball-tube feedback regulation is disordered, resulting in sodium and water retention in the body. In the chronic phase, it is mainly caused by the expansion of extracellular fluid volume and the increase of peripheral vascular resistance caused by water and sodium retention [26].

8.3.4 Clinical Manifestations

AVV is not a single disease, but a group of diseases, usually involving multiple systems, but there are certain commonalities. Patients often have nonspecific symptoms such as fever, fatigue, weight loss, anorexia, joint pain, myalgia, and other prodromal symptoms, which usually can last weeks to months. The main organs and tissues involved in the three AAV subtypes are different, and their clinical manifestations are different, as shown in Table 8.2.

Table 8.2 Clinical manifestations of three subtypes of AAV [26]

	GPA	EGPA	MPA
Ear, nose, throat	Necrotizing, destructive	Allergic	–
Lung	Nodule, cavity, infiltrate	Asthma, infiltrates, nodule	Infiltrates
Kidney	++++	+~++	++++
Nerve	++	++++	+++
Skin	++	+++	+++
Heart	+	++	+
Granuloma	++++	++++	–
Eosinophils	–	++++	–
ANCA	PR3+ 80%–95% MPO + 5%–20% ANCA(−)0%–20%	PR3+ 35% MPO + 40% ANCA(−)60%	PR3+ 35% MPO + 40%–80% ANCA(−)0%–20%

ANCA anti-neutrophil cytoplasmic antibodies, *AAV* ANCA-associated vasculitis, *GPA* granulomatous vasculitis, *EGPA* eosinophilic granulomatous vasculitis, *MPA* microscopic polyangiitis

8.3.4.1 Laboratory Test

1. Routine examination: ESR and C-reactive protein are commonly elevated. Leukocytosis, increased platelet and chronic anemia are frequently present. Urine sediment examination showed microscopic hematuria, proteinuria, and red blood cell tubular urine. Peripheral blood eosinophilia is one of the characteristic indicators of EGPA.
2. ANCA detection: It includes indirect immunofluorescence ITF method and ELISA method; c-ANCA is more common in GPA, its target antigen is protease 3 (PR3), p-ANCA is mainly found in MPA, and its main target antigen is myeloperoxidase (MPO) enzyme.
3. Imaging examination: Chest X-ray or high-resolution CT is of great significance for diagnosis and differential diagnosis. Pulmonary imaging showed lung shadow, pleural effusion, pleural thickening, interstitial pneumonia fibrosis, and nodular cavities.
4. Pathological biopsy: The basic pathological features of AAV are oligo-immune complex deposition and necrotizing small vasculitis.

8.3.5 Diagnosis and Differential Diagnosis

The current diagnosis is based on clinical manifestations, serological examination (ANCA) and pathological biopsy (mainly renal biopsy). The diagnostic criteria for GPA and EGPA mainly use the 1990 ACR standard and the 2012 CHCC naming and definition. Currently, there is no diagnostic criteria for MPA, mainly based on (1) multiple organ involvement; (2) biopsy showed necrotizing vasculitis of small blood vessels and glomerulonephritis with less or no immune complex deposition; (3) no granuloma formation in the respiratory system [21, 25].

Differential diagnosis: AAV needs to be associated with vasculitis (PAN), other types of glomerulonephritis (lupus kidney, anti-glomerular basement membrane syndrome, etc.), pulmonary hemorrhagic-nephritis syndrome, asthma, eosinophilia Identification of diseases.

8.3.6 Treatment

The treatment of primary disease is divided into three stages: induction remission, maintenance remission, and treatment of recurrence [22, 23, 27].

Induction remission: Studies have shown that the combination of glucocorticoid and cyclophosphamide has significant effects, especially in patients with renal involvement and severe respiratory diseases, which should be the preferred treatment. (1) Glucocorticoid: Prednisone 1.0–1.5 mg/kg/day was used in the active phase, and the dose was gradually reduced and maintained at a small dose after 4–6 weeks of remission. For serious diseases such as central nervous system vasculitis, respiratory diseases with hypoxemia such as alveolar hemorrhage, progressive renal failure, and shock therapy can be used: methylprednisolone 1.0 g/day for

3 days, and the fourth day is changed to oral administration(1.0 to 1.5 mg/kg/day), and then gradually reduced according to the condition. (2) Immunosuppressant: Usually given oral cyclophosphamide 1–3 mg/kg/day, can also be used cyclophosphamide 200 mg, once every other day. For patients with stable disease, it can be maintained at 1 mg/kg/day. For severe cases, cyclophosphamide was administered intravenously with a body surface area of 0.5–1.0 g/m^2, once every 3–4 weeks. Oral cyclophosphamide 100 mg per day is also given. Cyclophosphamide is the basic drug for the treatment of AAV. It can be used for 1 year or several years. After withdrawal, patients can be relieved for a long time. During the medication, the adverse reactions, such as bone marrow suppression and secondary infection, need to be observed. It can also be applied to azathioprine, methotrexate, mycophenate, leflunomide, etc. (3) Biological agents: Rituximab is a monoclonal antibody that specifically reduces the number of B cells, has been shown to induce remission or partial remission of recurrent and refractory vasculitis in several clinical trials and case reports. Rituximab has become one of the potential drugs for the treatment of ANCA-associated vasculitis. In 2016, European Union of Rheumatology (EULAR) recommended that cyclophosphamide and rituximab had similar efficacy in inducing remission in AAV patients with life-threatening or severe organ damage. Plasma exchange may be used for patients with rapidly progressive renal failure or severe diffuse alveolar hemorrhage, if possible.

Maintenance remission: For maintenance therapy, low-dose glucocorticoids combined with azathioprine or rituximab, or methotrexate or mycophenolate mofetil are recommended to maintain remission in patients with AAV. Azathioprine is the best choice.

Recurrence: Treatment is the same as induced remission.

8.3.6.1 Treatment of Hypertension [28]

The mechanism of hypertension induced by AVV is the same as renal substantive hypertension. On the basis of the treatment of primary hypertension, ACEI, ARB, CCB, beta receptor blockers, diuretics, and other drugs were actively applied to reduce blood pressure. Single drug is very difficult to reach the standard, often combined drug. Dialysis or ultrafiltration may be considered for refractory hypertension caused by irreversible renal failure.

ACEI/ARB: Considering the important role of RAS in chronic kidney disease, blocking RAS has become the main intervention to control blood pressure and delay renal damage. ACEI/ARB can effectively reduce blood pressure and urinary protein excretion. In addition, ACEI can also reduce the accumulation of renal extracellular matrix, antagonism glomerulosclerosis, and renal interstitial fibrosis, and delay the progression of renal damage. Creatinine levels should be closely monitored during the administration. If the increase exceeds 25%, ACEI/ARB should be reduced or discontinued.

Calcium channel antagonists: CCB can dilate blood vessels and increase urinary sodium excretion, which is very effective in the control of renal substantive hypertension. In addition, CCB has many other effects besides direct blood pressure lowering, such as inhibiting proliferation of mesangial cells, inhibiting cytokine secretion and its effects, inhibiting inflammatory mediators, reducing the generation

of reactive oxygen species, inhibiting hypercoagulability, and protecting the kidney.

Receptor blocker: It mainly reduces the patient's heart rate, myocardial contractility, cardiac output, and plasma renin activity, thus lowering blood pressure. The drugs did not affect renal blood flow or glomerular filtration rate.

Diuretics: Diuretics reduce blood pressure mainly through removing sodium, reducing extracellular volume and reducing peripheral vascular resistance. It is divided into thiazide, loop diuretic, and potassium retention diuretic. The application of thiazide diuretics is limited because of the adverse effect of thiazide diuretics on metabolism at high doses.

8.3.7 Prognosis

The mortality of untreated AVV is higher, and the prognosis of AAV is significantly improved after treatment with glucocorticoids and immunosuppressive agents, but recurrence is common. The main causes of death are uncontrolled disease activity, renal failure, and uncontrolled secondary infections and lung involvement.

8.4 Other Vascular Diseases and Hypertension Nutcracker Phenomenon

Bin Zhu

Nutcracker phenomenon (NCP), also known as left renal vein compression syndrome, is a high-pressure syndrome caused by blood reflux obstruction after compression of left renal vein (LRV) [29].

8.4.1 Anatomical Basis

Anatomically, the left renal vein is longer than the right renal vein. The right renal vein flows directly into the inferior vena cava (IVC), which is short and straight, while the left renal vein needs to pass through the angle between the abdominal aorta and the superior mesenteric artery and inject IVC. Under normal conditions, the angle was 45–60°, and the left renal vein was not squeezed by mesenteric fat, lymph nodes, and so on. However, in some cases, such as excessive body growth in adolescence, excessive spinal extension or lymph node enlargement, and tumor compression, the left renal vein is squeezed, the reflux is blocked, and the internal pressure is increased and dilated, resulting in left renal blood stasis. The clinical manifestations are due to abnormal communication between the blood stasis venous system and the urine collection system, or the thinning and rupture of the venous sinus wall of the calyx dome.

8.4.2 Clinical Manifestations

1. **Hematuria and/or proteinuria:** Multiple cases were 13 to 15 years old, most of them were male, the ratio of male to female was 24 to 5, most of them were unilateral (left) hematuria, the degree of bleeding was different, and most of them were found because of sudden hematuria. Asymptomatic microscopic hematuria is also often found in routine urine tests. In addition, some patients can also show hematuria with proteinuria or simple proteinuria.
2. **Characteristics of hypertension:** Because of the hyperemia of renal vascular bed after LRV compression, the renin-angiotensin-aldosterone system is affected, and the adrenal vein blood stasis and sympathetic catecholamine level are caused by LRV compression, which leads to the increase of blood pressure. In general, mild to moderate increase of blood pressure is more common, clinical observation of blood pressure is related to posture, blood pressure after exercise and standing for a long time is significantly higher than that before exercise and lying position.

8.4.3 Auxiliary Inspection

1. **Color Doppler ultrasonography:** B-ultrasound combined with color and pulse Doppler was superior to B-ultrasound alone in the diagnosis of nutcracker phenomenon. Color Doppler could directly reflect the pressure difference between left renal vein and inferior vena cava. The measured pressure difference ≥ 4 kPa can be used as a criterion for the diagnosis of nutcracker phenomenon.
2. **CT and MRI:** CT or MRI showed dilatation of the distal end of the left renal vein, and the left renal vein between the abdominal aorta and the superior mesenteric artery suddenly became thinner and angled. The contrast medium was concentrated in the left renal sinus and lower pole area, and the distal dilatation of the left renal vein could be seen by B-ultrasound, which could indicate the phenomenon of nutcracker [30, 31].
3. **Renal venography:** It is used to observe the compression and dilatation of left renal vein directly. At the same time, the internal pressure of inferior vena cava and left renal vein can be measured directly. When the pressure of left renal vein is greater than 0.4 kpa, the pressure of left renal vein can be considered.

8.4.4 Diagnosis and Differential Diagnosis

At present, the diagnostic criteria of nutcracker phenomenon have not been unified. The imaging examination of NCP included Doppler ultrasound (DUS), CT, MRI, venography, and intravascular ultrasound (IVUS). However, the diagnosis of NCP can not only be based on imaging examination, clinical symptoms and signs are also particularly important [32].The specific diagnostic flowchart is shown in Fig. 8.3.

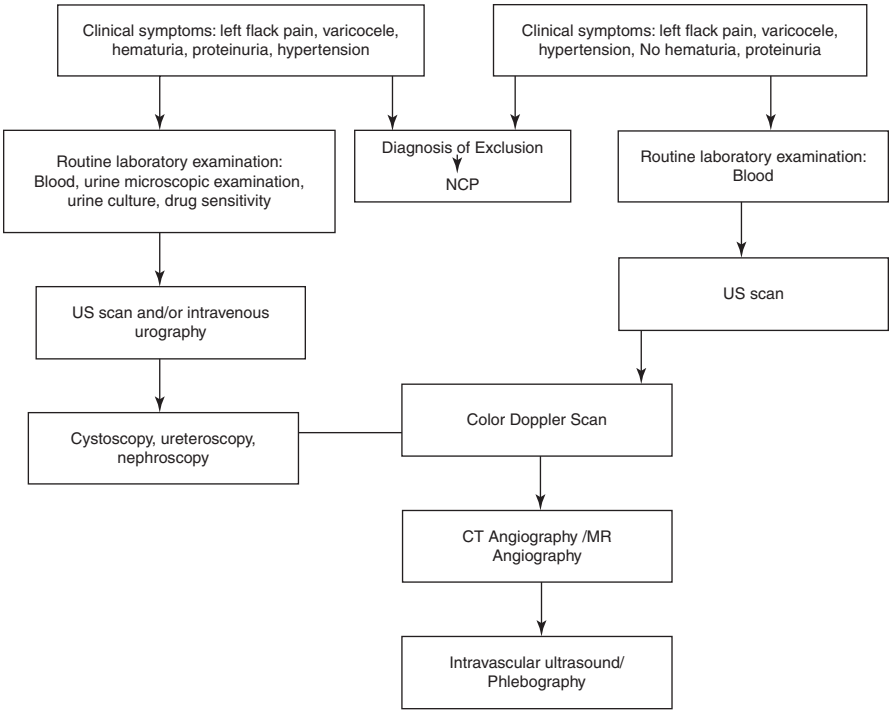

Fig. 8.3 Flowchart showing how NCP is diagnosed following a pathway from initial symptomatic presentation to a series of tests from the least invasive to most invasive

8.4.5 Treatment

At present, there is no unified understanding of the treatment of nutcracker phenomenon; the general treatment can be divided into conservative treatment, interventional therapy, and surgical treatment. Conservative treatment can be divided into two types: clinical observation without drugs and drug treatment.

Drug therapy: Infusion of silver nitrate into the renal pelvis can block abnormal communication between the venous system and the urine collection system. Interventional therapy mainly includes trans-vena cava balloon angioplasty and stenting in the stenosis of left renal vein.

Surgical treatment: Left renal fixation, resection of varicose veins around renal pelvis, renal vein bypass, left renal vein transfer-inferior vena cava end-to-side anastomosis, superior mesenteric artery suspension external fixation, autologous renal transplantation, nephrectomy, etc.

Treatment of hypertension: The increase of blood pressure in patients with nutcracker phenomenon is mainly caused by the activation of renin-aldosterone system, sympathetic nerve excitation, and the increase of catecholamine. Angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, and β receptor blockers can be selected for antihypertensive therapy.

8.4.6 Prognosis

Patients with nutcracker phenomenon underwent at least one abdominal ultrasound examination and renal function examination at least once in 1–2 years. For patients with hypertension complicated with vascular diseases, the treatment plan and antihypertensive treatment should be determined according to different vascular diseases.

8.4.7 Arteriovenous Fistula

There is an abnormal channel between artery and vein, which is called arteriovenous fistula (AVF). Because the normal blood channel of the artery flows into the accompanying vein, it can cause the local vascular disease of the fistula and the hemodynamic changes of the local, peripheral circulation and the whole body system of the fistula.

8.4.7.1 Clinical Manifestations

1. **Common symptoms and signs:** Acute arteriovenous fistula can occur immediately after injury, or after clot dissolution in arteriovenous communication, hematoma in the injury area, most of them tremor and murmur. Arterial pulsation can still be palpable in the limbs at the distal end of arteriovenous fistula, but weaker than that in the contralateral side. The affected limbs of patients with chronic arteriovenous fistula are swollen, numb, painful, and weak. There is a buzzing in the pulsatile mass. Heart failure can have chest tightness, palpitations, and shortness of breath.
2. **Hypertension characteristics:** Once patients with arteriovenous fistula complicated with hypertension, often manifested as serious, persistent hypertension, blood pressure can be above 170/130 mmHg, accompanied by dizziness, panic, and other manifestations, and symptoms can be progressively aggravated. If the arteriovenous fistula is large, the systolic blood pressure is significantly increased and the pulse pressure difference is widened [33].

8.4.7.2 Auxiliary Inspection

1. **Ultrasonic examination:** It is the first choice for peripheral arteriovenous fistula. Color Doppler flow imaging is easier to show fistula than two-dimensional ultrasound, the blood flow at the fistula is multicolored, the color blood flow in the artery near the heart of the fistula is bright, but the color blood flow in the artery at the distal end of the fistula is dim. The venous blood flow in the proximal end of the fistula was also accelerated and the flow channel was widened [34].
2. **Measurement of finger pressure fistula:** Finger pressure fistula to block blood shunt, measure the heart rate and blood pressure before and after blocking shunt, and compare them. After blocking the blood shunt, the heart rate slowed down significantly.
3. **Measurement of mean arterial pressure at the distal end of arteriovenous fistula:** When the fistula was large and the collateral circulation was small, the

mean arterial pressure decreased significantly, and the mean arterial pressure at the distal end of the fistula changed little when the fistula was small and the collateral circulation was abundant.

4. **Arteriography:** The location and size of the fistula, as well as the expansion of nearby blood vessels and collateral circulation can be determined.

8.4.7.3 Diagnosis and Differential Diagnosis

The diagnosis of arteriovenous fistula is generally not difficult. In the history of penetrating trauma, the patient can find his own pulsatile mass, and there is a local buzzing. The possibility of arteriovenous fistula should be taken into account when one side of the limb is swollen, varicose veins and venous valve dysfunction, and the local skin temperature of the limb is higher than that of the contralateral side. When there are scars, murmurs, and tremors in the injured site, the possibility of arteriovenous fistula should be taken into account.

8.4.7.4 Treatment

1. **Surgical treatment.** After the diagnosis has been determined, the patient is generally allowed to undergo early surgery. Patients with acute arteriovenous fistulas may undergo fistula repair, or anastomosis of the two ends of the artery after fistula resection or use autologous great saphenous vein transplantation according to different conditions of arterial injury. For the patients with chronic stage, the surgical methods of arteriovenous fistula include arteriovenous fistula ligation and closure, arteriovenous fistula resection and vascular reconstruction and fistula open artery artificial vascular transplantation and so on.
2. **Treatment of hypertension.** For the mild to moderate hypertension secondary to chronic arteriovenous fistula, the main mechanism of hypertension is the increase of blood volume and the activation of renin, so diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor antagonists can be used. Vasodilators can be used to treat refractory severe hypertension.

8.4.7.5 Prognosis

Patients with arteriovenous fistula generally have good surgical results, but need to be followed up for life.

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Endocrine Hypertension

9

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9.1 Pituitary Diseases and Hypertension

Weiwei Zhang

Pituitary gland, located in the sella pituitary fossa of the skull base, is the most important endocrine gland in the body, secreting hormones and regulating other endocrine glands. The pituitary gland is divided into neurohypophysis (posterior pituitary) and adenohypophysis (anterior pituitary). The neurohypophysis can also be divided into the middle part and the nerve part. The pituitary gland is connected with the hypothalamus through the pituitary stalk to form the hypothalamus neurohypophysis system. There are five main endocrine cells in adenohypophysis, which secrete seven different hormones, including growth hormone (GH), thyrotropin, (TSH), suprarenal adrenocortical hormone (ACTH), follicle-stimulating hormone, (FSH), luteinizing hormone (LH), prolactin (PRL), promoted melanin (MSH), and so on. All kinds of pituitary diseases, resulting in abnormal hormone secretion or increased intracranial pressure, can lead to increased blood pressure. Summary of pituitary hormones related to hypertension as shown in Table 9.1.

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Table 9.1 The effect of pituitary hormone and its relationship with blood pressure regulation

Pituitrin	Target gland	Physiological action	Relationship with blood pressure
GH	Several glands	Promote the growth of the body and bones and increase blood sugar Promote protein synthesis and mobilize fat	Related
PRL	Several glands	Lactation, osmotic pressure regulation, immune regulation, etc	Probably related
ACTH	Adrenal gland	Remote adrenocortical hyperplasia Stimulating steroid synthesis and release	Probably related
TSH	Thyroid gland	Hypertrophic thyroid hypertrophy Synthesis and release of thyrotropin	Probably related
FSH	Sexual gland	Promote follicular maturation (female) Promote sperm production (male)	Uncorrelated
LH	Sexual gland	Synergetic FSH to promote follicular maturation and ovulation Sex-stimulating hormone synthesis and secretion	Uncorrelated
AVP	Several glands	Regulating water metabolism and promoting smooth muscle contraction	Probably related
MSH	Melanocyte	Promote melanin synthesis, lower blood pressure, slower heartbeat	Probably related

The hypothalamic paraventricular nucleus secrets oxytocin (oxytocin), and the supraoptic nucleus secretes vasopressin (AVH, ADH), which stores and releases these hormones. Vasopressin and oxytocin directly act on the effector organs. The pituitary gland is not needed as an intermediate link.

9.1.1 Disease of Pituitary Gland

There are many diseases of hypothalamus-pituitary, including neuroendocrine diseases, pituitary tumors, adenohypophysis, hypophysis, vacuolar sella syndrome, and so on. Pituitary lesions can lead to a variety of endocrine diseases. All kinds of pituitary diseases, resulting in abnormal hormone secretion or increased intracranial pressure, can lead to increased blood pressure. Clinically, pituitary adenomas are the most common. The incidence of pituitary adenoma was the second in intracranial tumors, accounting for 15% of intracranial tumors. The incidence of pituitary adenomas was 8.2–14.7% in population and 20–30% in routine continuous autopsies. According to Peking Union Hospital, men are slightly more than women, and the age of onset is mostly between 31 and 40 years old.

9.1.2 Pituitary Tumor Classification

There are many types of pituitary adenomas. For a long time, they have been classified mainly on the basis of histopathology, immune markers of related hormones, and ultrastructural characteristics. In recent years, with the discovery of transcription factors (PIT1), SF1 and TPIT are very important in the regulation of pituitary cell differentiation and specific pituitary hormone secretion. 2017 WHO classifies pituitary adenomas based on the origin of pituitary adenomas (Table 9.2) [76].

9.1.3 Pathogenesis of Pituitary Adenoma

The pathogenesis of pituitary adenomas is not clear, but it is generally believed that this is a multi-factor process, which involves the abnormal expression of genes, abnormal proliferation of cells, the participation of many kinds of cytokines, and so on. At present, the development of pituitary adenoma can be divided into two stages: the initial stage and the promoting stage, that is, the pituitary cell mutation occurs first, and the mutant cell proliferation is promoted by internal and external factors, which develops into pituitary tumor. The deficiency of pituitary cells in the initial stage is the main cause of the disease, and it plays a major role in the disorder of hypothalamus regulation in the promoting stage.

9.1.4 Mechanism of Pituitary Adenoma Leading to Hypertension

The increase of blood pressure caused by pituitary adenoma is mainly related to the abnormal secretion of hormone and the increase of intracranial pressure. The mechanism of hypertension caused by excessive growth hormone secretion is unclear.

Table 9.2 The 2017 WHO classification of pituitary adenoma

Adenoma type	Immunophenotype	Transcription factors and other co-factors
Growth hormone cell adenoma		
Dense granular growth hormone cell gonadoma[a]	GH ± PRL ± α-subunit LMWCK: perinuclear or diffuse	PIT1
Sparse granular growth hormone cell adenoma	GH ± PRL LMWCK: Dot (fibrous body)	PIT1
Prolactin growth hormone cell adenoma	GH ± PRL (in the same cell) ± α-subunit	PIT1, ERα
Prolactin cell adenoma		
Sparse granular gonadotropin cell adenoma[a]	PRL	PIT1, ERα
Dense granular prolactin cell adenoma	PRL	PIT1, ERα
Eosinophilic stem cell adenoma	PRL, GH (local and unstable LMWCK: fibrous body	
Thyrotropin cell adenoma	TSH-β, α-subunit	PIT1, GATA2
Corticotropin cell adenoma		
Dense granular corticotropin cell adenoma[a]	ACTH, LMWCK: suffuse	TPIT
Sparse granular corticotropin cell adenoma	ACTH, LMWCK: suffuse	TPIT
Crooke cell adenoma	ACTH, LMWCK: cyclic annular	TPIT
Gonadotropin cell adenoma		
Sparse granular gonadotropin cell adenoma[a]	TSH-β, LH-β, α-subunit	SF1, GATA2, Era (different degrees)
Null cell adenoma	Non	Non
Polyhormone cell adenoma		
PIT1-positive polyhormone cellular adenoma[b]	GH, PRL, TSH-β ± α-subunit	PIT1
Rare adenomas with a combination of immunohistochemical expression	various combination	Other transcription factors (different degrees)
Double hormone cell adenoma		
With two different hormone cell adenomas	PRL/ACTH	PIT1 and TPIT

Note: LMWCK low molecular weight cytokeratin; TSH-β thyrotropin β subunit; ACTH corticotropin; FSH-β follicle-stimulating hormone β subunit; LH-β luteinizing hormone β subunit; ER receptor; a is the most common subtype; b previously known as silent adenoma type 3; c refers to the almost identical alpha subunit of four glycoprotein hormones, namely, FSH, LH, and TSH in the pituitary and chorionic gonadotropin in the placenta

The incidence of hypertension in patients with acromegaly is higher than that in normal controls. It may be related to the following factors: growth hormone has the effect of sodium retention. High level growth hormone can promote the secretion of aldosterone and increase the level of renin-angiotensin (renin-angiotensin), which leads to the increase of peripheral resistance due to the thickening of blood vessel wall. The excessive secretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) by growth-stimulating melanoma (GH) leads to increased basal metabolic rate (BMR) and hyperplasia of tissues and organs. Hypertrophic nose, hyperplastic lip and thick tongue, tonsil, uvula and thickening of soft palate, changes of nose, tongue, and pharynx caused respiratory obstruction. Sleep apnea syndrome was involved in the increase of blood pressure. ACTH adenomas can cause secondary cortisol over-secretion, excessive cortisol can lead to water and sodium retention, activate and maintain the renin-angiotensin-aldosterone system. Increased glomerular filtration resulted in glomerulosclerosis and proteinuria, increased activity of vasoconstrictor substances, and increased blood pressure. At the same time, corticotropin itself has the effect of increasing heart rate. Hypersecretion of thyrotropin causes pituitary hyperthyroidism. Thyroid hormone stimulates the excitability of sinoatrial node, increases myocardial contractility and cardiac output, and then leads to increased systolic blood pressure. Prolactin is associated with the regulation of osmotic pressure, and PRL through renin-blood. The regulation of saline corticosteroids by angiotensin system may be the cause of increased blood pressure, which needs further study.

9.1.5 Pathology

According to the routine pathological staining, pituitary adenomas can be divided into four categories: chromophobe, eosinophils, basophilic, and mixed. The current guidelines emphasize the need for histopathological analysis of tumors, including pituitary hormones, transcription factors, and proliferation markers, such as Ki-67, p53, and mitotic index, to determine tumor proliferation and invasive activity [2]. Tumor Ki-67 $\geq$ 3% is combined with p53 (+) or Ki-67 $\geq$ 3% with increased mitosis index, suggesting poor prognosis [3]. For young patients with a family history of endocrine tumors such as pituitary tumors, species genetic detection is recommended.

9.1.6 Clinical Manifestation

There are few clinical manifestations in the early stage of pituitary adenoma. Pituitary adenomas without biologically active hormone secretion mainly include two clinical manifestations: (1) the extension of tumor to the outside of the sella compresses adjacent tissue structure, and this kind of symptom is the most common reasons for patients seeking medical treatment; (2) the hypofunction of adenohypophysis caused by compression and destruction of normal pituitary tissue around the tumor. Pituitary adenomas with bioactive hormone secretion have one or more clinical manifestations of pituitary hormone hypersecretion.

Pituitary compression: due to the enlargement of adenomas, the pituitary tissue outside the tumor was compressed and atrophied, resulting in decreased secretion of other pituitary hormones and atrophy of the corresponding surrounding target glands.

Peripituitary tissue compression: Common symptom is headache, often occurs in both temporal, frontal, posterior eyeball and nasal roots. The main cause of headache is the traction of the sellar septum and the surrounding dura mater due to the upward growth of the tumor. Pain may decrease or disappear when the tumor breaks through the saddle septum. Depending on the size and direction of tumor growth, the following symptoms may also occur: Vision loss, visual field defect, fundus change (mainly temporal hemianopia or bilateral superior temporal hemianopia), diabetes insipidus, abnormal sleep, hyperorexia or hypoorexia, thermoregulation disorder, autonomic nervous dysfunction, precocious puberty, hypogonadism, personality change, etc.

Hormone secretion abnormality: hyperpituitarism and hypophysis.

Hypertension: The characteristics of hypertension caused by pituitary adenomas are related to endocrine types of pituitary adenomas. Blood pressure increased in 25–60% of pituitary growth-stimulating melanoma patients and 60% died of hypertension-related cardiovascular disease. The incidence of hypertension in patients with acromegaly is higher than that in normal subjects (30–63%). ACTH tumors are often associated with increased blood pressure. The severity of hypertension is related to the course of disease, and the blood pressure in patients with acromegaly is increased to a certain extent, with the prolongation of the course of disease. The incidence of hypertension increased, and the severity of hypertension increased. A few patients had severe hypertension in the early stage, and this was the first symptom to seek medical treatment. The systolic blood pressure increased, the diastolic blood pressure decreased, and the pulse pressure difference increased due to pituitary hyperthyroidism.

Pituitary apoplexy: When pituitary tumors bleed, necrosis, can lead to pituitary apoplexy. May appear blurred mind, orientation disorder, neck ankylosis, or even coma or death.

9.1.7 Imaging Examination

CT is of great value in the diagnosis of pituitary adenomas.MR is more sensitive than CT. MR is the first choice of imaging examination for finding microadenomas of 3 mm. MR can clearly display pituitary and its surrounding soft-tissue structure, distinguish optic chiasma from sella septum, clearly show whether cerebrovascular and pituitary tumors invade cavernous sinus and sphenoid sinus, and whether pituitary stalk is compressed, etc. PET can observe physiological and biochemical processes, such as blood flow, local glucose metabolism, amino acid metabolism, protein synthesis, receptor density, and distribution. PET can distinguish tumor necrosis from recurrence. But PET costs higher. The plasma ACTH level was measured by intubation of anterior elbow vein to inferior petrosal sinus vein and compared with the plasma ACTH level of peripheral vein. The method of measuring ACTH concentration gradient by intravenous catheterization is helpful to the diagnosis of ACTH tumor and is one of the differential diagnostic methods for the etiology of cortisol hyperplasia [4].

9.1.8 Examination of Endocrine Function

Functional examination is essential. The following factors should be taken into account in assessing the results of the examination of adenohypophysis: (1) adenohypophysis hormones are secreted and released in a pulse manner; (2) there are many factors affecting the secretion of adenohypophysis hormone, the time of blood sample extraction, whether to eat, stress, sleep state or awakening state, age, growth stage, and so on; (3) explain the change of the hormone level of a certain adenohypophysis, it must be considered as a link in the hypothalamic-pituitary-target axis to be analyzed as a whole; (4) the range of normal values of adenohypophysis hormone varies from laboratory to laboratory; (5) when one pituitary hormone secretion is abnormal, other adenohypophysis hormones should be detected comprehensively; (6) functional and imaging examinations must be combined; (7) the heterogeneity of adenohypophysis hormone component in blood circulation can cause the inconsistency of immune activity and biological activity and lead to the inconsistency between laboratory examination and clinical manifestation.

9.1.9 Diagnosis

The diagnosis of pituitary adenoma is not difficult, and some patients can make the correct judgment according to the clinical manifestation. Some microadenomas are difficult to diagnose. There was no significant increase in hormone secretion in microadenomas. Accurate and complete diagnosis includes detailed medical history, careful physical examination (including nervous system, fundus, visual acuity, visual field examination), various pituitary hormones, and their dynamic function tests.

9.1.10 Treatment

Therapeutic goal: Alleviate or eliminate the influence of tumor occupying lesions, correct the excessive secretion of hormone by the tumor, and preserve pituitary function as much as possible. Treatment includes basic treatment and symptomatic therapy. There are three basic therapies: drug therapy, surgical treatment (transcranial or transsphenoidal), and radiotherapy.

Prolactinoma is usually first treated with drugs. With the exception of prolactinoma, all pituitary adenomas, especially macroadenomas and functional tumors, especially compression of the central nervous system and optic tract, should be considered for those with ineffective or intolerable drug therapy. There are transcranial and transsphenoidal approaches. With the development of microsurgical technique, transsphenoidal approach gradually replaces transcranial approach and becomes the main method of pituitary adenoma resection. Through transsphenoidal approach, direct nasal approach with less damage was used. It was reported that the remission rate of microadenoma was about 59–95%, macroadenoma was 26–68%, and the total response rate was 34–74% [5].

Surgical treatment of pituitary adenomas generally depends on the following four aspects: (1) experience and level of surgeons; (2) size of mass; (3) invasion of bone or dura mater; (4) previous treatment. Surgical complications include cerebrospinal fluid rhinorrhea, loss of vision, stroke or cerebrovascular injury, meningitis or abscess, ophthalmoplegia, and hypophysis.

In the patients with hypofunction, appropriate hormone replacement therapy was given according to the damage of the target gland. For people with hyperfunction, different drugs are given according to the circumstances to reduce hormone release. Drug therapy is mainly used in prolactin and growth hormone adenomas. The main drugs are bromocriptins and somatostatin, the former inhibits the synthesis and secretion of prolactin, the latter inhibits the synthesis and secretion of growth hormone, and also inhibits the growth of tumor. It is beneficial to the operation and postoperative adjuvant therapy to control the high secretion of growth hormone after operation [6–8].

Radiotherapy is an adjunct therapy for pituitary adenomas, including conventional radiotherapy, radiotherapy (RT), stereotactic radiosurgery/radiotherapy, and stereotactic radiosurgery (SRS)/radiotherapy (SRT). Side effects of radiotherapy include adenohypophysis (requiring long-term follow-up and hormone replacement therapy), optic neuritis and vision loss as well as brain atrophy and cognitive impairment.

The treatment principle is the same as the general secondary hypertension, first of all, it is necessary to choose the corresponding treatment for the basic diseases, and the use of antihypertensive drugs is the same as primary hypertension.

9.1.11 Prognosis

Pituitary adenoma patients have a long course and good prognosis, especially early diagnosis, early treatment, and the quality of life is not affected. Pituitary adenoma secondary hypertension, especially acromegaly, the hypotension effect is not ideal; some patients have serious target organ damage and poor prognosis.

9.2 Thyroid Dysfunction and Hypertension

Ying Wang

Thyroid dysfunction can cause common endocrine hypertension, and it is a potentially reversible cause of hypertension. Clinical studies have shown that hyperthyroidism and hypothyroidism can cause elevated blood pressure, especially in women, the prevalence in the population can reach 1.0–1.6% and 1.0–4.6%, respectively. Proficiency in the pathogenesis, specific clinical manifestations and related screening methods of hypertension caused by abnormal thyroid function will greatly reduce the misdiagnosis, and achieve the purpose of correct diagnosis and treatment. The following is a summary of the relationship between thyroid dysfunction and hypertension.

9.2.1 Hyperthyroidism and Hypertension

Hyperthyroidism is a group of common endocrine diseases caused by hyperthyroidism and/or the increase of thyroid hormone level in blood circulation caused by many causes. The disease is more common in young and middle-aged women. Clinically, it is characterized by hypermetabolic syndrome, goiter, exophthalmos, dysfunction of nerve, and cardiovascular system. Pathologically, thyroid gland can be diffuse, nodular, or mixed enlargement. In a ten-year etiological survey of hypertension in Xinjiang Uygur Autonomous region people's Hospital, one of the largest comprehensive Grade 3A hospitals in Xinjiang, it was found that about 1 % of the patients were secondary hypertension caused by hyperthyroidism. The results are basically consistent with the etiological analysis of hypertension in inpatients in many hospitals in China. However, the refinement of the current social medical discipline may make this type of hypertension patients be diverted to endocrinology and thyroid surgery and other related departments, so the data may be underestimated.

9.2.1.1 Epidemiology

Thyroid disease is a common disease, mainly due to different regional diet containing iodine and clinical manifestations are different. The epidemiological study of thyroid diseases is limited by a variety of limitations, including the definition of thyroid dysfunction and subclinical thyroid dysfunction, and different criteria for selecting specimens for detection. And there are relatively few statistical data on the incidence of thyroid hormones due to different methods of determination of thyroid hormones.

Hyperthyroidism is a frequently occurring and common disease of the endocrine system. The incidence of hyperthyroidism is about 0.5%, which is more common in urban residents than in rural population. According to a British data set, 1.6% of men suffer from the disease; the annual incidence of women is estimated at 2–3%. Epidemiological data on thyroid dysfunction in Europe show that the prevalence of undiagnosed clinical and subclinical hyperthyroidism in women is 1.71%, 0.49%, and 0.42%, compared with men is 1.81%, 1.67%, and 0.27% [9]. In China, the prevalence of hyperthyroidism is between 1.2 and 2%, while the incidence of subclinical hyperthyroidism is between 1.1 and 3.9%, which depends on iodine intake [10]. The prevalence of hyperthyroidism in Germany was 0.4% [11]. In the United States, the prevalence of hyperthyroidism is about 1.2% (0.5% obvious, 0.7% subclinical) [12]. Epidemiological investigation in China shows that the total incidence of hyperthyroidism is 3%, 4.1% in women, and 1.6% in men. In recent years, it has been found that with the development of society, the main inducing factors of hyperthyroidism, such as the increasing pressure of social work, mental stress, and trauma, lead to the increase of the incidence of hyperthyroidism. A large number of studies have shown that hyperthyroidism with hypertension is one of the characteristic manifestations of the disease. According to the relevant literature, the highest incidence of the disease can reach 30%, the main manifestations are the increase of systolic blood pressure, pulse pressure, with the correction of thyroid function and blood pressure can return to normal.

9.2.1.2 Etiology and Pathogenesis

According to the etiology and pathogenesis of hyperthyroidism, it can be divided into the following five categories (Table 9.3):

As mentioned above, the most common cause of hyperthyroidism is diffuse toxic goiter, Graves' disease (hereinafter referred to as GD). Clinically, it was found that the disease had a significant genetic tendency. It was found that GD was associated

Table 9.3 Five categories

Category	Pathogenesis characteristics
Hyperthyroidism	
Diffuse goiter with hyperthyroidism	The most common, about 85%, is mainly due to the autoimmune mechanism. Thyroid-stimulating hormone receptor antibody (TRAb) is often detected in patients
Nodular goiter with hyperthyroidism	The etiology is unknown and is common in patients who have suffered from thyroid nodules for many years. It is more common in the elderly, the onset of the disease is slow, symptoms are mild, exophthalmos rare. Thyroid radionuclide imaging showed a slight diffuse increase in thyroid uptake of 131 I, but a scattered nodular concentration. TSH or exogenous thyroid hormone could not change its iodine uptake function
Autonomous and highly functional thyroid adenoma or nodule	The etiology is unknown, the vast majority of patients with single adenoma, but also occasionally multiple nodules. Most of them were found in middle-aged women. The onset of the disease was slow, the symptoms were mild, no exophthalmos was found, and T3 type hyperthyroidism was more common. Thyroid radionuclide imaging showed that the thyroid presented as a single "hot nodule" and occasionally multiple "hot nodules," which were not regulated by TSH
Neonatal hyperthyroidism	The incidence of hyperthyroidism in infants born to pregnant women with hyperthyroidism is closely related to the concentration of TRAb in the mother's body. One month after birth and 3 months after birth, it is often self-reliant
Iodine-induced hyperthyroidism	As a result of long-term overconsumption of iodine. Mild symptoms, rare exophthalmos, common thyroid nodules
Hyperthyroidism caused by primary thyroid cancer	Some primary thyroid cancer can secrete a large amount of thyroxine, which can lead to hyperthyroidism
Secondary hyperthyroidism	
Pituitary hyperthyroidism	Extremely rare as a result of pituitary adenomas secreting a large amount of TSH
Ectopic TSH secretion syndrome	It occurs occasionally in women with choriocarcinoma or hydatidiform mole, or in men with testicular choriocarcinoma, as well as in some cancers of the bronchus and digestive tract. Thyroid hyperthyroidism is caused by the secretion of TSH-like substances by cancer tissue
Allogenic hyperthyroidism	Other parts of the body have thyroid hormone-secreting tissue, but the thyroid itself has no pathological changes. Including: (1) hyperthyroidism caused by goiter of ovarian teratoma; (2) metastasis of thyroid
Drug-induced hyperthyroidism	These include: (1) excessive use of thyroxine; (2) excessive use of iodine
Thyroiditis with hyperthyroidism	Due to the destruction of thyroid follicles, excess thyroid hormones stored in follicles enter the blood circulation, resulting in hyperthyroidism. Most of them are temporary and can be converted into hypothyroidism at the later stage

with histocompatibility complex (MHC) gene, and environmental factors might be involved in the occurrence of GD. The direct evidence of the immune mechanism of hyperthyroidism is that a variety of antibodies against thyroid cell components can be detected, such as thyroid-stimulating antibody (TISI), against TSH receptor or TSH receptor antibody (TRAb). It binds to TSH receptors or their associated tissues. Further activation of cAMP enhances thyroid function, an antibody that can pass through placental tissue, causing neonatal hyperthyroidism, or persistent antibody positivity. There are sensitized T lymphocytes for thyroid antigen in the blood of patients with hyperthyroidism. Lymphocytes activated by phytohemagglutinin (PHA) can excite T lymphocytes and then stimulate B lymphocytes, thus producing immunoglobulin which can excite thyroid function and lead to hyperthyroidism. The indirect evidence was: (1) a large number of lymphocytes and plasma cells infiltrated in the thyroid gland and behind the eyeball, (2) the number of lymphocytes in the peripheral blood circulation increased. May be accompanied by lymph nodes, liver and spleen reticuloendothelial tissue hyperplasia; (3) patients and their relatives at the same time or successively develop some other autoimmune diseases; (4) blood antithyroid antibodies and anti-gastric parietal cell antibodies in patients and their relatives. (5) IgG, IgA, and IgM were increased in thyroid gland and blood.

9.2.1.3 Pathophysiology

The thyroid gland of GD is diffuse enlargement, which can be symmetrical or asymmetric. In addition, there is a complete capsule, smooth surface, rich blood flow, follicular and follicular epithelial cell proliferation. Interstitial lymphocytes and plasma cells infiltrated. Lead to hyperplasia and enlargement of the liver, spleen, thymus and lymph nodes. Under electron microscope, the number of microvilli, glial droplets, Golgi apparatus, rough endoplasmic reticulum, mitochondria, and lysosomes in thyroid follicular epithelial cells increased, and the thyroid gland showed active function.

In hyperthyroidism, the multi-system organs are involved, the whole body striated muscle steatosis, edema, stria disappear, vacuole degeneration, the nucleus is degenerative. It leads to myocardial degeneration, myocyte necrosis, monocyte infiltration and mucopolysaccharide deposition. Exophthalmos, lymphocyte infiltration, mucopolysaccharide deposition, optic nerve edema or atrophy. Symmetrical thickening, subcutaneous edema, swelling of collagen fibers, cleavage and separation can occur in the skin. The staining of extracellular mucopolysaccharide was enhanced and monocytes increased, most of which occurred in the anterior tibia and lower extremities. The liver was enlarged, the hepatocytes showed fat degeneration, and the liver glycogen decreased. Endocrine glands can be involved, gonads and adrenal glands can occur in severe patients with hypofunction. Osteoporosis and bone decalcification are more common, osteoclast activity is enhanced, bone resorption is more than bone formation, bone deformity, and pathological fracture can also occur in serious cases, especially in elderly women.

9.2.1.4 Mechanism of Hypertension Caused by Hyperthyroidism

Excessive thyroid hormones in blood circulation, resulting in increased excitability and hypermetabolism of neuromuscular, circulatory, digestive and other systems, is

the initial link in the occurrence and development of hypertension. The mechanisms of hyperthyroidism leading to the increase of blood pressure are as follows: (1) To increase the protein synthesis of myocardial cells, increase myocardial contractility and cardiac output, manifested as increased systolic blood pressure. (2) The structure of thyroxine is similar to that of catecholamine, which can increase the activity of sympathetic nervous system, increase the binding of adrenergic receptor to catecholamine, and enhance the inotropic (vasoconstriction) of myocardium and blood vessels. (3) The increase of sympathetic activity in hyperthyroidism can increase the synthesis and release of renin and contribute to the occurrence of hypertension. (4) When the thyroid hormone in blood reaches a certain extent, it can increase the production of hepatic angiotensin, which can lead to the increase of RAAS activity. (5) Increase the level of serum atrial natriuretic peptide, which can inhibit the production of vasopressin, thus indirectly affecting renal blood flow, glomerular filtration rate, and sodium homeostasis to increase blood pressure.

As mentioned above, in addition to the direct action of the cardiac blood vessels, thyroxine also acts on many systems involved in the regulation of blood pressure, thereby increasing the stroke volume and systolic blood pressure of the heart, while thyroxine acts on the periphery, the heat dissipation increases, and the peripheral blood vessels dilate, and diastolic blood pressure is slightly lower or normal, resulting in a significant increase in pulse pressure, resulting in high output hypertension.

9.2.1.5 Clinical Manifestation

Hyperthyroidism can occur at any age, most of the ages are 20–40 years old, and women generally have a higher incidence than men, about 4:1. However, in the endemic goiter area, women are only slightly more than men, about 4:3. Young women often have thyroid hyperthyroidism with mild symptoms. Some people are untreated and can heal themselves after puberty. In recent years, the elderly with hyperthyroidism is increasing. Older patients are more prone to occult or apathy hyperthyroidism. The clinical symptoms are mild, the course of disease is prolonged after the onset, the recurrence rate is high, and various complications can occur. In general, hyperthyroidism is complicated by multiple systems, and the clinical manifestations are variable. The main clinical manifestations are shown in Table 9.4.

1. Multi-system hypermetabolic syndrome: patients often have fatigue, fear of heat and sweating, wet skin, more food and hunger, weight loss, hyperactivity, tension and anxiety, irritability, insomnia, lack of concentration, hand and eyelid tremors. Tremor, palpitation shortness of breath, tachycardia, elevated blood pressure, increased defecation frequency, fatigue and periodic paralysis caused by thyroid toxicity, and so on. Thyrotoxic periodic paralysis occurs in Asian men aged 20–40 years old. The inducements include strenuous exercise, high carbohydrate diet, insulin injection, and so on. The lesions mainly involve the lower limbs and have hypokalemia. The course of disease is self-limited. In addition, a small number of patients with hyperthyroidism myopathy, myasthenia gravis more involved in the proximal scapular and pelvic band muscle groups. In addition, 1% GD is associated with myasthenia gravis, which is an autoimmune disease as well as GD.

Table 9.4 Involved tissues and clinical manifestations of hyperthyroidism

Affected tissues and systems	Clinical manifestation
Central nervous system	Neuroticism, irritability, emotional instability
Thyroid gland	Nodular swelling
Cardiovascular system	Palpitation, tachycardia, atrial fibrillation; blood pressure increases by systolic pressure and pulse pressure
Digestive system	Increased gastrointestinal peristalsis, hyperappetite and hunger; increased defecation, diarrhea
Skin and metabolic system	Skin damp-heat, sweating, heat-resistant; hair fine and easy to take off; body metabolism exuberant, weight loss
Muscle motor system	Muscle tremor, especially in both hands; the proximal muscle is weak and prone to fatigue

2. Goiter of different degrees: generally symmetrical, a few asymmetric enlargement, divided into I, II, III enlargement, most of them showed diffuse enlargement, often vascular murmur and tremor. The thyroid gland may not be enlarged, or the thyroid gland has cystic and nodular enlargement.
3. Different types of eye signs: exophthalmos beyond 16 mm is exophthalmos. About 25% of GD patients had exophthalmos. Generally can be divided into simple exophthalmos and infiltrative exophthalmos. Simple exophthalmos is common. The etiology is related to the increase of sympathetic excitability caused by thyrotoxicosis, including the following manifestations: (1) mild exophthalmos: exophthalmos 19–20 mm; (2) Stellwag sign; (3) upper eyelid contracture and widening of eyelid fissure; (4) von Graefe's sign; (5) Joffroy's sign (6) Mobius sign. However, infiltrative exophthalmos is relatively rare in clinic and the prognosis is poor. The general patient complained of foreign body sensation, distension and pain, photophobia, tears, diplopia, strabismus, and visual acuity decline; examination showed exophthalmos, eyelid swelling, conjunctival congestion and edema, limited eye movement, and in severe cases, eye fixation, eyelid insufficiency, corneal exposure and corneal ulcer, total ophthalmitis, and even blindness. In general, the incidence of male is higher than that of female.
4. Characteristics of hypertension: as mentioned earlier, hypertension secondary to hyperthyroidism is mainly related to the increase of cardiac stroke volume, accompanied by peripheral vascular dilatation, so the patient shows elevated contraction, slightly lower or normal diastolic blood pressure, and a significant increase in pulse pressure.

9.2.1.6 Laboratory and Auxiliary Examinations

The results of thyroid function examination may vary according to region, age, and measurement method. The main monitoring items and their clinical significance are as follows:

1. Serum total thyroxine (TT4): it is the most basic screening index to judge thyroid function. T4 was all produced by thyroid gland, of which 80–90% bound to thyroid hormone binding protein (TBG). TT4 is a hormone that binds to this

part of the protein, so changes in the amount of serum TBG and the binding capacity of the protein to the hormone will affect the results of the determination. Pregnancy, estrogen, acute viral hepatitis, and congenital factors can cause the increase of TBG, leading to the increase of TT4; androgen, glucocorticoid, hypoproteinemia, and so on can cause the decrease of TBG, resulting in the decrease of TT4. The normal values of adults measured by radioimmunoassay (RIA) were 65–156 nmol/L.

2. Serum total triiodothyronine TT3: about 80% TT3 is converted from T4 in peripheral tissue. The concentration of TT3 is parallel to that of TT4, which is a specific index for diagnosis, especially sensitive to treatment observation, recurrence after withdrawal and T3 hyperthyroidism. More than 99.5% of T3 in serum exists in the form of binding to protein, so the value is also affected by the content of TBG. The normal value of 1.8~2.9 nmol/L in adults was determined by RIA method.
3. Serum-free thyroxine (FT4) and free triiodothyronine (FT3): free thyroid hormone is the main part to realize the biological effect of this hormone. It is the first-choice index for the diagnosis of clinical hyperthyroidism. However, because the contents of FT4 and FT3 in blood are very small, the stability of the determination is not as good as that of TT4 and TT3.
4. Serum reverse T3 (γ T3): γ T3 is a metabolite of T4 in tissues, which is consistent with T4, which can be used as an index to understand thyroid function and is of significance in the differential diagnosis of low T3 syndrome.
5. The change of serum TSH concentration of thyrotropin (TSH): is the most sensitive index to reflect thyroid function. At present, uTSH has become the first-line index for screening hyperthyroidism, and the TSH of hyperthyroidism is usually smaller than that of 0.5 mU/L.
6. ^{131}-I uptake rate: ^{131}-I uptake rate is a traditional method for the diagnosis of hyperthyroidism, which has been replaced by uTSH and other measurement techniques. In hyperthyroidism, ^{131}-I uptake rate showed an increase in total uptake and a shift in the peak of uptake. This method is now mainly used to identify the etiology of thyrotoxicosis: the uptake rate of ^{131}-I in thyrotoxicosis with hyperthyroidism is increased.
7. Determination of thyroid autoantibody: TSH receptor antibody (TRAb) is one of the indexes to distinguish the etiology of hyperthyroidism and diagnose GD. 75%~96% TRAb was positive in GD patients. It should be noted that TRAb includes irritant (TSAb) and inhibitory (TSBAb) antibodies, but the detected TRAb can only reflect the existence of autoantibodies against TSH receptors, but cannot reflect the function of this antibody.
8. Imaging examination: ultrasound, CT, and MRI are helpful to the diagnosis of thyroid, ectopic thyroid, and retrobulbar lesions. In particular, ocular CT and MRI can exclude exophthalmos caused by other causes and evaluate the involvement of extraocular muscles.
9. Thyroid radionuclide scan: it is of significance in the diagnosis of thyroid autonomic hyperfunctional adenoma. A large number of nuclides were concentrated in the tumor area, and there was no radionuclide absorption in the thyroid tissue and contralateral thyroid tissue outside the tumor area.

10. Basal metabolic rate: measured by instrument or calculated. The determination of basal metabolic rate (BMR) showed that the basal metabolic rate of patients with hyperthyroidism was significantly higher than 15%, which was equal to that of hyperthyroidism.

In a word, the increase of TT3 in hyperthyroidism is often earlier than that of TT4, and TT3 is more sensitive to mild hyperthyroidism, early hyperthyroidism and recurrence of hyperthyroidism after treatment. TT4, TT3, TSH, ^{131}I uptake rate, basal metabolic rate, TRAb, TSAb, thyroid CT and MRI, thyroid radionuclide scanning have specific diagnostic and differential diagnostic value. In addition, the determination of blood lipid and cholesterol, 24 h muscle uric acid, T3 inhibition test, and TRH (thyrotropin-releasing hormone) test are also helpful for the diagnosis.

9.2.1.7 Diagnosis

The general diagnosis is divided into three steps: (1) diagnosis of thyrotoxicosis: determination of serum TSH and thyroid hormone levels; (2) determination of whether thyrotoxicosis originates from hyperthyroidism; (3) determination of the causes of hyperthyroidism, such as GD, nodular toxic goiter, thyroid autonomic hyperfunctional adenoma, and so on.

The diagnosis of hyperthyroidism is relatively simple, based on: (1) hypermetabolic symptoms and signs; (2) goiter; (3) the increase of serum TT4 and FT4 and the decrease of TSH. With the above three, diagnoses can be established. Special attention is paid to the fact that the hypermetabolic symptoms of indifferent hyperthyroidism are not obvious, only manifested as obvious emaciation or atrial fibrillation, especially in elderly patients, in addition, a small number of patients do not have goiter; on the other hand, only the level of serum TT3 was increased in T3 hyperthyroidism.

9.2.1.8 Differential Diagnosis

About 20% of patients with hyperthyroidism have atypical clinical manifestations, especially older patients with chronic diseases, as well as patients with early and mild hyperthyroidism. Common manifestations of atypical hyperthyroidism are as follows:

1. Cardiovascular type: cardiovascular symptoms as the prominent symptoms, the main manifestations of patients with tachycardia, arrhythmia, angina pectoris, or heart failure. More common in women or older patients and toxic nodular hyperthyroidism patients, clinical diagnosis of coronary heart disease, hypertensive heart disease, arrhythmia, and other diseases.
2. Neurotype: neuropsychiatric symptoms as a prominent performance, patients neurotic, inattention, emotional impatience, restlessness, insomnia, and even mania, depression, hallucinations, and other mental symptoms. It is more common in women and is easy to be misdiagnosed as neurosis or climacteric syndrome.

3. Muscular type: characterized by myasthenia, physical weakness, and periodic paralysis, often without exophthalmos, goiter and other signs and symptoms of hyperthyroidism, or symptoms appear later, more common in middle-aged men. Most of the patients after a full meal and intake of a large number of carbohydrates occur.

Special attention is paid to the differentiation between hyperthyroidism and pheochromocytoma. Paroxysmal secretion of catecholamine in pheochromocytoma can lead to paroxysmal hypertension due to paroxysmal secretion of catecholamine from tumor or hyperplastic tissue. The patients generally have no goiter and abnormal function. The examination of catecholamine in blood and urine and imaging examination of adrenal gland are helpful for differential diagnosis.

9.2.1.9 Therapy

The main purpose of the treatment of hyperthyroidism is to reduce the concentration of thyroid hormone in blood and re-establish the normal metabolic state of the body. There are three treatment methods for hyperthyroidism, namely, antithyroid drugs (ATD), ^{131}I and surgical treatment. The effect of ATD is to inhibit the synthesis of thyroid hormones, ^{131}I and surgery is through the destruction of thyroid tissue, reduce the production of thyroid hormones to achieve the purpose of treatment. The three have their own advantages and disadvantages. Before choosing the treatment plan, we must carefully consider the age, sex, condition, complications, and other factors of the patients.

1. Treatment of antithyroid drug (ATD): ATD treatment is the most widely used in China at present. It has the advantages of convenient dose adjustment, low price, no need for special equipment and low incidence of persistent hypothyroidism after treatment; the disadvantage is that the course of treatment is long, the recurrence rate is high after withdrawal, and sometimes serious drug side effects can be produced. There are two kinds of commonly used drugs: thiourea including propylthiouracil (PTU) and methionine (MTU), imidazole including methimidazole (MMI) and carbimazole (CMZ), and so on. The half-life of MMI was 4~6 h, which could be used once a day, and the half-life of PTU plasma was 60 min, and the conversion of T4 to T3 could be inhibited by peripheral tissue, so the effect was faster than that of MMI, but it must be given every 6~8 h. PTU binds closely to the protein and is not easy to pass through the placenta and enter the milk, so it is preferred when combined with pregnancy.

   Indications: (1) mild to moderate patients; (2) mild to moderate enlargement of thyroid gland; (3) age < 20 years; (4) pregnant women, advanced age, or unsuitable for operation due to other serious diseases; (5) preparation before operation and ^{131}I treatment; (6) recurrence after operation and not suitable for ^{131}I treatment. The common adverse reactions were: (1) granulocytopenia, (2) rash, and (3) toxic liver disease. The indexes of drug withdrawal were mainly based on clinical symptoms and signs. At present, it is believed that ATD maintenance therapy can be discontinued for 18–24 months. The following indicate that hyperthyroidism may be cured: (1) goiter is significantly reduced and (2) TSAb (or TRAb) becomes negative.

2. Radioactive ^{131}I therapy: it has become the main method for the treatment of hyperthyroidism in western countries. This method is simple, safe, economical, effective, low recurrence rate, similar to surgery, but easy to cause hypothyroidism, so we must carefully select cases.

   Indications: (1) adult Graves' with goiter above degree II; (2) failure or allergy of ATD treatment; (3) recurrence of hyperthyroidism after operation; (4) heart disease of thyrotoxicosis or hyperthyroidism with other causes of heart disease; (5) hyperthyroidism complicated with leukopenia and/or thrombocytopenia. Hypothyroidism or pancytopenia; (6) senile hyperthyroidism; (7) hyperthyroidism with diabetes mellitus; (8) toxic multinodular goiter; (9) autonomic functional thyroid nodules with hyperthyroidism. The main adverse reactions were hypothyroidism, the incidence of which was 50–70%.
3. Surgical treatment: the surgical treatment of patients with hyperthyroidism is mainly subtotal thyroidectomy. The indications are: (1) moderate or severe hyperthyroidism, ineffective for a long time, or relapse, or cannot adhere to the medication; (2) significant goiter with compression symptoms; (3) retrosternal goiter; (4) polynodular goiter with hyperthyroidism. The cure rate of general surgical treatment was about 95%, and the recurrence rate was 0.6–9.8%. The main complications were hypoparathyroidism and recurrent laryngeal nerve injury caused by surgical injury. The incidence can be greatly reduced by experienced doctors.

   Treatment of hyperthyroidism hypertension: it is a curable hypertension, the fundamental treatment of which is to cure hyperthyroidism, but the treatment of antithyroid drugs will take some time to be effective, so β receptor blocker is the first choice. It can not only reduce blood pressure, but also slow down the heart rate and improve the symptoms of hyperthyroidism.

9.2.1.10 Prognosis

There are three kinds of prognosis of hyperthyroidism: about one-third of the patients can be cured after treatment, one-third of the patients show fluctuating progress, or become chronic course of disease, or persistent hyperthyroidism does not heal for a long time. For more than 10 years, most of the patients with hyperthyroidism had recurrence and family history, and the patients with hyperthyroidism were still aggravated by treatment, and various complications occurred, such as hyperthyroidism crisis, the fatality rate was higher than that of the patients with hyperthyroidism, and the mortality of patients with hyperthyroidism was higher than that of patients with hyperthyroidism, and the mortality of patients with hyperthyroidism was higher than that of patients with hyperthyroidism.

9.2.2 Hypothyroidism and Hypertension

Hypothyroidism is a systemic hypometabolic syndrome caused by low-thyroid hormone or thyroid hormone resistance. Its pathological feature is the accumulation of mucopolysaccharide in tissue and skin, manifested as mucinous edema. It can occur in all age groups, most of which are women. A coma caused by

hypothyroidism is called mucoedema coma. Hypothyroidism in the embryonic stage known as cretinism. In the etiological composition of patients with secondary hypertension in our hospital, it was found that about 0.5% of the patients were caused by this disease.

9.2.2.1 Epidemiology

The prevalence of clinical hypothyroidism reported by foreign countries is 0.8–1.0%, the incidence is 3.5/1000, while the prevalence of clinical hypothyroidism reported by Chinese scholars is 1.0%; the incidence is 2.9/1000. The prevalence of hypothyroidism in Germany was 0.7% [11]. Hypothyroidism (0.3% OH and 4.3% SCH) [13] was found in 4.6% of the population in the United States, compared with 1.9% in a Japanese study. The prevalence of subclinical hypothyroidism was 0.6% [14]. As mentioned earlier, hyperthyroidism can cause systolic hypertension, while hypothyroidism can also cause hypertension, mainly diastolic hypertension, low pulse pressure, the incidence can reach 50%. Hypothyroidism has become the cause of less than 1% of hypertensive patients [15]. Studies have shown that diastolic hypertension caused by hypothyroidism accounts for 1–2% of diastolic hypertension in the population. This kind of hypertension can return to normal after correction with hypothyroidism treatment.

9.2.2.2 Etiology and Pathogenesis

Hypothyroidism can be divided into three types according to the location of the lesion: primary hypothyroidism, central hypothyroidism, and thyroid hormone resistance syndrome. According to the causes of the lesions, they can be divided into drug-induced hypothyroidism, postoperative hypothyroidism, ^{131}I hypothyroidism after treatment, idiopathic hypothyroidism, pituitary or hypothalamic tumor after surgery hypothyroidism and so on. Comprehensive analysis, the main causes of adult hypothyroidism are as follows: (1) autoimmune injury; (2) thyroid destruction; (3) iodine excess; (4) antithyroid drugs.

9.2.2.3 Pathophysiology

Thyroid hormones have a wide range of effects on the whole body, so the pathophysiological changes of thyroid hormone deficiency are very complex. The main contents were as follows: (1) the basal metabolic rate was decreased; (2) mucopolysaccharide was deposited under subcutaneous, submucous, and subendothelial conditions; (3) the level of serum cholesterol was increased, which was related to the decrease of cholesterol metabolism; (4) anemia; (5) high carotene; and (6) decreased renal excretion of calcium and magnesium. The main pathophysiology of hypothyroidism is mucinous edema; about 55% of hypothyroidism patients develop systemic mucinous edema.

9.2.2.4 Mechanism of Hypertension Caused by Hypothyroidism

Hypothyroidism leads to the increase of blood pressure, which is generally believed to be related to the following factors: (1) The levels of serum T3 and T4 in patients with hypothyroidism are low, the basal metabolic rate is low, and the cardiac work

of mucinous edema is reduced. Compensatory vascular tension increases, peripheral resistance vasoconstriction, resulting in increased systemic circulatory resistance. (2) the accumulation of mucopolysaccharide in tissue and skin resulted in the retention of sodium and water, the increase of extracellular fluid capacity, and the increase of blood pressure. (3) T3 is considered to be a vasodilator, and its lack can lead to vasoconstriction. (4) Abnormal lipid metabolism in hypothyroidism patients leads to atherosclerosis, which reduces the compliance of arterial bed and leads to the increase of blood pressure. In addition, patients with hypothyroidism often lead to obstructive sleep apnea syndrome due to mucinous edema, which ultimately mediates the formation of hypertension. Other scholars believe that the occurrence of hypothyroidism hypertension is the result of the activation of sympathetic nervous system and adrenal gland and the increase of peripheral vascular resistance.

In a word, hypothyroidism hypertension is mainly low renin hypertension, which can occur in the early stage of hypothyroidism. Because of the increase of peripheral vascular resistance, the diastolic blood pressure is increased, and the systolic pressure is normal because of the decrease of cardiac output, so the clinical manifestation is hypertension with small pulse pressure difference.

9.2.2.5 Clinical Manifestation

It usually depends on age. Adult hypothyroidism mainly affects metabolism and organ function, and timely diagnosis and treatment are reversible lesions. Hypothyroidism, which occurs in fetuses and infants, can lead to short stature and mental retardation due to the impact on brain and bone development, most of which belong to irreversibility. Patients with adult hypothyroidism often have a history of thyroid surgery, ^{131}-I treatment, Graves' disease, Hashimoto's thyroiditis, and so on. The incidence of hypothyroidism is more concealed and the course of disease is longer. Many patients lack specific symptoms and signs.

The main clinical features are opposite to hyperthyroidism. Patients are generally characterized by fatigue, fear of cold, weight gain, slow response, drowsiness, depression, constipation, irregular menstruation, muscle fatigue, and spasms. Physical examination showed indifferent expression, anemia, dry and cool skin, face, eyelid and hand skin edema, hoarse voice, sparse hair, and so on.

In the cardiovascular system, bradycardia is common in clinical patients, and electrocardiogram (ECG) shows low voltage. In addition, due to myocardial interstitial edema, nonspecific myocardial fiber swelling, left ventricular dilatation, and pericardial effusion lead to cardiac enlargement, which often appears as "hypothyroidism heart disease." In hypothyroidism, coronary heart disease and hypertension also showed high incidence signs. Diastolic hypertension is caused by hypothyroidism, and diastolic blood pressure is significantly correlated with T3 and T4 levels. For hypertension caused by typical hypothyroidism, blood pressure can return to normal after drug treatment of hypothyroidism.

9.2.2.6 Laboratory Examination

Laboratory examinations are necessary for the diagnosis of hypothyroidism and include the following items:

1. Blood routine: most of them were mild to moderate orthochromic anemia.
2. Biochemical examination: serum triglyceride, total cholesterol, LDL-C increased, HDL-C decreased, homocysteine increased, serum CK and LDH increased.
3. Thyroid function examination: serum TSH increased, TT4, TT3 decreased, early TT3 can be normal. In general, the decrease of TT4 is more obvious, which plays a key role in the diagnosis of hypothyroidism.
4. ^{131}I uptake rate: decreased.
5. Thyroid autoantibodies: the positive results of serum thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb) suggest that hypothyroidism is caused by autoimmune thyroiditis.
6. TRH stimulation test: it is mainly used to distinguish primary hypothyroidism from central hypothyroidism. After intravenous injection of TRH, the patients with no increase of serum TSH suggested pituitary hypothyroidism, the patients with delayed increase were hypothalamic hypothyroidism, and the serum TSH was further increased on the basis of the increase, suggesting primary hypothyroidism.

In short, the most commonly used test indicators are TT4, TT3. In general, the decrease of TT4 occurs earlier than TT3 (compensation of the body). Normal TT4 and TT3 cannot deny primary hypothyroidism because of subclinical primary hypothyroidism, only the increase of TSH. FT4 and FT3 should be added in patients with liver and kidney insufficiency. The increase of blood lipid (especially TC and TG) is often an auxiliary diagnostic index of primary hypothyroidism.

9.2.2.7 Diagnosis

Diagnostic criteria: (1) Symptoms and signs of hypothyroidism. (2) Laboratory examination of serum TSH increased, FT4 decreased, primary hypothyroidism can be established. Further search for the cause of hypothyroidism. If TPOAb is positive, hypothyroidism can be considered because of autoimmune thyroiditis. (3) Laboratory examination showed that serum TSH was decreased or normal, TT4 and FT4 were decreased. Considering central hypothyroidism, TRH stimulation test could confirm the diagnosis. Further search for pituitary and hypothalamic lesions.

In addition, in recent years, it has been found that subclinical hypothyroidism shows an increasing trend with age, which is more common in women. Most of the patients had no abnormal symptoms and signs in clinic, but the serum TSH was increased and FT4 was decreased in laboratory examination. At present, most scholars believe that “subclinical hypothyroidism” can progress to clinical hypothyroidism, at the same time, it can promote the occurrence and development of atherosclerosis and cardiovascular diseases, including hypertension. Moreover, “subclinical hypothyroidism” during pregnancy may affect the neurointellectual development of its offspring, causing great harm, so special attention should be paid to the early diagnosis and treatment of the disease.

9.2.2.8 Differential Diagnosis

1. Identification of low T3 syndrome: low T3 syndrome is a group of clinical syndromes with low circulating thyroid hormone levels caused by non-thyroid diseases. The changes of thyroid hormone levels are mainly caused by serious systemic diseases, malnutrition, hunger, trauma, and psychological diseases, which reflect the adaptive response of the endocrine system to diseases. The severity of the disease is generally related to the degree of decrease in TT3. Thyroid hormone replacement therapy is not required for the disease. The basic diseases of general patients gradually return to normal after treatment; however, transient increase of TSH can occur in the convalescent period, which also needs to be differentiated from primary hypothyroidism. The main manifestations of laboratory examination were the decrease of serum TT3 and FT3 levels, the increase of rT3, and the normal levels of serum T4 and TSH.
2. Central hypothyroidism and primary hypothyroidism identification: mainly rely on the identification of basic TSH, the former TSH decreased, the latter increased. When central hypothyroidism is characterized by normal or mild elevation of TSH, a TRH stimulation test is needed for identification. Typical hypothalamic hypothyroidism, TSH secretion curve after TRH stimulation showed a peak delay (60–90 min after injection), and continued high secretion state to 120 min; TSH response was slow after pituitary hypothyroidism TRH stimulation, increased <2 times or increased ≤4.0 mIU/L, showing a low flat curve.

In addition, when the symptoms of hypothyroidism are not typical, attention should be paid to the need to distinguish from anemia, edema, pericardial effusion, and sella turcica caused by other diseases.

9.2.2.9 Hypothyroidism with Sleep Apnea-Related Hypertension

Obstructive sleep apnea (OSA) is characterized by intermittent repetitive cessation of pulmonary airflow due to pharyngeal airway closure, accounting for approximately 24–42% of adults, and is considered hypertension, cardiovascular and cerebrovascular disease, and metabolic syndrome to be the independent risk factors [16]. There is growing evidence of a two-way relationship between OSA and thyroid dysfunction, especially between clinical and subclinical hypothyroidism, which is associated with atherosclerosis and hypertension. Cardiovascular disease is associated with metabolic disorders [17]. In a recent meta-analysis, the prevalence of hypothyroidism was 8% in OSA patients and 11% in subclinical hypothyroidism [18]. The prevalence of clinical hypothyroidism in patients with hypertension was increased with the severity of OSA, including 6.94% in non-OSA group, 13.4% in mild OSA, 15.2% in moderate OSA, and 17% in severe OSA [19]. Hypothyroidism leads to OSA mainly by increasing mucin deposition in the upper respiratory tract [20]; in addition, it may be involved in changes in the regulatory control of pharyngeal dilator muscles due to neuropathy [21] causes obesity and abnormal central ventilation control. On the other hand, OSA may also have an effect on the hormone axis, which may lead to hypothyroidism [20]. Nocturnal respiratory abnormalities, such as snoring, asphyxia, and severe apnea/hypopnea, occur in 25–35% of patients

with hypothyroidism [20]. A study found that the prevalence of hypothyroidism in patients diagnosed with OSA was 1.5–11%, and 25–35% of patients with hypothyroidism could develop OSA [22].

9.2.2.10 Therapy

Regardless of the reason for the treatment of hypothyroidism, most of them need to use thyroid hormone preparation for life replacement at the same time of etiological treatment. Levothyroxine (L-T4) is the first choice for replacement therapy. The thyroid-stimulating hormone (TSH) in young subjects should be maintained between 1.0 and 3.0 mIU/L, and in the elderly or vulnerable patients should be maintained at the normal upper limit. According to clinical experience and current guidelines, fasting status is necessary for optimal dissolution and absorption of LT4 tablets [23]. Serum TSH, body weight, and cardiac function were measured 4–6 weeks after thyroid hormone supplementation. The dose of LT4 was then adjusted according to the results of the examination until the treatment goal was achieved. After the treatment reached the standard, the relevant hormone indexes were reexamined every 6–12 months in order to stabilize the curative effect. For hypothyroidism secondary to hypothalamus and pituitary, TSH cannot be used as a therapeutic index, but serum TT3 and FT3 to reach the normal range as the goal of treatment. Hypertension caused by hypothyroidism is cured with the cure of hypothyroidism, such as high blood pressure (about 40%) after hypothyroidism, suggesting that hypothyroidism leads to increased arterial stiffness and the existence of essential hypertension. Antihypertensive drugs can be given.

9.2.2.11 Prognosis

The prognosis of patients with hypothyroidism varies according to the cause of the disease. Actually, most hypothyroidism patients disappear after thyroid hormone supplementation, the metabolism of the body returns to normal, and the prognosis is good. Among them, patients with transient hypothyroidism may stop taking drugs after the clinical symptoms are alleviated, hypothyroidism symptoms and signs do not recur, and some hypothyroidism patients need to take a certain dose of thyroid hormone maintenance therapy for life after the clinical symptoms are alleviated to maintain thyroid function at a normal level.

If hypothyroidism is not diagnosed in a timely manner, it may further aggravate hypothyroidism and even develop mucoedema coma when combined with a variety of inducing factors, such as infection, cold, anesthesia, and sedative and hypnotic drugs. The fatality rate can be as high as 50%.

9.3 Hyperparathyroidism and Hypertension

Zhen Wei

Hyperparathyroidism, (PHPT) is caused by the parathyroid gland itself or other lesions (such as renal function insufficiency, bone softening, and small intestine

diseases such as malabsorption) lead to parathyroid hormone (PTH) synthesis and secretion of calcium, phosphorus, and bone metabolic disorders caused by a kind of systemic disease, clinically characterized by increased bone resorption of bone lesions, nephrolithiasis, hypercalcemia, and low phosphorus concentration, etc. Hypertension is common in patients with primary hyperparathyroidism. In different studies, the prevalence of primary hyperparathyroidism combined with hypertension varies greatly, ranging from 20 to 80% [24–29]. More and more evidences show that high PTH concentration is related to the risk of cardiovascular disease [30–32], and PTH may be an independent risk factor of cardiovascular disease. The mechanism of hypertension may involve PTH, which may be one of the causes of blood pressure rise or an important factor to accelerate the process of blood pressure rise. Therefore, some scholars believe that hyperparathyroidism is one of the basic diseases of secondary hypertension.

9.3.1 Epidemiology

Since the mid-1960s, a growing number of patients with primary hyperparathyroidism have been diagnosed with hypercalcemia for other unrelated reasons, increasing the incidence of PHPT 4–5 times. According to the data, the adult prevalence is between 1 in 500 and 1 in 1000.The disease is more common in women, male and female ratio about 1:3, most of the patients for postmenopausal women, the onset of the disease in postmenopausal 10 years, but also can occur at any age. Childhood onset is rare, and the possibility of hereditary endocrine diseases should be considered if the disease occurs in this age group [33].

9.3.2 Classification

Hyperparathyroidism (HPT) consists of primary hyperparathyroidism (PHPT), secondary hyperparathyroidism (SHPT), or tertiary hyperparathyroidism (THPT) [33–35].

Primary parathyroid function already (primary hyperparathyroidism, PHPT), hereinafter referred to as primary near a port, is a parathyroid tissue primary lesions caused by parathyroid hormone hypersecretion (parathyroid hormone, PTH), caused by a group of clinical syndrome, including hypercalcemia, increased renal calcium reabsorption and urine phosphorus excretion, kidney stones, renal calcinosis, and predominantly skin bone absorption increase. Pathologically, the most common type of single parathyroid adenoma is hyperplasia of parathyroid gland or parathyroid carcinoma.

Secondary hyperparathyroidism is often caused by hypocalcemia that stimulates hypertrophy of parathyroid gland and excessive secretion of PTH, which is seen in chronic kidney disease, osteomalacia, intestinal malabsorption syndrome, vitamin D deficiency and hydroxylation disorders.

Tertiary hyperparathyroidism (THPT), sometimes referred to as tertiary hyperparathyroidism, is sometimes found in chronic kidney disease and kidney transplantation. It is sometimes found on the basis of secondary hyperparathyroidism because the glands are constantly stimulated and develop into hyperplasia or tumor with autonomic function, which can be caused by excessive secretion of PTH.

9.3.3 Etiology and Pathophysiological Mechanism [33–35]

9.3.3.1 Etiology

Most PHPT is sporadic, and a few are manifestations of familial or some hereditary syndromes, that is, a family history or as part of some hereditary tumor syndromes, the latter of which has a clear pathogenesis.

1. Familial/syndromic PHPT
   Most of these PHPT are single-gene lesions caused by inactivation of tumor suppressor genes or activation of proto-oncogenes. The confirmed genetic syndromes associated with PHPT and their pathogenic genes are shown in Table 9.5 [36].
2. Sporadic PHPT
   Parathyroid adenoma or adenocarcinoma are mostly monoclonal neoplasms, which are caused by the change of the original cancer and/or tumor suppressor

Table 9.5 Pathogenic subsets of familial PHPT [36]

Syndrome (OMIM)	Chromosome localization	Disease genes	Encoding protein	Mutation type
MEN-11 (131100)	11q13	MEN1	Menin	The deactivation
MEN-2A2 (171400)	10q11.3	RET	RET	The activation
MEN-43 (610755)	12p13	CDKN1B	p27kipl	The deactivation
FHHI/NSHPT/ NHPT4 (145,980/239200)	3q13.3-q21	CαSR	CaSR	The deactivation
ADMH5 (601199)	3q13.3-q21	CαSR	CaSR	Atypical inactivation
FHH2 (145981)	19q13.3	GNA11	Gα11	The deactivation
FHH3 (600740)	19q13.32	AP2S1	AP2σ2	The deactivation
HPT-JT6 (145001)	1q25-q31	HRPT2	Parafibromin	The deactivation
FIHPT7 (145000)	11q13,1q25-31,3q13.3-q21/2p13.3-14, Unknown locations	CαSR, HRPT2, MEN1	–	The deactivation

Mens-1 multiple endocrine adenoma type1, MEN-2A multiple endocrine adenomatosis type2A (multiple endocrine neoplasia type2A), Men-4 multiple endocrine neoplasia type 4, FHH familial low urinary calcium hypercalcemia (familial hypocalciuric hypercalcemia), NSHPT neonatal severe hyperparathyroidism, NHPT neonatal hyperparathyroidism, ADMH autosomal dominant moderate hyperparathyroidism, HPT-JT hyperparathyroidism–jaw tumors syndrome, FIHPT familial isolated primary hyperparathyroidism, OMIM online Mendelian inheritance in men

basis in a parathyroid cell, but the reason is not completely clear. A few patients have a history of external neck irradiation or the use of lithium in the decades before the onset.

9.3.3.2 Pathophysiological Mechanism

Several possible mechanisms have been proposed to explain the association between PHPT and hypertension. Part of the hypothesis is that this link is due to one or two major biochemical abnormalities of PHPT, hypercalcemia, and elevated parathyroid hormone levels. Another part of the theory attributed this association to hypertension-related complications, such as renal insufficiency, hypomagnesemia, and the effect of PTH on the renin-aldosterone system. The following are several possible pathophysiological mechanisms associated with hypertension induced by PHPT.

1. Hypercalcemia is considered to be the basis of the association between hypertension and PHPT, and some data suggest that in non-PHPT populations, acute hypercalcemia induced by calcium infusion in healthy volunteers may lead to increased systolic blood pressure [37]. In this study, dose-dependent hypercalcemia resulted in impaired vascular endothelial diastolic function, suggesting that stress changes in vascular diastolic function may account for elevated blood pressure. In addition, calcium ions may cause increased blood pressure through the contraction of vascular smooth muscle cells [38]. Similarly, PTH may play an indirect role in the association between PHPT and hypertension. Studies have found that in the normal blood pressure, slow continuous injection of PTH can cause hypercalcemia and hypertension [39, 40]. PTH effect on vascular smooth muscle cells, it may be indirectly through the stimulation of renin activity, directly through prostimulatory effect (mediated by calcium ions or through the activation of renal 1-hydroxylase via PTH), or through tprosclerotic effect, to involve in the mechanism of increased blood pressure [41, 42].
2. Renal impairment may be PHPT also play a role in contact with high blood pressure, in one study found that 54.8% of patients with PHPT hypertension, including PHPT patients with hypertension, urea nitrogen, and creatinine levels significantly higher than the pure PHPT patients [43]; in addition, in all patients with PHPT, systolic blood pressure is associated with serum urea nitrogen level, however, the blood pressure and found no relationship between PTH or calcium ions. A similar relationship between blood pressure and renal impairment has been reported in another PHPT study, but whether renal impairment caused by hypertension is still unclear, or another potential link exists between PHPT and hypertension [44].
3. Increased blood pressure in PHPT patients may be associated with hypomagnesemia [45, 46]. Both experimental and epidemiological data suggest an association between hypomagnesemia and hypertension [47, 48]. In PHPT patients, hypercalcemia can lead to decreased renal magnesium resorption leading to hypomagnesemia. Hypomagnesemia leads to increased intracellular calcium levels, which may cause vascular smooth muscle contraction. In addition,

decreased magnesium ions themselves may be associated with calcium signaling channels [48]. In an observational study of PHPT patients undergoing parathyroidectomy, mean serum magnesium levels in the hypertensive group were significantly lower than those in the normotensive group [45]. However, whether hypomagnesemia plays a role in PHPT and hypertension is still uncertain.

4. More and more evidence shows that there is a two-way and positive relationship between RAAS and PTH [49, 50]. It has been speculated that aldosterone may directly stimulate the parathyroid gland and induce the secretion of PTH since the glucocorticoid receptor has been found to be expressed in the parathyroid gland [51, 52]. Many case reports describe the occurrence of primary hyperparathyroidism with primary aldosteronism, suggesting that aldosterone may play a role in the pathogenesis of hyperparathyroidism [51, 53]. In addition, aldosterone may induce hypercalcemia and subsequent hypocalcemia (secondary hyperparathyroidism) by indirectly stimulating PTH secretion by acting on the nephrons [54–58]. Elevated PTH is also associated with vascular dysfunction and cardiovascular outcomes [59–62]. The mechanism behind this association, however, remains unclear. In addition to the effect of RAAS on PTH, evidence supports the direct effect of PTH on the composition of RAAS [49, 63]. Similar stimulatory effects of PTH on renin were observed in vitro experiments [64, 65], suggesting that PTH may enhance the activity of RAAS through a variety of methods.

9.3.4 Clinical Manifestations [33–35]

9.3.4.1 The Clinical Manifestation of Primary Hyperparathyroidism

PHPT disease degree is different, and clinical manifestations is also different, which involve multiple systems of the body, as follows:

1. Nonspecific symptoms

   Fatigue, weight loss and loss of appetite.
2. Skeleton

   It is usually manifested as diffuse and gradually aggravated pain in the bone and joint, and the pain in the weight-bearing part of the bone is more prominent, such as lower extremity and lumbar spine. Patients with a longer course of disease may have skeletal deformities, including chest collapse, scoliosis, pelvic deformation, limb bending, etc. Patients can grow shorter. Pathologic fractures are caused by minor external forces, or spontaneous fractures occur. Fibrocystic osteitis tends to occur in the jawbone, ribs, clavicle and long bones of the limbs, and the lesion site is prone to fracture. The lesions of the larger extremities of fibrocystic osteitis may be touched and have tenderness. The patient's mobility was significantly reduced or even limited. Loose or falling teeth.
3. Urinary system

   Patients often appear polydipsia, polyuria; recurrent and multiple urinary calculi can cause renal colic, ureteral spasm, gross hematuria, and even gravel-like

calculi in urine. Patients are also prone to recurrent urinary tract infections, and a small number of long-term or severe cases can lead to renal insufficiency.

4. Digestive system

   The patient had symptoms such as poor appetite, nausea, vomiting, dyspepsia, and constipation. Some patients can appear repeated peptic ulcer, upper abdominal pain, black stool, and other symptoms. Some hypercalcemia patients may be accompanied by acute and chronic pancreatitis, with clinical manifestations such as epigastric pain, nausea, vomiting, poor appetite, diarrhea, and even onset of acute pancreatitis.

5. Cardiovascular system

   Hypercalcemia can promote the contraction of vascular smooth muscle, and vascular calcification can cause the increase of blood pressure. Hypertension is the most common cardiovascular system manifestation of PHPT, which can be improved after PHPT is cured. A few patients with PHPT may have tachycardia or bradycardia, ST segment shortening or disappearance, q-t interval shortening, and severe hypercalcemia may have obvious arrhythmia.

6. Neuromuscular system

   The patient of hypercalcemia can appear indifferent, depressed, be agitated, reaction is slow, memory drops, serious person even appears the central nervous system symptom such as psychedelic, manic, and coma. Patients are prone to limb fatigue and muscle weakness, which are mainly manifested as the decrease of muscle strength mainly at the proximal end of the limbs. Some patients also present with muscle pain, muscle atrophy, and decreased tendon reflexes.

7. Mental state

   Patients may show mental abnormalities such as burnout, lethargy, emotional depression, neuroticism, decreased social skills, and even cognitive impairment. After the treatment of PHPT, the manifestations of psychological abnormalities can be significantly improved.

8. The blood system

   Some patients with PHPT may be associated with anemia, especially those with longer PHPT or parathyroid carcinoma.

9. Other metabolic abnormalities

   Some patients may be accompanied by abnormal glucose metabolism, manifested as abnormal glucose tolerance, diabetes or hyperinsulinemia, presenting corresponding clinical symptoms.

9.3.4.2 Clinical Manifestations of Secondary Hyperparathyroidism

The clinical manifestations of SHPT have changed significantly in the past 30 years due to the early measures to prevent and treat SHPT, common in the past the bone pain, muscle pain, muscle weakness, itching, bone calcification, spontaneous tendon, calcified defense and skeletal deformation image is very rare, restricted to persistent, severe hyperphosphatemia and (or) 1, 25-(OH)-2 D3 lack, PTH rise very significantly, accompanied by biochemical abnormalities. Hyperphosphatemia and calcification defense are two difficult problems to be solved in clinic.

1. Hyperphosphatemia: Hyperphosphatemia is a very common and serious complication in dialysis patients, with an incidence of over 50%. Block et al. divided dialysis patients into five groups according to their blood phosphorus levels and found that the higher the blood phosphorus, the higher the mortality. The mortality of > group with 2.1 mmol/L was significantly increased ($p = 0.03$), and that of > group with 2.6 mmol/L was higher ($p < 0.0001$). Hypercalcemia did not affect mortality, and its clinical significance was obviously different from hyperphosphatemia. High phosphorus can directly stimulate the secretion of PTH and the proliferation of parathyroid cells.
2. Calcified defense: Calcification defenses are commonly seen in patients after maintenance dialysis or kidney transplantation. It is a bilateral symmetrical superficial lesion with persistent pulsation at the distal end. It is usually a painful, freckled rash resembling a reticular green spot. Purple nodules can be seen on the surface of the tip of the finger, ankle, knee or buttocks, and may further develop into hemorrhagic foci after skin gangrene occurs, finger skin pain may occur. On biopsy of the skin nodules, calcium deposits in the arteriole wall are seen with lobular fat necrosis, calcification, and infiltration of neutrophils, lymphocytes, and macrophages.
3. Hypertension: SPHT often leads to refractory moderate to severe hypertension due to primary lesions, which is chronic renal.

9.3.5 Laboratory and Auxiliary Examination [33–35]

9.3.5.1 Laboratory Examination

The laboratory examinations characteristic of PHPT were hypercalcemia, hypophosphatemia, hypercalcemia, hyperphosphaturia, and hyper PTH. Common laboratory inspection items are as follows:

1. Serum calcium and blood-free calcium.
   (a) The normal reference value of serum calcium (total calcium, usually called blood calcium) is 2.2–2.7 mmol/L of 8.8–10.9 mg/dL), the serum calcium level can be continuously increased or fluctuated to be increased at PH, and the blood calcium value of a few patients is continuously normal (normal blood calcium PHPT), so repeated measurement is required if necessary. Serum albumin levels should be corrected when determining serum calcium levels. When the serum albumin concentration is lower than 40g/L (4 g/dL), every 10 L (1.0 g/dL) decrease will cause a 0.20 mmol/L (0.8 mg/dL) decrease in serum calcium level. Calculation method: corrected serum calcium (mg/dL) = measured serum calcium (mg/dL) +0.8 [4. - measured serum albumin (g/dL)].
   (b) The serum-free calcium level of normal people was (1). 18+/−0.05) the tendency for L. Blood-free calcium test is more sensitive to the diagnosis of hypercalcemia than blood total calcium test and is not affected by albumin level. As the equipment conditions are not yet popular, it is not a routine

examination item for the diagnosis of hypercalcemia, but it is helpful for the determination of hypercalcemia in patients with PHPT suspected clinically due to the normal total blood calcium value after multiple examinations.

2. Serum phosphorus

   The normal reference value of serum phosphorus was (0.97–1.45) mmol/L for adults (3.0–4.5 mg/dL) and (1.29–2.10) mmol/L for children (4.0–6.5 mg/dL). Hypophosphatemia is one of the biochemical characteristics of PHPT. In hyperparathyroidism, the renal reabsorption of bicarbonate decreases due to PTH, and the reabsorption of chlorine increases, leading to hyperchloremia, and the blood chlorine/phosphorus ratio will increase, usually >33.

3. Serum alkaline phosphatase

   The normal reference value of serum alkaline phosphatase in adults is (32–120) U/L, and the normal value in children is 2–3 times higher than that in adults. Hyperalkaline phosphatemia is another feature of PHPT. The increase of alkaline phosphatase in blood usually indicates the presence of bone lesions, and the increase of alkaline phosphatase in bone is more specific, and the higher the level, the more serious bone diseases or rickets/osteomalacia.

4. Calcium urine

   Most patients with PHPT have increased urinary calcium excretion (except for familial hypocalcemia), 24 h urinary calcium >250 mg in women, 300 mg in men, or 24 h urinary calcium excretion >4 mg/kg. Urinary calcium excretion may not increase in hyperparathyroidism with osteomalacia and severe vitamin D deficiency.

5. Blood creatinine (Cr) and urea nitrogen (BUN) levels

   Determination of blood Cr and BUN and other renal function tests is helpful to distinguish primary from secondary and tertiary hyperparathyroidism. Elevated levels of Cr and BUN can also be found in patients with hyperparathyroidism accompanied by dehydration or kidney injury.

6. Blood parathyroid hormone (PTH)

   There are four main forms of PTH in blood circulation.

   (a) Complete PTH1-84, accounting for 5–20%, has biological activity.
   (b) N-terminal PTH1-34 (i.e., PTH-N. They are also bioactive in small amounts.)
   (c) C-terminal FFH 56-84 (i.e., PTH-c, which can be divided into several fragments of different lengths).
   (d) Middle PTH (i.e., PTH-m)

   The heterogeneity of PTH molecules in blood circulation, as well as the source of antiserum and antigens used, make the normal reference range of FFH of serum in different laboratories have great differences, and the units used are not uniform (Table 9.6 [36]). PTH determination is very important for the diagnosis of hyperparathyroidism. The diagnosis of primary hyperparathyroidism should be considered in patients with hypercalcemia accompanied by higher PTH level than normal or in the normal range. For hypercalcemia, which is not caused by hyperparathyroidism caused by tumor, since modern complete PTH detection has no cross-reaction to PTH-

Table 9.6 Normal reference range of several commonly used PTH detection methods [36]

Methods	Reference range
Roche Elecsys PTH intact or Elecsys PTH intactstat	1.6–6.9 pmol/L (15–65 pg/mL)
Roche Elecsys PrH (1-84) bio-intact (the third generation)	1.58–6.03 pmol/L (14.9–56.9 pg/mL)
DPC2000 intact PTH	1.3–6.8 pmol/L (12–65 pg/mL)
Centaurintact H (The third generation)	1.48–7.63 pmol/L (14–72 pg/mL)

related egg whites, PTH secretion is inhibited at this time, and blood PTH level is lower than normal or undetectable.

7. Blood vitamin D

Patients with PHPT are prone to vitamin D deficiency, which may be accompanied by severe vitamin D deficiency when combined with rickets/osteomalacia. Blood levels of 25 hydroxyvitamin D (25-(OH)D) are lower than 20 ng/mL or even 10 ng/mL. However, due to excessive PTH, the blood level of 1,25-(OH)2D3 may be higher than normal.

The reference range of the above indicators may vary with different laboratories and testing methods.

9.3.5.2 Imaging and Positioning Inspection

1. Bone lesions
   (a) Bone X-ray examination

   About 40% and above patient X-ray shows bone abnormal change. There are mainly osteoporosis, osteomalacia, osteosclerosis, subperiosteal absorption, and bone cystic degeneration. In addition, the disease can involve joints, joint surface bone erosion like changes. It should be noted that not every patient has the above X-ray manifestations of bone changes; different patients have different bone changes; X-ray cannot see the negative exception of the disease; primary or secondary hyperparathyroidism cannot be distinguished by X-ray findings alone.

   (b) Bone imaging

   Bone imaging is a kind of nuclear medical imaging technology with high sensitivity and can reflect bone lesions.

   (c) Imaging evaluation of urinary system.

   Urinary calculi may occur in 15–40% of PHPT patients. Nephrolithiasis mainly occurs in the collection system, and occurs in the renal parenchyma stone called renal calcinosis. X-ray radiography is the most commonly used imaging examination. Calculi can be found by abdominal plain film, excretory urography, retrograde pyelography, and percutaneous renal puncture radiography.

   (d) Positioning inspection.
2. Neck ultrasound (including fine needle puncture).

(a) Parathyroid ultrasound

Ultrasonic examination is an effective method for preoperative localization of hyperparathyroidism. Ultrasonography is a effective method for localization for PTPH before the operation, PTH determination of ultrasound-guided helps determine whether the lesion is of parathyroid origin.

(b) Radionuclide examination

Parathyroid dynamic imaging is a nuclear medical imaging technique for PHPT localization diagnosis. 99mTc-MIBI (99mTc, Methoxyl isobutyl isonitrile) is the most widely used imaging tracer for parathyroid gland. The uptake of 99mTc-MIBI in hyperfunctional parathyroid tumor tissues was significantly higher than that in normal thyroid tissues, while the elution rate was significantly slower than that in surrounding thyroid tissues. Therefore, delayed imaging and comparison with early imaging can be used to diagnose hyperfunctional parathyroid lesions.

3. CT and MR

CT and MR are helpful in locating parathyroid lesions (mostly adenomas). Thin-slice enhanced CT and MR images are helpful for the detection of smaller lesions. CT and MR are mainly used to determine the specific location of the lesion, the relationship between the lesion and surrounding structures, and the morphological characteristics of the lesion itself.

4. Selective thyroid vein blood sampling for PTH

It is a means of invasive PHPT localization examination. Blood was collected at different sites (such as the superior, middle and inferior thyroid veins, thymic veins, and vertebral veins), and peripheral blood was collected for control. The peak value of PTH in blood reflected the location of the parathyroid gland, and an increase of 1.5–2 times was significant.

5. Intraoperative PTH monitoring

Rapid intraoperative determination of PTH level changes can determine whether hyperfunctional parathyroid tissues are removed during the operation, especially suitable for preoperative positioning, small neck incision, or minimally invasive parathyroid gland resection.

9.3.6 Diagnosis and Differential Diagnosis [33–35]

9.3.6.1 Diagnostic Clues of PHPT

PHPT diagnosis should be considered if:

1. Recurrent or active urinary calculi or renal calcium salt deposition.
2. Unexplained osteoporosis, especially with subperiosteal cortical bone resorption and/or alveolar bone plate resorption and bone cyst formation.
3. “Giant cell tumor” of long bone diaphysis, rib, jaw, or clavicle, especially for multiple patients.
4. Patients with unexplained nausea and vomiting, chronic peptic ulcer, refractory constipation, or recurrent pancreatitis.

5. Unexplained psychoneurotic symptoms, especially those accompanied by thirst, urination, and bone pain.
6. Positive family history and mothers of newborn children with tetany.
7. Hypercalcemia due to long-term application of lithium preparation.
8. Hypercalcemia with or without hypercalcemia.
9. Hypercalcemia occurs when taking calcium supplements, vitamin D preparations, or thiazide diuretics.

9.3.6.2 Diagnosis

Qualitative diagnosis can be made based on the history, skeletal lesions, clinical manifestations of urinary calculi and hypercalcemia, and the co-existence of hypercalcemia and hyper PTH (except primary hyperparathyroidism with normal serum calcium). In addition, the diagnosis of primary hyperparathyroidism was supported by elevated alkaline phosphatase level, hypophosphatemia, increased excretion of urinary calcium and phosphorus, and specific changes of X-ray images. After the qualitative diagnosis is clear, the location diagnosis of parathyroid lesions can be completed through ultrasound, radionuclide scanning, and other related location examination to understand the location.

9.3.6.3 Differential Diagnosis

It mainly includes the differentiation with other types of hyperparathyroidism and its clinical manifestations.

1. Differentiation from other types of hyperparathyroidism.
   (a) Secondary hyperparathyroidism: it is a chronic compensatory clinical syndrome in which the parathyroid gland secretes excessive PTH stimulated by hypocalcemia in order to increase blood calcium, and the blood calcium level is low or normal. Common causes include chronic renal insufficiency, vitamin D deficiency, intestinal malabsorption syndrome, pregnancy, and lactation.
   (b) Triple hyperparathyroidism: on the basis of long-term secondary hyperparathyroidism, the parathyroid tissues that are strongly and persistently stimulated have developed into functional autonomic hyperplasia or adenoma, and the blood calcium level is higher than normal, often requiring surgical treatment.
   (c) Hyperparathyroidism: hyperparathyroidism is caused by excessive spontaneous secretion of PTH (rather than PTHrP) by some non-parathyroid tumors. The causes of ectopic hyperparathyroidism include lung cancer, ovarian cancer, pancreatic cancer, liver cancer, thyroid papillary cancer, and so on.
2. Identification of clinical manifestations.
   (a) Differential diagnosis of hypercalcemia: first, if the serum albumin level is abnormal, the corrected total blood calcium should be calculated by the formula, or the diagnosis of hypercalcemia should be determined by the determination of free calcium. Secondly, the causes of hypercalcemia were

preliminarily determined based on the blood PTH level measured at the same time. If PTH was decreased, malignant tumors, sarcoidosis, hyperthyroidism, vitamin D poisoning, and other causes were considered. If PTH is normal or elevated, hypercalcemia associated with thiazide diuretics or lithium preparations should be excluded. The ratio of calcium clearance rate/creatinine clearance rate can be further determined. If the ratio is >0.01, the diagnosis of primary hyperparathyroidism can be preliminarily determined. If the ratio < 0.01, familial hypocalcemia and hypercalcemia should be considered.

(b) Differential diagnosis of bone lesions: patients with bone pain, fracture, or bone malformation should be differentiated from primary osteoporosis, rickets/osteomalacia, renal osteodystrophy, bone fibrosis, and other diseases, mainly based on medical history, physical signs, X-ray manifestations, and laboratory examinations.

(c) Differential diagnosis of urinary calculi: the disease often starts with recurrent unilateral or bilateral urinary calculi, which can be distinguished from other diseases causing urinary calculi by detailed medical history inquiry, physical examination, blood biochemistry and urine examination, image diagnosis, and analysis of stone components.

9.3.7 Treatment [33–35]

Treatment for PHPT includes surgery and medication.

9.3.7.1 Surgical Treatment

Surgery is the preferred treatment for PHPT. Surgical indications include:

- Symptomatic PHPT patients.
- Asymptomatic PHPT patients are associated with either of the following conditions: (1) hypercalcemia with serum calcium 0 above the normal upper limit 25 mmol/L (1 mg/dL); (2) renal damage with creatinine clearance rate less than 60 mL/min; (3) the BMD value of any part is 2.5 standard deviations lower than the peak bone mass (*T* value <-2.5), and/or a brittle fracture; (4) less than 50 years old; (5) routine follow-up was not acceptable.
- No surgical contraindication and definite lesion location.
- Whether PHPT patients who do not meet the above surgical indications need surgical treatment is controversial. Surgical intervention needs to be based on the principle of individualization, which can be comprehensively considered according to the patient's age, life expectancy, surgical risk, surgical willingness, risk of target organ damage, and other factors.
- Postoperative monitoring and follow-up: after the successful resection of the diseased parathyroid gland, the serum calcium and PTH were reduced to normal within a short period after surgery, and even hypocalcemia occurred. The time of regular postoperative reexamination is once every 3–6 months, and it can be

extended to once a year in patients with stable condition. The contents of follow-up observation included symptoms, signs, blood calcium, blood phosphorus, bone conversion index, creatinine, urinary calcium, bone density, etc.

9.3.7.2 Drug Treatment

Patients with PHPT should be treated in time if they have severe hypercalcemia or even hypercalcemia crisis. For patients who cannot or refuse surgery, drug treatment and long-term follow-up may be considered.

1. Hypercalcemia treatment

   The most radical treatment for hypercalcemia is removal of the etiology, i.e., parathyroidectomy. In general, patients with mild hypercalcemia and those without clinical symptoms do not need special treatment. Patients with moderate hypercalcemia presenting symptoms and signs should be treated actively. When blood calcium >3. At 5 mmol/L, effective measures should be taken immediately to reduce blood calcium level regardless of clinical symptoms. Treatment principles include dilation, promoting urinary calcium excretion and inhibiting bone resorption. Treatment principle is: (1) dilation, promote urinary calcium excretion; (2) application of drugs to inhibit bone absorption such as bisphosphonate, pamidronate sodium, zoledronic acid, ibandronate sodium, and so on; (3) calcitonin: it is mostly suitable for patients with high-calcium crisis and can reduce the level of serum calcium in a short time; (4) can also use low calcium or no calcium dialysis fluid peritoneal dialysis or hemodialysis.
2. Long-term treatment.
   (a) Patients who cannot be operated on or do not receive surgery

   Treatment of PHPT patients who cannot or do not undergo surgery aims to control hypercalcemia and reduce complications associated with hyperparathyroidism. Drink plenty of water, avoid high-calcium diets, and avoid lithium and thiazide diuretics. Drug therapy, including bisphosphonates, estrogen replacement therapy, selective estrogen receptor modulators, and calcium mimic compounds, is suitable for patients with asymptomatic PHPT who cannot be treated surgically.

   (b) Postoperative medication

   Hypocalcemia is one of the common complications after parathyroidectomy. The main cause of postoperative hypocalcemia is transient and transient parathyroid insufficiency. Therefore, this hypocalcemia is usually transient, and the normal parathyroid gland, whose preoperative function is inhibited, can gradually recover its function after surgery, so that the blood calcium can return to normal.

9.3.7.3 The Efficacy of Surgery to Improve Blood Pressure in Patients with Hypertension Combined with PHPT Is Still Uncertain

If there is a direct link between primary hyperparathyroidism and hypertension, successful parathyroidectomy may eventually be able to reverse hypertension. In some earlier studies in the 1970s and 1980s, it was reported that up to 50% of patients had improved blood pressure after parathyroidectomy [27, 28, 66]. However, in these

studies, the average serum calcium content was significantly higher than what we see today, up to 12.75 mg/dL [52]. Even in earlier studies, postoperative improvements in blood pressure were uncommon in patients with parathyroidectomy with higher serum calcium levels. For example, a retrospective study in 1982 (preoperative blood calcium level 11.7 mg/dL) showed that only 2 out of 15 patients with hypertension had postoperative hypertension reversal [26]. The data obtained from recent studies showed that, for patients with less severe hyperparathyroidism, the results of the curative effect on blood pressure after surgical treatment were also inconsistent [29, 48, 67]. Therefore, the curative effect of parathyroidectomy on blood pressure still needs to be studied further.

For hypertension associated with either PHPT or SHPT, even if PHPT is given active surgical treatment (as mentioned above), the patient's hypertension is relatively stubborn and the antihypertensive treatment is relatively difficult. Generally, ACEI/ARB should be combined with a variety of antihypertensive drugs with different mechanisms of action in order to effectively control blood pressure.

9.3.8 Prognosis [33–35]

Postparathyroid hypercalcemia and hyper PTH were corrected after surgical resection of the lesion, and the level of bone resorption index decreased rapidly. Bone pain began to decrease 1 to 2 weeks after surgery and improved significantly in 6 to 12 months. Most patients with limited preoperative activities were able to resume normal activities and work 1 or 2 years after surgery. Bone density increased significantly after surgery, especially in the first year after surgery. The incidence of urinary calculi after successful PHPT surgery has been reported to be reduced by 90%, while the remaining 5%-10% of patients with recurrent calculi may have other factors besides hyperparathyroidism. The stone that has formed won't disappear, the kidney function harm that has caused also is not easy to restore, and blood pressure of some patients may be reduced or return to normal.

9.4 Pheochromocytomas and Paragangliomas (PPGLs)

Guijuan Chang

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine chromaffin-cell tumors that usually produce catecholamines and arise from the adrenal medulla (80–85%) or from paravertebral ganglia of the sympathetic chain (15–20%), respectively [68, 69]. Paragangliomas located in the neck and the skull base are usually hormonally inactive, but some produce dopamine. There are two biochemical phenotypes: adrenergic and noradrenergic tumors [70, 71]. Adrenergic tumors are located in the adrenal medulla and usually produce epinephrine and varying amounts of norepinephrine. Noradrenergic tumors are located either in the adrenal medulla or are extra-adrenal and produce norepinephrine.

9.4.1 Epidemiology

The prevalence of PPGLs in the general population is extremely low (1.5–1.6 per 10,000 persons). The prevalence is higher in patients who present with hypertension (20–60 per 10,000 patients). However, it is still a rare neoplasm that a general physician will rarely encounter in clinical practice. In some patient groups, the prevalence is much higher (e.g., 500 PPGLs per 10,000 of patients who also have an incidentally discovered adrenal mass) [72]. The diagnosis of PPGLs is frequently missed, as the prevalence of PPGLs in autopsy studies is five per 10,000 persons [73]. In children with hypertension, the prevalence of PPGLs is approximately 1.7% [74]. The prevalence of PPGLs in individuals carrying a germline mutation in PPGLs susceptibility genes may be around 50%. Patients with hereditary PPGLs typically present with multifocal disease and at a younger age than those with sporadic neoplasms [75, 76]. Multiple endocrine neoplasia type 2 (MEN2) is associated with underlying mutations in the rearranged during transfection (RET) proto-oncogene. It is divided into three subclassifications: MEN2A, MEN2B, and familial MTC. Patients with MEN2B have a 50% chance of developing PHEO, but also typically present with a marfanoid body habitus and mucosal ganglioneuromas [76, 77].

9.4.2 The Clinical Importance of PPGLs [78–82]

1. It is important to suspect, confirm, localize, treat, and resect these tumors for several reasons. Most of these tumors hypersecrete catecholamines, and if untreated, cardiovascular morbidity and mortality are high.
2. Also, PPGLs enlarge with time and may cause mass-effect symptoms by encroaching upon or extending into adjacent tissues and organs.
3. Another reason to encourage case detection is that, for familial disease, detection of a tumor in the proband may result in earlier diagnosis and treatment in other family members.
4. Finally, some PPGLs have malignant potential. Malignancy is defined as the presence of metastases in nonchromaffin tissue; the prevalence varies between 10% and 17%.

9.4.3 The Clinical Presentation of PPGLs [83]

The clinical presentation of patients with PPGLs varies widely from no symptoms, to minor discrete symptoms, to catastrophic life-threatening clinical conditions. When present, the classic triad of pounding headache, profuse sweating, and palpitations occurs in spells that last from several minutes to 1 h. There is complete relief of symptoms between spells. The frequency of spells may vary from several times a day to a few times per month, occurring either spontaneously or being provoked by a variety of physical or chemical triggers, such as general anesthesia, micturition, and medications (e.g., b-adrenergic inhibitors, tricyclic antidepressants,

glucocorticoids) [84]. Enhanced blood pressure (BP) variability is reflected by paroxysmal hypertension in about 35%of the patients. Other patients may experience severe high BP peaks, sometimes superimposed on sustained hypertension and potentially evolving into a hypertensive crisis. These high BP surges, and the underlying episodes of tumoral catecholamine release, are thought to be responsible for the high prevalence of cardiovascular emergencies, such as myocardial infarction, stroke, and heart failure [79, 81].

9.4.4 Biochemical Testing [83]

PPGLs tumors produce, store, synthesize, and metabolize catecholamines. Although previous methods of diagnosis relied on the measurement of catecholamines in the plasma or urine, these are not always the most effective measurements. Many tumors have fluctuating levels of catecholamine release, which can lead to false-negatives during periods of low catecholamine release [85]. Instead, the measurement of plasma or urine metanephrines, the metabolites of catecholamines, are the most accurate test currently available. Although catecholamine release fluctuates, their metabolism remains fairly constant, leading to a steady release of metanephrines [86].

1. We recommend that initial biochemical testing for PPGLs should include measurements of plasma-free metanephrines or urinary fractionated metanephrines.
2. We suggest using liquid chromatography with mass spectrometric or electrochemical detection methods rather than other laboratory methods to establish a biochemical diagnosis of PPGL.
3. For measurements of plasma metanephrines, we suggest drawing blood with the patient in the supine position and use of reference intervals established in the same position.
4. We recommend that all patients with positive test results should receive appropriate follow-up according to the extent of increased values and clinical presentation.

9.4.5 Imaging Studies [83]

1. We recommend that imaging studies to locate PPGL should be initiated once there is clear biochemical evidence of a PPGL.
2. We suggest computed tomography (CT) rather than magnetic resonance imaging (MRI) as the first-choice imaging modality because of its excellent spatial resolution for thorax, abdomen, and pelvis.
3. We recommend MRI in patients with metastatic PPGL, for detection of skull base and neck paragangliomas, in patients with surgical clips that cause artifacts when using CT, in patients with an allergy to CT contrast, and in patients in whom radiation exposure should be limited (children, pregnant women, patients

with known germline mutations, and those with recent excessive radiation exposure).
4. We suggest the use of ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy as a functional imaging modality in patients with metastatic PPGL detected by other imaging modalities when radiotherapy using ^{131}I-MIBG is planned, and occasionally in some patients with an increased risk for metastatic disease due to large size of the primary tumor or to extra-adrenal, multifocal (except skull base and neck PPGLs), or recurrent disease.
5. We suggest the use of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/CT scanning in patients with metastatic disease. ^{18}F-FDGPET/CT is the preferred imaging modality over ^{123}I-MIBG scintigraphy in patients with known metastatic PPGL.

9.4.6 Genetic Testing [83]

Besides the three classical PHEO-associated cancer syndromes, namely, multiple endocrine neoplasia type 2 (MEN2), von Hippel-Lindau (VHL) disease, and neurofibromatosis type 1 (NF1), new entities have been associated with PHEO: the PGL syndrome types 1 to 5 [(PGL1–5) caused by mutations in succinate dehydrogenase (SDH) subunits D/AF2/C/B/A genes (SDHx), resp. [87]. The susceptible genes were sequenced according to the germline mutation frequency: SDHB (10.3%), SDHD (8.9%), VHL (7.3%), RET (6.3%), and NF1 (3.3%). The high rate of malignancy with SDHB mutations (40%) demands extensive initial diagnostic surveys and a close surveillance program [88]. Similarly, the greater likelihood of recurrent tumors in pediatric patients with VHL and SDHD mutations needs a proactive long-term follow-up. Nearly one-third of all patients with PHEO have germline mutations and this number is significantly higher at younger ages [89].

1. We recommend that all patients with PPGLs should be engaged in shared decision-making for genetic testing.
2. We recommend the use of a clinical feature-driven diagnostic algorithm to establish the priorities for specific genetic testing in PPGL patients with suspected germline mutations.
3. We suggest that patients with paraganglioma undergo testing of succinate dehydrogenase (SDH) mutations and that patients with metastatic disease undergo testing for SDHB mutations.
4. We recommend that genetic testing for PPGL be delivered within the framework of health care. Specifically, pretest and post-test counseling should be available. All tests for PPGL genetic testing should be performed by accredited laboratories. (Ungraded recommendation).

9.4.7 Perioperative Medical Management [83]

1. We recommend that all patients with a hormonally functional PPGL should undergo preoperative blockade to prevent perioperative cardiovascular complications.
2. We suggest adrenergic receptor blockers as the first choice.
3. We recommend preoperative medical treatment for 7 to 14 days to allow adequate time to normalize blood pressure and heart rate. Treatment should also include a high-sodium diet and fluid intake to reverse catecholamine-induced blood volume contraction preoperatively to prevent severe hypotension after tumor removal.
4. We recommend monitoring blood pressure, heart rate, and blood glucose levels with adjustment of associated therapies in the immediate postoperative period.
5. We suggest measuring plasma or urine levels of metanephrines on follow-up to diagnose persistent disease. We suggest lifelong annual biochemical testing to assess for recurrent or metastatic disease.

9.4.8 Surgery [83]

1. We recommend minimally invasive adrenalectomy (e.g., laparoscopic) for most adrenal pheochromocytomas. We recommend open resection for large (e.g., >6 cm) or invasive pheochromocytomas to ensure complete tumor resection, prevent tumor rupture, and avoid local recurrence. We suggest open resection for paragangliomas, but laparoscopic resection can be performed for small, noninvasive paragangliomas in surgically favorable locations.
2. We suggest partial adrenalectomy for selected patients, such as those with hereditary pheochromocytoma, with small tumors who have already undergone a contralateral complete adrenalectomy to spare adrenal cortex to prevent permanent hypocortisolism.

9.5 Primary Aldosteronism

Qin Luo

Primary aldosteronism (PA) is a group of disorders in which aldosterone production is inappropriately high, relatively autonomous from the renin-angiotensin system, resulting in suppression of plasma renin, hypertension, sodium retention, and potassium excretion, with or without hypokalemia [90, 91].

9.5.1 The Prevalence of PA in Hypertension Patients

PA is usually diagnosed between 20 and 60 years of age. PA was previously considered to be a rare disease accounting for less than 1% in unselected hypertensive

patients. With the widespread application of aldosterone/renin ratio (ARR), the prevalence of PA is currently reported between 5 and 13% in general population [92–94], and higher prevalence of 17–23% in resistant hypertensive patients [95–97]; therefore, it could be speculated that the actual number of PA patients might be a considerable number.

9.5.2 Subtype Classification and Pathogenesis

9.5.2.1 Subtype of Primary Aldosteronism

PA includes five subtypes: Aldosterone-producing adenoma (APA), bilateral idiopathic hyperaldosteronism (IHA), primary adrenal hyperplasia (PAH), aldosterone-producing adrenocortical carcinoma, familial hyperaldosteronism (FH) (Table 9.7). APA and IHA are the two most common subtypes of PA. The other subtypes are rare. PA can be divided into unilateral (largely represented by APA) and bilateral (largely represented by IHA) adrenal disease by using bilateral adrenal venous sampling (AVS). The Endocrine Society Clinical Practice Guidelines recommend that using laparoscopic adrenalectomy for unilateral disease and for those with bilateral disease, targeted medical therapy lowers both BP and the deleterious effects of aldosterone hypersecretion [90, 91].

9.5.2.2 Pathogenesis of PA

At present, the pathogenesis of familial hyperaldosteronism type I (FH-I) is clear, the pathogenesis of other types of PA is still unclear [98].

Table 9.7 Types of primary aldosteronism

Type of primary aldosteronism	Cases
Aldosterone-producing adenoma (APA)	30%
Bilateral idiopathic hyperplasia (BAH or IHA)	60%
Primary (unilateral) adrenal hyperplasia (PAH)	2%
Aldosterone-producing adrenocortical carcinoma	<1%
Familial hyperaldosteronism (FH)	
Glucocorticoid-remediable aldosteronism (FH type I)	<1%
FH type II (APA or IHA)	<6%
FH type III (germline KCNJ5 mutations)	<1%
Ectopic aldosterone-producing adenoma or aldosterone-producing carcinoma	<0.1%

1. Idiopathic aldosteronism (IHA): The most common type, accounting for about 60% of PA. The pathogenesis of this type is unclear. It is found that the pathogenesis of IHA is associated with aldosterone cluster-like cell aggregation (APCC) and CACNA1D gene mutation.
2. It is found that about 40% of sporadic APA has KCNJ5 somatic mutations, which is higher in Asian population (60–70%), CACNA1D accounts for about 10%, and ATP1A1, ATP2B3, and CTNNB1 somatic mutations are 2–5%, these mutations are thought to specifically drive aldosterone excess.
3. Familial hyperaldosteronism, FH (including type I, type II, and type III):
   (a) FH type I: glucocorticoid-remediable aldosteronism (GRA) inherited by autosomal dominant, the pathogenesis has been clear, it is related to some aldosterone synthase gene (CYP11B2) and 11β-hydroxylase gene (CYP11B1) occur formation of a chimeric gene by non-peer exchange. Normally, the genes encoding 11β-hydroxylase and aldosterone synthase are located on chromosome 8, and the DNAs in the coding regions are 95% identical. CYP11B2 is expressed in zona glomerulosa (zG), CYP11B1 is normally expressed in zona fasciculata (zF), and the latter is regulated by ACTH. The 5′ end of the chimeric gene is the regulatory sequence of CYP11B1, and the 3′ end is the coding sequence of CYP11B2. The product of transcriptional translation of the chimeric gene has aldosterone synthase activity, and its 5′ end contains ACTH-regulated sequence, thus resulting in ectopic synthesis and secretion of aldosterone in zF, then it is regulated by ACTH. The use of exogenous glucocorticoids can inhibit pituitary ACTH secretion, the expression level of chimeric gene products is decreased, and the secretion of aldosterone is also reduced, so type of these patients can be controlled by exogenous dexamethasone.
   (b) FH type II: it is called non-ACTH-dependent PA, also autosomal inheritance, more common than FH-I type, often occurs in adulthood, at least two members of the family are involved. There was no significant difference in clinical manifestations and treatment with non-familial PA. The secretion of aldosterone is affected by angiotensin II and erectile, but it is not regulated by ACTH, means it is not inhibited by dexamethasone. The pathogenesis of FH-II is not related to CYP11B2. Currently, the linkage analysis maps its gene to chromosome 7 (7p22), but its pathogenic gene has not been elucidated.
   (c) FH type III: rarely, characterized by severe hypertension in early childhood with typical high aldosterone, hypokalemia, and severe target organ damage. The adrenal gland of FH-III patients is significantly enlarged 3–6 times than the normal adrenal gland. Pathological examination showed diffuse hyperproliferation of the adrenal fascicular zone and atrophy of the globular zone, and the secretion of several adrenocortical hormones was also significantly increased. Its pathogenesis is related to germline mutation of KCNJ5 gene lead the loss of ion selectivity, Na^+ influx, cell membrane depolarization, and increased intracellular Ca^{2+} concentration.

(d) FH type IV: caused by heterozygous variant in the CACNA1H gene encoding a gain-of-function Cav3.2-Met1549Val mutation. The clinical phenotypes manifest as severe early onset hypertension, elevated ARRs, and no evidence of an adrenal mass or hyperplasia at imaging.

4. Primary adrenal hyperplasia (PAH): a rare form of unilateral PA, whose pathological morphology is adrenal cortical nodular hyperplasia, its endocrine and biochemical characteristics are between APA and IHA, currently considered to be with APCC and CACNA1D mutations, some scholars believe that it may be the early stage of adenoma.
5. Aldosterone cortical cancer: rare, can be seen at any age, the diameter of the cancer is often greater than 3 cm, easy to occur lung and liver metastasis. In addition to secreting aldosterone, tumors can secrete other corticosteroids, and clinical manifestations vary according to secreted hormones.

9.5.3 Clinical Manifestations and Harm of PA

1. Hypertension: The most common and earliest symptom, mainly moderate to severe hypertension. The initial manifestations are dizziness, headache, fatigue, tinnitus, and other nonspecific symptoms, and the conventional antihypertensive treatment is not effective.
2. Hypokalemia: In the past, hypokalemia was considered to be a hallmark of PA. In recent years, hypokalemia has been found to account for only about 30%. Hypokalemia can cause polydipsia, increased nocturia, and can cause periodic episodes of muscle weakness, paralysis, respiratory muscle paralysis, numbness of the extremities, and muscle spasms.
3. Target organ damage: Long-term excessive secretion of aldosterone in PA patients can increase body volume load, damage vascular endothelial function, induce oxidative stress, inflammatory reaction, and myocardial tissue and vascular remodeling and fibrosis, resulting increased risk of cardiovascular and cerebrovascular damage independent of hypertension, such as arrhythmia, heart failure, coronary artery disease, renal insufficiency, stroke, etc. A recent meta-analysis of 31 clinical studies involving 3838 patients with PA and 9284 patients with EH showed significantly increased risk of stroke [odds ratio (OR) = 2.58], coronary artery disease (OR = 1.77), atrial fibrillation (OR = 3.52), and heart failure (OR = 2.05) [99] in APA and IHA patients compared with EH patients. In addition, PA also increased the risk of diabetes (OR = 1.33), metabolic syndrome (OR = 1.53), and left ventricular hypertrophy (OR = 2.29). Moreover, a large number of studies have shown that PA can also cause mental illness in patients and affect the quality of life of patients [100–105].

9.5.4 PA Screening and Diagnosis Process (Fig. 9.1)

1. According to an endocrine society clinical practice guideline [91, 92], PA should be screened in patients with following situations:

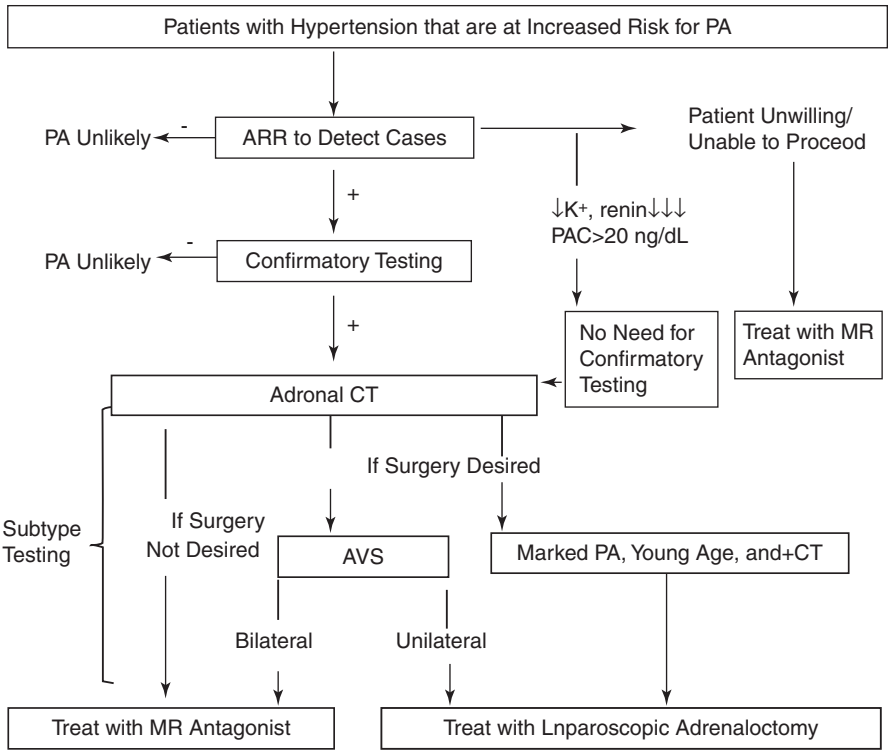

Fig. 9.1 Diagnostic process of PA

(a) Blood pressure persistence >150/100 mmHg or resistant hypertension (when combined with three antihypertensive drugs including diuretics, blood pressure is still higher than 140/90 mmHg, or when combined with four or more antihypertensive drugs, blood pressure is lower than 140/90 mmHg).
(b) Hypertension with spontaneous hypokalemia or induced by diuretics.
(c) Hypertension with obstructive sleep apnea.
(d) Hypertension with adrenal adenoma.
(e) Hypertensive patients with family history of early onset hypertension or with family history of early onset cerebrovascular accident less than 40 years old.
(f) First-degree relatives suffer from PA.

At present, it is generally accepted that aldosterone/renin ratio (ARR) is the most widely used, reliable, and ideal screening index for PA. Most centers use the cutoffs of 20–40 (ng/mL/h)/(ng/dL) (taking blood under sitting conditions in midmorning) [106, 107]. However, ARR still has some limitations. The accuracy of ARR is affected by many factors, such as different postures, measurement time, antihypertensive drugs, blood potassium level, sodium intake, kidney function, age, sex, menstrual cycle, contraceptives

and antidepressants, and detection methods [108–113]. Therefore, in order to ensure the reliability of laboratory results, it is necessary to determine the time and position of blood extraction, sodium intake, and other pretest preparations: (1) Try to correct the blood potassium to the normal range. (2) Maintain normal sodium intake. (3) Withdrawal of ARR drugs had a significant impact on ARR for at least 4 weeks: aldosterone receptor antagonists (spironolactone, ipridone), potassium-preserving diuretics (amiloride, aminophenylpyridine), potassium-excreting diuretics (hydrochlorothiazide, furosemide), and glycyrrhiza extracts. (4) Angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor antagonist (ARB), calcium antagonist (CCB), and other drugs can increase renin activity and reduce aldosterone, leading to false-negative ARR. Therefore, PA cannot be excluded from ARR-negative, and the above drugs should be discontinued for at least 2 weeks before testing. (5) Because beta-blockers, central alpha-2 receptor blockers (clonidine or methyldopa), non-steroidal anti-inflammatory drugs, and so on can reduce renin activity, leading to false-positive ARR, it is recommended to stop taking beta-blockers for at least 2 weeks, such as patients with coronary heart disease or arrhythmia, and clinicians decide whether to stop taking beta-blockers or not according to the patient's condition. (6) If blood pressure is not well controlled, alpha receptor blockers and non-dihydropyridine CCB (e.g., verapamil, doxazosin, terazosin) can be given to control blood pressure. (7) Oral contraceptives and artificial hormone replacement therapy may reduce direct renin concentration (DRC). Contraceptives are generally not discontinued unless better and safer contraceptive measures are available. At present, there is no uniform cutting value for screening PA. Different cutting values of ARR are used in different centers, ranging from 20 to 100 ng/dL per ng/mL/h. In some centers, ADRR (aldosterone/renin concentration) was calculated by measuring plasma renin concentration instead of plasma renin activity, ranging from 26.35 to 59.66 ng/dL per ng/dL [114–116].

(g) Factors that may lead to false-positive or false-negative ARR results (Table 9.8 [91]).

2. PA Confirmation Test

As a screening test for PA, ARR has a certain false-positive, so it is necessary to select one or several confirmatory tests for further diagnosis of PA-positive patients. At present, there are four kinds of diagnostic tests used at home and abroad, including hydrofluorocortisone test (FST), oral high-sodium diet, saline infusion test (saline load test, SIT), and captopril test. These four tests have their own advantages and disadvantages, among which FST is considered to be the most credible, but the operation is cumbersome and are not available in China. Oral high-sodium diet and fluorocortisone test are complicated and take a long time to prepare. Most centers use intravenous saline loading test as diagnostic test. Recently, Stowasser et al. reported that the accuracy of SIT in sitting position was significantly better than that in recumbent position, especially for postural reactive PA, which is expected to be a simple alter-

Table 9.8 Factors that may lead to false-positive or false-negative ARR results

Factor	Effect on aldosterone plasma levels	Effect on renin levels	Effect on ARR
Medications			
β-Adrenergic blockers	↓	↓↓	↑(FP)
Central agonists (e.g., clonidine, α-methyldopa)	↓	↓↓	↑(FP)
NSAIDs	↓	↓↓	↑(FP)
K^+-wasting diuretics	→↑	↑↑	↓(FN)
K^+-sparing diuretics	↑	↑↑	↓(FN)
ACE inhibitors	↓	↑↑	↓(FN)
ARBs	↓	↑↑	↓(FN)
Ca^{2+}blockers (DHPs)	→↓	↑	↓(FN)
Renin inhibitors	↓	↓↑	↑(FP) ↓(FN)
Potassium status			
Hypokalemia	↓	→↑	↓(FN)
Potassium loading	↑	→↓	↑
Dietary sodium			
Sodium restriction	↑	↑↑	↑(FN)
Sodium loading	↓	↓↓	↑(FP)
Advancing age	↓	↓↓	↑(FP)
Premenopausal	→↑	↓	↑(FP)
Women (vs. males) other conditions			
Renal impairment	→	↓	↑(FP)
PHA-2	→	↓	↑(FP)
Pregnancy	↑	↑↑	↓(FN)
Renovascular HT	↑	↑↑	↓(FN)
Malignant HT	↑	↑↑	↓(FN)

NSAIDs non-steroidal anti-inflammatory drugs, K^+ potassium; ACE angiotensin-converting enzyme, ARBs angiotensin II type 1 receptor blockers, DHPs dihydropyridines, PHA-2 pseudohypoaldosteronism type 2 (familial hypertension and hyperkalemia with normal glomerular filtration rate), HT hypertension, FP false-positive, FN false-negative

native to FST [117, 118]. However, it should be noted that high-sodium stress test is not suitable for uncontrolled patients with severe hypertension, renal insufficiency, cardiac insufficiency, arrhythmia, and severe hypokalemia. In addition, because hypokalemia can decrease aldosterone secretion, it is necessary to supplement potassium adequately before the test, and keep the blood potassium within the normal range before the diagnostic test can be carried out. Captopril test is a simple and safe diagnostic test, but there is a certain false-negative in this test. Aldosterone levels in some IHA patients can be decreased [119]. It should be pointed out that the interference of drugs should be excluded before the above diagnostic tests, and the matters needing attention should be the same as the determination of ARR.

3. Subtype Classification

The endocrine society clinical practice guideline recommended that all patients with PA undergo adrenal CT as the initial method for subtype testing to exclude large masses that may represent adrenocortical carcinoma and to assist the interventional radiologist and surgeon where anatomically appropriate. Adrenal venous sampling (AVS) is the gold standard method to differentiate unilateral from bilateral forms and performed in patients who are candidates for surgery. The procedure of AVS can be difficult, especially in terms of successfully cannulating the right adrenal vein. With experience, the success rate varied is between 90% and 96%. The main the complication of AVS is adrenal hemorrhage, the risk of thromboembolism is very low.

Successful AVS is determined by calculating the selective index (SI) and Lateralization of aldosterone secretion is determined by the lateralization index (LI) Protocols for AVS: a) unstimulated sequential or simultaneous bilateral AVS, b) unstimulated sequential or simultaneous bilateral AVS followed by bolus cosyntropin-stimulated sequential or simultaneous bilateral AVS, and c) continuous cosyntropin infusion with sequential bilateral AVS.Assessment of Successful Catheterization: a) the cutoff value for the SI should be ≥2.0 under unstimulated conditions;b) the cutoff value for the SI should be ≥3.0 during cosyntropin stimulation.

Assessment of Lateralization: most centers used LI between 2.0 and 4.0 under unstimulated conditions and between 2.6 and 4.0 during cosyntropin stimulation; Most of centers used baseline, unstimulated LI values ≥2.0.

SI = PCC_{side}/PCC_{IVC}; LI = PACDom/PCCDom:PACNondom/PCCNondom (IVC, inferior vena cava; Dom, dominant side; Nondom, nondominant side; PCC, plasma cortisol concentration).

9.5.5 Differential Diagnosis of PA

1. Differentiation between hypertension and hypokalemia:
   (a) Renal potassium loss: hypokalemic interstitial nephritis, renal tubular acidosis, and other causes of obvious renal function changes and changes in blood pH value.
   (b) Secondary aldosteronism: usually caused by renal ischemia, acute or malignant hypertension and renin secretion tumors; resulting in hypertension and hypokalemia.
   (c) Liddle syndrome: So called pseudoaldosteronism. Because of the mutation of the regulatory sequence of sodium channels in the epithelial cells of distal renal tubules and collecting ducts, the sodium channels are overactivated, the sodium reabsorption is increased, and the abnormal transport of sodium and potassium ions causes hypertension and hypokalemia, but aldosterone secretion is normal or slightly lower than normal.
   (d) Hypertension and hypokalemia caused by non-antihypertensive drugs: For example, patients who take glucocorticoids, estrogen or contraceptives for a long time can cause drug-induced hypertension and hypokalemia. The identification needs to be judged from the history of taking drugs, blood pressure, and blood potassium returning to normal after withdrawal (Table 9.9).

Table 9.9 The influencing factors of false-positive or false-negative for ARR

Confirmatory tests		Operation method	Procedure	Concerns
Unrepressed tests Aldosterone elevation in plasma and 24-h urine	Oral salt loading test (oral SLT)	Sodium intake >200 mmol/day (~6 g/day) for 3 days. After taking potassium chloride sustained-release tablets to adjust the normal range of blood potassium, 24-h urine is collected from the morning of the third day to the morning of the fourth day of the experiment. Urinary aldosterone levels are measured	PA can be excluded when urine aldosterone is less than 10 μg/24 h, and PA can be diagnosed when urine aldosterone is more than 12 μg/24 h (Mayo Clinic Center standard) and 14 μg/24 h (Cleveland Clinic Center standard)	Severe hypertension patients are not effectively controlled; refractory hypokalemia patients are not corrected; severe arrhythmia; heart failure and moderate to severe renal insufficiency patients should not be used
	Intravenous salt infusion test (SIT)	On the basis of general diet or balanced meal test, blood potassium is corrected to normal before the test. 0.9% saline (2000 mL) is administered intravenously, and aldosterone in plasma is measured before and after infusion	The plasma aldosterone concentration <5 ng/dL after saline can exclude PA; the plasma aldosterone concentration after saline is 5–10 ng/dL, which is an uncertain PA. The diagnosis should be based on clinical manifestations (including hypokalemia, high potassium urinary excretion, adrenal CT). Prompt nodules or low-density foci); plasma aldosterone concentration ≥10 ng/dL after saline can diagnose PA	Severe hypertension is not effectively controlled; patients with stubborn hypokalemia are not corrected; severe arrhythmia; patients with heart failure and moderate to severe renal insufficiency should not be used
	Captopril test (CAPT)	Blood samples are taken to measure renin and aldosterone after sitting or standing for 1 h. Blood samples are taken for renin activity and plasma aldosterone concentration 1 h and 2 h after taking 25–50 g captopril tablets. The patients remain seated until the end of the experiment	The guideline suggests that PAC suppression percentage ≤30% as the diagnostic criteria. Differences may be seen between patients with APA and those with IAH. Some centers prefer to use ARR or PAC post-CCT.	Taking 50 mg captopril on the basis of the original standardized antihypertensive program may cause hypotension
	Fluorohydrocortisone inhibition test (FST)	Patients take 0.1 mg of fluorohydrocortisone tablets every 6 h for 4 days, and oral potassium supplementation is also given. (The adjustment of blood potassium is close to 4.0 mmol/L by daily close monitoring; 30 mmol/L sodium chloride sustained-release tablets added to three meals a day (Monitor urinary sodium daily to maintain urinary sodium excretion rate (>3 mmol/kg). Cortisol is measured at 7:00 in the morning on the fourth day of the experiment; renin activity, aldosterone concentration, and cortisol are measured at 10:00 a.m. in the sitting position	1. The plasma aldosterone concentration is higher than 6 ng/dL after the experiment 2. Renin activity is less than 1.0 ng/mL/h after the test 3. The cortisol measured at 10:00 am on the fourth day of the experiment is lower than that at 7:00 a.m.	Patients with intractable hypokalemia not corrected should not be used

(continued)

Table 9.9 (continued)

Confirmatory tests		Operation method	Procedure	Concerns
Reduced renin activity without being excited	Furosemide provocation test (FPST)	Patients lie on their back for at least 2–6 h before 8:00 a.m., take blood at 8:00 a.m. to determine renin and aldosterone, stand at 9:00 a.m. and push furosemide 40 mg intravenously, and take blood after 2–4 h to determine renin and aldosterone	Renin activity is less than 2.0 ng/mL/h after the experiment	Patients with intractable hypokalemia not corrected should not be used
	Postural stimulation test (PST)	Patients lie on their back for at least 2–6 h before 8:00 a.m., take blood at 8:00 a.m. to determine renin and aldosterone, and take blood at 9:00 a.m. to determine renin and aldosterone after standing for 2–4 h	The renin activity is less than 0.8 ng/mL/h after the experiment	Postural hypotension may occur when alpha 1 receptor blockers are used in elderly men with hypertrophy of the prostate
Other	Spirono-lactone test	The patient is given oral spironolactone tablets 300–400 mg daily for 3–4 weeks, and blood pressure is monitored and recorded daily, and blood potassium is measured once in every 2–3 days	1. The blood potassium returns to normal in the first 1–2 weeks; 2. Blood pressure drops to normal in the 2–3 weeks	Patients with renal insufficiency are contraindicated in this trial to avoid hyperkalemia

2. Differential diagnosis of adrenal hypertension:
   (a) Cushing syndrome commonly caused by adrenal tumors or hyperplasia and secretion of large amounts of cortisol, it can be manifested as hypertension, hypokalemia, some patients with typical centripetal obesity, polycythemia appearance, skin purple lines, acne and other signs, and increased blood, saliva, urine cortisol levels, through dexamethasone test can be further identified.
   (b) Pheochromocytoma: It is a rare disease, but it is the main disease of adrenal medulla. About 50–60% of the patients have persistent hypertension, of which half are paroxysmal exacerbation; 40–50% have paroxysmal hypertension. Hypertensive attack with headache, palpitation, and hyperhidrosis is of great significance in the diagnosis of pheochromocytoma. Hypokalemia can be measured by sweating and loss of appetite. Detection of urinary vanillary amygdalate or blood 3-methoxy-epinephrine and methoxy-norepinephrine during seizures may be helpful in the identification.
   (c) Congenital adrenocortical hyperplasia: It is a common autosomal recessive hereditary disease caused by the congenital deficiency of enzymes required in the process of corticosteroid synthesis. The inadequate synthesis of cortisol lowers the blood concentration, and the negative feedback stimulates the pituitary to secrete more adrenocorticotropic hormones, resulting in bilateral adrenocortical hyperplasia. The proliferative cortex continuously synthesizes androgens and salt corticosteroids which cause hypertension. Clinical symptoms such as hypertension, hypokalemia, and gonadal dysplasia occur. Therefore, it can be differentiated from medical history, signs, chromosomes, and laboratory examinations.

9.5.6 Treatment

The treatment of PA should be based on the diagnosis and classification of lateral diagnosis.

9.5.6.1 Drug Therapy

Mineralocorticoid receptor antagonists are mainly used. They are drugs that prevent the physiological effects of salt corticosteroids (e.g., aldosterone) by competing for salt corticosteroid receptors. It can reduce blood pressure and correct hypokalemia. It is a long-term plan for patients with bilateral PA and unilateral PA who are at high risk and unwilling to undergo surgery. It can also be used before and during adrenalectomy.

1. Mineralocorticoid receptor antagonism

   Spironolactone: Spironolactone dose ranges from 1 to 4 mg per kg body weight per day. Spironolactone has many side effects related to sex steroids, such as breast pain, menstrual disorders, decreased libido, and impotence. These side effects are dose related. If the daily dose is controlled at or below 50 mg, the incidence of side effects is about 6.2%. If the daily dose is equal to or more than 150 mg, the incidence of side effects increases to 50%.

Eplerenone: The routine oral dose is 50–100 mg, 1–2 times a day. For PA patients, oral doses of 50–300 mg for 1–2 days are usually used. Side effects are relatively small. Studies have shown that there is no significant difference in side effects between placebo and placebo.

2. Non-mineral corticosteroid receptor antagonists

Amilopril: It is a drug that antagonizes the endothelial sodium channel in the kidney. It can reduce blood pressure and increase blood potassium. It is considered to be selective to salt corticosteroid receptors.

Other drugs: calcium antagonists, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists all have small sample descriptions for the treatment of PA. They do not antagonize salt corticosteroid receptors; they have certain effect on hypotension, but cannot usually correct the hypokalemia caused by hyperaldosteronism. In addition, aldosterone synthase inhibitors may be a new target for future treatment.

9.5.6.2 Surgical Treatment

1. Guidelines recommend the best indications for surgical treatment

(1) Aldosterone tumors; (2) Unilateral adrenal hyperplasia; (3) Aldosterone-secreting adrenal cortical carcinoma or ectopic tumors; (4) Patients with idiopathic aldosteronism who cannot tolerate long-term drug treatment due to side effects of drugs.

2. Surgical methods

Laparoscopic adrenalectomy is recommended as the first choice for aldosteronism. Laparoscopic adrenalectomy is recommended for unilateral adrenal hyperplasia. Laparoscopic adrenalectomy is recommended for patients with idiopathic aldosteronism who are unable to adhere to medical treatment due to side effects of drugs. Surgery can be considered for patients with idiopathic aldosteronism who secrete more or larger adrenals.

9.5.6.3 PA with Pregnancy

For APA patients, laparoscopic adrenalectomy can be considered in the second trimester of pregnancy. Spironolactone is classified as pregnancy C drug by FDA. Animal experiments have found that it can induce feminization of male newborn mice. It has been reported in humans that polycystic ovary syndrome (PCOS) patients take Spironolactone from 5 weeks of gestation to cause male infants to have external genitals difficult to distinguish, so it is not recommended to use Spironolactone during pregnancy. Epristone is classified as pregnancy B drug by FDA. During pregnancy, it should be treated according to the standard of pregnancy with hypertension. Potassium supplements should be taken orally for hypokalemia. For APA patients who cannot be treated surgically, low doses of epristone should be considered.

9.5.7 Prognosis

So far, many studies have confirmed that targeted treatment of different subtypes of PA (including surgery and drug treatment) can significantly improve the cardiovascular prognosis and mortality of PA patients [120–123]. A recent large cohort study

involving 12 clinical centers involving 705 patients with unilateral PA based on AVS precise typing showed that: 37% of patients with unilateral PA were clinically cured after laparoscopic adrenalectomy (definition: normal blood pressure + no antihypertensive drugs). 47% of patients received partial clinical remission after operation [Definition: (1) Blood pressure remains unchanged + antihypertensive drugs decrease; (2) Blood pressure decreases compared with preoperative + antihypertensive drugs are the same or less], the biochemical cure rate was 94% (Definition: Hypokalemia, ARR returned to normal) [121]. Another PA cohort study from the United States, involving 602 patients treated with drugs (mineral corticosteroid receptor antagonists), showed that even if blood pressure was controlled at the same level, the risk of major cardiovascular events, diabetes, atrial fibrillation, and death was still about twice as high as that of EH patients. Further stratification by PRA revealed that the high risk mainly existed in PA patients whose renin was still below 1.0 ng/mL/h after taking the medicine. It is suggested that inadequate antagonism of salt corticosteroid receptor may be the cause of worse prognosis than that of patients undergoing EH and PA surgery [124].

9.6 Cushing Syndrome

Sha Tao

9.6.1 Introduction

Cushing syndrome denotes pathologic hypercortisolism as a result of excessive adrenocorticotropic hormone (ACTH) production, or autonomous adrenal production of cortisol. This potentially lethal disorder is associated with significant comorbidities, including hypertension, diabetes, coagulopathy, cardiovascular disease, infections, and fractures. As a result, even after cure of hypercortisolism, mortality rates may be increased. Because of this it is important to make the diagnosis as early in the disease course as possible to prevent additional morbidity and residual disease [125].

9.6.2 Epidemiology

Endogenous CS is an uncommon disorder, with population-based studies showing an incidence of 0.7–2.4 cases per million population per year. The female-to-male ratio is 3:1 except for the subtype of ectopic ACTH syndrome, which is equally common in male patients [3, 8, 9]. Subclinical CS refers to the presence of autonomous mild cortisol hypersecretion in a patient who lacks the classic or overt signs of CS and is present in 5–20% of patients with an incidental finding of an adrenal mass (adrenal incidentaloma) [126]. Hypertension is very common affecting about 80% of patients with Cushing [127]. In patients with resistant hypertension, less than 1% of patient suffered from CS [127].

9.6.3 Progress in Genetics of Cushing Syndrome

Great progress has been made in recent years to elucidate the genetic defects underlying CS of adrenal and pituitary origin. Frequent molecular abnormalities in adrenal lesions include cAMP/PKA and WNT/CTNNB1 signaling overactivation, whereas glucocorticoid resistance, abnormal expression of cell-cycle regulators, and overexpression of membrane receptors predominate in corticotropinomas. Although most of the patients present sporadically, CS is part of a growing number of syndromes of familial isolated CS or multiple endocrine and nonendocrine neoplasia. Moreover, it should be kept in mind that CS of adrenal and pituitary origin can coexist in the setting of some syndromic presentations, complicating the diagnosis [128].

9.6.4 Classification of Cushing Syndrome

CS can result from exogenous administration of glucocorticoids or endogenous overproduction of cortisol [129]. Endogenous CS is traditionally classified as ACTH dependent when pathologic ACTH secretion drives cortisol production, or as ACTH independent, when the adrenal glands autonomously secrete excessive cortisol [130]. The diagnosis of CS requires the confirmation of hypercortisolism, the differentiation between ACTH-dependent and ACTH-independent causes, and the differentiation between pituitary and ectopic sources of ACTH in ACTH-dependent CS [126].

9.6.4.1 Exogenous Cushing Syndrome

Exogenous or iatrogenic CS is more common than endogenous CS and results from the administration of supraphysiologic doses of glucocorticoids. Exogenous administration of glucocorticoids is used to treat inflammatory, autoimmune, and neoplastic disorders [130]. Administration of synthetic ACTH is prescribed less often these days.

9.6.4.2 Endogenous Cushing Syndrome

Adrenocorticotropic Hormone-Dependent Cushing Syndrome: ACTH-dependent CS accounts for approximately 80% of the endogenous causes and includes ACTH-secreting pituitary adenomas (Cushing disease), ectopic ACTH syndrome, and CRH-producing tumors [126].

Cushing disease: Cushing disease, which results from a pituitary adenoma-producing ACTH, accounts for approximately 80% of cases of ACTH-dependent CS. The ACTH-secreting pituitary adenoma stimulates the adrenal glands to secrete cortisol. Cushing disease typically occurs in the third or fourth decade of life although children and young adolescents can also develop Cushing disease. The frequency of Cushing disease is significantly higher among women [126].

Ectopic adrenocorticotropic hormone syndrome: Ectopic ACTH syndrome, which is due to ACTH production from nonpituitary tumors, accounts for approximately 20% of ACTH-dependent CS cases. It is crucial to distinguish ectopic ACTH syndrome from the more common Cushing disease (CD) and to localize the source of ectopic

ACTH secretion because surgical resection of the primary lesion has a high probability of cure, with complete remission in up to 80% of cases, and these extrapituitary tumors are frequently malignant. Tumors of the lung are the most likely source of ectopic ACTH, with small cell lung cancer and bronchial carcinoid tumors accounting for approximately 50% of ectopic ACTH-secreting tumors. Other causes of ectopic ACTH syndrome include nonlung neuroendocrine tumors (22.5%), including thymic, pancreatic, and gastrointestinal carcinoids; medullary thyroid carcinomas (7.5%); and pheochromocytoma (2.5%). Localization of the ectopic source of ACTH can be difficult and may be delayed for months to years, with consequent increased morbidity and mortality. In 12.5% of patients, the source of ectopic ACTH syndrome cannot be found, despite repeated clinical and imaging evaluations and long-term follow-up [126].

Corticotropin-releasing hormone-producing tumors: CS due to CRH-producing tumors is extremely rare, accounting for less than 1% of cases of ACTH-dependent CS [130]. In 20 cases reported in the literature, isolated CRH-producing tumors consisted of medullary thyroid carcinoma (33%), pheochromocytoma (19%), carcinoma of the prostate (14%), small cell lung carcinoma (9.5%), and carcinoid (5%), with single cases of sellar choristoma and gangliocytoma [131]. Although it is exceedingly rare, ectopic CRH syndrome should be included in the differential diagnosis for causes of CS.

9.6.4.3 ACTH-Independent Cushing Syndrome

ACTH-independent CS, accounting for approximately 20% of all endogenous causes, results from autonomous secretion of cortisol from an adrenal gland lesion, usually an adenoma, adrenocortical carcinoma (ACC), or, very rarely, ACTH-independent macronodular adrenal hyperplasia or primary pigmented nodular adrenal disease (PPNAD) [132].

Adrenal adenoma: Adrenal adenomas are benign neoplasms of adrenocortical cells that account for approximately 60% of adrenal causes of CS [8]. Adrenal adenomas can be hormonally silent or they can produce clinical syndromes of hypercortisolism (CS), hyperaldosteronism, or, rarely, virilization or feminization. They are often discovered incidentally on abdominal imaging studies or may be sought when patients present with symptoms of hormonal excess.

Adrenocortical carcinoma [133]*:* Adrenocortical carcinoma (ACCs) are rare often-aggressive tumors and account for approximately 40% of adrenal causes of CS. ACCs have an estimated annual incidence of two cases per million people with an estimated 5-year overall survival rate of 15–44%. ACC tends to occur in the fourth or fifth decades of life and only extremely rarely in children [9]. ACC can occur sporadically or may be syndromic and associated with Li-Fraumeni syndrome, Lynch syndrome, familial adenomatous polyposis, or Beckwith-Wiedemann syndrome among others. Up to 80% of children with ACC carry a germline *TP53* mutation found in Li-Fraumeni syndrome. Approximately 40% of ACCs are hormonally functioning and can secrete cortisol (most commonly), aldosterone, or androgens. Functioning tumors are associated with increased morbidity and poorer survival compared with nonfunctioning tumors.

Primary pigmented nodular adrenal disease (PPNAD): PPNAD is a rare cause of ACTH-independent CS and accounts for less than 1% of adrenal causes of CS [132]. PPNAD is most frequently seen in infants, children, or young adults. The clinical presentation may be atypical, with short stature, asthenic body habitus, severe muscle wasting, and advanced osteoporosis commonly present. The majority of PPNAD cases are part of a Carney complex, characterized by cardiac and cutaneous myxomas, spotty skin pigmentation and lentigines, PPNAD, testicular tumors, and growth hormone-secreting pituitary tumors [134]. Carney complex arises from a mutation in the *PRKAR1A* gene.

ACTH-independent macronodular adrenal hyperplasia: ACTH-independent macronodular adrenal hyperplasia accounts for less than 1% of adrenal causes of CS [132]. ACTH-independent macronodular adrenal hyperplasia occurs equally in male as in female patients, in contrast to the predominantly female distribution of most cases of CS, and has a higher mean patient age compared with adenomas, CD, or PPNAD, most frequently presenting in the fifth to sixth decades of life. Most cases of ACTH-independent macronodular adrenal hyperplasia are sporadic, and patients may be identified either after an incidental imaging finding or during the workup of adrenal over-secretion syndrome. Patients may have subclinical or overt CS [135].

Adrenal incidentalomas: Adrenal incidentaloma (AI) is a mass larger than 1 cm in diameter discovered incidentally on imaging not performed for suspected adrenal disease. Advances in imaging techniques raised the prevalence of AI to 4.4% in radiological series compared to autopsy data (1–8.7%) [136, 137]. Both nonfunctioning adrenal adenoma and subclinical Cushing syndrome are the common subtypes of adrenal incidentalomas.

9.6.4.4 Other Rare Cause

Cyclic CS: Cyclic CS is a rare variant of Cushing syndrome that demonstrates periodic cortisol excess. The underlying mechanism that triggers the development of the hypercortisolism is still unknown [138].

Subclinical CS: Subclinical CS refers to the presence of autonomous mild cortisol hypersecretion in a patient who lacks the classic or overt signs of CS and is present in 5–20% of patients with an incidental finding of an adrenal mass (adrenal incidentaloma) [139].

9.6.5 Pathophysiological Mechanism of CS

Hypertension: Arterial hypertension is a very common feature. The prevalence of this complication is about 80% in adult CS patients while in children and adolescents it is about 47% [140].

Cardiovascular complications: Cardiovascular complications are the main causes of mortality among CS patients. Cardiovascular risk in CS is mainly linked to the presence of complications resulting from cortisol excess such as hypertension, obesity, diabetes mellitus (DM), dyslipidemia, and coagulation disorders (see relative sections). Moreover, glucocorticoids (GC) play a direct role on the cardiovascular system through gluco- and mineralocorticoid receptors and seem to

directly influence vascular smooth muscle, endothelial cells, myocardium, and macrophages [141].

Coagulopathy: CS is associated with a hypercoagulable state leading to an increased incidence of venous thromboembolic events (VTE). The derangement of the hemostatic system is related to cortisol excess that induces prothrombotic changes in blood by several and complex mechanisms including quantitative and qualitative alterations in the clotting profile.

Obesity: CS is characterized by an increase in body weight associated with redistribution of adipose tissue at abdominal level and a decrease of subcutaneous fat in the limbs. Accumulation of central adipose tissue occurs above all in the intra-abdominal region, both in men and women resulting in disappearance of gender difference in visceral fat. Obviously, visceral obesity is a risk factor for reduced life expectancy. Cortisol directly stimulates adipocyte differentiation and adipogenesis by activation of key differentiation genes (lipoprotein lipase, glycerol-3-phosphate dehydrogenase, and leptin).

Impaired glucose tolerance and DM: GC excess induces impairment of glucose metabolism both by direct and indirect effects. Direct effects include: 1) stimulation of gluconeogenesis in the liver through the expression of several key enzymes, with consequent increase of glucose production; 2) reduction of insulin sensitivity by the impairment of the insulin receptor signaling pathway in peripheral tissues, and 3) enhancement of different hormones involved in glucose metabolism, in particular glucagon, whose actions lead to increased glucose production. Indirect effects mainly include the stimulation of proteolysis and lipolysis that contribute both to the development of insulin resistance and the increase of glucose production providing substrates for gluconeogenesis.

Dyslipidemia: GC regulate differentiation, function, and distribution of adipose tissue where they may stimulate both lipolysis and lipogenesis. The pathogenetic mechanisms of dyslipidemia are multifactorial, including direct and indirect cortisol action on lipolysis, decreased fatty acids β-oxidation, increased hepatic free fatty acid (FFA) production, VLDL synthesis, and fatty accumulation in liver.

Myopathy: GC-induced myopathy is a common complication of GC excess. This problem is one of the most discriminating elements characterizing CS and its prevalence varies between 40 and 80% in patients with endogenous CS [141].

Osteoporosis and fractures: Structural and functional impairment of the skeletal system is a relevant cause of morbidity and disability in patients with CS. The pathogenesis of GC-induced osteoporosis (GIO) is complex, multifactorial, and not fully understood. GC decrease the bone collagenous matrix reducing its synthesis and increasing its degradation. The decrease in osteoblast number and function seems to play a central role in bone loss; in fact, hypercortisolism inhibits the replication of osteoblastic lineage, decreases the production of new osteoblasts and induces apoptosis of osteoblasts and osteocytes and this contributes to a decreased number of mature osteoblasts.

Psychiatric disorders: GC have important effects also on the central nervous system; they affect neural activity and a number of specific biochemical processes. Increased levels of GC often produce behavioral disorders which are initially represented by insomnia and euphoria and later by depression.

Infections: Given the potent anti-inflammatory and immunosuppressive action of GC, it is not surprising that an excess of GC impairs immune function and predisposes to infectious complications.

Gonadal abnormalities: GC exert important effects on the reproductive function in a sex-dependent manner, whereas men tend to have true hypogonadotropic hypogonadism; both hyperandrogenism and hypogonadotropic hypogonadism may occur in women.

Thyroid abnormalities: The effects of hypercortisolism on thyroid function vary in degree and affect hypothalamic-pituitary adrenal (HPA) and T4 metabolism; moreover, GC can influence thyroid functionality by inhibiting immune response.

Others: CS is associated with blunted somatic growth and blocked GH secretion. Pediatric CS patients show short stature associated with increased BMI values. Given the great number of physical and neuropsychological consequences of hypercortisolism a significant impact on quality of life (QoL) is expected.

9.6.6 Pathogenesis of Hypertension in CS

The mechanisms involved in the development of hypertension are complex and only partially understood. Previous researches concluded that the renin-angiotensin system (RAS), the mineralocorticoid activity, the sympathetic nervous system, and the vasoregulatory system, together with indirect mechanisms, which contribute to the development of CS-related hypertension. The mechanisms through which hypercortisolism induces hypertension directly or indirectly, as well as the mechanisms by which specific treatments, which could counteract directly or indirectly the hypercortisolism-induced changes that contribute to the CS-related hypertension and consequent cardiovascular damage.

9.6.7 Clinical Features of Cushing Syndrome

Clinical manifestations of CS depend on the patient's age and the duration and degree of the hypercortisolism. CS is associated with poor quality of life, morbidity, and a fivefold excess mortality. In florid cases, patients may present with central obesity with dorsocervical and supraclavicular fat accumulation, thinned skin with wide purple striae, fatigue, proximal muscle weakness, hypertension, glucose intolerance, acne, hirsutism, and menstrual irregularities. Neuropsychological manifestations are frequent and include depression, sleep disturbances, emotional lability, and cognitive defects. In children, growth retardation is frequently observed. Because manifestations of CS are multiple and variable, the diagnosis may be challenging when signs and symptoms are subtle [126, 142] (Table 9.10).

9.6.8 Screening Tests for Cushing Syndrome

When the pretest probability of CS is high, and exogenous steroid exposure has been excluded, patients should undergo recommended first- and (as appropriate) second-line biochemical tests to screen for CS (Table 9.11) [144]. In general, these

Table 9.10 Signs and symptoms associated with Cushing syndrome grouped by system [143]

System	Comments
General	
Fatigue	
Growth	In children, typically a decrease in height percentile as weight percentile increases
Adipose	
Increased weight from baseline	BMI may be normal, overweight, or obese
Changes in adipose distribution	Increased temporal, supraclavicular or dorsocervical adipose; may lead to moon facies or central adiposity
Skin/hair	
Striae	Often with more severe hypercortisolism; significant if >1 cm and purple color; occur on abdomen, buttocks, upper arm/leg, breasts
Thin skin	Compare with age/sex controls (skin is thinnest in older women)
Hyperpigmentation	May be present in ACTH-dependent forms
Hirsutism (women)	Not typical for ACTH-independent adenomas
Balding (women)	Not typical for ACTH-independent adenomas
Acne	May be glucocorticoid (red) or androgen (pustular) related
Poor wound healing	
Increased bruising	
Flushed face	
Psychiatric/Cognitive	
Accentuation of previous personality/ disorder	Up to 80% of patients may have previous diagnosis
Increased irritability	Present in up to 86% of patients
Development of new psychiatric disorder	
Decreased memory	Short-term memory is particularly affected; may be assessed at bedside by recall of three cities or objects
Decreased cognitive ability	May be assessed at bedside by serial 7 s (consecutive subtraction of 7 from 100)
Infectious	
Increased number of infections	Including typical community-acquired infections as well as those seen more often in immunocompromised individuals; the latter most frequently in patients with more severe hypercortisolism
Renal	
Increased incidence of stones	
Metabolic	
Glucose intolerance/ diabetes	Both new and exacerbation of existing glucose intolerance seen
Cardiovascular/thrombotic	
Hypertension	Greatest diagnostic weight in children and older patients in whom it is difficult to control, as both are unexpected in the general population
Increased incidence CVA	

Table 9.10 (continued)

System	Comments
Increased incidence myocardial infarction	
Increased clotting	May result in deep venous thrombosis and pulmonary embolism, more common in severe hypercortisolism
Edema	
Reproductive	
Decreased libido	
Delayed or stuttering puberty (children)	
Infertility	Presumed to result from anovulation; role of hyperandrogenism not well-studied
Hypogonadism	Results from cortisol suppression of hypothalamic-pituitary function
Ophthalmologic	
Central serous chorioretinopathy	An uncommon feature of CS
Musculoskeletal	
Proximal muscle weakness	Tested by asking patients to rise from a chair without using upper extremities
Back pain	
Decreased BMD/ fracture	Greatest diagnostic weightif it occurs at an early age (<35 years)
Sleep	
Insomnia	May present as difficulty falling asleep, frequent wakening, or early wakening
Vivid dreams	
Obstructive sleep apnea	In one study, 50% prevalence in CS compared with 23% in controls

ACTH adrenocorticotropic hormone, BMD bone mineral density, BMI body mass index, CVA cerebrovascular accident

tests either measure baseline levels of cortisol (urine, saliva, serum) or evaluate the response of the hypothalamic-pituitary-adrenal axis to stimulatory (corticotropin-releasing hormone [CRH], desmopressin) or suppressive (dexamethasone [Dex]) agents. Interpretation of these tests relies on reference ranges for normal basal values and known responses to each of the provocative agents. The results also must be interpreted in light of the specific assay that is used for the outcome measure and with knowledge of confounding factors that result in abnormal (or falsely normal) results.

Most screening tests require that samples be collected at a specific time of day and that measurement of the response to a stimulatory/suppressive agent occurs at a fixed interval after its administration. Failure to adhere to strict timing can lead to false-positive or false-negative results. Guidelines on the diagnosis of CS suggest using at least two of the first-line tests, with two or more measurements of basal

Table 9.11 Recommended first- and second-line screening tests for the diagnosis of Cushing syndrome [143]

Measurement (name of test)	Stimulus/ suppressive agent	Time of day of collection or administration	Measurement time after administration	Cutoff point for normal response	Confounders
First-line tests					
Urine cortisol (UFC)	None	24 h	N/A	Assay ULN	Incomplete/overcollection, renal failure, mild/cyclic hypercortisolism, excess fluid intake
Salivary cortisol (bedtime or late-night salivary cortisol test)	None	Bedtime	N/A	Assay ULN	Older age, hypertension, diabetes, smoking, variable bedtime, mild/cyclic hypercortisolism
Serum cortisol (1 mg overnight Dex test)	Dex 1 mg po	23:00–00:00	8 h (07:00–08:00)	1.8 mg/dL (50 nmol/L)	CBG abnormalities, abnormal Dex metabolism, mild/cyclic hypercortisolism
Alternative approaches to first-line tests					
Serum cortisol (bedtime or late-night serum cortisol test)	None	Bedtime	N/A	7.5 mg/dL if awake	CBG abnormalities, variable bedtime, mild/cyclic hypercortisolism
Serum cortisol (2 mg, 2 day or low dose Dex test, LDDST)	Dex 0.5 mg po	q6h × 8 doses begin at noon	2 h after last dose	1.4 (38 nmol/L)	CBG abnormalities, abnormal Dex metabolism, mild/cyclic hypercortisolism
Second-line tests					
Serum cortisol (Dex-CRH test)	Dex 0.5 mg po and ovine CRH 1 μg/kg up to 100 μg IV	Dex q6h × 8 doses, begin at noon; give CRH at 09:00 after 06:00 Dex	−5, 0, 15 min relative to CRH administration	1.4 (38 nmol/L)	Mild/cyclic hypercortisolism, use of medications that affect Dex metabolism
Plasma ACTH ±cortisol (desmopressin test)	Desmopressin 10 μg IV	Morning	0, 10, 20, 30 min	Varies, see text	Ectopic ACTH secretion may respond, mild/cyclic hypercortisolism

CRH corticotropin-releasing hormone, Dex dexamethasone, IV intravenous, LDDST low-dose dexamethasone suppression test, N/A not applicable, UFC urine-free cortisol, ULN upper limit of normal

cortisol tests, if those are chosen [144]. By reviewing the confounders in (Table 9.11) the choice of tests can be individualized to minimize potential false results.

Severe, clinically overt CS is easier to diagnose than mild or cyclic cases or when underlying physiology changes the interpretation of tests. Such patients with a classic presentation of severe CS usually have similarly extreme abnormalities in cortisol, and there is little ambiguity in the diagnosis. The following conditions found in which it is often difficult to identify pathologic hypercortisolism: extremely mild or cyclic CS, renal failure, incidental adrenal masses, and pregnancy.

Figure 9.2 provides a flowchart for the diagnosis and management of CS. After the diagnosis of CS is confirmed and the possibility of exogenous glucocorticoid administration is excluded, the next step is to determine whether excessive ACTH secretion is the cause. ACTH levels are measured to identify the subtype of CS, whether ACTH dependent or ACTH independent [145]. A normal or high ACTH level is consistent with ACTH-dependent CS (corticotroph adenoma in the pituitary gland or a tumor elsewhere as an ectopic source of ACTH) because high cortisol levels would normally suppress ACTH. Abnormally low ACTH levels are consistent with ACTH-independent CS resulting from various adrenal abnormalities [126].

After the subtype of CS has been determined, imaging is the next step to identify the exact cause. Pituitary MRI is an initial imaging study in ACTH-dependent CS to differentiate between pituitary and ectopic causes of ACTH production. If MRI shows a pituitary lesion compatible with an adenoma, then the pituitary lesion is the most likely source of excess ACTH. If the pituitary MRI is negative or the initial biochemical workup is inconclusive, then bilateral inferior petrosal sinus sampling, the reference standard for differentiating between pituitary and nonpituitary sources of ACTH, or a CRH stimulation test, is undertaken [8]. Pituitary adenomas causing Cushing disease usually respond to CRH stimulation, whereas ectopic ACTH-secreting tumors do not, thereby enabling differentiation with the CRH stimulation test [126].

For patients with an adrenal incidentaloma who do not have overt clinical signs of CS, there is no consensus on the algorithm for establishing the diagnosis of subclinical CS, but inadequate suppression of cortisol in response to a 1-mg overnight dexamethasone suppression test is most commonly present [134]. In patients with bilateral adrenal masses and clinical or subclinical CS, adrenal venous sampling may accurately determine whether cortisol hypersecretion is unilateral or bilateral, which is critical when treatment with adrenalectomy is considered.

9.6.9 Imaging Evaluation of CS

9.6.9.1 Adrenocorticotropic Hormone-Dependent CS

Pituitary MRI—Once the diagnosis of ACTH-dependent CS is confirmed, a high-resolution pituitary MRI with gadolinium-based contrast agent should be performed for all patients [139]; this is used to confirm the presence or absence of a pituitary lesion and to differentiate the source of ACTH between pituitary adenomas and ectopic lesions.

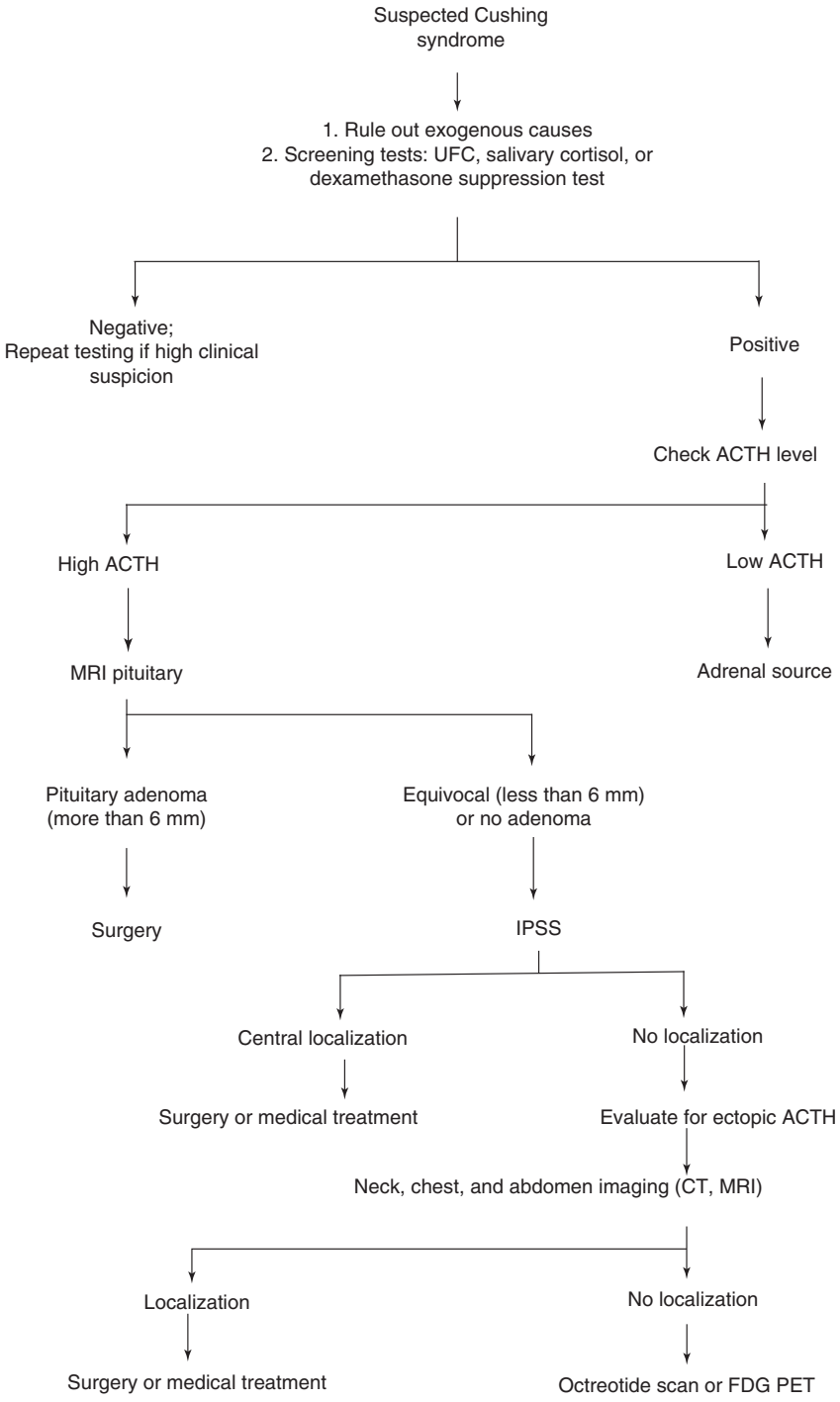

Fig. 9.2 An algorithm for the treatment of CS [144]

MRI reveals a discrete pituitary adenoma in up to 60% of patients with ACTH-dependent CS [146]. A pituitary adenoma is usually a microadenoma, defined as smaller than 10 mm in the longest dimension, with a mean size detected by MRI of 6 mm. It should be noted, however, that MR images may be interpreted as normal in up to 40–50% of patients with documented ACTH-secreting pituitary adenomas because of the small size of these adenomas [129]. Dynamic contrast-enhanced pituitary MRI improves detection relative to unenhanced MRI; however, not all potential adenomas will be identified.

Thus, additional testing is needed to clarify whether the source of ACTH is in the pituitary gland [129, 146]. Further tests include bilateral inferior petrosal sinus sampling, which can confirm the pituitary gland as the source of ACTH excess or additional biochemical testing (e.g., CRH stimulation test) [145, 146]. When a pituitary macroadenoma (> 10 mm) is present, normal glandular tissue may be difficult to detect; in these cases, any mass effect on the surrounding structures (e.g., the optic chiasm and cavernous sinus) should be assessed. CT is not used for first-line assessment of the pituitary gland owing to its lower sensitivity relative to MRI but can be used when MRI is contraindicated, such as when an aneurysm clip is present.

Bilateral inferior petrosal sinus sampling—Because transsphenoidal surgery is widely accepted as the primary treatment option for pituitary adenoma, bilateral inferior petrosal sinus sampling, with its high sensitivity (95–99%) and specificity for Cushing disease and a diagnostic accuracy of more than 90%, is performed as the reference standard to confirm the pituitary gland as the source of excess ACTH and to help exclude an ectopic source of ACTH [146]. Bilateral inferior petrosal sinus sampling should be pursued in patients with ACTH-dependent CS whose clinical, biochemical, or radiologic results are equivocal or discordant. Bilateral inferior petrosal sinus sampling should be performed only in specialized centers by an experienced radiologist because of its potential for significant complications, including vascular damage to the brainstem, deep venous thrombosis, pulmonary emboli, and cranial nerve palsies [147]. The procedure should be performed during active secretion of ACTH by the tumor, which can be determined by elevated levels of measured cortisol. After the radiologist catheterizes both inferior petrosal sinuses, blood samples for ACTH measurements are collected from both sides simultaneously, with another sample from a peripheral vein in the basal state and at subsequent timed intervals (i.e., 3, 5, and 10 min) after IV injection of CRH (100 μg) [147].

An inferior petrosal sinus-to-peripheral ACTH ratio greater than 2.0 in the basal state or greater than 3.0 after injection of CRH is diagnostic of Cushing disease [146]. Lower inferior petrosal sinus-to-peripheral ACTH ratios are highly suggestive of an ectopic ACTH-secreting tumor, with a specificity of 95–99% [146, 147].

9.6.9.2 Ectopic Adrenocorticotropic Hormone-Secreting Tumors

Thoracic sources of ectopic adrenocorticotropic hormone—When Cushing disease has been excluded by pituitary MRI or bilateral inferior petrosal sinus sampling, in the case of ACTH-dependent CS, the ectopic source of the ACTH is sought. Contrast-enhanced CT of the chest is the next study obtained to assess for intrathoracic tumors that could be the source of ACTH because the chest is the most

common body region for ectopic ACTH-secreting tumors [145]. Small cell carcinoma of the lung represents approximately 20–50% of these cases. Other thoracic tumors, such as bronchial and thymic carcinoids, as well as medullary thyroid carcinoma, may also secrete ACTH. Localization of the ectopic source of ACTH can be difficult and may be delayed for months to years, with resultant increased morbidity and mortality. Several reports have described the usefulness of selective pulmonary arterial sampling with ACTH measurement for localizing and confirming ectopic ACTH production by small bronchial carcinoid tumors when the diagnosis could not be confirmed by noninvasive modalities, including somatostatin receptor scintigraphy or ^{18}F-FDG PET [148]. Although MRI has limited value in detection of bronchial carcinoids in the chest, it could be valuable in diagnosing mediastinal lesions such as thymic tumors.

Abdominal sources of ectopic adrenocorticotropic hormone—After exclusion of more common intrathoracic sources of ACTH-secreting tumors, CT or MRI scan of the abdomen is performed to evaluate for intra-abdominal ACTH-secreting neoplasms. These tumors include gastroenteropancreatic neuroendocrine tumors, most commonly islet cell tumors of the pancreas and gastrointestinal carcinoids, and pheochromocytomas [145]. Islet cell tumors of the pancreas are usually small and intensely enhancing in the early arterial phase, and a specific diagnosis is suggested by the tumor markers and hormonal profile. Intestinal carcinoid tumors are suspected when a calcified mesenteric mass is seen, often with associated mesenteric fibrotic changes. These tumors may be associated with vascular compromise and mesenteric ischemia.

If one of these modalities fails to detect the ectopic focus, multiple imaging techniques (e.g., MRI plus octreotide scan or PET scan of the whole body) should be applied to localize the ectopic source of ACTH [145]. Selective venous sampling may help localize occult endocrine tumors and includes systemic and transhepatic intestinal, pancreatic, and portal venous sampling. Some cases may need image-guided biopsy confirmation when surgical planning is requested.

Nuclear Medicine Tests: Nuclear medicine functional imaging tests, including octreotide scan, FDG PET, and ^{68}Ga-somatostatin receptor PET/CT, improve the sensitivity of conventional CT and MRI when hormone-secreting tumors in CS prove difficult to detect. Molecular imaging can detect approximately 80% of tumors unidentified by conventional radiology [149].

9.6.9.3 Imaging for Adrenocorticotropic Hormone-Independent Cushing Syndrome

CT is the optimal noninvasive imaging modality for diagnosing adrenal lesions in ACTH-independent CS because adrenal adenoma, carcinoma, and ACTH-independent macronodular adrenal hyperplasia are invariably detectable by CT [132, 150]. An adrenal CT should be performed with thin (2.5–3 mm) CT slices before and after the IV administration of 100–150 mL of iodinated contrast material. MDCT scanners with 1 mm or smaller collimation and multiplanar reconstruction capabilities allow excellent delineation of adrenal anatomy and the anatomic relationship of an adrenal lesion. At CT, normal adrenal glands appear

homogeneous and symmetric with soft-tissue attenuation similar to that of the kidney. Adrenal MRI can provide a similar assessment as CT [126].

9.6.10 Treatment of Cushing Syndrome

The treatment guideline for CS was published by The European Society for Endocrinology in 2015 [151]. They recommend initial resection of primary lesion (s) as the first-line treatment options. In patients with overt Cushing syndrome (CS), the goal of treatment should be normalizing cortisol levels or action at its receptors to eliminate the signs and symptoms of CS and treating comorbidities associated with hypercortisolism.

First-line treatment options: They recommended initial resection of primary lesion(s) underlying CD, ectopic and adrenal (cancer, adenoma, and bilateral disease) etiologies, unless surgery is not possible or unlikely to significantly reduce glucocorticoid excess. The unilateral resection should be performed by an experienced adrenal surgeon for all cases of benign unilateral disease. The guideline recommended localizing and resecting ectopic ACTH-secreting tumors with node dissection as appropriate. They recommended measuring serum sodium several times during the first 5–14 days after transsphenoidal surgery (TSS), assessing free T4 and prolactin within 1–2 weeks of surgery to evaluate for overt hypopituitarism. A postoperative pituitary MRI scan should be obtained within 1–3 months of successful TSS. They recommended surgical resection of bilateral adrenal disorders and suggest medical therapy to block aberrant hormone receptors for bilateral macronodular adrenal hyperplasia (BMAH).

Remission and recurrence after surgical tumor resection: The individualized management approach based on whether the postoperative serum cortisol values categorize the patient's condition as hypocortisolism, hypercortisolism, or eucortisolism. The patients with persistent overt hypercortisolism should accepted additional treatments. Measure late-night salivary or serum cortisol in the patients with eucortisolism after TSS, including those cases where eucortisolism was established by medical treatment before surgery. Use tests to screen for hypercortisolism to assess for recurrence in patients with ACTH-dependent CS.

Glucocorticoid replacement and discontinuation, and resolution of other hormonal deficiencies: Hypocortisolemic patients receive glucocorticoid replacement and education about adrenal insufficiency after surgical remission. Follow-up morning cortisol and/or ACTH stimulation tests or insulin-induced hypoglycemia to assess the recovery of the HPA axis in patients with at least one intact adrenal gland, assuming there are no contraindications. We also recommend discontinuing glucocorticoid when the response to these test(s) is normal. Re-evaluate the need for treatment of other pituitary hormone deficiencies in the postoperative period.

Second-line therapeutic options: In patients with ACTH-dependent CS who underwent a noncurative surgery or for whom surgery was not possible, we suggest a shared decision-making approach because there are several available second-line therapies (e.g., repeat transsphenoidal surgery, radiotherapy, medical therapy, and

bilateral adrenalectomy). The patients with very severe ACTH-dependent disease who cannot be promptly controlled by medical therapy should be accepted bilateral adrenalectomy for occult or metastatic ectopic ACTH secretion (EAS) or as a life-preserving emergency treatment. Regularly evaluate for corticotroph tumor progression using pituitary MRIs and ACTH levels in patients with known CD who undergo bilateral adrenalectomy and in patients who undergo this procedure for presumed occult EAS (because some of the latter have a pituitary and not ectopic tumor). Repeat TSS, particularly in patients with evidence of incomplete resection, or a pituitary lesion on imaging. Confirm that medical therapy is effective in normalizing cortisol before administering radiation therapy (RT)/radiosurgery for this goal because this will be needed while awaiting the effect of radiation. RT/radiosurgery in patients who have failed TSS or have recurrent CD use RT where there are concerns about the mass effects or invasion associated with corticotroph adenomas. Measure serum cortisol or urine-free cortisol (UFC) off-medication at 6- to 12-month intervals to assess the effect of RT and also if patients develop new adrenal insufficiency symptoms while on stable medical therapy.

Medical treatment: Use steroidogenesis inhibitors under the following conditions as second-line treatment after TSS in patients with CD, either with or without RT/radiosurgery; as primary treatment of EAS in patients with occult or metastatic EAS; and as adjunctive treatment to reduce cortisol levels in adrenocortical carcinoma. Patients with CD who are inoperable or whose lesions persist after TSS should be treated with drugs that target the pituitary gland. Administer a glucocorticoid antagonist in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after TSS. Targeted therapies treat ectopic ACTH syndrome.

Approach for long-term follow-up: Treat the specific comorbidities associated with CS (e.g., cardiovascular risk factors, osteoporosis, and psychiatric symptoms) in all patients with CS throughout their lives until resolution. Test for recurrence throughout life, except in patients who underwent resection of an adrenal adenoma with a computerized tomography (CT) density of 10 Hounsfield units. Educate patients and families about the clinical features of remission. In patients with adrenal adenoma, implement follow-up tests for the specific comorbidities associated with CS if the adenoma density on CT was 10 Hounsfield units. For those with higher Hounsfield unit values or pathology consistent with possible carcinoma, evaluate for malignancy using imaging. Patients with Carney complex have lifelong follow-up tests for cardiac myxoma and other associated disease (testicular tumors, acromegaly, thyroid lesions).

9.6.10.1 Special Populations/Considerations

Accept urgent treatment (within 24–72 h) of hypercortisolism if life-threatening complications of CS such as infection, pulmonary thromboembolism, cardiovascular complications, and acute psychosis are present. The associated disorder(s) should be addressed as well (e.g., anticoagulation, antibiotics).

CS therapy during pregnancy is also challenging. Milder cases can be managed conservatively by controlling comorbidities. Pituitary or adrenal surgery should

ideally be performed during the second trimester and patients should then be treated for adrenal insufficiency. Experience with anticortisolic drugs is limited. Metyrapone was found to allow control of hypercortisolism, with a risk of worsening hypertension. Cabergoline may be an alternative option. The use of other drugs is not advised because of potential teratogenicity and/or lack of information. Non-hormonal (mechanical) contraception is recommended until sustained biological remission is obtained.

Blood Pressure Control for CS

In general, more than a single agent is required to reach the recommended target blood pressure (BP) levels. Thiazides and furosemide can worsen the hypokalemia and therefore should be avoided, unless adrenergic blockade and calcium channel antagonists are usually less effective. Because glucocorticoid hypertension may be augmented by the RAS, sartans, and ACE inhibitors are recommended. Until recently, spironolactone and his metabolites canrenone and potassium canrenoate were the only mineralocorticoid (MR) antagonists available, usually effective in the cases where mineralocorticoid excess is obvious. Eplerenone, a novel selective aldosterone antagonist with limited adverse effects, may be beneficial in the treatment of hypertension in CS, but it requires higher doses and repeated administration. The sartans also lower BP in CS patients, as do the ACE inhibitors, while no data are available for the direct renin inhibitor aliskiren. Blockade of the RAS with sartans or ACE inhibitors in hypertensive CS patients results in amelioration of hypertension and normalization of BP in approximately 50% of the cases. In general, hypertension can be difficult to treat or be resistant to treatment in the setting of CS without direct relief from the hypercortisolism [140].

9.6.11 Summary

The accurate diagnosis and characterization of CS requires a multimodality approach, including clinical assessment, biochemical analysis, and imaging studies. Treatment of CS is essential to reduce mortality and associated comorbidities. Effective treatment includes the normalization of cortisol levels or action. It also includes the normalization of comorbidities via directly treating the cause of CS and by adjunctive treatments.

9.7 Pancreatic Diseases and Hypertension

Yulan Chen

The pancreas is the second largest gland of the human body and possesses both exocrine and endocrine functions. For the exocrine function, the pancreas can secrete pancreatic juice with digestive action; for the endocrine function, the islets (containing a variety of cells) in the pancreas can secrete insulin, glucagon, somatostatin, pancreatic polypeptide, gastrin, and vasoactive intestinal peptide. These molecules

can regulate the metabolism of glucose, protein, and fat as well as the secretion of pancreatic juice, movement of biliary tract, and gastrointestinal functions. Some pancreatic lesions may cause exocrine and endocrine dysfunction of the pancreas, which often leads to hypertension. In this chapter, the relationship among pancreatitis, pancreatic tumors (two common pancreatic diseases), and hypertension is introduced, which may improve the understanding of symptomatic hypertension.

9.7.1 Physiological Function of the Pancreas

The pancreas is a strip-like organ and located in the retroperitoneal space of the upper abdomen at the level of the second lumbar vertebra (the pancreas is located in the upper abdomen directly behind the stomach). Generally, the pancreas in adults is about 12–20 cm in length and about 70–120 g in weight. It is composed of four parts: head, neck, body, and tail.

The pancreas is innervated by both sympathetic and parasympathetic nerves. The sympathetic nerve mainly controls the arterial system of the pancreas and affects the blood flow in the pancreas; the parasympathetic nerve efferent fibers end in the pancreatic acinar and islet cells and are responsible for the regulation of the endocrine and exocrine functions.

The pancreas has two main physiological functions: exocrine function (digestion) and endocrine function. Two functions depend on the different cell types in the pancreas. The pancreas consists of acinar cells, ductal cells, and islet cells. Among them, acinar cells account for more than 80% of pancreatic tissue and mainly secrete various digestive enzymes; ductal cells form intralobular ducts, interlobular ducts, and common ducts.

As the second largest digestive gland, the pancreas can secrete pancreatic juice with digestive action for exocrine. The pancreatic juice is a clear and isotonic solution with the pH of 7.4–8.4 and the specific gravity of 1.007–1.035. The amount of pancreatic juice secreted is about 1000 mL per day, and the pancreatic juice mainly contains water, bicarbonate, and digestive enzymes. The digestive enzymes in the pancreatic juice include amylase, trypsin, elastase, collagenase, carboxypeptidase, ribonuclease, deoxyribonuclease, lipase, and phospholipase. These enzymes are crucial for the digestion of macromolecular nutrients in food (such as protein, starch, fat, and nucleic acid) and the absorption of fat-soluble vitamins. The bicarbonate can not only neutralize gastric acid to protect the duodenal mucosa from strong acid-induced erosion, but also maintains the pH above 6 in the duodenum, providing an optimum pH for various digestive enzymes in the small intestine. The secretion of pancreatic juice during feeding is controlled by both vagus nerve and body fluid, but mainly regulated by body fluid.

9.7.2 Endocrine Function of the Pancreas

Although the islet only accounts for 1–2% of the pancreas, its blood supply is as high as 10–25% of the total blood supply to the pancreas. The capillaries for the islet perfusion form a network embedding the islets and acinus, which forms an

Table 9.12 Main endocrine hormones secreted by pancreas and functions of the pancreas

Hormones	Cell source	Main functions
Insulin	β cells	Lower glucose and increase protein and fat synthesis
Glucagon	α cells	Increase blood glucose, release gastric and intestinal smooth muscle, and Oddi sphincter
Somatostatin	δ cells	Inhibit gastrointestinal motility and secretion
Pancreatic polypeptide	PP cells	Inhibit pancreatic exocrine

islet-acinar portal system. The hormone secreted by the islets enters the portal system directly, achieving high hormone level around the acinus. In recent years, increasing evidence has shown that the pancreatic endocrine hormones can locally affect the exocrine function of the pancreas (Table 9.12).

Insulin is derived from the proinsulin which is synthesized in the endoplasmic reticulum ribosome of β(B) cells. Insulin is a protein with small molecular weight, consists of 51 amino acids, and has two chains (A and B) which are connected by a C-peptide. Insulin plays an important role in the metabolism of carbohydrates, fats, and proteins. In addition, insulin can also affect the blood pressure through following mechanisms: (1) It can promote the reabsorption of Na + and water by the distal nephron directly or indirectly via elevating the activity of the renin-angiotensin-aldosterone system, resulting in the increase in blood volume and cardiac output. (2) It can stimulate the ventral middle sympathetic nerve in the hypothalamus and promote the adrenal gland to secrete adrenaline and norepinephrine, thereby increasing blood catecholamine and leading to sodium water retention. (3) Insulin is also a growth factor that can enhance the activity of mitotic factors and promote the proliferation of vascular smooth muscle cells leading to blood vessel wall thicken, which result in increased vascular resistance. (4) In case of hyperinsulinemia, insulin can reduce the activity of Ca^{2+}-ATPase in the cell membrane which increases the intracellular Ca^{2+} and then enhances the excitation and contraction coupling, leading to the vasoconstriction or spasm. (5) Insulin at a high concentration can promote the mRNA expression of endothelin (a factor that can contract the blood vessel) in the blood vessel and increase its synthesis and release. (6) Insulin at a high concentration can inhibit the release of endothelium-derived relaxing peptide from the vascular endothelial cells, leading to the increased peripheral resistance.

Of note, the endocrine hormones secreted by the pancreas are able to regulate the exocrine function of the pancreas. Studies have shown that insulin can promote the synthesis of proteins in pancreatic acinar cells and stimulate the growth and differentiation of acinar cells. In addition, insulin can also stimulate the synthesis and secretion of trypsin. Thus, insulin can be regarded a hormone that can enhance the exocrine function of the pancreas. However, glucagon exerts an inhibitory effect on the exocrine function of the pancreas. In addition, glucagon can also inhibit the secretin-induced hormone secretion of the pancreas. Pancreatic polypeptide also confers a significant inhibition on the exocrine function of the pancreas, especially the secretion of bicarbonate and trypsin. This may reduce the amount of pancreatic juice secreted, but does not cause acinar atrophy. The somatostatin mainly inhibits

the secretion of pancreatic juice and trypsin. Vasoactive intestinal peptide (VIP) may also act as a neurotransmitter to regulate the exocrine function of the pancreas.

The above effects of hormones secreted by the islet on the pancreatic exocrine indicate that there is an endocrine-exocrine pathway in the pancreas. In case of acute or chronic pancreatitis, there may be pancreatic endocrine and/or exocrine dysfunctions. In short, various pancreatic diseases may affect their endocrine and/or exocrine functions, leading to a series of clinical manifestations [152].

9.7.3 Acute Pancreatitis and Hypertension

Acute pancreatitis (AP) is a common acute abdominal disease. The disease condition is complex and variable in AP patients. The mild AP is pathologically characterized only by pancreatic edema, which is more common in clinical practice, is often self-limiting and has a good prognosis. In severe cases, AP is pathologically characterized by pancreatic necrosis, and patients usually manifest concomitant peritonitis, shock, and secondary multiple organ failure, resulting in high mortality [153]. In recent years, studies have indicated that some AP patients develop hypertension which may resolve with the improvement of pancreatitis. Thus, this phenomenon has become a focus in clinical studies.

9.7.3.1 Risk Factors

There are some risk factors for AP, including biliary diseases, alcohol consumption, hyperlipidemia, and idiopathic acute pancreatitis

1. Biliary diseases: Biliary diseases account for more than 50% of courses of AP, and biliary disease-related AP is also known as biliary pancreatitis. The gallstones can block the terminal of the common bile duct. Thus, the bile can flow back into the pancreatic duct through the *common channel* to induce acute pancreatitis [154]. The causes of obstruction at the terminal of the common bile duct also include duodenal papilledema or stenosis caused by inflammation or surgery, Oddi sphincter spasm, tumors, and biliary mites.
2. Drinking: It is a common cause of AP. Ethanol can directly damage the pancreas, stimulate the secretion of pancreatic juice, and cause duodenal papilla edema and Oddi sphincter spasm. As a result, the pancreatic duct pressure increases and the pancreatic duct ruptures. Ethanol is able to activate the nuclear factor NF-κb in the inflammatory pathway, which increases the production of TNF-α, IL-1, and caspase (a protein related to apoptosis), and to increase the pancreatic microcirculatory disorder, resulting in acute pancreatitis [155].
3. Metabolic diseases: Hyperlipidemic pancreatitis (type I, IV, or V hyperlipoproteinemia) and hypercalcemia (hyperparathyroidism) are the important causes of AP. Currently, the prevalence of hyperlipidemia pancreatitis is increasing [156].
4. Duodenal reflux: When the duodenal pressure increases, the duodenal juice can flow back into the pancreatic duct. The causes of duodenal fluid reflux include duodenal diverticulum, anatomical abnormalities of the pancreatic duct and

biliary duct, annular pancreas, duodenal inflammatory stenosis, pancreatic uncinate tumor, obstruction of afferent loop after gastrectomy, ascaris infection, and other factors causing obstruction.

5. Iatrogenic factors: Endoscopic retrograde cholangiopancreatography (ERCP) can cause pancreatitis in about 2–10% of patients, and the anastomotic stenosis of the pancreatic duct and jejunum can also lead to residual pancreatitis [157].
6. Tumors: Intraductal papillary mucinous neoplasm (IPMN) and pancreatic cancer can cause pancreatic duct obstruction, resulting in AP.
7. Some drugs: 5-aminosalicylic acid, azathioprine, 6-oxime, cytarabine, dideoxyinosine, diuretics (such as furosemide, thiazide), estrogen, metronidazole, valproic acid, and acetaminophen can also cause AP.
8. Trauma: Upper abdominal blunt injury, penetrating injury, surgical trauma, etc.
9. Pancreatic circulation disorders: Hypotension, cardiopulmonary bypass, arterial embolism, vasculitis, and increased blood viscosity can cause pancreatic blood circulation disorders, resulting in AP.
10. Other factors: Diet, infection, and metabolic, endocrine, genetic, and autoimmune diseases associated with pregnancy are also risk factors of AP.
11. Unknown causes: AP of unknown causes is also clinically known as idiopathic acute pancreatitis (IAP). IAP may be associated with anatomical and genetic factors, such as pancreatic division, Oddi sphincter dysfunction, and genetic defects (such as trypsinogen gene mutation).

9.7.3.2 Pathogenesis: The Pathogenesis of AP Is Complex and Still Poorly Understood

Most investigators speculate that AP is a result of abnormal activation of pancreatic enzymes in the acinus. The activation of pancreatic enzymes in the acinus may induce self-digestion of the pancreatic parenchyma, in which alveolar cells release inflammatory cytokines such as tumor necrosis factor (TNF-α), IL-1, IL-2, IL-6, and other inflammatory mediators such as IL-10 and IL-1 receptor blockers. These factors may cause inflammatory cascade. In severe cases, there are hemorrhage and necrosis locally in the pancreas, which may result in systemic inflammatory response syndrome (SIRS) and even multiple organ failure [158].

In recent years, increasing attention has been paid to the role of pancreatic microcirculation disorders (mainly characterized by pancreatic ischemia) in the development of AP. In case of AP, the renin-angiotensin system (RAS) is activated, causing a significant increase in angiotensin II (Ang II), an important active product in RAS. Studies have shown that Ang II involves in the progression of AP through not only regulating peripheral blood circulation and pancreatic microcirculation, but also modulating the inflammatory process as a pre-inflammatory factor. As early as in 1991, studies on RAS found Ang II and angiotensinogen were expressed in the pancreatic tissues of dogs, and the concentration of Ang II in the pancreas was higher than that in peripheral blood. This indicates there is local Ang II synthesis in the pancreatic tissues of dogs. Some investigators have established AP model in rats through the duodenal ligation, and results have indicated the increase in Ang II is consistent with the pathological severity of the pancreas. The binding of Ang II to

AT1 receptor may cause significant vasoconstriction, which not only increases the peripheral vascular resistance, but also causes pancreatic microvascular spasm, pancreatic ischemia, and poor perfusion of pancreatic microcirculation, which promotes the progression of AP. Carlsson et al. [159] found that enalaprilate (ACE inhibitor) and sarlasin (non-selective Ang II receptor antagonist) in rats could increase blood flow in the pancreas, especially in the islet. Therefore, it has been proposed that RAS, especially its active product Ang II, plays an important role in the development of AP.

The pathogenesis of hypertension secondary to AP: Some patients with AP and normal blood pressure will develop hypertension, but the mechanism is still unclear. It is speculated that hypertension secondary to AP may be related to the following factors:

Hyperinsulinemia: Patients with AP usually develop hyperglycemia, and blood insulin is also at a high level. The pathogenesis of hyperinsulinemia-related hypertension may be related to the following factors: (a) It increases the reabsorption of sodium and water in renal tubules and elevates its sensitivity to sodium. (b) It enhances the performance of Na-H pump, attenuates the Na-K-ATPase activity, increases intracellular sodium and calcium, and elevates vascular tone. (c) It stimulates the growth factor production and promotes vascular smooth muscle hyperplasia. (d) It increases sympathetic nerve activity.

Endothelin (ET) involved in hypertension: ET has been shown to be a vasoactive polypeptide secreted and released by vascular endothelial cells. ET is a potent vasoconstrictor with long-lasting action. Some investigators have found that patients with mild AP have a slight increase in plasma ET, while the plasma ET in patients with severe AP increases by three- to fourfolds and significantly higher than in patients with mild AP. On the one hand, ET can exert vasoconstrictive effects to assure the blood supply to other organs, and on the other hand, ET can contract the pancreatic arterioles and induce vasospasm, resulting in insufficient blood supply to the pancreas, which aggravates pancreatic ischemia.

Abnormal blood lipid metabolism: Studies have confirmed that the abnormal lipid metabolism in obese individuals with insulin resistance also promotes the development of hypertension. This may be related to the blocking of insulin signaling and alteration of peroxisome proliferator-activated receptor (PPARs) expression due to the so-called lipotoxicity. In case-control studies, results show that blood purification and lipid lowering treatment can reduce the blood pressure to normal level in hyperlipidemia-induced pancreatitis patients with hypertension, which suggests abnormal lipid metabolism may be involved in the pathogenesis of hypertension.

In AP, patients can not rest well due to severe pain, and some patients have fear and mental stress, which activate sympathetic nerves, resulting in elevated blood pressure, and subsequent hypertension.

RAS activation: As mentioned above, RAS activation is present in AP, Ang II is abundantly produced in local pancreatic tissues, and the binding of Ang II to AT1 receptor may cause significant contraction of peripheral and pancreatic local arterioles and micro-arteries as well as vascular smooth muscle spasm and sympathetic activation, resulting in hypertension.

In summary, hypertension secondary to AP may be the result of interaction among multiple factors.

Pathology: The pathology of AP is characterized by edema of different extents, congestion, hemorrhage, and necrosis.

Acute edematous pancreatitis: The pancreatic lesion is mild and mostly confined to the body and tail of the pancreas. The pancreas become swollen, hard, and congested, the capsule becomes tight, and there is fluid around the pancreas. Miliary or plaque-like yellow-white saponified plaques (fatty acid calcium) can be observed in the abdominal adipose tissues, especially those in the greater omentum. The ascites is light yellow. Microscopically, interstitial hyperemia, edema, and inflammatory cell infiltration can be observed with localized fat necrosis.

Acute hemorrhagic necrotizing pancreatitis: The pancreatic lesion is characterized by pancreatic parenchymal hemorrhage and necrosis. The pancreas becomes swollen and dark purple, the lobulated structure is blurred, the necrotic area is grayish black, and the entire pancreas becomes black in severe cases. Saponified plaques and fat necrosis can be seen in the abdominal cavity, and extensive necrosis can be found in the retroperitoneum. There is brown or dark red bloody fluid or bloody turbid exudate in the abdominal cavity or retroperitoneum. Under the microscope, fat necrosis and acinar destruction are observed, and the structure of the acinar lobule is blurred. The small blood vessel wall also has necrosis in the interstitium which shows flaky hemorrhage and inflammatory cell infiltration.

Clinical manifestations: The clinical manifestations are related to the severity of AP.

1. Abdominal pain: It is a main symptom of AP. It often occurs abruptly after a meal or drinking, the abdominal pain is severe and mostly found in the left upper abdomen, can radiate to the left shoulder and left back.
2. Bloating: It often occurs concomitantly with abdominal pain.
3. Nausea and vomiting: They can occur at early stage of AP, vomiting is often severe and frequent, and abdominal pain does not relieve after vomiting.
4. Signs of peritonitis: In case of acute edematous pancreatitis, tenderness is limited to the upper abdomen; severe AP may present serious abdominal tenderness, which may be accompanied by muscular tension and rebound tenderness, involving the entire abdomen.
5. Others: There are other clinical manifestations such as fever, jaundice, and shock. In several patients with severe AP, Grey Turner's sign and Cullen sign may be observed, and even manifestations of DIC and symptoms of central nervous systems can be present.
6. Characteristics of hypertension: AP patients may develop hypotension and shock in the early and late stages of AP. However, of note, a small number of patients develop hypertension. It is speculated that the pathogenesis of hypertension in AP patients is multifactorial, and mainly related to the hyperinsulinemia, elevated endothelin secretion, increase in plasma-free fatty acids (FFA) and relevant lipotoxicity, severe pain, high mental stress, and subsequent sympathetic activation although some of these mechanisms are reported in case studies and there is still no consensus on it. Thus, more studies are needed to elucidate the pathogen-

esis of hypertension in AP patients, which may be important for the prevention and treatment of hypertension in AP patients.

9.7.3.3 Auxiliary Examinations

Laboratory Examinations

Trypsin assay: Detection of serum and urine amylase is the most commonly used diagnostic examination. Serum amylase begins to rise within a few hours after disease onset, peaks at 24 h and gradually decreases to normal level after 4–5 days; urine amylase begins to rise in 24 h, peaks at 48 h, decline slowly and returns to normal level after 1–2 weeks. The higher the amylase content, the greater the diagnostic accuracy is, but the magnitude of increase in amylase is not proportional to the severity of AP. Significant increase in serum lipase (normal range: 23–300 U/L) is specific and also an objective indicator in the diagnosis of AP [160].

Other examinations: Increase in white blood cells, hyperglycemia, liver dysfunction, hypocalcemia, and abnormal blood gas may be observed in AP patients. Diagnostic abdominal puncture may reveal bloody exudate and increase in amylase, which are helpful for the diagnosis of AP. In recent years, studies indicate microRNAs are also helpful for both the diagnosis of AP and the determination of severity of AP [161]. This is very important for the planning of treatments and the prediction of prognosis of AP.

Elevated C-reactive protein (CRP) (>150 mg/mL within 48 h) is indicative of severe condition in case of AP.

Imaging Examination

1. Ultrasonography: It can reveal pancreatic enlargement and peripancreatic fluid.
2. CT scanning: It is an imaging examination with the most diagnostic value. It can not only diagnose AP, but also identify the pancreatic necrosis.
3. MRI: It can provide information for the diagnosis of AP as in CT. MRCP can clearly display the bile duct and pancreatic duct, which plays an important role in the diagnosis of pancreatitis caused by biliary stones and anatomical abnormalities of the pancreatic ducts [162].

Diagnostic Criteria

AP can be diagnosed clinically once 2 of 3 following characteristics are present: (1) abdominal pain consistent with the clinical manifestations of AP; (2) serum amylase and/or lipase activity is at least threefolds higher than upper limit of normal; (3) imaging findings consistent with those of AP.

Severity of AP

1. Mild acute pancreatitis (MAP): It is edematous pancreatitis and accounts for 60% of AP. There is no organ failure and local or systemic complications in MAP patients. After timely treatment, MAP patients usually recover within 1–2 weeks, and the mortality rate of MAP patients is extremely low.

2. Moderately severe acute pancreatitis (MSAP): There is transient organ failure (self-recovery within 48 h) in MSAP patients. MSAP accounts for about 30% of AP and may present local or systemic complications. AP in early stage has a low mortality, but the presence of infection due to pancreatic necrosis in late stage may significantly increase the mortality rate.
3. Sever acute pancreatitis (SAP): SAP accounts for about 10% of AP and usually has sustained organ failure (longer than 48 h) which cannot recover autonomously. The organs that will develop failure include respiratory system, cardiovascular system, and kidney.

9.7.3.4 Differential Diagnosis

AP should be differentiated from cholelithiasis, peptic ulcer, myocardial infarction, and acute intestinal obstruction. Blood amylase and lipase can also increase in these acute abdominal diseases, but they usually are less than twice the normal reference in these diseases.

9.7.3.5 Treatments

Treatments are usually determined according to types, stages, and causes of AP.

1. Non-surgical treatments: Patients with mild AP and patients with moderate to severe AP and without indications to surgical intervention can receive non-surgical treatments. Patients with severe AP are often treated in intensive care unit due to severe disease condition and the requirement of organ support. Mechanical ventilation and bedside dialysis may be performed if necessary.
   (a) Fasting and gastrointestinal decompression: Continuous gastrointestinal decompression can prevent vomiting, reduce abdominal distension, and decrease intra-abdominal pressure.
   (b) Rehydration, prevention, and treatment of shock: Intravenous infusion, supplement of electrolytes, correction of acidosis, prevention and treatment of hypotension, maintenance of circulation stability, and improvement of microcirculation are also important.
   (c) Analgesia and spasmolysis: Antispasmodics and analgesics can be administered once definite diagnosis is made.
   (d) Inhibition of pancreatic secretion: Proton pump inhibitors (PPI) or H2 receptor blockers can indirectly inhibit pancreatic secretion; somatostatin (such as octreotide) and trypsin inhibitors may also inhibit pancreatic secretion.
   (e) Nutritional support: The nutritional support is mainly dependent on total parenteral nutrition (TPN) in fasting period. When the disease condition is stable and the intestinal function is restored, enteral nutrition may be administered as early as possible and the normal diet should be resumed as appropriate.
   (f) Application of antibiotics: Antibiotics can be administered empirically or in a targeted manner when there is evidence of infection.
   (g) Treatment with traditional chinese medicine: After control of vomiting, the Chinese herb can be administered intragastrically or by enemata.

2. Surgical treatments.
   (a) Indications to surgery: (1) AP is present, other acute abdominal disease cannot be excluded; (2) patients have concomitant lower common bile duct obstruction or biliary tract infection; (3) patients have concomitant intestinal perforation, heavy bleeding, or pancreatic pseudocyst; (4) there is infection secondary to pancreatic and peripancreatic necrosis.
   (b) Surgical methods: The most common method is the removal of necrotic tissues combined with drainage. Open surgery or endoscopy is an alternative.
   (c) Surgical treatment of biliary pancreatitis: The goal is to relieve obstruction and establish smooth drainage [163].
3. Treatment of secondary hypertension: Generally, it is recommended to control the primary disease and closely monitor blood pressure. Once the blood pressure continues to rise, sedation, pain relief block, and blocking of sympathetic activation may be administered to lower blood pressure. After the AP is controlled, the blood pressure may return to normal level.

9.7.3.6 Prognosis

The prognosis of AP is related to the severity of AP. The prognosis of mild AP is usually good, but the mortality rate of patients with severe AP is high. In addition, patients with severe AP may develop some complications, even after timely treatment, resulting in a poor prognosis. Early assessment of AP severity is critical to its prognosis and treatment. Generally, the hypertension secondary to AP is mostly temporary. It is recommended to closely monitor the blood pressure and strengthen the symptomatic treatment and pressure lowering treatment if necessary.

9.7.4 Chronic Pancreatitis and Hypertension

Chronic pancreatitis (CP) is an irreversible chronic inflammation of the pancreatic parenchyma and pancreatic duct caused by various causes and characterized by recurrent episodes of upper abdominal pain with concomitant progressive dysfunction or loss of pancreatic endocrine and exocrine. Long-term heavy drinking and smoking are the most common risk factors for CP, and ethanol and tobacco may exert toxic effects on the pancreas directly [164]. In addition, genetic factors, autoimmune, and various causes of pancreatic duct obstruction are also related to the pathogenesis of CP [165]. In a small number of patients with CP, the causes are unknown. The pancreatic endocrine dysfunction and pain-induced stress may indirectly cause hypertension in some patients with CP, but there is no consensus on it and more studies are needed to confirm this phenomenon.

9.7.4.1 Pathology

CP is pathologically characterized by pancreatic atrophy and fibrosis and irregular nodular sclerosis. Pancreatic duct stenosis may be present with segmental dilatation and formation of pancreatic stone or cyst. Microscopically, there are hyperplasia of fibrous tissues, loss of acinar cells, shrinkage of cell body, calcification and ductal

stenosis, deposition of dense collagen, fibroblast proliferation, and separated islet cells. In a small number of patients, the chronic inflammation of the pancreas may induce carcinogenesis [166].

9.7.4.2 Clinical Manifestations

CP is often clinically characterized by abdominal pain under the xiphoid or at left abdomen which often radiates to the lower back, showing a belt-like pain. The pain is long-lasting. There may be concomitant loss of appetite and weight loss. Some patients may develop insulin-dependent diabetes and steatorrhea. Generally, abdominal pain, weight loss, diabetes, and steatorrhea are often referred to as the tetralogy of CP. In some patients, the compression of the common bile duct due to pancreatic head fibrosis may cause jaundice [167].

Patients with AP may have concomitant hypertension, which may be ascribed to the essential hypertension, diabetes, or renal hypertension due to diabetic nephropathy. The pathophysiological pathogenesis of hypertension in case of CP is similar to that in essential hypertension and diabetic hypertension.

9.7.4.3 Diagnosis

CP may be considered based on the typical clinical manifestations.

Fecal examination can reveal fat droplets, indicative of steatorrhea (i.e., the fecal fat content is higher than 7 g/day when the daily intake of fat is 100 g within prior 3 days); fecal elastase-1 < 200 μg/g suggests pancreatic exocrine insufficiency.

Ultrasonography can reveal local pancreatic nodules, pancreatic duct dilatation, cyst formation, pancreatic enlargement or fibrosis; CP patients with concomitant pancreatic duct stones may display strong echo and accompanying shadow in the pancreas on ultrasonography.

Plain X-ray can show pancreatic calcification or pancreatic duct stones. CT can reveal pancreatic duct stones, scattered calcification in the pancreatic parenchyma, altered density of the pancreatic parenchyma and pancreatic duct dilatation; complications of CP (such as pancreatic pseudocyst, duodenal compression, and pancreatic portal hypertension) may also be observed. MRCP can display the main pancreatic duct, the branch pancreatic duct, and the common bile duct. EUS-ERCP may not only display dilatation or bead-like change in pancreatic duct, but also identify the abnormalities in the opening of cholangiopancreatic duct and help the biopsy and pancreatic duct drainage [168, 169].

9.7.4.4 Treatments

1. Non-surgical treatment: (1) Etiological treatment: Alcohol cessation and smoking cessation are necessary. (2) Analgesia: Non-steroidal anti-inflammatory drugs, tramadol or propoxyphenol analgesics may be administered. Anesthesia analgesics can be used if the pain cannot be alleviated. Intractable, non-obstructive pain can be treated by CT or ultrasound-guided celiac nerve block. (3) Diet therapy: Patients should have more meals a day but less food at each, the diet should be rich in protein and vitamins and has low fat, and the intake of carbo-

hydrate should be controlled. (4) Supplementation of trypsin: A large number of exogenous trypsin should be administered in case of indigestion, especially in patients with steatorrhea. (5) Control of diabetes: The food intake should be controlled, and insulin replacement therapy may be administered if necessary. (6) Nutritional support: In addition to diet therapy, parenteral and/or enteral nutrition support can be given in a planned manner. (7) In recent years, it has been reported that botulinum can regulate Oddi sphincter. Endoscopic injection of botulinum into Oddi sphincter may achieve the efficacy of as high as 80% in CP patients [170].

2. Surgical treatment: The main purpose is to relieve pain and delay the progression of AP, but it cannot reverse the pathological process. CP with biliary obstruction, duodenal obstruction, and suspected cancer should be treated as soon as possible [171].
   (a) Pancreatic duct drainage: (1) Transduodenal Oddi sphincter incision may relieve the ampullary stenosis, making the smooth flow of pancreatic fluid; Oddi sphincter incision can also be performed by ERCP. (2) Pancreatic duct–jejunum anastomosis: The pancreatic duct is opened, the stones are removed, and the pancreatic duct is anastomosed to the lateral side of the jejunum.
   (b) Pancreatectomy: Patients with severe pancreatic fibrosis and without pancreatic duct dilatation may receive surgical intervention based on the extent of the CP.
   (c) Pancreatic resection combined with pancreatic duct drainage: The inflammatory lesion at the head of the pancreas can be removed to relieve the compression on the surrounding tissues, reduce the pain, and assure the pancreatic duct drainage, which maximizes the endocrine and exocrine functions of the pancreas and preserves integrity of the common bile duct and duodenum.
   (d) Symptomatic treatments: For refractory severe pain, splanchnic neurotomy or injection of absolute ethanol at the splanchnic ganglion to control pain once the pain is non-responsive to other treatments.
3. Treatments of hypertension: Patients with AP or CP have the possibility to develop hypertension, which may be related to the pancreatic endocrine dysfunction damage and/or pain-induced stress. Thus, in the treatment of pancreatitis, the blood pressure should be closely monitored. Sedation and blocking of sympathetic activation may be administered to lower blood pressure, if necessary.

9.7.4.5 Prognosis

Relatively, the prognosis of CP is good. However, CP patients usually develop diabetes mellitus due to the pancreatic endocrine dysfunction, which may also cause a series of complications. Moreover, CP is an independent risk factor for pancreatic cancer, and patients with pancreatic cancer usually have a poor prognosis [172].

9.7.5 Insulinoma and Hypertension

9.7.5.1 Introduction

Insulinoma is a kind of functional pancreatic neuroendocrine tumor, which is characterized by recurrent hypoglycemia because the tumor secretes excessive insulin.

The disease can occur in all age groups, female incidence is slightly higher than male, the high incidence of 40–50 years old [173]. The incidence of insulinoma is 0.4 per 100,000 people per year, according to a 60-year observational study by the Mayo clinic and a series of subsequent patient studies [174, 175]. Insulinoma accounts for 25% of pancreatic endocrine, most of which are benign and 4–14% malignant [176, 177].

9.7.5.2 Etiology

The etiology of insulinoma is still unclear and may be related to genetic mutation, cell apoptosis, neurotransmitters, growth factors, gastrointestinal hormones, and other factors. Among them, gene mutation is an important cause of insulinoma. Chinese investigators have shown that mutations in *MLL3*, *H3F3A*, and *LMO2* and other high-frequency T372R mutation in the transcription factor YY1 (YIN-YANG 1) are associated with the pathogenesis of insulinoma [178].

9.7.5.3 Pathology

Macroscopically, the insulinoma is usually pink or dark red with clear boundary, slightly hard texture, smooth surface, and round or oval shape (occasionally irregular shape). Microscopically, the tumor cells are polygonal with unclear boundaries and sparse and translucent cytoplasm; the nucleus is round or elliptical with similar size and uniform distribution of chromatins, the nucleolus is generally hard to observe; the tumor cells are arranged in clusters and close to the capillaries forming small nodules or islands; the tumor cells can also be arranged in glandular cavity manner, which is in the shape of a chrysanthemum. Sometimes, red secretions can be observed in the glandular cavity. The cells are mostly columnar, and the nucleus is often found at the base. The tumor cells can also be distributed in patch manner. Under the electron microscope, the secreted particles are similar to the B particles. Tumor cells express insulin at about 10–30 IU per gram of tumor tissues (higher than 100 IU in a few patients [normal reference: 1.7 IU per gram of pancreatic tissues). Insulinoma can be benign or malignant. Generally, it is difficult to differentiate benign insulinoma from malignant one based on the cell morphology alone, and the presence of metastasis is indicative of malignant insulinoma.

9.7.5.4 Pathogenesis

The clinical symptoms of insulinoma patients are related to the elevated blood insulin, but these symptoms are caused by the normal physiological feedback in insulin secretion, not by the excessive insulin secretion alone. Under physiological conditions, normal blood glucose is regulated by insulin and glucagon. When the blood glucose reduces, the secretion of glucagon increases, and the secretion of insulin is inhibited. When the blood glucose is lower than 1.94 mmol/L, insulin secretion

almost completely stops. However, in patients with insulinoma, this normal physiological feedback is completely absent, and the tumor cells continue to secrete insulin, resulting in hypoglycemia. The metabolism of human brain cells is dependent glucose alone and the glycogen cannot be used by brain cells to produce calories. Therefore, when the blood glucose reduces, the metabolism of brain cells is first affected, causing central nervous system symptoms (such as lethargy, delirium, and even coma).

Mechanism underlying the insulinoma-induced hypertension

1. Excessive insulin secretion: Insulin can elevate blood pressure via a variety of ways (see Physiological Function of the Pancreas).
2. Compensatory sympathetic excitation secondary to hypoglycemia: Sympathetic excitation is a compensatory response to hypoglycemia, patients usually develop hypertension, and blood pressure may return to normal when the disease is relieved, which is similar to that in pheochromocytoma.
3. Seizures: Severe hypoglycemia may cause the abnormal excitation of cerebral cortex, resulting in seizures. In case of seizures, there is loss of consciousness, muscle spasm, increased vascular resistance, and elevated blood pressure.

9.7.5.5 Clinical Manifestations

Clinical symptoms are characterized by paroxysmal hypoglycemia, and 17.6% of patients have seizures.

1. Symptoms of compensatory sympathetic nervous system excitation secondary to hypoglycemia: Pale face, cold limbs, sweating, palpitation, hand tremor, leg weakness, and concomitant hypertension. The blood pressure may return to normal after the disease is relieved.
2. Psychotic symptoms: Hypoglycemia may cause the lack of glucose in brain cells, leading to the presence of psychotic symptoms such as absent-mindedness, lethargy, and coma; it may also cause insobriety, unresponsiveness, and hypophrenia. The repeated hypoglycemia may further inhibit the cerebral cortex, causing significant psychotic symptoms in severe cases, including visual hallucination, and thus it is sometimes misdiagnosed as mental diseases. Some patients present with seizures, which is the most serious neurological symptom. During seizures, patients present with loss of consciousness, closed jaws, limb convulsions, and incontinence.

   The typical clinical manifestations include: (1) episode of hypoglycemia or coma and psychotic symptoms; (2) blood glucose is less than 2.22 mmol/L at disease onset; (3) the symptoms disappear after oral or intravenous administration of glucose. These symptoms are also known as Whipple triad or insulinoma triad.

9.7.5.6 Diagnosis

Qualitative Diagnosis

The diagnosis of insulinoma can be considered when patients present with typical Whipple triad. If there is no episode of hypoglycemia, a 72-h starvation induction test can be performed. Diagnosis of insulinoma can be made when the patient

develops hypoglycemia after starvation and the following six manifestations are present: (1) blood glucose is ≤2.22 mmol / l (≤ 40 mg/dL); (2) insulin content is ≥6 μU/mL (≥ 36 pmol/l); (3) C-peptide content is ≥200 pmol/l; (4) proinsulin content is ≥5 pmol/l; (5) β-hydroxybutyric acid is ≤2.7 mmol/l; (6) there are no metabolites of sulfonylureas in the blood/urine.

Examinations for Localization

1. Noninvasive examinations: (1) Ultrasonography: Ultrasound examination is simple, noninvasive, and inexpensive, but has a poor performance in the localization of tumor. (2) Computed tomography (CT): CT is the most widely used noninvasive tool in the diagnosis of insulinoma, enhanced CT is more sensitive than plain CT, and dynamic CT is better to display the relationship of tumors with the pancreas and the common bile duct [179]. (3) Nuclear magnetic resonance (MRI): Its sensitivity is similar to that of CT. (4) Positron emission tomography (PET) and PET-CT: Studies have shown that PET can identify 84% of primary tumors. In particular, PET with ^{68}gallium-labeled somatostatin analogues is more sensitive than other tools. Thus, for newly diagnosed pancreatic neuroendocrine tumors, ^{68}Ga-PET-CT is recommended for staging [180].
2. Invasive examinations: (1) Selective celiac angiography: Because insulinoma is rich in blood, high-selective celiac angiography can clearly display the location of the tumor and reveal the round, clear boundaries (also known as "bulb sign"), which can diagnose up to 80% of patients. Especially, the combined use of new techniques such as digital subtraction (DSA) may further increase the diagnostic accuracy. (2) After percutaneous liver puncture, blood is collected from different segments of portal vein system for the measurement of insulin content, (also known as selective segmented blood sampling of the portal vein system), which may achieve a high rate of coincidence. (3) Intraoperative ultrasonography: This is especially applicable in the diagnosis of tumors located in the head of the pancreas or deep pancreas or small in size and may achieve the accuracy of 95%-100% for localization. (4) Selective arterial injection of methylene blue: It is helpful to identify the location of insulinoma. (5) Arterial Stimulation and Venous Sampling (ASVS): ASVS has a high accuracy in the preoperative localization of insulinoma with favorable safety, and is especially applicable for occult insulinoma with negative findings on morphological examinations.

9.7.5.7 Differential Diagnosis

1. Gastrinoma: Gastrinoma is also known as Zollinger-Ellison syndrome and derived from islet G cells, and often has concomitant lymph node or liver metastasis. Gastrinoma patients may have other endocrine tumors. The clinical manifestations are characterized by recurrent peptic ulcers and diarrhea. The laboratory examination of gastric juice shows that the basic hydrochloric acid (BAO) exceeds 15 mmol/h; the gastrin concentration significantly increases. CT, MRI, endoscopic ultrasonography, and somatostatin receptor imaging (SRS) are helpful to localize the tumor.

2. Type 1 multiple endocrine neoplasia (MEN1): It is also known as Wermer syndrome. It is an autosomal dominant tumor syndrome caused by 11q13 chromosome aberration. The parathyroid gland is the most common organ involved, followed by the pancreas, pituitary gland, adrenal gland, and thyroid gland. MEN1 patients have a long history, complicated clinical manifestations, and generally family genetic predisposition. The family history should be recorded in detail, and the MEN1 gene mutation can be tested to confirm the diagnosis.

9.7.5.8 Diagnosis

1. Surgical treatments: Early surgical treatment to remove the tumor is importance once diagnosis is confirmed.
   (a) Simple tumor resection: Simple tumor resection is applicable for superficial, small, single benign insulinoma.
   (b) Resection of the pancreatic body and tail: When the tumor is located in the tail or body of the pancreas, large and deep in the pancreas, multifocal, or hard to be differentiated from malignant tumor, resection of the pancreatic body and tail may be preferred.
   (c) Wedge resection may be employed for a benign insulinoma at the head of the pancreas.
   (d) Blind resection of the pancreatic body and tail can be performed when the tumor is not identified after thorough and careful examinations.
   (e) If pathological examination shows islet cell proliferation, it is often necessary to remove more than 80% of pancreatic tissues.
   (f) For insulinomas larger than >2 cm in diameter and having concomitant metabolic symptoms, RO resection (including adjacent organs) and regional lymph node dissection are preferred.
2. Endoscopic treatment.
   (a) Ultrasound endoscope (EUS)-guided ethanol injection is a safe, minimally invasive treatment for benign insulinoma with low medical cost, no radiation, and favorable clinical efficacy [181].
   (b) Ultrasound endoscope (EUS)-guided radiofrequency ablation is also a safe and minimally invasive new treatment with favorable clinical efficacy and less complications. It has a broad prospect in the clinical treatment of insulinoma.
3. Pharmacotherapy: Pharmacotherapy is performed mainly to rescue and control hypoglycemia symptoms.
   (a) Octreotide: It not only inhibits insulin secretion, but also suppresses the secretion of glucagon and growth hormone.
   (b) Streptozotocin: It may inhibit DNA synthesis and thereby suppresses gluconeogenesis and pyridine nucleotide synthesis, exerting therapeutic effects on malignant insulinoma.
   (c) Diazoxide: It is a thiazide diuretic derivative and capable of opening ATP-sensitive K^+ channels, directly inhibit the secretion of insulin by β-cells, activate β-adrenergic nerves to induce gluconeogenesis, and reduce peripheral glucose utilization to raise blood glucose.

(d) Everolimus and sunitinib: They are used in metastatic insulinomas and can raise blood glucose, control tumor growth, and prevent tumor recurrence with favorable efficacy.

4. Hypertension treatment: In view of the pathogenesis of hypertension, both ACEI/ARB and calcium ion antagonists can be used to treat hypertension, but further investigations are needed due to the lack of clinical findings.

9.7.6 Type 1 Multiple Endocrine Neoplasia (MEN1) and Hypertension

9.7.6.1 Introduction

MEN1 is also known as Wermer syndrome with an incidence of 2–20/100,000. It consists of different endocrine tumors such as parathyroid tumor, pancreatic tumor, adrenal tumor, and pituitary tumor. If at least one of the first-degree relatives also has parathyroid adenoma, entero-pancreatic endocrine tumor or pituitary tumor, this tumor may be diagnosed with family type MEN1. Sporadic MEN1 may be diagnosed if there is no family history.

9.7.6.2 Pathogenesis

MEN1 is an autosomal dominant disease. The MEN1 gene is located in chromosome 11 (11q13). It is 9 kb in length, contains 10 exons, and encodes a menin protein consisting of 610 amino acids [182]. The MEN1 gene is a −/− tumor suppressor gene, the gene defects are diverse, may cover the entire gene, and often cause non-functional menin due to truncated mutation. In addition to genetic defects found in cells throughout the body, loss of another allele is also found in MEN1 tumor. Thus, mutations may be found in two alleles in MEN1 tumor: one is hereditary and can be found in any type of cells; another is acquired mutation and only found in the tumor tissues. In the MEN tumor, two alleles are non-functional, resulting in cell proliferation and tumorogenesis, which is consistent with the "two-hit" theory.

9.7.6.3 Clinical Manifestations

The clinical manifestations of MEN1 are related to the organs affected. The main clinical manifestations of MENl patients are parathyroid adenoma, intestinal pancreatic neuroendocrine tumor, pituitary tumor, etc. [183].

1. Parathyroid adenoma: About 85% of patients with MENl have parathyroid adenoma as the first symptom, and primary hyperparathyroidism (PHPT) secondary to parathyroid adenoma is the most common clinical manifestation in MENl patients. Moreover, the age of onset is young in MENl patients [184]. PHPT can lead to increased secretion of parathyroid hormone (PTH), bone and kidney are the main target organs of PTH, and there are concomitant high blood calcium, hypophosphatemia, and elevated PTH. Based on the main clinical manifestations, MENl can be divided into bone type, kidney type, and mixed type.

2. Intestinal pancreatic neuroendocrine tumor: It is the second most common type of MEN1 and can be functional or non-functional. It includes following tumors: gastrinoma accounts for 50%-60% of MEN1 pancreatic neuroendocrine tumors, gastrinoma is malignant in most patients; it is characterized by refractory, recurrent, or atypical peptic ulcers and high gastric acid secretion; and it is also known as Zollinger-Ellison syndrome. Insulinoma accounts for 10%–30% of MEN1 pancreatic neuroendocrine tumors, it is benign and unifocal in most patients, most insulinoma patients are younger than 40 years at onset, and 10% of insulinoma patients have other endocrine tumors. It is characterized by Whipple triad. The incidence of MEN1 glucagonoma is low, and it is clinically characterized by weight loss and rash. Some patients may have no corresponding symptoms, but the clinical examinations indicate positive results. The incidence of MEN1 vasoactive intestinal peptide tumor is low, and it is often located in the tail of the pancreas. The main clinical manifestations are the hypokalemia and diarrhea. The incidence of MEN1 non-functional pancreatic tumors is lower than that of above tumors; it often has no corresponding symptoms or slight increase in pancreatic-related hormones, which makes the diagnosis difficult. The prognosis of MENl non-functional pancreatic tumor is worse than that of the functional tumor.
3. Pituitary tumors: The incidence of pituitary tumors is about 25%, and mostly pituitary tumor is prolactinoma with or without elevated growth hormone secretion. Growth hormone tumor, non-functional tumor, and ACTH tumor with Cushing syndrome have relative lower incidences as compared to prolactinoma in pituitary tumors. Rarely, pituitary tumors in MEN1 are malignant, and their diagnosis and treatment are the same as sporadic MEN1.
4. Adrenal adenomas and other lesions: Adenomas that secrete cortisol can also be found in MEN1. There are three possibilities for the presence of Cushing's syndrome in MEN1: (1) adrenal adenoma; (2) pituitary ACTH tumor; (3) carcinoid with ectopic ACTH syndrome. Pituitary tumor is more common. In MEN1, thyroid adenomas and other thyroid diseases are also common. Among the family members of MEN1, about 30%–90% of patients develop subcutaneous lipoma, skin collagenoma, and multiple facial angiofibroma. These manifestations are helpful to screen these individuals and identify the individual carrying MEN1 deficiency.

Hypertension can be seen in patients with MEN1 involving any of above-mentioned areas.

9.7.6.4 Auxiliary Examinations

1. Laboratory examinations: The laboratory examinations are dependent on the organs involved in MEN1 patients. Detection of blood calcium and PTH is applicable in parathyroid adenoma patients; detection of fasting insulin and blood glucose can be employed in insulinoma patients; detection of fasting gastrin is applicable in gastrinoma patients; monitoring of PRL and IGF1 can be used in pituitary adenomas patients; for patients with clinical symptoms or the tumor larger than 1 cm, detection of aldosterone and cortisol is recommended; monitor-

ing of glucagon, chromogranin A, and pancreatic polypeptide is recommended for patients with other type of pancreatic MEN1.
2. Endoscopic ultrasonography: It has the highest sensitivity and can identify the tumor as small as 0.3 cm in diameter, but it is an invasive procedure. Of note, it has a poor sensitivity in the diagnosis of left pancreatic lesion. In fact, for non-functional tumors smaller than 1 cm, clinical observation is recommended in clinical practice.
3. Octreotide scanning: It can be used for the diagnosis of pancreatic neuroendocrine tumors.
4. Other imaging examinations: CT and MRI have different sensitivities in the diagnosis of MEN1 involving different regions. There is evidence showing that CT perfusion and enhanced MRI are superior to CT three-phase scanning [185], and CT perfusion can be employed to assess the tumor blood perfusion. The latest findings from Peking Union Hospital [186] reveal the new tracer-labeled PET-CT (such as 68Ga-Exendin 4) is more sensitive than traditional tools [187].

9.7.6.5 Diagnosis

1. Parathyroid adenoma: The youngest patient is 8 years old at disease onset, 95% of patients present with hyperparathyroidism before 40 years old, and most patients are asymptomatic, or manifest as hypercalcemia, urinary calculi, abnormal bone metabolism, and weakness.
2. Insulinoma: The clinical manifestations are mainly the triad of hypoglycemia. In the examinations for localization, somatostatin receptor scanning, intraoperative ultrasonography, and ASVS are helpful for the identification of the tumor.
3. Gastrinoma: The symptoms include diarrhea, esophageal reflux, and peptic ulcer. The fasting serum gastrin content increases. The gastrin content increases by 114 pmol/L (200 pg/mL) after secretin stimulation.

9.7.6.6 Differential Diagnosis

1. MEN2 is a rare autosomal dominant genetic disease and also known as Sipple syndrome. Subtypes of MEN2 include MEN2A, MEN2B, and familial medullary thyroid carcinoma (FMTC). The RET proto-oncogene germline mutation is closely related to the occurrence and development of MEN2 [188]. MEN2 is mainly characterized by medullary thyroid carcinoma (MTC) and may have concomitant pheochromocytoma and hyperparathyroidism. Parasitic tumor syndrome can be found in a small number of patients. Blood catecholamine detection, imaging examination, ^{131}I-m-iodobenzylamine (MIBG), and other examinations are helpful for the diagnosis of MEN2 pheochromocytoma, and MEN2 is mainly managed by surgery.
2. MEN4 is caused by CDKN1B gene mutation and is an autosomal dominant genetic disease. MEN4 can manifest as parathyroid adenoma, pituitary adenoma, intestinal pancreatic neuroendocrine tumor, angiofibroma, and other tumors. Biochemical examinations, imaging examinations, and CDKN1B gene detection

are helpful for the diagnosis of MEN4 [189]. At present, the main treatment for MEN4 is surgery, and radiotherapy and chemotherapy serve as adjuvant therapies of MEN4.

9.7.6.7 Treatments

1. Non-surgical treatments: (1) Proton pump inhibitor: Gastroinoma is more sensitive to proton pump inhibitors in patients with MEN1 gastrinoma. (2) Octreotide: For patients with insulinoma who cannot undergo surgery, refuse surgery, have postoperative remission or recurrence, or being waiting for surgery [190], octreotide can be used. (3) Somatostatin analogues and molecular-targeted therapy [191] (sunitinib and everolimus): These can be used for the treatment of pancreatic neuroendocrine tumors (P-NETs).
2. Surgical treatments: Surgery is the most effective treatment for parathyroid adenoma, neuroendocrine tumor of the pancreas (except for gastrinoma), and pituitary adenoma caused by MENl. The guideline recommends that non-functional tumor larger than 1 cm in diameter or with rapid growth should be removed by surgery [190].
3. Treatments at late stage: Local treatments may be administered such as tumor cell reduction, radiofrequency ablation, and hepatic artery embolization.
4. Treatment of hypertension: According to medical history, clinical manifestations and laboratory findings, qualitative, localization and functional examinations are performed to identify the cause of hypertension and elucidate the functional status of target organs. Antihypertensive drugs are selected based on the pathogenesis of hypertension.

9.7.6.8 Screening

Family members of MEN 1 patients should undergo comprehensive reviewing of medical history and physical examination [192]. Important laboratory examinations include the detection of blood calcium concentration or the total blood calcium after correction by plasma protein. This examination is initiated at 15 years old. In addition, detection of prolactin, gastrin, and fasting blood glucose is also helpful for the diagnosis. The detection of MEN1 mutations is complicated and expensive, and only applicable in qualified laboratories.

9.8 Rare Adrenal Hypertension

Hongjian Li

A large number of studies have confirmed that the adrenal gland is closely related to hypertension. Adrenal lesions, whether cortical or medulla, can cause hypertension. Common lesions include primary aldosteronism, pheochromocytoma, hypercortisolism, etc. Rare lesions include glucocorticoid resistance syndrome, congenital adrenal hyperplasia, such as 11β hydroxylase deficiency (CYP11B deficiency),

CYP17A deficiency (17α-hydroxylase/17,20-lyase deficiency), and adrenal deoxycorticosterone secretory tumor can also lead to hypertension. This section mainly summarizes the relationship between glucocorticoid resistance syndrome and hypertension.

9.8.1 Glucocorticoid Resistance Syndrome

Glucocorticoid resistance syndrome (GRS), also known as glucocorticoid hormone insensitivity syndrome (GCIS), is a syndrome with a series of clinical manifestations due to glucocorticoid resistance caused by congenital or acquired factors. Since glucocorticoids play an important role in the physiological processes of the human body, almost every tissue can be affected. If glucocorticoids do not work at all to the target tissue, life will end, therefore only partial or incomplete glucocorticoid resistance exists. The characteristic clinical manifestations of GRS are cortisol in plasma and urine is significantly elevated without hypercortisolism.

9.8.1.1 Etiology and Pathogenesis

GRS can be divided into two categories: primary and secondary [193, 194]. Primary glucocorticoid resistance syndrome (PGRS), also known as Chrousos syndrome, originally reported by Chrousos in 1968, there have been only dozens of reports so far, and the incidence is often familial. Studies have shown that the pathogenesis of PGRS may be related to the mutant NR3C1 gene, which encoding human glucocorticoid receptor (GR) [195]. Secondary glucocorticoid resistance syndrome is associated with defects in glucocorticoid receptor function caused by acquired factors, and is common in some psychological and pathological diseases such as major depression, chronic obstructive pulmonary disease, asthma, rheumatoid arthritis, sepsis, acute lymphocytic and leukemia [196–199].

The exact pathogenesis of GRS is not clear. Studies have shown that PGRS may be associated with a mutation in the GR gene that causes a decrease in receptor binding to glucocorticoid/DNA and GR polymorphism/post-receptor defects reduce glucocorticoid sensitivity [194]. The glucocorticoid receptor is encoded by a glucocorticoid receptor gene located on the fifth pair of autosomes, mutation of the receptor gene can cause abnormalities in the glucocorticoid receptor protein. It is generally believed that if the glucocorticoid receptor gene is mutated, the spatial conformation of the glucocorticoid receptor protein is significantly altered, resulting in abnormal binding of the glucocorticoid receptor to the glucocorticoid or binding to the DNA binding region, that is, the binding affinity is reduced or lost, clinically manifested as glucocorticoid resistance syndrome. If the glucocorticoid receptor mutation has no significant effect on the binding of the two, there is no obvious clinical manifestation. Glucocorticoid receptor genotype (polymorphism) can affect the sensitivity of glucocorticoids, the difference in the function of the glucocorticoid receptor and the role of the glucocorticoid receptor makes the metabolism of glucocorticoids and their effects on blood pressure different. Secondary glucocorticoid resistance is mainly associated with taking steroids and chronic diseases. Steroids act on both receptors at the same time. Long-term application can

lead to down-regulation of glucocorticoid receptor-α expression, and the half-life of glucocorticoid receptors is significantly reduced, causing glucocorticoid resistance [193]. Some chronic diseases such as asthma and rheumatoid arthritis can reduce the expression of glucocorticoid receptor-α and decrease the sensitivity of glucocorticoid receptors leading to glucocorticoid resistance [200–202]. In addition, changes in the mineralogical hormone 11β-hydroxysteroid dehydrogenase 2 are also associated with glucocorticoid resistance [203].

9.8.1.2 Pathophysiology

Glucocorticoids are synthesized and secreted by adrenal cortical bundles. They mainly bind to GR in the body and play a physiological role, which is regulated by the feedback of the hypothalamic-pituitary-adrenal axis. Under physiological conditions, corticotropin-releasing hormone stimulates pituitary adrenocorticotropic hormone-secreting cells to secrete adrenocorticotropic hormone through the pituitary portal vein. The increase in ACTH levels can also excite the adrenal cortical bundle to secrete glucocorticoids, which increases the concentration of glucocorticoids in the blood, while the elevated glucocorticoid concentration in turn acts on the hypothalamus, inhibiting the secretion of corticotropin-releasing hormone. And inhibit the secretion of ACTH in the pituitary, thereby reducing the secretion of glucocorticoids from the adrenal gland and maintaining the dynamic balance among the three. Due to defects in the GR gene or abnormalities in the GR receptor caused by certain chronic diseases, the target tissue is not sensitive to glucocorticoids and causes glucocorticoid resistance, so the body is in a relatively insufficient state of glucocorticoids. The body is regulated by the hypothalamic-pituitary-adrenal axis feedback; ACTH and glucocorticoid secretion are compensatory, in the meantime. At the same time, the secretion of precursor substance with mineralocorticoid (such as deoxycorticosterone, corticosterone) and adrenal androgens (such as androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate) secreted by the adrenal glands are increased [204].The glucocorticoid secretion balance is regulated by the negative feedback of the hypothalamic-pituitary-adrenal axis, and the hypothalamic-pituitary-adrenal axis is set in a highly functional state to compensate for the insensitivity of the target tissue to glucocorticoids. The secretion of ACTH in the pituitary gland increases, the secretion of glucocorticoids also increases. At the same time, increased ACTH increased the levels of the mineralocortic hormone-producing precursors (deoxycorticosterone, corticosterone) and adrenal androgen levels. Because the body does not resist mineralocorticoids and sex hormones, it eventually leads to the corresponding mineralocorticoid hyperactivity and hyperandrogenism [205].

9.8.1.3 Clinical Manifestation

The clinical manifestations of PGRS are diverse, which is related to the degree of glucocorticoid resistance, increased adrenal mineralocorticoid and androgen-compensatory secretion, and the sensitivity of target tissues to both. Most patients have no clinical symptoms, only laboratory indicators are abnormal, and some patients have only chronic fatigue, weakness [205]. Patients with excessive secretion of mineralocorticoid may have hypertension, hypokalemia, and metabolic alkalosis;

patients with excessive androgen secretion may have hairy, acne, baldness, precocious puberty, female pseudohermaphroditism, and decreased fertility. In women, amenorrhea and menstrual disorders can occur, and men can have oligozoospermia; children can present with febrile seizures and abnormal growth and development [206–208]. The clinical manifestations of secondary cortisol resistance syndrome may be masked by the primary disease.

9.8.1.4 Auxiliary Inspection

1. Biochemical indicators detection: blood lipids, blood sugar, electrolytes, blood gas analysis.
2. Hormone testing: serum total cortisol and free cortisol levels were significantly elevated, 24-h urinary free cortisol, and 17-hydroxyketone steroid levels were also significantly elevated, cortisol rhythm was normal, androgen levels were elevated, ACTH levels were normal or elevated, and aldosterone and renin levels were normal.
3. Dexamethasone inhibition test: can be used for diagnosis and experimental treatment.
4. Pituitary, adrenal imaging studies can help with differential diagnosis.
5. Glucocorticoid receptor gene testing helps to identify the cause of PGRS.

9.8.1.5 Diagnosis and Differential Diagnosis

Because the clinical manifestations of glucocorticoid resistance are often not obvious, they are often difficult to detect. The following clinical manifestations can be used as early diagnosis clues: (1) blood or urinary-free cortisol is significantly increased but no typical clinical manifestations of Cushing syndrome; (2) female hairy and male precocious puberty without obvious etiology; (3) hypertensive patients with severe hypokalemia alkalosis after taking diuretics; (4) patients with hypertension and hypokalemia are associated with elevated blood or urine cortisol. Screening for GRS from cases of elevated blood cortisol is generally considered to be based on the following points: (1) cortisol in blood or urine is significantly increased and not inhibited by low-dose dexamethasone; (2) with or without blood ACTH, androgen, estrogen, and deoxycorticosterone increased; (3) elevated blood cortisol, but normal circadian rhythm, normal response to elevated blood cortisol for insulin hypoglycemia, normal aldosterone in blood and urine; (4) glucocorticoid receptor gene mutation; (5) secondary glucocorticoid resistance syndrome has clinical manifestations of primary disease.

GRS should be differentiated from ACTH resistance syndrome, familial simple glucocorticoid deficiency, and CAH. ACTH resistance syndrome, although both GRS and ACTH resistance syndrome may present the clinical manifestations of glucocorticoid deficiency, but ACTH resistance syndrome presents a decrease in serum cortisol and an increase in blood ACTH, GRS is shown as serum cortisol increased, blood ACTH could not be measured (See the Table below). In addition, ACTH resistance syndrome can be manifested as skin pigmentation; ACTH resistance syndrome can also cause hypoglycemia in children; ACTH resistance syndrome also shows that exogenous ACTH cannot increase the secretion of cortisol.

According to clinical manifestations, GRS should also be differentiated from other diseases that cause hypertension and hypokalemia. Determination of plasma cortisol and aldosterone is helpful in diagnosis.

Identification of ACTH resistance syndrome, GRS, and Addison disease

	ACTH resistance syndrome	GRS	Addison disease
Cause	ACTH receptor mutation Post-MC2R defect	Glucocorticoid receptor mutation or post-receptor defect	Primary adrenal lesion or autoimmune multiple endocrine adenosis
Cause of hormone deficiency	Adrenal cortical MC2R or post-receptor functional deficit	Glucocorticoid receptor deficiency or post-receptor defect	Adrenal girdle and reticular lesions may be associated with aldosterone reduction
Identification points	Excessive secretion of aldosterone adrenal hormone shows gender deformity (male), amenorrhea, obesity	Female: masculine or obese	Mostly adult onset, adrenal or autoimmune disease
Laboratory inspection			
Blood ACTH	↑	↓	↑
Blood cortisol	↓	↑	↓
Blood aldosterone	↑	constant	↓/constant
Blood androgen	↑	indefinite	↓/constant
Dexamethasone inhibition test	Not suppressed	Not suppressed	Not suppressed
Treatment method	Glucocorticoid and mineralocorticoid	Glucocorticoid replacement therapy	Glucocorticoid and mineralocorticoid

Familial simple glucocorticoid deficiency: can be manifested as primary adrenal insufficiency, generally without mineralocorticoid deficiency. Most patients have skin pigmentation and recurrent hypoglycemia, serum ACTH is significantly elevated, cortisol is reduced, but the renin-angiotensin-aldosterone system functions normally. Familial glucocorticoid deficiency is often associated with tall builds.

Cushing syndrome: GRS has many similarities in clinical manifestation and laboratory examination, and the syndrome is often misdiagnosed as Cushing disease. The diagnosis of the two in clinic is the clinical manifestation of the former no typical Cushing syndrome, such as full moon face, buffalo back, cardiac obesity, skin purple grain, and glucose tolerance test abnormalities, can have plasma anaerobic cortisol and glucocorticoid receptor defects; blood cortisol circadian rhythm is normal.

Congenital adrenal hyperplasia: female patients with the clinical manifestation of androgen increase and male pseudo-precocious puberty should be identified with congenital adrenal cortical hyperplasia, the latter blood cortisol normal or low.

9.8.1.6 Treatment

No treatment is required for asymptomatic PGRS patients [209]. For symptomatic PGRS patients, the current method is to give dexamethasone a lifetime replacement treatment. Dexamethasone is a synthetic long-acting glucocorticoid with the smallest effect of endogenous salt corticosteroids in the current synthetic glucocorticoid. Dexamethasone can combine and activate genetically defective glucocorticoid receptors to play the physiological role of glucocorticoids, thereby inhibiting the body's compensatory ACTH secretion, reducing the levels of salt corticosteroids and androgens secreted by the adrenal glands, and relieving clinical symptoms. The commonly used dose of GRS patients in the literature is 1–3 mg/days, serum ACTH and cortisol levels can be restored to normal, and clinical symptoms can be alleviated [210, 211]. However, treatment should be individualized, according to the patient's clinical performance and laboratory examination indicators, different patients choose different doses of dexamethasone, and ultimately to control clinical symptoms as the goal. New drugs to correct glucocorticoid resistance, such as creatine phosphate -3-kinase delta inhibitors and p38MAP kinase inhibitors, are being developed. Interleukin-10, vitamin D, theophylline, and antioxidants have a certain adjuvant therapeutic effect.

For secondary glucocorticoid resistance syndrome, it is necessary to actively treat the original onset of the disease. Lesovaya and other reports bortezomib help restore the sensitivity of some secondary glucocorticoid resistance in patients with glucocorticoid receptors [212]. The recent Wilkinson has proposed the application of the SEMOGRAM-SEDIGRAM strategy to secondary glucocorticoid resistance to the development of new drugs, which has helped to reduce the side effects of low-sugar corticosteroid therapy [213].

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General Discussion on Neurogenic Hypertension

10

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The nervous system is closely related to blood pressure regulation. A variety of central and peripheral systemic lesions can lead to hypertension. The mechanism is mainly related to the increase of intracranial pressure, which increases the sympathetic nervous system impulse and autonomic dysfunction in the vasomotor center. Early intracranial lesions It manifests as an increase in reflex or compensatory blood pressure, and once brain damage is aggravated, especially in the medullary cardiovascular center failure, blood pressure drops rapidly and life is threatened.

10.1 Increased Intracranial Pressure and Hypertension

Sheng Li

10.1.1 Intracranial Pressure

The normal adult cranial cavity is a cavity composed of the skull base and the skull bone, which has the function of accommodating and protecting its contents. In addition to the vascular system (especially the jugular vein) and the base of the skull (especially the large occipital foramen) communicating with the cranial cavity, the cranial cavity can be regarded as a completely closed container, and the skull that constitutes the cranial cavity is hard and cannot be expanded. Therefore, the volume of the cranial cavity of each person is constant, about 1400–1500 mL. The contents of the cranial cavity have brain tissue, cerebrospinal fluid, and blood. The brain

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tissue is 1400 mL, accounting for 80–90% of the total volume of the cranial cavity; the blood volume in the cerebral blood vessels per unit time is about 75 mL, which accounts for 5.5% of the volume of the cranial cavity; the cerebrospinal fluid of the ventricle, cerebral cistern, and intracranial subarachnoid space is about 75 mL, about 5.5% of the volume of the cranial cavity. Under normal physiological conditions, the volume of the cranial cavity and the volume of its contents are adapted and remain relatively stable throughout the skull. The pressure generated by the contents of the cranial cavity on the cranial wall is the intracranial pressure (Intracranial Pressure, ICP) [1].

Since the cerebrospinal fluid present in the subarachnoid space and the cerebral cistern is between the cranial wall and the brain tissue, and communicates with the subarachnoid space in the ventricle and the spinal cord cavity, the cerebrospinal fluid is in the case of a smooth subarachnoid space of the spinal canal. Hydrostatic pressure can represent ICP. Puncture the cisterna magna or lateral ventricle, the reading measured by the pressure tube or pressure gauge, which is the clinical intracranial pressure. This pressure is close to the cerebrospinal fluid pressure measured by the lumbar puncture in the lateral position, so it is clinically represented by the cerebrospinal fluid pressure in the lateral position. Normal adult ICP is 80–180 mmH_2O. When the ICP continues to exceed 200 mmH_2O, it is clinically known as an increase in intracranial pressure. When the volume of the cranial cavity is increased or the volume of the cranial cavity is reduced by more than 8–10% of the volume of the cranial cavity, severe intracranial pressure will increase. Can lead to a series of physiological dysfunction and pathological changes, showing typical symptoms such as headache, nausea, vomiting, papilledema, severe intracranial pressure can also be complicated by complications such as pulmonary edema; can also cause compression or destruction due to cerebral palsy The hypothalamus causes autonomic dysfunction and can be life-threatening in a short period of time, which is the main cause of death from neurosurgical diseases.

10.1.2 Blood Pressure and Cerebral Blood Flow

Cerebral blood flow (CBF) depends on cerebral perfusion pressures (CPP) and cerebral vascular resistance. Cerebral blood flow (CBF) = [mean arterial pressure (MAP) − intracranial pressure (ICP)]/cerebrovascular resistance (CVR), mean arterial pressure (MAP) − intracranial pressure (ICP), also known as CPP, when ICP unchanged, CPP was positively correlated with mean arterial pressures (MAP). That is, CPP = MAP – ICP [2].

Under normal circumstances, CPP fluctuates widely. Between 70 and 90 mmHg, CBF remains relatively stable due to the presence of autoregulatory mechanisms, which is achieved by contraction and relaxation of the cerebral arteries. Studies have shown that cerebrovascular resistance mainly depends on the size of the small arteries. When the CPP is increased, in order to maintain the CBF at 50 mL/100 g/min, the body's cerebrovascular resistance is increased by the contraction of the

small arteries; on the contrary, when the CCP is lowered, the arterioles dilate and the cerebral vascular resistance decreases, which is the Bayliss effect [3]. The automatic adjustment system only works within a certain range. When the MAP fluctuates from 50–60 mmHg to 150–160 mmHg, the CBF can be guaranteed to be relatively stable. However, when the MAP is lower than 50–60 mmHg, the diastolic function of the blood vessel has reached the limit. At this time, the CPP will decrease with the further decrease of MAP, and the cerebral ischemia will occur. Conversely, when the MAP exceeds 150–160 mmHg, the systolic function of blood vessels reaches the limit, and CPP will increase as MAP continues to rise, which will lead to cerebral edema and blood-brain barrier function, such as hypertensive encephalopathy and/or cerebral hemorrhage [4].

10.1.3 The Pathogenesis of Hypertension Caused by Intracranial Hypertension

10.1.3.1 Increased Intracranial Pressure Itself

The increase of any component in the cranial cavity caused by various causes can lead to increased intracranial pressure. When the intracranial pressure increases to 35 mmHg (1 mmHg is equal to 13.6 mmH_2O), the cerebral perfusion pressure is below 40 mmHg, the cerebral blood flow is reduced to 1/2 or less of normal, the brain is in a state of severe hypoxia, $PaCO_2$ is more than 50 mmHg, and the autoregulation function of the cerebral blood vessels is basically lost, and it is paralyzed. The human body uses the autonomic nervous system to contract the blood vessels around the body. Increased blood pressure and heart rate to improve cerebral perfusion pressure in order to improve cerebral perfusion pressure. At the same time, the breathing rhythm is slowed down, and the breathing depth is increased, so that the gas in the alveoli is fully exchanged, and the blood oxygen saturation is improved. This triple reaction, which increases arterial pressure with slowing heart rate, increased cardiac output, and slowing of respiratory rhythm, is called systemic vasopressor response or Cushing's three main signs. Increased blood pressure is more common in patients with acute craniocerebral injury or acute intracranial injury, blood pressure is not obvious in patients with chronic head injury or intracranial injury [5].

10.1.3.2 Central Vasomotor Dysfunction

The cardiovascular systolic center is located in the medulla oblongata, and the pons, midbrain, hypothalamus, cerebral cortex, and cerebellum above the medulla have high-level integrated centers that regulate cardiovascular movement, especially the hypothalamic autonomic nerve center. Whether it is mechanical (extrusion, pulling, damage), or biological (pathogenic bacteria and their toxins), physical (temperature), and chemical (CO_2) damage involving these parts, can cause blood pressure changes. Increased the heart rate, peripheral vasoconstriction, elevated blood pressure; it also has a slow heart rate, peripheral vasodilation, and a drop in blood pressure; or alternating between the two situations [1].

Cause of Disease

1. Cerebrovascular disease: Including cerebral hemorrhage, subarachnoid hemorrhage, extensive cerebral thrombosis, cerebral embolism, and intracranial venous sinus thrombosis.
2. Intracranial infectious diseases: Meningitis, encephalitis, brain abscess, etc. caused by viruses, bacteria, tuberculosis, fungi, etc.
3. Craniocerebral injury: Such as brain contusion, intracranial hematoma, surgical trauma, extensive skull fracture, craniocerebral firearm injury, traumatic subarachnoid hemorrhage, etc.
4. Intracranial space-occupying lesions: Including various cancers, abscesses, hematomas, granuloma, cysts, brain parasites, etc.
5. Traffic and non-communicating hydrocephalus caused by various reasons.
6. Ischemic hypoxia-metabolic encephalopathy caused by various causes: Such as respiratory obstruction, asphyxia, and cardiac arrest. Hepatic encephalopathy, acidosis, carbon monoxide poisoning, lead poisoning, acute water intoxication, and hypoglycemia.
7. The of status epilepsy cannot be effectively controlled.
8. Increased benign intracranial pressure: Arachnoid encephalitis is more common, which occurs in the posterior cranial fossa, the most significant increase in intracranial pressure.
9. Congenital anomalies: Such as the developmental deformity of the aqueduct, skull base depression and congenital cerebellar tonsil malformation, etc., can cause cerebrospinal fluid reflux obstruction, thus secondary hydrocephalus and increased intracranial pressure, due to cranial stenosis, which hinders the normal development of the brain, it may also increase intracranial pressure.

10.1.4 Clinical Manifestation

10.1.4.1 Symptoms and Signs Associated with Increased Intracranial Pressure

(1) Headache; (2) Vomiting; (3) Optic papilledema; (4) Disorder of consciousness; (5) Cushing reaction: It refers to the rise of blood pressure, slow heart rate, and slowing of breathing when severe intracranial pressure increases. The result is to ensure a certain cerebral perfusion pressure, so that alveolar O_2 and CO_2 are fully exchanged, increasing brain oxygen supply, which is the performance of the body's total mobilization and active compensation. (6) Diplopia; (7) Twitching and going to the brain; (8) Visual field defect; (9) Cerebral palsy: The intracranial pressure rises to a certain extent, part of the brain tissue is displaced, and the dura mater or the occipital foramen is squeezed, and the nearby nerves, blood vessels, and brainstem are compressed, resulting in a series of symptoms and signs.

1. The cerebral inferior palsy: The cerebral hemisphere is buckled back and the forehead is moved back to the contralateral side through the free edge of the cerebral palsy. The anterior cerebral artery and its branches are compressed, mainly showing contralateral lower extremity paralysis and dysuria.

2. Subcerebellar tentorial hiatus hernia: The hippocampus inside the temporal lobe and the hook back into the cerebellar hiatus, the midbrain, oculomotor nerve, and blood vessels are squeezed and displaced, mainly manifested as disturbance of consciousness, oculomotor nerve paralysis and contralateral limb paralysis.
3. Upcerebellar tentorial hiatus hernia is in the upper part of the cerebellum and the anterior cerebellum is retrogradely displaced upward through the cerebellum, compressing the tetrad and the large cerebral vein. Mainly manifested as disturbance of consciousness, bilateral drooping face, upper eye visual disorder, the pupil is big and the light response is slow or disappear, late go cerebrum rigidity and breath stops suddenly.
4. Occipital foramen: Cerebellar tonsils and adjacent cerebellar tissue are inserted into the spinal canal through the occipital foramen, and the medulla is compressed. The main manifestations is consciousness, changes in vital signs such as heart rate, respiration, and blood pressure, nystagmus and balance disorders, frequent vomiting and dysphagia, etc.

10.1.4.2 Symptoms and Signs Associated with Primary Intracranial Lesions

Mainly related to the neurological stimulation symptoms or focal signs associated with the lesion, such as epilepsy, aphasia, mental retardation, dyskinesia, sensory disturbance, autonomic dysfunction, etc.

10.1.4.3 Cardiovascular Systolic and Central Disorders Symptoms and Signs

Can be expressed as blood pressure high or low, or alternating between the two, up to 220/140 mmHg or more, the lowest is below 90/60 mmHg; with tachycardia, bradycardia, or arrhythmia. Heart rate or rhythm, blood pressure have large fluctuations, instability and sensitivity to drug intervention.

10.1.4.4 Symptoms and Signs Associated with Increased Blood Pressure

Headache, dizziness, palpitations, shortness of breath, tinnitus, fatigue, etc.; can also appear more serious symptoms such as blurred vision, nose bleeding, and even the performance of target organs such as heart, brain, kidney, and eye caused by high blood pressure. Cerebrovascular accidents caused by hypertension, especially prone to the middle cerebral artery of the bean vein artery, the central artery of the base artery, and the cerebellar dentate nucleus. Target organ damage such as retinal exudation and hemorrhage.

10.1.5 Diagnosis

According to the typical manifestations of headache, vomiting, and papilledema, it is not difficult to clinically diagnose the increase of intracranial pressure. However, in the early stage of acute intracranial hypertension or increased intracranial pressure, the papilledema is often ignored, which is easy to be misdiagnosed and has

serious consequences. If there is an increase in blood pressure, a slow pulse, and a slow breathing on the basis of increased intracranial pressure, consider the diagnosis of Cushing reaction, that is, intracranial disease secondary to hypertension. Because the degree of increased intracranial pressure is closely related to the location and extent of intracranial lesions. Only when the cause diagnosis is made as soon as possible can the problem of increased intracranial pressure be fundamentally solved. Etiological diagnosis is considered from the following aspects according to the nature of the lesion [6]:

10.1.5.1 Craniocerebral Injury

Brain contusion, cerebral edema, and intracranial hematoma caused by any cause of craniocerebral injury can increase intracranial pressure. Increased intracranial pressure can occur in the early stage of acute severe craniocerebral injury. A small number of patients may have intracranial hypertension later, such as chronic subdural hematoma. After craniocerebral injury, patients often quickly enter a coma with vomiting. Symptoms and signs such as hemiplegia, aphasia, and seizures may occur depending on the location.

10.1.5.2 Cerebrovascular Disease

Mainly for hemorrhagic cerebrovascular disease, hypertensive cerebral hemorrhage is most common. Generally, the onset is more urgent, and the increase in intracranial pressure is peaked within 1–3 days. Patients often have varying degrees of disturbance of consciousness. It is characterized by headache, dizziness, vomiting, limb paralysis, aphasia, incontinence, and so on. There is often a significant increase in blood pressure at the time of onset. Most patients have positive meningeal irritation. Cerebrospinal fluid pressure is increased and often bloody. Most patients have risk factors for cerebrovascular disease such as hypertension, arteriosclerosis, coronary heart disease, and diabetes. Intracranial venous sinus occlusion, such as sagittal sinus thrombosis, intracranial venous thrombosis, and occlusion of extracranial large veins, can cause increased intracranial pressure.

10.1.5.3 Hypertensive Encephalopathy

Hypertensive encephalopathy refers to an acute, comprehensive brain dysfunction caused by a sudden increase in blood pressure. Common in acute hypertension, acute and chronic nephritis or eclampsia, occasionally due to pheochromocytoma or taking monoamine oxidase inhibitors while taking tyramine-containing foods, lead poisoning, Cushing's syndrome. Frequently, the blood pressure suddenly increased significantly to above 250/150 mmHg, and the increase in diastolic blood pressure was more significant than systolic blood pressure. Symptoms of increased intracranial pressure such as severe headache, nausea, vomiting, and neck stiffness often occur at the same time. Neuropsychiatric symptoms include visual impairment, hemiplegia, aphasia, epilepsy-like convulsions or limb muscle rigidity, and disturbance of consciousness. The fundus may have hypertensive fundus, retinal artery spasm, and even retinal hemorrhage, exudate, and papilledema. CT examination showed cerebral edema and narrowing of ventricles.

10.1.5.4 Intracranial Tumor

It can be divided into primary intracranial tumors and metastases in which malignant tumors metastasize to the brain. The common feature of intracranial pressure caused by brain tumors is the chronic progressive typical intracranial pressure. Although the symptoms may be slightly up and down during the course of the disease, the general trend is gradually increasing. A small number of patients with increased chronic intracranial pressure can suddenly turn into an acute attack. According to the tumor growth site can be accompanied by different symptoms and signs, such as changes in visual field of vision, pyramidal tract damage, seizures, aphasia, sensory disturbances, mental symptoms, and cerebellopontine angle syndrome.

10.1.5.5 Brain Abscess

There are often primary infections, such as otogenic, nasal, or traumatic. At the beginning of blood supply, there may be systemic symptoms of acute inflammation, such as high fever, chills, meningeal irritation, increased white blood cells, blood sedimentation, and increased number of white blood cells in the cerebrospinal fluid of the lumbar spine. However, after the abscess matures, the above symptoms and signs disappear, showing only an increase in chronic intracranial pressure.

10.1.5.6 Brain Infectious Disease

It refers to inflammatory diseases of the brain and meninges caused by bacteria, viruses, parasites, rickettsia, and spirochetes. Acute or subacute intracranial pressure increased, a small number of patients appear of increased chronic intracranial pressure, such as brain arachnoiditis. Symptoms of infection often occur at the onset, such as fever, general malaise, leukocytosis, or lymphocyte predominance, or neutrophils predominate; some cases have consciousness disorders, mental confusion, myoclonus and seizures, etc. Developed into a deep coma in the day. Frequent symptoms and signs such as hemiplegia, aphasia, binocular deviation, partial epilepsy, involuntary movement, and meningeal irritation. Cerebrospinal fluid often has inflammatory changes, such as cerebrospinal fluid leukocytosis, increased protein, or decreased sugar or chloride.

10.1.5.7 Hydrocephalus

Due to various reasons, the cerebrospinal fluid in the ventricular system is increasing, and the brain parenchyma is correspondingly reduced. When the ventricle is enlarged and accompanied by increased intracranial pressure, it is called hydrocephalus. Ventricular angiography showed a marked enlargement of the ventricles. CT examination can detect tumors, accurately observe the size of the ventricles, and show the degree of edema around the ventricles.

10.1.5.8 Benign Intracranial Hypertension

Also known as “pseudo-brain tumor,” the patient has only symptoms and signs of increased intracranial pressure, but no space-occupying lesions exist. The cause may be arachnoiditis, otogenic hydrocephalus, venous sinus thrombosis, endocrine

disease, etc., but often cannot determine the cause. Clinical manifestations, in addition to increased chronic intracranial pressure, generally no focal signs.

10.1.5.9 Systemic Diseases

Various systemic diseases such as toxic diseases caused by various bacterial infections, drug or food poisoning, water, electrolytes and acid-base balance disorders, uremia, diabetic coma, and hepatic coma. Increased intracranial pressure usually occurs when the systemic disease progresses to a severe stage. Evidence of systemic disease can be found in combination with detailed medical history, physical signs, and auxiliary examination results.

10.1.6 Auxiliary Inspection

Intracranial pressure monitoring can determine the level of intracranial pressure, and the lumbar cerebrospinal fluid test can help determine the cause. In addition, there are head X-ray films, EEG, computed tomography (CT), magnetic resonance imaging (MRI), and digital subtraction angiography (DSA), which mainly identify the lesions. CT and MRI examinations also have some help for qualitative diagnosis.

10.1.6.1 Intracranial Pressure (ICP) Monitoring

Intracranial pressure monitoring is the most rapid, objective and accurate method for diagnosing intracranial hypertension. It is also important to observe changes in the patient's condition, early diagnosis, time to determine surgery, guide clinical drug treatment, and judge and improve prognosis. Its monitoring methods are both traumatic and non-invasive. Lumbar puncture and intraventricular monitoring are the most commonly used methods of traumatic ICP monitoring [4].

1. Lumbar puncture: Lumbar puncture measurement of ICP began in 1897. The method is simple and easy to operate. However, when cerebrospinal fluid circulatory disorders occur, the measured pressure does not necessarily reflect the changes in intracranial pressure, and the lumbar puncture can only reflect the pressure at that time and cannot be continuously monitored. In addition, it is necessary to strictly control the indications, all suspected severe intracranial pressure or signs of cerebral palsy, shock, exhaustion or endangered state and local skin inflammation, posterior fossa space-occupying lesions are taboo.
2. Intraventricular monitoring: It is the gold standard for ICP monitoring. Place the catheter containing the fiber optic probe in the lateral ventricle and the other end connected to a pressure transducer for measurement. The method is simple, direct and objective, accurate in pressure measurement, and can drain cerebrospinal fluid and can be continuously monitored. The disadvantage is that when the ICP is increased, the brain swelling causes the ventricle to be narrowed, displaced, or even disappeared, and the ventricle puncture and catheterization are difficult; and the probability of infection is greatly increased after 5 days of catheterization.
3. Non-invasive intracranial pressure monitoring technology: Including flash visual evoked potential and non-invasive brain electrical impedance monitoring, can

achieve continuous intracranial pressure monitoring, but indirectly through the electrophysiological method to estimate intracranial pressure, by age and brain metabolism. The impact of various factors such as intracranial lesions, disease types and systemic conditions, and the accuracy needs further study.

10.1.6.2 X-Ray Film

The skull X-ray film of patients with chronic intracranial hypertension can detect the sella, especially the saddle back and the anterior and posterior sacral bone destruction or absorption; the diffuse thinning of the skull; the increase and deepening of the cerebral gyrus.

10.1.6.3 Electroencephalogram Examination

EEG examination is helpful in finding the cause of increased intracranial pressure and has a great diagnostic value for epilepsy, encephalitis, and encephalopathy.

10.1.6.4 Computerized Tomography (CT)

It is a non-invasive and effective examination method that clearly shows intracranial space, cerebral edema, hydrocephalus, cerebral infarction, and intracranial hemorrhage.

10.1.6.5 Magnetic Resonance Imaging (MRI)

MRI imaging has better resolution and contrast than CT, and can obtain information on multiple different sections. The diagnosis of posterior fossa lesions is significantly better than CT.

10.1.6.6 Digital Subtraction Angiography (DSA)

DSA has important diagnostic value for cerebrovascular disease, especially for the diagnosis of aneurysm, arteriovenous malformation, intracranial venous sinus, and cerebral venous thrombosis.

10.1.7 Complication

Severe intracranial pressure may result in visceral complications due to hypothalamic and brainstem dysfunction, more common are upper gastrointestinal bleeding, neurogenic pulmonary edema, acute renal failure, diabetes insipidus, cerebral sodium retention, and brain sodium deficiency syndrome. The serious complications are cerebral palsy and central circulatory respiratory failure leading to deterioration of vital signs.

10.1.8 Treatment

The treatment of primary intracranial disease is the fundamental to relieve high blood pressure caused by increased intracranial pressure, and reducing intracranial pressure is a direct means of lowering blood pressure, such as surgical removal of

intracranial hematoma, abscess, granuloma, tumor, and other intracranial masses. Ventricle puncture drainage or cerebrospinal fluid shunt, improve cerebrospinal fluid circulation; local thrombolysis of cerebral venous thrombosis, promote cerebral venous return [7, 8]. In most cases, as the intracranial pressure drops, blood pressure returns to near normal. Therefore, the regulation of blood pressure should be cautious, and blind drug intervention should not be blindly administered. Treatment of intracranial pressure reduction should be a balanced, step-by-step process [9]. Starting from simple measures, intracranial pressure therapy should monitor intracranial pressure and blood pressure simultaneously to maintain cerebral perfusion pressure > 70 mmHg. The specific measures are as follows [10]:

10.1.8.1 Raise the Head Position

The bed head is raised by 30°, which can reduce the cerebral blood flow volume, increase the jugular venous return, reduce the cerebral venous pressure and intracranial pressure, and is safe and effective. The ideal head position should be based on the individual response of the patient's ICP monitoring. If the occipital is too high or the neck is too tight, ICP may increase and should be avoided.

10.1.8.2 Pain Relief and Sedation

When intracranial pressure compliance is reduced, sedation, resistance to restraint, tracheal intubation, or other invasive procedures can increase intrathoracic pressure and jugular venous pressure, increase intracranial pressure; in addition, anxiety or fear makes the sympathetic nervous system function hyperactive, leading to tachycardia, increased blood pressure, increased brain metabolic rate, increased cerebral blood flow, increased intracranial pressure. Therefore, it is especially important to actively carry out sedation treatment. Parenteral sedatives are at risk for respiratory depression and blood pressure lowering, so endotracheal intubation and arterial blood pressure monitoring must be performed before medication. Propofol is an ideal intravenous sedative with a short half-life and does not affect the patient's neurological clinical assessment, as well as anti-epilepsy and free radical scavenging. Paralytic neuromuscular blockers should be avoided as they affect the correct assessment of nervous system function.

10.1.8.3 Rehydration

Patients with increased intracranial pressure can be infused with isotonic saline or hypertonic saline, and hypotonic fluid such as 5% dextran or 0.45% saline is prohibited. The hypotonic state of the body (<280 mOsm/L) should be actively corrected, and the mild hypertonic state (>300 mOsm/L) is beneficial to the condition. A decrease in CPP can increase the reflectivity of the ICP, and an isotonic solution can be infused to correct the hypovolemia. 5% or 10% glucose solution should not be used. It is contraindicated to use 50% hypertonic glucose solution because it will increase the accumulation of lactic acid in brain tissue, aggravating brain edema and neuronal damage. Of course, the clinician should dynamically adjust the type of rehydration and the amount of rehydration according to the patient's blood glucose and plasma electrolyte content.

10.1.8.4 Lower Intracranial Pressure

1. Osmotic diuretics: Osmotic diuretics are non-electrolyte substances, have no pharmacological activity, and are hardly metabolized in the body. After intravenous input, the plasma osmotic pressure is increased in a short time. When the blood-brain barrier is good, an osmotic pressure difference is formed between the plasma and the brain tissue fluid, so that the water in the brain tissue rapidly shifts to the blood circulation, thereby reducing the volume of the brain. Permeable diuretics in the kidney is filtered by the glomerulus, but not reabsorbed by the renal tubules, the osmotic pressure in the renal tubules is increased, the reabsorption of water is reduced, and the urine is increased, thereby achieving the purpose of dehydration, diuresis, and reduction of intracranial pressure.
   (a) Mannitol: Mannitol is fast-acting and has strong dehydration effect. It is currently recognized and the most widely used osmotic diuretic. The usual concentration of mannitol is 20%, which makes the osmotic pressure 4 times. After intravenous infusion, it takes effect after about 20 min, and the action time is short (2–3 h peak, maintain 6–8 h). After glomerular filtration, it is not reabsorbed by renal tubules, so that water and electrolyte are discharged through the kidney. There is a relatively obvious rebound phenomenon. Mannitol at a dose of 0.25–1 g/kg can effectively control elevated ICP. Arterial pressure should be avoided (systolic pressure < 90 mmHg). For the deterioration of progressive neurological function caused by cerebellar incision or non-cranial causes, mannitol should be restricted before ICP monitoring. Common mannitol side effects: aggravate cardiac load, induce heart failure or pulmonary edema; hypovolemic shock; acute tubular necrosis, and water and electrolyte disorders. Therefore, in the use of mannitol, it is necessary to note that patients with small lesions and high intracranial pressure symptoms may not be used or used in small doses. Generally, the control is below 20 g/day, and it is divided into 4–6. For patients with large lesions and high intracranial pressure, each dose is 1–2 g/kg. The severe dose can be larger. After 3–5 days application, it should be reduced, the use time should not be too long, and 7–10 days is appropriate. The infusion rate should not be too fast, claiming that 250 mL will be lost within 30 min. Urine color, urine routine, plasma electrolyte, renal function, plasma osmotic pressure and fluid intake and output should be monitored during the application.
   (b) Glycerol: It can reduce brain edema, reduce intracranial pressure, and improve cerebral blood flow and neuroprotection. After glycerol injection, a part of glycerol is converted into glucose in the liver to provide a certain amount of heat, and the other part is excreted by the kidney. It promotes diuresis and is considered to be a better dehydrating agent. Clinically, glycerol fructose injection is commonly used. Glycerin has the functions of providing heat card, scavenging free radicals, and enhancing red blood cell deformability, and has protective effect on ischemic brain tissue. Fructose has the function of preventing dehydration of cell membrane and reducing hemolysis, so compatibility of glycerin with fructose can reduce the side effects of glycerol. Usually intravenous infusion of 250–500 mL, 1 time/12–

24 h, infusion time is 1–1.5 h. Use with caution in patients with severe circulatory system dysfunction, diabetes insipidus, and diabetes. In addition, when using glycerin fructose, it should be noted that the drug contains 0.9% sodium chloride, that is, 500 mL of glycerin fructose contains 4.5 g of sodium chloride, and the patient's salt intake should be paid attention to when taking the drug. Adverse reactions to glycerol preparations include hemolysis, hemoglobinuria, renal failure, and hyperosmolar coma. Due to the lack of evidence of long-term prognosis, routine application of glycerol to reduce intracranial pressure is not recommended.

(c) Hypertonic Saline (HS): The main component is sodium chloride, which has obvious effects of increasing plasma osmotic pressure and osmotic diuresis. Regarding the mechanism of action of HS to reduce intracranial pressure, foreign scholars believe that sodium ions cannot pass through the intact blood-brain barrier. After inputting HS, a continuous osmotic gradient is formed inside and outside the cell. This continuous osmotic gradient removes water from brain cells and interstitial cells. The gap moves toward the capillary network, thereby reducing brain water volume and reducing intracranial pressure. Animal experiments have confirmed that infusion of HS can increase plasma tension, promote the absorption of cerebrospinal fluid, and reduce the damage of inflammatory substances to the brain. In addition, HS can also improve regional cerebral blood flow, repair residual cell membranes, and restore intracellular sodium and potassium concentrations to normal. Therefore, in theory, HS should be a more effective osmotic dehydrating agent than mannitol. In recent years, domestic and foreign literatures have reported that hypertonic saline has a certain effect on the treatment of intracranial hypertension, especially for patients with refractory intracranial hypertension after traumatic brain injury, and 7.5% of physiological saline is more effective than 20% of mannitol [11, 12]. Chinese scholars reported that 3% hypertonic saline and 20% mannitol can rapidly reduce intracranial pressure [13], but 3% hypertonic saline lasts longer than 20% mannitol, and can effectively improve central venous pressure and mean arterial pressure. However, there is no uniform conclusion on the high sodium level that produces the best osmotic effect, and there is no evidence of large sample, randomized, double-blind, controlled clinical studies of hypertonic saline. Therefore, routine use is still not recommended clinically. HS can be considered for use in a life-threatening situation, such as patients with hemorrhagic shock and traumatic brain injury fails to respond to conventional treatment with fluid resuscitation or high cranial pressure, during neurosurgery, resuscitation maintenance fluid in the intensive care unit of neurology, etc. If liquid or the like is maintained, it can be considered for use. During neurosurgery, Resuscitation of hypotension in acute spinal cord injury, maintenance fluid in the intensive care unit of neurology, etc., may be considered.

2. Human albumin: Under normal physiological conditions, albumin accounts for 80% of plasma osmotic pressure. Application of human serum albumin can significantly increase plasma colloid osmotic pressure and transfer interstitial water

to blood vessels, thereby reducing brain edema and reducing intracranial pressure. It is especially suitable for intracranial hypertension and cerebral edema with insufficient blood volume and hypoproteinemia. Usually intravenous infusion of 10 g, 1 time/8–24 h; infusion rate does not exceed 2 mL/min; within the first 15 min, the infusion rate should be slower. Use with caution when acute heart disease, cardiac insufficiency, severe hypertension, severe anemia, or renal insufficiency.

3. Medullary diuretic: Mainly furosemide (furosemide), acting on the cell membrane of the medullary medulla of the medullary sac, inhibiting Na + and Cl- reabsorption, rapid diuresis, and plasma protein binding rate 91–97%, 5 min after intravenous administration, peak time is 0.33–1 h. The duration of action was 2 h, 88% was excreted by the kidneys in the original form, and 12% was excreted by the liver through the metabolism of the liver. Each intravenous injection of 20–40 mg, the minimum interval of repeated use is 1–1.5 h, usually 1/6–12 h, but diuretic effect is weakened after 7–10 d[6]. Intravenous injection should be diluted with sodium chloride injection, not glucose injection. The effect of furosemide diuresis is stronger than that of mannitol, but the dehydration effect is poor. Synergistic with a dehydrating agent. Especially for patients with intracranial hypertension with heart and kidney failure, diuretic should be used first to reduce blood volume, and then combined with dehydrating agent. The most common adverse reactions are water and electrolyte imbalances, such as hyponatremia, hypokalemia, hypomagnesemia, and hypovolemia.
4. Glucocorticoids: Mainly the use of glucocorticoids to stabilize membrane structure reduces lipid peroxidation induced by free radicals, thereby reducing cerebral vascular permeability, restoring vascular barrier function, and increasing blood flow in the injured area. And improve the function of Na^+-K^+-ATPase to improve brain edema. However, studies have confirmed that glucocorticoids are sensitive to vasogenic cerebral edema caused by brain tumors and brain abscesses, but not to cytotoxic cerebral edema or cerebral infarction, cerebral hemorrhage, or head trauma. Therefore, glucocorticoids should not be used as a routine treatment for increased intracranial pressure. Glucocorticoids are not recommended to improve prognosis or reduce ICP. For patients with severe head injury, high-dose methylprednisolone is contraindicated because it is associated with increased mortality.

10.1.8.5 Barbiturates

Barbiturates have the ability to contract cerebral blood vessels, reduce brain metabolic rate, inhibit cerebrospinal fluid secretion, reduce brain oxygen consumption and cerebral blood flow, and inhibit free radical-mediated lipid peroxidation. Large doses of barbital can reduce intracranial pressure. Clinical trials have confirmed that the input dose of pentobarbital is 5–20 mg/kg, and the maintenance dose is 1–4 mg/(kg h), which can improve the refractory intracranial pressure. The US and European stroke guidelines recommend high-dose barbiturates for the treatment of refractory high intracranial pressure, but patients with cardiovascular disease should not be used.

10.1.8.6 Ventilation Therapy

Hyperventilation reduces the partial pressure of carbon dioxide in the alveoli and blood, leading to hypocapnia, which reduces brain vasoconstriction and cerebral blood flow, thereby reducing brain volume and intracranial pressure. It is also believed that the negative pressure of increasing the breathing causes the central venous pressure to drop, and the cerebral venous blood is easily returned to the heart. Thus, the cerebral blood volume is reduced. However, when $PaCO_2$ is lower than 30 mmHg, it will cause cerebral vasospasm, leading to cerebral ischemia and hypoxia, and aggravating intracranial hypertension. 2016 US Guidelines for the Treatment of Severe Head Injury (Fourth Edition) does not recommend prolonged use of preventive hyperventilation (carbon dioxide partial pressure $\leq$ 25 mmHg). Hyperventilation is recommended as a temporary measure to reduce intracranial hypertension. Hyperventilation should be avoided when cerebral blood supply is significantly reduced within 24 h of injury [14].

In hyperventilation, it is recommended to measure jugular venous oxygen saturation or brain tissue oxygen partial pressure to monitor oxygen supply.

10.1.8.7 Mild Hypothermia Treatment

Animal experiments have confirmed that elevated temperature increases brain oxygen metabolism rate, cerebral blood flow, and intracranial pressure, especially ischemia and hypoxia. Generally, for every 1 °C reduction, brain oxygen consumption and blood flow decreased by 6.7%. There are data indicating that when the body temperature drops to 30 °C, the brain oxygen consumption is 50–55% of normal, and the cerebrospinal fluid pressure is decreased 56% than cooling down before [15]. Therefore, first, patients with elevated body temperature should be treated with cooling (using acetaminophen, cooling blanket, indomethacin, etc.). In recent years, with the development of modern intensive care technology, research on sub-hypothermia and intracranial pressure therapy has developed rapidly. Whether it is a general increase in intracranial pressure or an increase in refractory intracranial pressure, hypothermia treatment is effective, and systemic cooling is more effective than isolated head cooling. The depth of cooling depends on the condition of the disease. It is appropriate to use 32–34 °C. The temperature is too high to reduce the temperature. If it is too low, there is a risk of ventricular fibrillation. During the cooling process, chills, frostbite, and water and electrolyte imbalance should not be avoided. Generally, the physical cooling can be stopped after 3–5 days, so that the patient can naturally rewarn and gradually reduce the medication or even stop the drug. It has been promoted in countries such as Europe, the United States, and Japan [16]. However, in order to improve the prognosis of patients with diffuse severe head injury, prophylactic hypothermia is not recommended in the early (2.5 h) and short term (48 h after injury).

10.1.8.8 Reduce Cerebrospinal Fluid

To quickly reduce intracranial pressure and relieve the disease. It is also one of the commonly used auxiliary rescue measures before craniocerebral surgery.

1. External drainage of cerebrospinal fluid: An important measure to rescue patients with cerebral palsy. Continuous closed ventricular drainage can cause the cerebrospinal fluid to slowly flow out to control the intracranial pressure within the normal range, thereby avoiding sudden pressure drop and causing ventricular collapse, cerebellar palsy, cerebral congestion, increased cerebral edema, or dynamic balance of intracranial pressure. The disorder is also conducive to keeping the drainage smooth. Closed drainage helps prevent infection.
2. Cerebrospinal fluid shunt: Obstructive or traffic hydrocephalus caused by any cause, cannot remove the cause of cerebrospinal fluid shunt. According to different parts of the obstruction, the cerebrospinal fluid can be bypassed to the surface of the brain and then absorbed by the arachnoid granules to reduce the intracranial pressure. Or the cerebrospinal fluid is drained to the right atrium or abdominal cavity and absorbed. If the shunt is successful, the effect is quite positive. At present, the most common clinical use is lateral ventricle-peritoneal drainage.
3. Acetazolamide: A carbonic anhydrase inhibitor that reduces cerebrospinal fluid production by 50%, thereby reducing intracranial pressure. The usual dose is 0.25 g each time, 3 times a day.

10.1.8.9 Intracranial Space-Occupying Lesions

Intracranial space-occupying lesions such as tumors and brain abscesses should be surgically removed. If they cannot be removed, ventricular drainage or cranial incision can be considered to reduce the intracranial pressure.

10.1.8.10 Decompression of Large Bone Flap

Can make the brain tissue bulge in the direction of the decompression window to reduce the pressure of the brain structure by the intracranial hypertension, especially the brain stem and hypothalamus, to save the patient's life. This procedure has been shown to reduce ICP and shorten ICU hospital stays. In order to reduce the mortality of patients with severe head injury and improve the prognosis of neurological function, it is recommended to use large amount of dome decompression (not less than 12 × 15 cm or 15 cm in diameter) compared with small decapitation.

10.1.8.11 Prophylactic Antiepileptic Treatment

More and more clinical studies have shown that the use of preventive antiepileptic drugs will not reduce the incidence of epilepsy after craniocerebral injury, but also increase brain damage and cause serious side effects. Severe brain contusion and laceration in the brain after hematoma removal is still controversial, and there is no evidence of large-scale clinical research. Foreign scholars do not advocate preventive antiepileptic treatment [17]. However, if epileptic seizures occur in patients with craniocerebral injury, antiepileptic drugs should be used regularly.

10.1.8.12 Hyperbaric Oxygen Therapy

When the arterial carbon dioxide partial pressure is normal and the oxygen partial pressure is increased, the cerebral blood vessels can be contracted and the brain volume can be reduced, thereby achieving the purpose of reducing intracranial

pressure [18]. Oxygen inhalation at two atmospheres increases the partial pressure of arterial oxygen above 1000 mmHg, reducing the increased intracranial pressure by 30%. However, this treatment is only present when oxygen partial pressure is maintained. If the blood vessels are already paralyzed, hyperbaric oxygen will not work. It has been reported in the literature that due to the increase of oxygen pressure difference between alveolar and pulmonary veins after hyperbaric oxygen inhalation, the amount of blood oxygen diffusion can be increased by nearly 20 times, thereby greatly increasing the tissue oxygen content [19], and interrupting brain edema caused by cerebral ischemia and hypoxia. It can promote the awakening of patients with coma, reduce the number of hospital stays, can significantly improve the cognitive dysfunction of patients with brain injury, is conducive to the recovery of the body function, and has a good effect on saving lives and improving the quality of life.

10.1.8.13 Regulating Blood Pressure

The relationship between systemic arterial blood pressure and intracranial pressure and cerebral perfusion pressure should be considered when regulating blood pressure. In particular, the blood pressure management and treatment of the acute phase of brain stroke is still inconclusive. Due to the adequate blood supply to the brain tissue surrounding the lesion, it is essential to save the endangered brain cells in the ischemic penumbra. At this time, the CBF self-regulation mechanism is impaired, and CPP is heavily dependent on MAP, but high blood pressure can also cause damage to the blood-brain barrier and other related organ function damage. A large number of studies have shown that more than 75% of stroke patients have elevated blood pressure in the acute phase, especially those with a history of hypertension. Within 1 week after the onset of stroke, blood pressure has a tendency to decline on its own, and in some patients, blood pressure is significantly reduced within a few hours. Therefore, the acute period of stroke blood pressure should be taken a cautious attitude, rather than simply reduce blood pressure [20–22]. The 2018 version of the guidelines for the diagnosis and treatment of ischemic stroke in China and the recommended guidelines for the diagnosis and treatment of acute cerebral hemorrhage in China are as follows [23]:

1. Blood pressure management in patients with ischemic stroke

   Patients with elevated blood pressure within 24 h after ischemic stroke should be treated with caution. Should deal with nervous anxiety, pain, nausea and vomiting, and increased intracranial pressure. Blood pressure continues to rise to systolic blood pressure ≥ 200 mmHg or diastolic blood pressure ≥ 110 mmHg, or patients with severe cardiac insufficiency, aortic dissection, and hypertensive encephalopathy, can be treated with antihypertensive treatment, and closely observe blood pressure changes. Labelol and Nikadi equal intravenous drugs can be used. It is recommended to use a microinfusion pump to give antihypertensive drugs to avoid the use of drugs that cause a sharp drop in blood pressure. For thrombolysis and bridging intravascular thrombectomy, blood pressure should be controlled at systolic blood pressure < 180 mmHg and diastolic

blood pressure < 100 mmHg. Blood pressure management for patients who are scheduled to undergo intra-arterial therapy without intravenous thrombolysis can refer to this standard, control postoperative blood pressure levels according to vascular access, and avoid over-perfusion or hypoperfusion. The specific target needs further study. If the condition is stable after stroke, if the blood pressure continues to ≥140/90 mmHg, there is no contraindication. You can resume the use of antihypertensive drugs taken before the onset of the disease or start the antihypertensive treatment after several days of onset.

2. Blood pressure management in patients with cerebral hemorrhage

   Patients with cerebral hemorrhage often have a significant increase in blood pressure, and the increase usually exceeds that of patients with ischemic stroke, and is associated with increased risk of death, disability, hematoma enlargement, and neurological deterioration. Unlike ischemic stroke, cerebral hemorrhage emphasizes early enhancement of blood pressure. When systolic blood pressure is >220 mmHg in patients with acute cerebral hemorrhage, intravenous antihypertensive drugs should be actively used to lower blood pressure; when systolic blood pressure > 180 mmHg, intravenous blood pressure can be used to control blood pressure, and the blood pressure can be adjusted according to the patient's clinical performance. 160/90 mmHg can be used as a reference for the buck target value. For patients with cerebral hemorrhage with systolic blood pressure of 150–220 mmHg and no contraindications for acute antihypertensive therapy, it is safe to reduce systolic blood pressure to 140 mmHg in the acute phase and to effectively improve functional outcomes. Intravenous rapid antihypertensive drugs can be selected from urapidil, labetalol, esmolol hydrochloride, enalapril, and the like. During the antihypertensive treatment, changes in blood pressure levels should be closely observed, and blood pressure monitoring should be performed every 5–15 min. In order to prevent excessive hypotension and lead to insufficient cerebral perfusion pressure, the blood pressure can be reduced by 15–20% on the basis of hypertension at admission. This stepwise step-down method can be used for reference.

10.2 Autonomic Nervous Dysfunction and Hypertension

Yuanyuan He

10.2.1 Fatal Familial Insomnia

Fatal familial insomnia is a rare familial human prion disease. It is an autosomal dominant hereditary disease and one of the human transmissible spongiform encephalopathy which has attracted much attention in recent years. In 1986, Lugaresi et al. of the Medical College of Bologna University, Italy, first reported and described the first case of this disease in detail. Progressive sleep disorders and autonomic nervous disorders were the main manifestations. Autopsy confirmed that

a large number of thalamic neurons were lost, which was named fatal familial insomnia. With the development of gene monitoring technology and in-depth understanding of prion diseases, the number of sporadic cases and family reports of FFI is increasing worldwide. The prevalence of FFI is about one millionth of a year. As of 2004, 82 patients from 27 families were reported in the world [24]. According to incomplete statistics, China reported the first case of FFI in 2005. So far, only 2 cases of FFI patients have been reported in Chinese and 2 families have been reported in English. The total number of cases is not more than 10 [25, 26]. The mutations that cause disease found by FFI in about 50 families around the world are very rare [27]. FFI can show signs of hypertension due to autonomic nervous dysfunction, and can lead to abnormal circadian rhythm of blood pressure due to severe sleep disorders.

10.2.1.1 Etiology and Pathogenesis

Studies in recent decades have confirmed that PrP is the pathogen of FFI. In 1992, it was found that FFI was A mutation of the 532-bit base from G to A in the coding region of prion protein (PRNP) gene, leading to the mutation of the 178-bit amino acid from aspartic acid (Asp) to asparagine (Asn), namely D178N, and the 129th codon was methionine (Met) [28]. Causes PRNP gene product PrP_c. The structure is unstable and easy to be transformed into PrP_{SC}, start the chain reaction and the result is PrP_{SC}. In the central nervous system (CNS), especially the thalamus, there is a large amount of deposition, including neuron degeneration, vacuolation, and glial hyperplasia. A recent report in the journal rodriguez-martinez suggested that the prion gene D178N variant was associated with FFI, and identified 38 cases (27 families) in three European countries by seven single nucleotide polypeptides (SNPs). To study and put forward two FFI haploid genotypes, all case in Spain and Italy Tuscany family share a common haploid genotype, and nine patients with Germany and Italy Veneto area family own a second haploid genotype, The anastomosis test suggested that there might be differences between the Spanish FFI case and the Spanish control facility. Based on the above results, two independent original PRNP D178N mutations were inferred to be the cause of FFI cases in Europe.

Because the deposition of PrP^{SC} is more prominent in the thalamus, the increased blood pressure caused by the involvement of the autonomic nerve center is the possible mechanism of FFI causing hypertension. At the same time, severe sleep disturbance may lead to abnormal blood pressure circadian rhythm.

10.2.1.2 Pathological

The most characteristic change is *selective thalamic degeneration*, in which a large number of thalamic nerve cells are lost and glial cells proliferate, especially the thalamus dorsal kernel and anterior abdominal nucleus. In severe cases, the loss of nerve cells can reach more than 95%. In addition, there may be nerve cell loss and glial cell proliferation in the subbulbar olive nucleus. Sometimes, cerebral cortex and cerebellar neurons are lost, and cerebellar purkinje cells are slightly reduced. The cerebral cortex of FFI patients with sponge-like deformation has been reported. Other studies have found PrP in the temporal lobe, frontal lobe, and basal ganglia of the brain in addition to the thalamus^{sc}. The most deposition was in temporal lobe.

10.2.1.3 Clinical Manifestations

The age of onset of FFI and the natural course of disease have been reported in different literatures. Most scholars reported the age of onset at 36–62 years old, with an average age of 51 years old, and the effect on both males and females was the same. The course of the disease ranged from 8 to 72 months, with an average course of 18 months. Some scholars also reported that the age of onset ranged from 20 to 72 years old, with an average age of 49 years old. The average duration of the disease was 11 ± 4 months for the patients with short disease, and 23 ± 9 months for the elderly. Compared with heterozygous Met-Val, patients with homozygous Met-Met variants showed a shorter mean survival time. Domestic reports showed that the onset of FFI was relatively early and the course of the disease was short, indicating that FFI's onset age and course of the disease are variable, and the disease may occur from young to old. The duration of the illness, defined as starting with insomnia, is defined as the sudden death of some patients while fully awake, while others fall into a mechanical phase of life that can lead to death when respiratory or systemic infections occur. The main clinical manifestations are as follows:

1. Sleep disorder: Sleep disorder is the most prominent symptom of the disease and found earlier, difficulty in falling asleep, significantly reduced sleep time, more dreams, lack of sleep spindles, etc. were the main manifestation and insomnia increased with the development of the disease.
2. Autonomic nervous disorder: Autonomic nervous dysfunction is one of the early symptoms of FFI, including fever, hyperhidrosis, tachycardia, tearing, salivation, hypertension, irregular breathing, and even dyspnea. Men are more often accompanied by impotence. At present, the characteristics of FFI blood pressure have not been reported in foreign literatures. Two domestic patients with FFI have been reported with blood pressure levels of 130/100 mmHg and 148/87 mmHg, respectively, and their blood pressure circadian rhythm is abnormal due to severe sleep disorders.
3. Endocrine changes: Due to the disturbance of human cycle rhythm, endocrine hormone abnormalities can be accompanied, such as adrenal cortical hormone (ACTH) level decreased, cortisol and catecholamine levels increased, growth hormone, melatonin, prolactin secretion disorders. Women in Spanish families even have amenorrhea.
4. Dysarthria, up to slurred speech, dysphagia, choking on water, ataxia, myoclonus, dystonia, hyperreflexia, and Babinski sign. Diplopia occurs occasionally with abductor palsy. The terminal stage is silent, extremely thin and exhausted and even coma.
5. Cognitive impairment and psychobehavioral disorder: Often manifested as rapidly progressive dementia (RPD), may have hallucinations and delusions.
6. Recently, professor Yuping Wang of Xuanwu hospital in China together with many domestic experts and professor Serge Gauthier of Canada and other experts published expert consensus on FFI clinical diagnostic criteria, summarized its core clinical characteristics and divided them into three groups of symptoms. The symptoms of each group and their frequency of clinical occurrence are shown in Table 10.1 [29]:

Table 10.1 Clinical features of FFI patients

Symptoms	Very common	Rare	Common
Group A symptoms—sleep-related symptoms			
Insomnia			+
Sleep-related involuntary movement			+
Sleep-related dyspnea			+
Pharyngeal wheeze			+
Group B symptoms—neuropsychiatric symptoms			
RPD			+
Mental symptoms		+	
Ataxia		+	
Pyramidal tract symptoms		+	
Parkinson's disease	+		
Symptoms of group C—progressing sympathetic symptoms			
Hypertension		+	
Sweat		+	
Tachycardia	+		
Irregular breathing	+		

10.2.1.4 Laboratory and Auxiliary Examination

1. Blood routine examination: most were normal.
2. Electrocardiogram: common sinus tachycardia.
3. Electroencephalogram (EEG):

   Epileptic discharge, periodic sharp wave, and nonspecific slow wave can be observed. Periodic synchronous discharge is rarely found. Nonspecific slow waves increased significantly. The periodic spike complex (PSWC) can signal prion disease, but only in a small number of patients with inherited prion disease. Pathogenic variants with distinct spongiform degeneration and clinical manifestations similar to CJD are more likely to have positive electroencephalogram. FFI nonspecific patients show systemic slowdowns without periodic sharp wave complexes.
4. Polysomnogram (PSG):

   Two types of sleep disorders can be manifested. Both electroencephalograms show decreased spindles and K complex waves. In patients with a disease course shorter than 1 year, PSG monitoring showed that the normal sleep structure disappeared and was replaced by periodic rapid eye movement (REM) sleep without hypotonic muscle tone for less than 1 min. In patients with a longer course of the disease, it was found that total sleep time, including non-rapid eye movement (NREM) sleep and REM sleep, decreased and disappeared completely in the later stage of the disease. In NREM sleep, spindles decrease in progressiveness, delta theta increases, radical changes in the normal sleep cycle, rapid shifts in wakefulness and sleep, or abrupt shifts in delta theta. Drug-induced sleep activity was not produced in these patients. Polysomnography can also monitor respiratory disorders, which are characterized by abnormal breathing patterns during wakefulness or sleep, and alternate

between non-breathing and irregular breathing. The above phenomenon is caused by the loss of brainstem neurons, which is called Biot's breathing.

5. Single photon emission computed tomography (SPECT) scan: showed decreased glucose metabolism in the thalamus.
6. Positron emission tomography (PET) examination revealed hypometabolism in the thalamus, sometimes with extensive cortical (including cerebellar) hypometabolism. Studies have found that the metabolism of FFI patients in the thalamus and cingulate area before the onset is lower than normal, and there is a more significant decline after the onset, suggesting that PET is of great value in the detection of FFI before and after the onset.
7. Computed tomography (CT) and magnetic resonance imaging (MRI) have limited value in the diagnosis of FFI, but may help to exclude other neurological disorders. Because of glial hyperplasia, the presence of reduced thalamic diffusions on diffusion MRI is possible. As the disease progresses, atrophic changes may become apparent [27].
8. Abnormal endocrine hormone levels: Decreased ACTH levels, increased cortisol and catecholamine levels, abnormal 24 h rhythm of growth hormone, prolactin and melatonin.
9. Dynamic blood pressure: Increased blood pressure and abnormal circadian rhythm of blood pressure.
10. PrP gene test: Helpful for diagnosis.
11. Cerebrospinal fluid (CSF) study: The CSF study of markers such as 14-3-3 protein is nonspecific and can be seen in a variety of diseases that cause neuron death.

10.2.1.5 Diagnosis

Due to the diverse clinical features, heterogeneity, and low sensitivity of various diagnostic methods, especially the lack of positive family history and incomplete gene manifestation in some patients, the diagnosis is very difficult. Early and accurate diagnosis of the disease is crucial, not only to help patients and their families to carry out risk assessment, but also to provide a basis for potential diagnosis and treatment research.

According to the clinical characteristics, family history, and laboratory examination results of FFI patients, clinical diagnosis is divided into three possibilities: possible FFI, probable FFI, and diagnosed FFI. The diagnostic criteria are as follows [28]:

1. Possible FFI diagnostic criteria:
   Somatic sleep-related disorders (group A symptoms) +1 or 2 other core characteristics (group B/C symptoms):
   (a) Somator-related sleep disorders: Insomnia, loss of deep sleep, fragmented sleep, reduction or loss of REM sleep, laryngeal wheezing, sleep breathing disorders, and involuntary movements.
   (b) RPD: With or without ataxia, pyramidal tract signs or extrapyramidal symptoms/signs and mental symptoms.

(c) Progress of sympathetic symptoms: Hypertension, sweating, tachycardia, irregular breathing.

2. Probable FFI diagnostic criteria:

If one or more of the following suggestive characteristics are present, and two or more of the above core characteristics (symptoms in group A/B/C) are present, a probable FFI can be diagnosed.

These suggestive features include:

(a) positive family history of RPD and insomnia.
(b) somatic insomnia, sleep-related dyspnea, laryngeal wheezing, and involuntary movements confirmed by polysomnography.
(c) SPECT or PET imaging showed decreased thalamic glucose uptake.

3. FFI diagnostic criteria for diagnosis:

FFI can be diagnosed if the prion gene (RPNP) test is positive. RPNP gene test showed D178N gene mutation, accompanied by 129 codon methionine polymorphism.

10.2.1.6 Differential Diagnosis

For those with the above clinical manifestations but no family history, should be alert to the possibility of sporadic fatal insomnia. In addition, FFI should be differentiated from the following diseases: hepatolenticular degeneration, infectious dementia (corticostriatum-spinal degeneration, neurosyphilis, AIDS, etc.), encephalitis of various properties, and encephalopathy. In evaluating patients with FFI, it is important to consider other prion diseases due to overlap of symptoms.

10.2.1.7 Treatment

Treatment focuses on symptom relief and palliative care. It is important to block medications that may exacerbate memory disorders and/or insomnia. Patients with FFI respond poorly to sedatives. Patients with dysphagia may require nasal feeding tubes. Tinuper P [30] described the lack of effect of CMB or benzodiazepines in EEG in FFI patients. Reder AT [31] reported hydroxybutyric acid (GHB) was found to induce short-wave sleep (SWS) in FFI patients. Studies have also included several other therapeutic agents using compounds such as pentosan polysulfate, quinacrine, and amphotericin B, with uncertain results. A study from Italy using doxycycline as a treatment option lasted nearly 10 years. For the control of blood pressure, since there is no large-scale clinical research evidence for the type and dose selection of antihypertensive drugs at present, the author believes that the treatment of hypertension caused by other autonomic nervous dysfunction (e.g., Guillain–Barre syndrome) can be used for reference.

10.2.1.8 Prognosis

Fatal familial insomnia is a progressive disease, and all cases reported so far have been fatal. The prognosis is dire. The course of the disease lasted from 7 to 36 months, with an average duration of 18 months, and eventually death.

10.2.2 Guillain–Barre Syndrome and Hypertension

Guillain–Barre syndrome (GBS) is an immune-mediated acute inflammatory peripheral neuropathy. Clinical features of acute onset, symptoms peaked in 2 weeks or so, mainly for hair nerve root and peripheral nerve damage, there is often a cerebrospinal fluid protein-cell separation phenomenon, more than a single-phase self-limiting course, intravenous immunoglobulin (IVIg) and plasma exchange (PE) therapy is effective. The disease also includes Acute inflammatory demyelinating polyneuropathies(AIDP), Acute motor axonal neuropathy(AMAN), acute motor - chipmaker axonal neuropathy(AMSAN), Miller Fisher syndrome (MFS), Acute neuropathy (ASN) and other subtypes. Among them, AIDP and ASN often damage the autonomic nerve and cause many symptoms and signs of autonomic nerve dysfunction including blood pressure fluctuation. The incidence of GBS autonomic nerve injury was 65% in foreign reports, 54% in domestic reports by Qingcheng Yang, and 39.4% in reports by Hanbing Lu, which was slightly lower than that in foreign reports.

10.2.2.1 Epidemiology

The annual incidence of GBS is 0.6–1.9 per 100,000, slightly more for males, and higher for whites than blacks. Different regions have different incidence of GBS, and 90% of cases in Europe and North America are AIDP. On the contrary, AMAN is the most common type in China and Japan. In India, although AMAN is more common in young patients, the incidence of AIDP and AMAN is basically balanced. In the United States, the incidence of GBS occurs at the age of 16 to 25 and 45 to 65, and the development trend in Europe is similar. At present, there is no large-scale epidemiological data in China, but most of them are children and young adults. No obvious seasonal tendency in foreign countries reported, our country GBS disease seems to have a regional and seasonal trends, Yan Shen analyzed the long-term epidemiological trend of GBS patients in XinLe city from 1975 to 1995 and compared with the epidemiological trends of European and American studies. He found its epidemiological characteristics significantly different from Europe and the United States. It is characterized by significant fluctuations in long-term morbidity. There is a two epidemic peaks and an epidemic period. There were obvious seasonal and periodic cluster phenomenon in summer and autumn, which had the characteristics of high incidence among adolescents. Though rare, it has major implications for the health care system. Medical costs for GBS patients are estimated to be as high as $318,966. Overall, the cost of treating patients with GBS is estimated at $1.7 billion per year. Men were slightly more affected than women. Every year, an estimated 100,000 patients worldwide have GBS [32, 33].

10.2.2.2 Etiology

The etiology and pathogenesis of GBS have not been fully understood. It was previously believed to be related to viral infection, such as upper respiratory tract

infection and diarrhea. At present, it is believed that multiple causes can cause the disease. In the literature, Cytomegalovirus (CMV), Epstein–Barr Virus (EBV), Mycoplasma Pneumonia (MP), Hepatitis B Virus (HBV), and Campylobacter Jejuni (CJ) is the most fully studied infectious agent, but the serological evidence of CJ infection reported by different laboratories in different countries is far different (7–76%), but most of them are about 30%. In the pathogenesis of GBS, most scholars believe that cellular immunity plays a very important role in the pathogenesis of cytokines involved in cellular immunity, especially by macrophage activation of T cells and of plasma tumor necrosis factor alpha (TNF-α) and interleukin 2 (IL-2), is to cause inflammation and tissue damage induced by including selective damage of peripheral nerve myelin neurotransmitter. These inflammatory mediators and their activated inflammatory cells can directly exert cytotoxic effects on peripheral nerves and Schwann cells. Ganglioside (GS) is an important link in contact with the pathogenesis of GBS, At present, many studies around the world have suggested that the LPS of campylobacteriae jejuni has a molecularmimicry between the molecular structure and the GS epitopes of human peripheral nerves, which leads to the cross-reaction of the body to produce anti-ganglioside antibodies, which is the most common reason for the pathogenesis of GBS.

10.2.2.3 Pathogenesis

Pathogenesis of GBS autonomic nerve injury:

1. Sympathetic nerve function hyperfunction or decrease: Sympathetic ganglion damage can cause arrhythmia and peripheral circulation failure, and sympathetic nerve root damage and tachycardia and elevated blood pressure. Catecholamine and renin are increased in some patients with hypertension.
2. Parasympathetic hyperfunction or hypofunction: Parasympathetic damage is very common in GBS autonomic disorder, which can lead to unstable blood pressure, arrhythmia, gastrointestinal dysfunction, and sphincter dysfunction.
3. Brain stem autonomic nerve damage: Clinical manifestations of GBS autonomic nerve disorder are mostly episodic. This change is presumed to be caused by damage to the autonomic nerve center of the brain stem.

10.2.2.4 Pathological

Spinal nerve roots showed extensive segmenting demyelination and inflammatory cell infiltration, with relatively light axonal changes, only swelling and distortion. The anterior root of spinal nerve is more damaged and heavier than the posterior root, the proximal end of peripheral nerve is heavier, and the distal end is lighter. Early stage of the disease is mainly neuroedema, lymphocytes and macrophages form perivascular sheath, spinal nerve roots and peripheral nerves are also infiltrated and increased by monocytes, monocytes and macrophages destroy the basal membrane of Schwann cells, resulting in extensive segmental demyelination, occasionally involving the spinal cord. In the middle stage of the disease, prominent hyperplasia of endoneurofibroblasts is seen. Schwann cell proliferation is seen late in the disease. In some explosive cases, axonal injury, fracture, or even granulation

may occur in the acute phase due to a strong immune response, and a few cases have severe axonal degeneration in the recovery period (6–7 weeks). According to domestic and foreign literatures, pathological examination of GBS accompanied with autonomic nerve damage found that sympathetic and parasympathetic nervous system damage was extremely extensive in such patients. Lesions were found in the lateral columns, nerve roots, sympathetic ganglia, sympathetic chain and peripheral nerves. It is manifested as edema, inflammatory cell infiltration, chromolysis of spinal lateral horn cells, segmental demyelination, Waller degeneration, etc. Parasympathetic nerve injury includes edema, lymphocyte and plasma cell infiltration in vagus, glossopharyngeal nerve, parasympathetic ganglion and autonomic ganglion, edema and inflammatory cell infiltration in cardiovascular activity center of brain stem.

10.2.2.5 Clinical Manifestations

AIDP is the most common type of GBS, also known as classic GBS. The main lesions were polygenic nerve root and peripheral ganglion demyelinating. Often involve autonomic nerve, appear accordingly blood pressure change. Its main features are:

1. It can occur at any age and in any season. Symptoms of fever, diarrhea, and upper respiratory tract infection are common, including campylobacter jejuni, cytomegalovirus, mycoplasma pneumoniae, or other pathogen infections, vaccination, surgery, and organ transplantation. Acute onset, the condition reached a peak in about 2 weeks.
2. Flaccid limb muscle weakness is the core symptom of AIDP. Muscle weakness develops from lower limbs to upper limbs in most patients and gradually worsens within a few days. Muscle tension can be normal or reduced, tendon reflex reduced or disappeared, and often in the muscle strength is still good, tendon reflex has been significantly reduced or disappeared, abdominal wall reflex, cremasterism reflex more normal, no pathological reflex. Muscle atrophy gradually appeared after 2–3 weeks. Some patients may have varying degrees of cerebral nerve motor dysfunction, which may be treated as the first symptom; a very small number of patients have difficulty opening the mouth, inadequate tongue extension and weak strength, as well as eye paralysis. Serious cases can appear the weakness of neck and breath muscle, bring about breath difficulty, even dying for respiratory failure. Patients who seek treatment with sensory impairment as the first symptom may also be seen. They are mainly subjective sensory disorders, limb distal sensory disorders, lower limb pain or pain, dry nerve tenderness and tension pain. On objective physical examination, the patient may have significant muscle tenderness (especially in bilateral gastrocnemius muscles). Mittens, garters and/or hypoesthesia may occur in the trigeminal innervation area. Of course, there can be no sensory barriers. It is one of the characteristics of this disease that sensory disorder is much lighter than motor disorder.
3. The clinical manifestations of autonomic nerve damage mainly include two aspects:

(1) the manifestations of cardiovascular system, which are more common and severe, mainly manifested as tachycardia, bradycardia, acute arrhythmia, and nonspecific ECG changes; unstable blood pressure, hypertension, hypotension, or alternation of hypertension and hypotension, blood pressure fluctuation more than 50/20 mmHg throughout the day. (2) other aspects of abnormal sweating, sphincter dysfunction, facial flushing or pale, salivation, intestinal obstruction, hair loss, nail thinning, and other nutritional disorders. It has been reported in literature that patients with GBS and autonomic nerve damage have a high fatality rate. Therefore, most physicians recommend monitoring for arrhythmias or blood pressure instability in these patients in moderate or intensive care units. In addition, the involvement of the inferior cranial nerves (glossopharyngeal, vagus, and sublingual) or of the nerves to the respiratory muscles may result in the need for artificial ventilation. Respiratory failure can occur in up to 30% of patients, often resulting in prolonged hospitalization and recovery time [34]. About 3–14% of patients with persistent autonomic dysfunction die from acute cardiovascular dysfunction. Domestic literatures reported that GBS patients died of elevated blood pressure accompanied by respiratory failure.

10.2.2.6 Auxiliary Examination

1. Blood routine and ESR: The total number of white blood cells increased and ESR increased faster, more serious disease or pulmonary complications.
2. It can be manifested as sinus tachycardia, sinus bradycardia, atrioventricular block, premature beats and other arrhythmias.
3. Cerebrospinal fluid examination: (1) Most protein increased and the cell number is normal or close to normal protein-cell separation phenomenon, is one of the characteristics of GBS, The content of CSF protein in most patients is normal within a few days after onset, and CSF protein in 2~4 weeks will increase in different degrees, but less than 1.0 g/L; sugar and chloride are normal; the white blood cell count is generally less than 10×10^6/L. However, this pattern was present in 80% of patients only 2 weeks after symptom onset. Therefore, the absence of this classic finding does not preclude diagnosis. (2) Part of patients with cerebrospinal fluid oligoclonal zone. (3) Some patients had positive cerebrospinal fluid anti-ganglioside antibody. However, these laboratory studies often take some time to get results, so they may not be helpful in decision-making when patients are admitted. Elevated cerebrospinal fluid protein can increase the rate of cerebrospinal fluid production, damage the absorption capacity of arachnoid villi, increase the circulation speed and volume of cerebrospinal fluid, and abnormal local distribution of cerebrospinal fluid all affect the prognosis of GBS. The increase of cerebrospinal fluid protein may easily cause the adhesion of nerve roots and affect the repair and regeneration of myelin sheath. Therefore, the higher the content of cerebrospinal fluid protein in patients with GBS, the worse the prognosis.
4. Serological examination: (1) A small number of patients showed mild elevation of creatine kinase (CK) and mild abnormal liver function. Part of the patients'

serum anti-ganglioside antibody is positive. Some patients' serum can detect anti-campylobacter jejuni antibodies, anti-cytomegalovirus antibodies, etc.

5. Fecal examination: Campylobacter jejuni can be isolated and cultured in the feces of some patients.
6. Neuroelectrophysiology: Mainly based on the measurement of motor nerve conduction, it indicates the presence of demyelinating lesions in peripheral nerves, and the presence of conduction block or abnormal waveform dispersion in the non-impaction site is more valuable for the diagnosis of demyelinating lesions. The median, ulnar, tibial, and common peroneal nerves on one side are usually selected. Neuroelectrophysiological test results must be interpreted in conjunction with clinical practice. The degree of electrophysiological changes is related to the severity of the disease.

   Nerve electrophysiological diagnostic criteria: (1) Motor nerve conduction: At least two motor nerves have at least one of the following parameters in the abnormal: A. The distal incubation period is more than 25% longer than the normal value; B. Motor nerve conduction velocity is more than 20% slower than normal value; C. The incubation period of f wave is more than 20% longer than normal value and/or the occurrence rate is reduced; D. Partial conduction block of the motor nerve: The negative phase amplitude of compound muscle action potential (CMAP) decreased by more than 20% and time duration increased by <15% compared with the distal end of peripheral nerves. E. Abnormal waveform dispersion: Compared with the proximal and distal ends of peripheral nerves, the duration of CMAP negative phase wave widens by more than 15%. When the amplitude of CAMP negative phase wave is less than 20% of the lower limit of normal value, the reliability of detecting conduction block decreases. (2) Sensory nerve conduction: Generally normal, but abnormal cannot be excluded from the diagnosis. (3) Needle electrode EMG: If secondary axonal damage occurs, abnormal spontaneous potentials may occur on EMG between 10d and 2 weeks after onset. With nerve regeneration, the motor unit potential duration, high wave amplitude, multiphase wave increase, and motor unit loss occurred.
7. Neurobiopsy: No neurobiopsy is required to confirm the diagnosis. Sural nerve biopsy revealed demyelination of myelinated fibers, partial phagocytic infiltration, and inflammatory cell infiltration around small vessels. Segmentalized demyelination is seen in a dissected single fiber.
8. Magnetic Resonance Neurography (MRN): It can clearly display the lumbar plexus nerve and its major branches. Conventional MRI examination showed that 80% of GBS patients had varying degrees of enhancement of the cauda equina nerve, indicating the destruction of the blood-nerve barrier due to inflammation in GBS. Typical performance of GBS patients with cauda equina nerve enhancement is up to 95%. MRN uses magnetic resonance to perform thin layer high resolution scanning of peripheral nerves, add fat saturation, remove fat high signal, and display high signal neural structure in muscle low signal background. MRN examination of GBS patients can reveal spinal nerve root enhancement, but its sensitivity and specificity are questionable. The "frog" sign is the obvious acute inflammatory exudation of GBS, and the fusion of multiple branches of

nerves with the inflammatory lesions around the nerves and the common "frog" appearance of the spinal canal are the typical manifestations of GBS, but the occurrence rate is not high (23.8%), and its specificity needs to be further studied. However, MRI utility in GBS is most useful in excluding other causes of tetraplegia or facial biplegia, such as transverse myelopathy or intracranial disease.

10.2.2.7 Diagnosis and Differential Diagnosis

Diagnosis

1. Often have a history of prodrome infection, acute onset, progressive aggravation, more than 2 weeks up to the peak.
2. Symmetry limb and medulla oblong muscle innervation, facial muscle weakness, severe cases can have respiratory muscle weakness, limb tendon reflex decreased or disappeared.
3. Can be accompanied by mild sensory abnormalities and autonomic dysfunction.
4. Cerebrospinal fluid protein-cell separation phenomenon.
5. Electrophysiological examination suggests prolonged latency of distal motor nerve conduction, slow conduction speed, abnormal F wave, conduction block, abnormal waveform dispersion, etc.
6. The course of illness is self-limited.

The diagnosis of GBS is generally not supported if the following manifestations occur:

(1) Significant and persistent asymmetric limb muscle weakness. (2) Bladder and rectal dysfunction as the first symptom or persistent bladder and rectal dysfunction. (3) The number of cerebrospinal fluid mononuclear cells exceeds 50×10^6/L. (4) Cerebrospinal fluid lobulated nuclear leukocyte. (5) There is a clear sense of plane.

Differential diagnosis: It needs to be distinguished from myelopathy, periodic paralysis, multiple myositis, poliomyelitis, myasthenia gravis, acute rhabdomyolysis, diphtheria neuropathy, lyme disease, porphyria peripheral neuropathy, hysterical paralysis, and toxic peripheral neuropathy, such as heavy metal, drugs, botulinum toxin poisoning and other diseases.

10.2.2.8 Treatment

General Treatment

GBS is one of the most common acute diseases in the department of neurology. Acute respiratory failure, infection, arrhythmia, and autonomic nervous dysfunction caused by respiratory muscle paralysis are common risk factors for death. Therefore, critical patients should be admitted to the intensive care unit, received electrocardiogram monitoring, strengthen respiratory tract management, patients with dyspnea and bulbar innervation of muscle paralysis should pay attention to maintain the

airway patency, especially pay attention to strengthen sputum aspiration and prevent aspiration. For patients with rapid progress of the disease accompanied by respiratory muscle involvement, the disease should be closely observed. In case of obvious dyspnea, significant decrease in vital capacity (vital capacity decreased to less than 1 L), and significant decrease in blood oxygen partial pressure (oxygen partial pressure lower than 70 mmHg), tracheal intubation or tracheotomy should be performed as soon as possible with mechanical assisted ventilation. Patients with paralysis of the medulla oblongata innervating muscles or dysphagia and coughing over drinking water, need to give nasal feed nutrition, in order to assure daily enough quantity of heat, vitamin, prevent electrolyte disorder. Patients with gastrointestinal bleeding or gastroenteroplegia should be given intravenous nutrition support. Keep your bowels open. Patients with urinary retention may be indwelling a catheter to assist in urination. For patients with neuropathic pain, appropriate use of drugs to alleviate pain. In case of pulmonary infection, urinary tract infection, bedsore, and deep vein thrombosis of lower limbs, active treatment should be given to prevent aggravation of the disease. Depression due to difficulty in verbal communication and severe limb weakness should be given psychological treatment, if necessary, antidepressant treatment. Strengthen the nursing of the paralyzed limb to prevent contracture deformity of the affected limb; start rehabilitation as soon as possible.

Immunotherapy

1. Plasma exchange (PE): It is the first confirmed effective for GBS, and has become the reference for the efficacy evaluation of GBS treatment trials. The mechanism of PE is to remove the pathogenic antibodies, lymphoid factors, and inflammatory mediators in the plasma circulation of patients, so as to restore the function of lymphocytes, promote the balance of immunoglobulin, restore the function of phagocytes, and reduce the immune response and its damage. The 2010 guidelines for the diagnosis and treatment of Guillain–Barre syndrome (Guillain–Barre syndrome) in China recommended the early application of PE in patients with conditions [35].

   Side effects: Hepatitis after transfusion, transfusion reaction, electrolyte disturbance, local infection, anaphylaxis, blood pressure changes due to hemodynamic changes, arrhythmias, pneumothorax and hemorrhage due to central catheter use, and possible sepsis.

   There are the following cases with caution or disabled: (1) severe electrolyte disorder with arrhythmia; (2) bleeding; (3) hypotension (not recovered after fluid replacement); (4) recently had myocardial infarction or suspected of myocardial infarction; (5) serious infection, liver and kidney failure.
2. Intravenous immunoglobulin (intravenous immunoglobulin, IVIg): Immunoglobulin can reduce antibody activity, and combination in different areas of the IgG, to speed up the process of decomposition, finally to achieve the purpose of reduce pathogenic. Many studies have proved that IVIg is an effective method to treat GBS. Although IVIg is expensive, it is simpler and easier to operate than PE, does not require complex equipment, and is relatively safe, so it has been recommended as a first-line drug for patients with severe GBS. The

2010 guidelines for diagnosis and treatment of Guillain–Barre syndrome (Guillain–Barre syndrome) in China recommended the early application of IVIg for patients with conditions. Methods: Human blood immunoglobulin, 400 mg/(kg. d), once/d, intravenous infusion for 3 to 5 days.

Side effects: Mild headache, nausea, chills, fever, vomiting, myalgia, erythema, and transient abnormal liver function are common.

Contraindications: Congenital IgA deficiency, immunoglobulin allergy, or other severe allergic history. Use with caution or caution in patients with fever.

3. Glucocorticoid: The possible mechanism of glucocorticoid treatment of GBS: (1) strong inhibition of the human immune system; (2) on the membrane structure to promote the stability of the membrane; (3) reduce demyelinating degree, improve nerve conduction function to reduce inflammation and edema. However, there is still some controversy over the treatment of GBS with glucocorticoid at present. The results of a number of foreign clinical trials all showed that there was no clear efficacy in the treatment of GBS with glucocorticoid alone, and there was no significant difference between the combined treatment with glucocorticoid and IVIg and the treatment with IVIg alone. Therefore, foreign GBS guidelines do not recommend the application of glucocorticoid therapy for GBS. However, in China, due to economic or medical conditions, some patients cannot receive IVIg or PE treatment. At present, many hospitals are still using glucocorticoid to treat GBS, especially in early or severe patients. The efficacy of glucocorticoid in the treatment of GBS and different types of GBS remains to be further explored. You can try methylprednisolone 500 mg/day intravenously for 5–7 days, or dexamethasone 10 mg/day intravenously for 7–10 days as a course of treatment.

   PE and IVIg combined applications are generally not recommended. A small number of patients who showed no improvement or progress after 1 course of PE or IVIg treatment, or the recovery process again aggravated, can extend the treatment time or increase 1 course of treatment.
4. Immunosuppressive agents: There have been many reports on the treatment of GBS with immunosuppressive agents in recent years. In China, it has been reported that 106 cases of severe GBS were treated with cyclophosphamide, and good results were obtained, with a total effective rate of 90.6%. However, there is no evidence of large-scale clinical studies.
5. Cerebrospinal fluid filtration: Cerebrospinal fluid (CSF) filtration is an immunotherapy method. Some studies have found that CSF filtration can significantly shorten the length of hospital stay and reduce sequelae in patients with GBS, but evidence from large-scale clinical studies is also lacking.

Neuronutrition

The 2010 guidelines for the diagnosis and treatment of Guillain–Barre syndrome in China recommend that B vitamins should always be used, including vitamin B_1, Vitamin B_{12} (cyanocobalamin, mecobalamine), vitamin B_6, and so on.

Rehabilitation Treatment

In order to prevent disuse of muscular atrophy and joint contracture, normal nerve function rehabilitation exercise should be carried out in the early stage after the condition is stable.

Treatment of Autonomic Nerve Injury

There is no special treatment for autonomic nerve injury, mainly symptomatic treatment. For those with elevated blood pressure (mean arterial pressure close to 125 mmHg) and persistent, low dose receptor blockers and angiotensin-converting enzyme inhibitors may be considered; however, long-acting calcium antagonists should be used carefully, especially in patients with alternating hypertension and hypotension. Hypotension should maintain blood volume and avoid the use of diuretics. Arrhythmia can be selected according to the situation of antiarrhythmic drugs; bradycardia can be increased by atropine or Chinese medicine; tachycardia up to 100–120 beats/min is not treatable, and severe bradycardia or sinus arrest requires pacemaker therapy. Gastrointestinal motility disorder occurs in 15% of severe GBS patients. Nausea, vomiting, and dyspepsia can be treated with gastrointestinal motility drugs and digestive AIDS, such as metoclopramide and motilin.

10.2.2.9 Prognosis

The disease is self-limited and has a single-phase course, which generally reaches a peak around 2 weeks, and begins to recover after several days to several weeks, with a few patients experiencing fluctuations in the recovery process. A handful of patients will experience remission - recurrence. Seventy to seventy-five percent of patients recover completely, 25% are left with minor neurological deficits, and 5% die, often from complications such as respiratory failure, infection, and severe arrhythmias. The prognosis of patients with early evidence of campylobacter jejuni infection was poor, and the course of the disease was delayed and the recovery was incomplete. The prognosis of senile patients with acute onset or assisted ventilation is poor. It is believed that with the further research on GBS, the cure rate will be higher and higher.

10.2.3 Autonomic Epilepsy

Autonomic epilepsy is also known as diencephalic epilepsy, visceral epilepsy, and so on. The diencephalon is located above the midbrain, the caudate nucleus, and the medial side of the inner capsule, which can be divided into five parts, namely, the thalamus, the upper thalamus, the bottom thalamus, the posterior thalamus, and the lower thalamus, the latter being the autonomic nerve center. Diencephalic epilepsy refers to the paroxysmal symptoms caused by the lesion in this area. In fact, the lesion does not involve the entire diencephalon. But this name has been used for a long time, it is still used clinically. In 1925, HeKo reported the first case of

diencephalic epilepsy, and in 1929 Penfield proposed the concept of diencephalic epilepsy. This is a kind of periodic paroxysmal autonomic nervous dysfunction syndrome caused by hypothalamic lesions of different causes. Like other autonomic neuropathy, this kind of epilepsy can cause paroxysmal increase of blood pressure, and its clinical manifestations are complex and diverse, lacking specificity and easy to be misdiagnosed.

10.2.3.1 Epidemiology

Clinically, it is common in children and extremely low in adults. It has been reported in the literature that the incidence of diencephalic epilepsy accounts for about 3.6% of epilepsy patients.

10.2.3.2 Etiology and Pathogenesis

There is no consensus on the pathogenesis of autonomic epilepsy. Some scholars believe that this type of epilepsy originated directly or indirectly from the structure of cortical or subcortical autonomic nerve network, including limbic system and subcortical connective fiber hypothalamus, midbrain periaqueductal gray, pons, and medulla autonomic nucleus [36]. Xinde Wang et al. believed that diencephalic epilepsy was related to basal frontal gyrus or insula. Most scholars, such as Xianli Zhu, believe that diencephalic epilepsy may be related to hypothalamus invasion. Hypothalamus is the superior autonomic nerve center under cortex, which is closely related to cerebral cortex, midbrain central gray matter, reticular structure and autonomic nerve center of spinal cord, and mainly regulates sympathetic and parasympathetic activities to maintain the balance of internal environment. Hypothalamus rich capillary network, but the blood-brain barrier structure is not sound, capillary permeability is high in other parts of the brain, to ischemia, trauma, infection, poisoning, and increased intracranial pressure were more sensitive, easy to produce the lesions such as edema, inflammation and hemorrhage, these all can become diencephalon epilepsy pathology foundation, can cause seizures. Hypothalamic lesions, however, can lead to autonomic nerve dysfunction, which can eventually lead to secondary hypertension [37].

In addition, autonomic seizures can also be caused by lesions in the higher centers of the autonomic nerve, such as the insular gyrus, cingulate gyrus, and amygdala. Only a few patients with primary diencephalic epilepsy have a family history, and the common secondary causes include various kinds of encephalitis, brain tumors, parasites, craniocerebral trauma, cerebrovascular diseases, poisoning, degeneration, metabolic disorders, and high fever.

10.2.3.3 Classification and Clinical Manifestations

Autonomic epilepsy is a partial seizure in the international classification of epilepsy. According to its attack symptoms can be divided into abdominal epilepsy, headache epilepsy, limb pain epilepsy, and vertigo epilepsy. According to whether the most prominent symptoms of autonomic attacks are accompanied by non-autonomic symptoms, they can be divided into simple type and mixed type. People with diencephalic epilepsy may have one or more of the following symptoms, with seizures

occurring several times a day or once a few days. The order that the symptom appears when same patient erupts every time and accompanying symptom are basic and consistent, namely Stereotyped - like. Most patients experience fatigue, drowsiness, deep sleep, or drowsiness after the onset. There were no symptoms during the intermission. One of the causes of sudden epileptic death is autonomic seizures and status epilepticus, which are characterized by cardiac and circulatory symptoms [38].

1. Simplex: presenting only as paroxysmal autonomic symptoms.
   (a) Vascular dyskinesia: The main manifestations are skin and mucous membrane vascular motor dysfunction, the skin is significantly pale or flushed with blood, but also can turn from pale to congestion, accompanied by local fever, especially obvious head and neck skin, the skin congestion is diffuse redness, can also be massive or large patches of erythema. Another typical manifestation of pallor is located in the trigone region of the nose and mouth. The rest of the face is significantly reddened with distinct boundaries. The conjunctiva and mucous membranes of the eyes may also be congested.
   (b) Abnormal exocrine gland secretion: Local or systemic sweating, excessive or reduced saliva secretion, abnormal exocrine gland secretion, tears, salivation, etc.
   (c) Visceral dysfunction: Visceral dysfunction of viscera function disorder, such as palpitations, chest tightness, heart rate and rhythm changes, changes of arterial blood pressure, visceral dysfunction, breathing too fast, hyperventilation, apnea and onset asthma and respiratory function disorder, suppress stomach rising gas, nausea, vomiting, diarrhea or digestive system symptoms such as abdominal pain, and urine, urinary incontinence, compulsive during urination or bowel movements, etc.
   (d) Thermoregulation disorder: Most of them are manifested as increased body temperature, some of them are accompanied by chills, a small number of them are accompanied by hypothermia and thermoregulation disorder.
   (e) Eating disorder: Manifested as gluttony, polydipsia, and polydipsia, a small number of appetite loss.
   (f) Sleep disorders: Symptoms include paroxysmal drowsiness, yawning, lethargy, and a few cases of continuous wakefulness and sleep disorders.
2. Mixed type: In addition to paroxysmal autonomic nerve manifestations, this type may be accompanied by mild disturbance of consciousness, paroxysmal muscle weakness, localized tonic spasm and paroxysmal paresthesia.

   Elevated blood pressure may occur during the seizure of diencephalic epilepsy. Domestic literatures reported that the blood pressure during the seizure of diencephalic epilepsy can reach 150–200/90–120 mmHg, but the duration of increased blood pressure is short, and the blood pressure during the seizure is more likely to return to normal. A case of autonomic epilepsy in adults with episodic hypertension caused by thalamic hemorrhage has been reported in China [39].

   Autonomic epilepsy is generally believed to be symptomatic in adult patients, especially in elderly patients; most pathological lesions of epilepsy can be found

by imaging examination. The most important auxiliary examination of diencephalic epilepsy is electroencephalogram. In general, epileptic discharge may occur during the onset, but also paroxysmal fast wave or slow wave, diffuse fast wave or slow wave, 14 weeks and 6 weeks/second positive phase spike. It has been reported in the literature that the EEG during a diencephalic seizure shows bilateral synchronous resynchronization rhythm, with a frequency of 4–7 times/second, and the frequency of 6–7 times/second accounts for the majority, suggesting that there is dysfunction in the deep middle line, supporting the diencephalopathy. But there are also patients with normal EEGs. EEG is of great value for the diagnosis of epilepsy, but it is not the only means of diagnosis. There are 20% of patients with epilepsy who do not have epileptiform discharge in the routine EEG during the intermittent seizures, and the probability of finding epileptic electrical activity in a single EEG record is generally less than 50%. Diencephalic epileptic lesions are located deep in the brain, and electroencephalogram (EEG) is not easy to detect epileptic electrical activity. Therefore, normal EEG cannot exclude epilepsy. If the disease is highly suspected clinically, it should be repeatedly examined and recorded by deep electrode. If possible, dynamic EEG or video EEG monitoring can be carried out to improve diagnosis rate and avoid missed diagnosis.

10.2.3.4 Diagnosis and Differential Diagnosis

Clinical diagnosis is based on clinical symptoms and EEG examination, as well as the effective diagnosis of antiepileptic drug therapy.

Diagnostic basis: (1) Repeated attacks of autonomic nerve symptoms, each attack has relatively inflexible, after the attack can be as usual activities, no residual symptoms, some cases can be accompanied by hazy consciousness or a sex consciousness loss, after the attack can have narcolepsy. (2) EEG can appear spike wave and other epileptic discharge. (3) Some patients may appear hypothalamus or third ventricle bottom lesions. (4) Antiepileptic therapy is effective. (5) It can have a family history of epilepsy.

Diencephalic epilepsy should be differentiated from pheochromocytoma: Blood catecholamine, adrenalin levels and electroencephalogram (EEG) examination at the time of seizure can help distinguish this disease from pheochromocytoma.

10.2.3.5 Treatment

The goal of diencephalic epilepsy therapy is to rapidly control the symptoms of sympathetic hyperactivity, reduce secondary damage, and promote patient recovery. Autonomic nerve sex epileptic attack duration is not long, can stop by oneself more, general antiepileptic medicaments is treated effectively. Generally, no intervention is needed for hypertension accompanied by the onset. If the blood pressure remains high, central antihypertensive drugs (e.g., clonidine) can be used. Long-term use of antihypertensive drugs is generally not required.

10.3 Spinal Cord Injury and Hypertension

Tilakezi Tuersun

Orthostatic hypotension is a common clinical complication. It can be secondary to spinal cord disease, heart failure, endocrine disorders, or after using antihypertensive drugs. In patients with spinal cord injury above the T6 level, the incidence of orthostatic hypotension is high. Statistics show that orthostatic hypotension affects 75% of patients with spinal cord injury and seriously hinders the progression of rehabilitation [40]. The treatment of orthostatic hypotension after spinal cord injury is an important part of the rehabilitation of spinal cord injury. At present, the cause of orthostatic hypotension after spinal cord injury is not clear, there is no uniform standard for diagnosis and measurement, and there is no specific method for treatment.

10.3.1 Pathogenesis

1. Neurogenic factors: Mainly because the spinal cord injury can lead to the interruption of the normal sympathetic outflow pathway. Studies have shown that spinal cord injury can cause the interruption of the conduction pathway between the vascular motor center and the sympathetic preganglionic neurons, resulting in a normal central nervous system short-term blood pressure regulation mechanism [41].
2. Angiogenic factors: Mainly caused by blood stasis in the lower limbs when standing. It has been reported that in patients with spinal cord injury, functional electrical stimulation induces a decrease in muscle contractility, which aggravates blood pressure regulation after spinal cord injury [42]. The possible mechanism is that in patients with spinal cord injury, due to paralysis of the lower extremities, the blood vessels of the lower limbs lose the squeezing effect of the skeletal muscles, causing the blood to accumulate in the lower limbs and reduce the amount of blood returning.
3. Cardiogenic factor: Mainly due to long-term bed rest caused by low heart work. In patients with spinal cord injury who have been bedridden for a long time, the pressure exerted by the heart contraction on the blood does not need to resist the hydrostatic pressure caused by the gravity of the earth. The heart is in a lower working state for a long time, resulting in a continuous decrease in the contractile force of the heart; when the patient re-stands, the symptoms of hypotension occur.
4. Body fluid factor: Mainly related to the reduction of blood pressure hormone levels. In patients with high-segment spinal cord injury, plasma catecholamine levels, especially plasma norepinephrine, are found to be low at rest [43]. In addition, a synthetase dopamine hydroxylase that can synthesize norepinephrine

at the nerve endings is also at a normal lower limit in patients with cervical spinal cord injury. These can affect the regulation of norepinephrine on blood pressure when the body position changes [44].

5. Recent studies have shown that a strong vasodilator, nitric oxide (NO), may be responsible for orthostatic hypotension [45]. NO is produced by endothelial nitric oxide synthase (iNOS) for some stimuli such as shear stress, bradykinin, acetylcholine, etc. [40]. In the study of rodent responses to microgravity, it was found that the expression of iNOS in the aorta, heart, and kidney increased, resulting in NO-related hypotension [46–48].

10.3.2 Clinical Manifestation

The clinical manifestations of orthostatic hypotension after spinal cord injury can be divided into symptomatic and asymptomatic. Symptomatic type is mainly caused by insufficient blood supply to the brain due to decreased blood flow in the middle cerebral artery [49]. Therefore, the common manifestations are mainly symptoms of cerebral ischemia, such as dizziness, blurred vision, headache, neck or head (occipital) discomfort, nausea, muscle weakness, etc. [50]. It is worth noting that some patients can be characterized by atypical symptoms such as weakness, fatigue, and cognitive delay. Asymptomatic type means that although the blood pressure has decreased, but there is no shortage of blood supply to the brain, there is no corresponding symptom.

10.3.3 Diagnostic Criteria

There are currently two diagnostic criteria:

1. Traditional diagnostic criteria were developed by the American Society of Neurology/American Academy of Neurology: A reduction in systolic blood pressure of at least 20 mmHg (1 mmHg = 0.133 kPa) within 3 min of standing, or a decrease in diastolic blood pressure of at least 10 mmHg, or 60° in the upright tilt test, a reduction in systolic blood pressure of at least 20 mmHg within 3 min, or a decrease in diastolic blood pressure of at least 10 mmHg [51].
2. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) was proposed by the American Society of Hypertension Education Program Coordinating Committee on July 7th, 2003. Oral hypotension criteria: Systolic blood pressure drops $\geq$10 mmHg in standing position, and those with symptoms of dizziness or weakness. According to the diagnostic criteria of JNC-7, patients whose blood pressure drops have not reached the traditional standard but have clinical symptoms have been covered.

10.3.4 Treatment

Since the mechanism of postural hypotension is not completely clear, there are no specific treatments, although there are many types of treatment. The current treatment of orthostatic hypotension is primarily aimed at improving the patient's functional status, rather than simply stressing the rise of blood pressure to a specific standard [52].

1. Non-drug treatment: Mainly use of non-pharmacological treatment in the clinical. At present, the commonly used treatment methods are slant bed standing training, abdominal belt and elastic stockings, bath therapy, manual therapy, etc. [53].
2. Medical treatment: When non-drug therapy does not alleviate the symptoms of orthostatic hypotension, medication should be added [54, 55]. The principle is also to improve symptoms.
   (a) Fluorohydrocortisone is a mineralocorticoid that causes sodium water to be stored and expands the amount of blood vessels. Studies have shown that it may improve blood pressure by increasing the sensitivity of alpha-adrenergic receptors. Its side effects include hypokalemia and edema. It is more commonly used and more effective than rice medorate, is an α1-receptor agonist, by activating the α-adrenergic receptors of the arterial and venous vasculature, causing blood vessels to contract, thereby raising blood pressure.
   (b) Methotrexate inhibits the activity of monoamine oxidase and increases the activity of norepinephrine, thereby increasing blood pressure.
   (c) Clonidine is an alpha2-adrenoreceptor agonist with central hypotensive action that can be used to improve orthostatic hypotension in some patients with spinal cord injury.
   (d) Indomethacin can increase blood pressure in patients with orthostatic hypotension by increasing the reflexive contraction of blood vessels. It may increase blood pressure by inhibiting the synthesis of prostaglandins.

10.3.5 Prevention

Prevention is particularly important because of the high incidence of orthostatic hypotension in high spinal cord injury and the lack of specific treatments. Prevention of orthostatic hypotension after spinal cord injury is recommended to do the following [56]:

1. During bed rest, attention should be paid to the passive activities of the limbs, and the seat training should be started as early as possible while ensuring the stability of the fracture site.
2. Before getting out of bed, it is best to perform active and passive activities on both lower limbs in the bed to improve blood circulation.

3. Properly arrange the time of standing training. Many patients have higher blood pressure in the morning, so the training can be arranged at noon or afternoon.
4. Spinal cord injury patients can gently raise the bedside when sleeping, so that the renin-angiotensin system can be partially activated.

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Mental Illness and Hypertension

11

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It is well known that the rise and fluctuation of blood pressure are closely related to mood and psychology. In addition to physical factors, psychosocial factors play an important role in the pathogenesis of hypertension. Long-term depression, insomnia, stress, anxiety, or sharp and intense trauma are also important causes of hypertension as research suggested. To pay full attention to the relationship between hypertension and mental health status and to identify and give effective psychological, social, and drug intervention in mental and psychological disorders and hypertension caused by it at an early stage is helpful to further improve the level of prevention and treatment of hypertension. It is of great significance to improve the prognosis.

11.1 Definition and Classification of Mental Disorders

In China, the current criteria for Classification of Mental Disorders and Mental Disorders are the tenth edition of the International Classification system for Diseases—ICD-10 and the fifth edition of the diagnosis and Statistics of Mental Disorders in the United States—DSM-V. Mental disorder is a kind of diagnostic mental problems characterized by cognitive emotional and behavioral changes which can be accompanied by painful experience or functional impairment and even increase the risk of death and disability of the patient. Psychological disorder refers to the abnormal behavior of a person's psychological process and abnormal

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personality characteristics caused by physiological, psychological, or social reasons. Depression is a common mood disorder characterized by depression, mental retardation, hypoactivity, and somatic symptoms. Anxiety disorder is a neurosis characterized mainly by anxiety, characterized by widespread and persistent anxiety or recurrent panic attacks, often accompanied by autonomic nervous disorders, muscle tension, and motor anxiety. There are two main forms: generalized anxiety disorder and panic disorder (PD). Insomnia is a disorder of sleep initiation and sleep maintenance that results in sleep quality not meeting individual needs. Posttraumatic stress disorder (PTST), due to unusually threatening, catastrophic psychological trauma, leads to delayed or long-lasting mental disorders.

11.2 The Relationship Between Psycho-psychological Disorders and Hypertension

The relationship between psychology and cardiovascular diseases is complicated, including the influence of psycho-psychological factors on cardiovascular system and the influence of cardiovascular system changes on psycho-psychological state. There are several biological ways to explain the link between psycho-psychological factors and the incidence and prognosis of cardiovascular diseases: first, psycho-psychological disorders can lead to unhealthy lifestyles such as smoking, unhealthy diets, and reduced physical activity. This leads to the development of major cardiovascular risk factors (such as obesity, hypertension, hyperglycemia, and hyperlipidemia). Second, psycho-psychological disorders can cause a series of pathophysiological changes, including autonomic nervous dysfunction, hormone imbalance, metabolic abnormalities, inflammation, insulin resistance, and endothelial dysfunction, which increase the risk of cardiovascular disease. Third, mental disorders such as depression, anxiety, treatment compliance is poor, leading to cardiovascular disease progression. In a word, mental disorders are closely related to hypertension. Mental disorders are a contributing factor to hypertension, and hypertension aggravates mental illness and psychological disorders.

Psycho-psychological disorder can cause disturbance of function of vegetative nervous system and function of hypothalamus-pituitary-adrenaline axis. Severity can even cause sudden death or cerebrovascular accident. Prolonged tension and anxiety increase vascular tone, and increased vascular resistance leads to increased blood pressure. Meanwhile, long-term sympathetic nerve excitation causes the continuous contraction of glomerular arteries and the formation of hypertension. The results showed that tension, depression, anger and hostility were closely related to lymphocyte β-adrenoceptor density, and β-adrenoceptor density was negatively correlated with anxiety and depression. When anxiety and depression increased, the density of β-adrenoceptor decreased significantly, which showed that heart rate increased and blood pressure increased [1]. In the early years, through anti-anxiety treatment on anxiety-induced hypertension rats, the French scholars returned to normal blood pressure, which provided a direct basis for secondary hypertension in patients with mental disorders [2]. On the other hand, the prevalence of anxiety and depression in patients

with hypertension is also high. It is speculated that the reason for emotional disorder caused by hypertension may be: firstly, because hypertension is basically a life-long disease, with the prolongation of the time of illness, some patients were too worried and nervous about their own condition, the psychological burden was aggravated, and the degree of anxiety and depression or the degree of original anxiety and depression was aggravated. Second, hypertension patients are often accompanied by bad life patterns, such as smoking, drinking, etc., these bad habits are an unhealthy psychological and mental performance. In short, psychological factors and hypertension affect each other, cause and affect each other, forming a vicious circle.

11.3 The Pathological Mechanism of Hypertension Caused by Psycho-mental Disorders

Early studies on the etiology of hypertension, which is, whether in normal blood pressure or hypertension, the body's neural and humoral mechanisms are involved in the regulation of blood pressure. And this regulation mechanism is extremely complex. The traditional theory of pathogenesis of hypertension is mentioned as follows: psychogenic theory, neurogenic theory, endocrine theory, kidney source theory, excessive sodium intake theory, etc. Among them, the psychogenic theory thinks that internal and external adverse factors stimulate, when patients have long-term or repeated obvious emotional changes such as stress, anxiety, irritability, etc., the cerebral cortex excites, suppresses the imbalance, and cannot normally exercise the function of regulating and controlling the central activity under the cortex, and the sympathetic nerve activity is enhanced. The central outflow of vasoconstriction is dominated by the impulse of vasoconstriction, which leads to the contraction of the small arteries, the rise of the resistance of the peripheral vessels, and the rise of blood pressure. The theory of spiritual origin emphasizes that the nervous system plays an important role in the regulation of blood pressure.

According to the neurogenic theory, the center of the medulla oblongata vasculature has pressure zone, decompression zone and sensory zone. The medullary vascular center main management the vascular center regulation with the involvement of the pons, the hypothalamus and the more advanced central nucleus. It can lead to high blood pressure. It can lead to high blood pressure such as all levels of central issued vasoconstrictor impulse increase or the increase of the vasoconstrictor signal from various receptors or the resistance vessels overreact to neuromediators. Long-term hypertension can make vascular smooth muscle proliferation, hypertrophy, vascular wall thickening and vascular cavity smaller, induce the electrical activity of blood vessel cell membrane, strengthens the vasoconstriction response, sympathetic nerve action on renal proximal bulb cells, Which lead to increases renin release to maintain high blood pressure. The theory of neurogenesis holds that peripheral arterioles are the target organs of the reflex arc of autonomic nervous system regulating blood pressure.

The mechanism of hypertension related to psycho-psychological factors is mainly focused on the theory of psychogenic and neurogenic sources. The mechanism of psychological stress leading to hypertension mainly involves sympathetic

adrenomedullary system (SAM) excitation, hypothalamic-pituitary-adrenal cortex (HPA) axis, renin-angiotensin-aldosterone system (RAS) activation, as well as the activation of genetic susceptibility and other aspects, and the activation of genetic susceptibility. It has been found that stress hypertension is closely related to the increase of norepinephrine (NE). NE is a monoamine neurotransmitter that regulates the sympathetic nervous system. Fifty percent of the NE neurons in the central nervous system are located in the locus coeruleus, and 90% of the neurons in the locus coeruleus are noradrenergic neurons whose fibers project to the cerebral cortex and limbic system. NE can function alert system in the locus coeruleus. In stress state, locus coeruleus receives external stimulation, produces excessive excitation, causes stress response, activates locus coeruleus-norepinephrine-sympathetic nervous system, and increases the release of norepinephrine. Increased sympathetic activity leads to increased blood pressure, anxiety and fear responses, causing alertness. In turn, animal experiments confirmed this process by electrical stimulation of the locus coeruleus nucleus. This suggests that the increased activity of NE in the central nervous system may be an important pathological mechanism of anxiety disorder. Previous studies have shown that NE function is significantly enhanced in anxiety patients, especially in panic disorder. It is inferred that the incidence of hypertension is closely related to NE. In addition, this theory has been found in the cerebrospinal fluid, blood, and urine of anxiety patients, and the role of norepinephrine in anxiety has been confirmed by drug trials.

A large number of studies have confirmed that the hypothalamic-pituitary-adrenocortical (HPA) axis plays an important role in the integration of stress behavior, autonomic, and endocrine responses. The hypothalamus receives visceral sensory impulses from the brainstem and spinal cord, and when individuals are exposed to chronic psychological stress, the activity of HPA axis increases, leading to an increase in the secretion of adrenocortical hormones. Glucocorticoid is one of the major stress hormones. The mechanism of glucocorticoid increasing hypertension includes many aspects. Glucocorticoid can increase the activity of phenylethanolamine N2 methyl transferase (PNMT) and inhibit the activity of catecholamine oxymethyltransferase (COMT). The concentration of epinephrine in plasma was increased. Glucocorticoid can also affect the expression of adrenaline α receptor, enhance the effect of catecholamines, and reverse regulate the secretion of corticotropin releasing hormone (CRH) through the effect on the central nervous system. It also inhibited the synthesis of prostaglandin, bradykinin and 5-HT, histamine, which in turn caused vasoconstriction. The increase of glucocorticoid secretion can also promote renal tubule reabsorption, increase blood volume, and thus raise hypertension. With the development of stress, the sympathetic-adrenal medulla system was excited, the whole-body blood was redistributed, the renal blood flow was reduced, the RAS system was activated, the level of angiotensin II in plasma was significantly increased, and finally hypertension was raised.

The study of psycho-psychological disease and cardiovascular disease, especially hypertension, has been reported more in type A behavior and stressful life events. The concept of type A behavior pattern was first proposed by Fridman in 1958. Many years of research have confirmed the relationship between behavioral

characteristics and cardiovascular disease. Patients with essential hypertension were more than two times more likely to have type A behavior than non-A type. Behavior characteristics directly affect people's response to changes in the environment. People in type of A behavior is characterized by a sense of urgency, extreme competitiveness, irritability, and hostility,who often deal with work and life in a highly stressful state of mind. Often deal with work and life with a high degree of stress. At the same time, it is easy to show tension, irritability, and obvious emotional changes, resulting in the neuroendocrine system often in a high wake-up state, sympathetic-adrenal system tension increase, and lead to an increase in blood pressure. Intense sex events, as a ***stimulating effect***, can cause blood pressure to rise in patients. Especially, the stress caused by stressful life events and anxiety state can increase the risk of hypertension. Under the stress state, the stress emotional experience of continuous tension and anxiety may be an important psychological factor that leads to the ***induced effect*** of blood pressure increase. When psychological stress reached a certain extent, the function of neuroendocrine system and autonomic nervous system were obviously changed, which promoted the activation of adrenal medulla, cortex, and RAS, and secreted catecholamine transmitters. The secretion of glucocorticoid and angiotensin is increased. These substances can cause vasospasm, sodium retention, and elevated blood pressure.

11.4 Anxiety Neurosis and Hypertension

Shaohong Zou

Anxiety neurosis (AN) is a neurosis characterized by anxiety that is clinically divided into two main forms: generalized anxiety disorder (GAD) and panic disorder (PD). It is characterized by extensive and persistent anxiety or recurrent panic disorder that is often accompanied by autonomic nervous disorder, muscle tension, and motor disturbance. Studies have shown that anxiety neurosis is not only one of the provocative and aggravating factors of hypertension, but also a common type of secondary hypertension. Hypertension caused by anxiety is mainly manifested as paroxysmal or continuous increase of blood pressure, accompanied by psychological and emotional abnormalities, poor effect of conventional antihypertensive drug treatment (therefore, it is often diagnosed as intractable hypertension), while the blood pressure of placebo treatment and sedation and anti-anxiety treatment is significantly decreased. At the same time, there was no evidence of organic disease in the examination.

The etiology and pathophysiological mechanism of anxiety disorder are complicated as current studies mainly focus on psychosocial factors, genetic factors, neurobiochemical, neuroendocrine, and immune mechanisms. It is generally believed that anxiety neurosis is mainly related to hyperfunction of 5-hydroxytryptamine (5-HT) and adrenergic (NE) system, deficiency of gamma-aminobutyric acid (GABA) function (neurotransmitter hypothesis), and abnormal activity of hypothalamus-pituitary-adrenal (HPA) axis and hypothalamus-pituitary-gonad (HPG) axis (neuroendocrine dysfunction hypothesis). Personality characteristics,

defense mechanism, social support, and life events also play an extremely important role in the onset of anxiety neurosis.

The mechanism of hypertension caused by anxiety neurosis is related to many factors. First, anxiety neurosis increases sympathetic tension. Heart rate variability (HRV) analysis of patients with anxiety neurosis and healthy volunteers showed that the average heart rate of patients with anxiety disorder was higher than that of normal control group. It was confirmed that the autonomic nervous function of patients with anxiety disorder decreased, mainly the vagal nerve tension decreased, while the sympathetic nerve activity was relatively hyperactive [3]. It has been proved that the stability of arterial blood pressure mainly depends on the role of some central nuclei. In the loop of blood pressure changes caused by emotion and stress, the central amygdala is the center, and its final pathway controls sympathetic nervous tension through the ventrolateral pressor area of the medulla oblongata [4]. Further studies have found that the secretion of adrenaline increases relatively in fear and anxiety, resulting in an increase in cardiac output and a marked increase in systolic blood pressure; when anger and hostility occur, the concentration of noradrenaline in the blood increases, resulting in an increase in peripheral vascular resistance and a marked increase in diastolic blood pressure. If hostility is forced to block, the levels of noradrenaline and adrenaline in the blood are significantly increased. It causes not only cardiac output increased, but also peripheral blood vessels contracted, blood pressure increased [5]. Secondly, increased sympathetic tension activates the hypothalamus-pituitary-adrenal/gonadal axis and promotes a series of hormone secretion (including RAAS system) [6]. In the study of the relationship between white coat hypertension and anxiety, researchers found that tension caused increased serum cortisol secretion, which significantly increased blood pressure in white coat hypertension. In addition, patients with anxiety often have sleep disorders, manifested as difficulty in falling asleep, easy to wake up, insomnia, early awakening, causing sleep structural disorders and increasing the number of micro-awakening, At last, leading to elevated blood pressure [7].

Generally, short-term anxiety often leads to paroxysmal elevation of blood pressure or deterioration of the original hypertension. Once psychosocial or emotional stimulation is relieved, the physiological changes affecting blood pressure will quickly and automatically return to normal. But if psychosocial stress or emotional stress is strong and lasting, it will destroy the regulation mechanism of blood pressure such as nerve, body fluid, and endocrine, and lead to repeated fluctuations of blood pressure for months or even years, eventually forming persistent hypertension [8].

Generalized anxiety disorder, also known as chronic anxiety disorder, is the most common manifestation of anxiety disorder. Often slow onset, with frequent or persistent anxiety as the main clinical phase. Its clinical manifestations include: (1) mental anxiety, which is the core of anxiety symptoms. It manifests itself in the constant fear of some dangerous or unforeseen event that may happen in the future. Patients often have a sense of panic. They are distracted, worried, and restless all day and seem to be in danger. (2) Physical anxiety, manifested as restlessness of movement (such as inability to sit still, walking constantly) and a variety of physical symptoms (such as headache, muscle soreness, diarrhea, etc.). (3) Increased arousal is manifested by excessive vigilance, sensitivity to external stimuli, difficulty in

concentrating, difficulty in falling asleep, irritability of emotions, sensory allergies, etc. (4) Other symptoms. Panic disorder is also known as acute anxiety disorder. It is characterized by unpredictability and sudden onset, strong reaction, patients often experience fear and fear of a catastrophic outcome, and termination is also rapid. During the attack, the consciousness is clear and highly alert. After the attack, there are still palpitations and fear of recurrence.

11.4.1 The Feature of Blood Pressure in Anxiety Disorder

Most anxiety patients are accompanied by elevated blood pressure, which is usually mild to moderate, and fluctuates greatly, which is closely related to patients' mental state. Especially in panic disorder attack, blood pressure sharply increased, systolic and diastolic blood pressure are increased, pulse pressure increased, and even can have water pulse, arterial gunshot sound, capillary pulse, and other high dynamic circulation state; accompanied by chest tightness, tachycardia, headache, and sweating, it is easy to be misdiagnosed as pheochromocytoma. Previous studies have found by using ambulatory blood pressure monitoring that the average blood pressure of hypertension patients with anxiety during the day and at night is higher than that of the control group, and the blood pressure varies greatly.

11.4.2 Therapy

Psychotherapy, pharmacotherapy, and physiotherapy can be used to treat anxiety neurosis.

1. Psychotherapy: Understand the causes of anxiety disorders, and use various methods, such as psychological counseling, relaxation training, biofeedback therapy, to transfer or relieve mental stress.
2. Drug therapy: Medication can be given for those with severe anxiety, including benzodiazepines (BZ), selective serotonin reuptake inhibitor (SSRI), norepinephrine and serotonin reuptake inhibitor (SNRI) and tricyclic antidepressants.
3. Physical therapy: Including biofeedback therapy, high potential therapy, transcranial magnetic stimulation therapy, brain wave therapy, brain reflex therapy, etc.
4. Hypertension treatment: The effect of conventional antihypertensive drugs on hypertension caused by anxiety disorder is poor. Physicians should recognize the psychological factors of patients when they encounter patients with poor compliance to a variety of antihypertensive drugs. Antianxiety therapy can cooperate with beta-blockers, such as metoprolol tablets have a better effect on alleviating somatic symptoms such as palpitation, tachycardia, tremor, hyperhidrosis and shortness of breath caused by hyperautonomic nervous function in patients with anxiety disorder. However, caution to the possibility that beta-blockers may affect patients' sleep and aggravate their condition. It is better to choose highly selective beta-blockers as far as possible and drugs that do not penetrate the blood–brain barrier may be better.

In conclusion, the prevalence of anxiety neurosis is high, especially in general hospitals and cardiovascular symptoms dominate anxiety neurosis. Previous studies have shown that the detection rate of anxiety neurosis can reach 30% in patients with hypertension, and about 5–12% of them are secondary hypertension caused by anxiety neurosis. These figures suggest that it is a difficult task to differentiate between anxiety neurosis and hypertension. In clinical practice, special attention should be paid to identifying the relationship between hypertension and anxiety, and to the use of psychotherapy and anti-anxiety drugs. It will be conducive to the control of blood pressure and the improvement of physical diseases.

11.5 Depression and Hypertension

Shaohong Zou

Depression is a common mood disorder that mainly shows low mood, slow thought, decrease of the willing activity, and somatic symptoms. Depression is closely related to many diseases. Patients who have depression are susceptible to cardiovascular diseases, especially hypertension, which is a special symptom in some patients.

Until now, the cause of depression is not so clear. Many studies at domestic and overseas have found that depression is closely related to many diseases, especially cardiovascular diseases. Epidemiological investigation confirms that there is a close relationship between hypertension and depression. Foreign researchers have found that the incidence of depression in hypertension is 20–30% [9]. Domestic studies such as Wei-Tiemin showed that the prevalence of depression was 15.8% in patients with hypertension, the course of disease was more than 3 years. Severe hypertension, and those who had a history of hospitalization had a higher depression score. Depression is not only an important factor in the occurrence and development of hypertension, but also affects the outcome, prognosis, and medicinal efficacy of hypertension. Zhang-Yucong et al. found that the incidence of depressive symptoms was 3.0% in the urban and rural elderly in Beijing, 2.9% with isolated systolic hypertension, 16.9% with systolic blood pressure (>160 mmHg), and 18.4% with diastolic blood pressure (>90 mmHg). The data of each group showed a significant increase, which verified that the significant correlation between hypertension and depression in the elderly. It also reminds that the existence of depressive symptoms in elderly hypertensive patients can't be ignored [10, 11].

11.5.1 Pathological Mechanism of Hypertension Induced by Depression

The relationship between depression and blood pressure may be related to the function of autonomic nervous system. Studies have confirmed that enhanced sympathetic nerve activity plays an important role in the pathogenesis of essential hypertension, and norepinephrine as a marker of sympathetic nervous tension is

significantly increased in patients with essential hypertension. Other studies have indicated that sympathetic nerve activity increased in patients with essential hypertension by measuring the blood circulation of skeletal muscle with microelectrodes. Current studies have also found that the levels of norepinephrine in plasma and its main metabolite, MHPG, are significantly increased in patients with depression, indicating that there are abnormal autonomic nervous function in patients with depression, manifested by increased activity of sympathetic nervous system and decreased vagal nerve tension. Studies have shown that the heart rate variability of depressive patients is reduced, which also reflects the existence of depressive patients with increased sympathetic nerve activity and/or decreased vagal nervous system activity. At present, most researchers believe that the mechanism of depression causing the hypertension may be related to the decrease of vagal nerve tension, the enhancement of sympathetic nerve activity, and hypothalamic dysfunction. However, some studies have not found the relation between depression and blood pressure. Cross-sectional data from a large study in Dutch on depression and anxiety show that depression is associated with lower blood pressure and using of the antidepressant increases the risk of hypertension [12].

Prospective studies have shown that depression is an independent risk factor for hypertension. The incidence of hypertension in patients with depression increases, and depressive mood is associated with high blood pressure. In order to assess the relationship between depression and hypertension, the American Health and Nutrition Examination Survey conducted a long-term follow-up of 2992 patients with normal blood pressure for 7–16 years. It was found that patients with high depressive symptoms score had a doubled risk of hypertension [13]. Similarly, the incidence of depression in patients with hypertension is also increasing. Once patients have hypertension, they often have various psychological reactions, which can easily cause panic, anxiety, or anger and other negative emotions, resulting in different degrees of depression.

The clinical manifestations of depressive episode are emotional depression (mainly manifested as significant and persistent emotional depression, depression, and pessimism), slow thinking (patients with slow thinking association speed, slow reaction), decreased volitional activity (patients with significant and lasting inhibition of will activity), and physical symptom (basically have morpheus obstacle, anorexia, weight to drop, sexual desire drops, the ache of any place in the body, lack of power to wait).

11.5.2 The Blood Pressure Characteristic of Depressed Patient

It can be found that some patients with depression have elevated blood pressure, which is mainly manifested as mild to moderate elevated blood pressure. In addition, patients with elevated blood pressure at night are more common. Dynamic blood pressure studies have shown that depression can affect blood pressure circadian rhythms, and that depression is associated with increased systolic and diastolic blood pressure and decreased day/night blood pressure ratios. The results may be

related to abnormal autonomic nervous function and hormone regulation. Lu-Lingchun et al. showed that the average blood pressure in the day and night of the primary hypertension complicated with anxiety group and the depression group was higher than that of the control group, and the increase in blood pressure at night was more obvious, and the circadian rhythm curve was more common in the non-arytenoid type. Blood pressure of depressed patients taking sleeping pills was tested, and it was found that the blood pressure level at night decreased significantly and the ratio of day/night blood pressure increased. However, there was no significant difference in blood pressure rhythm between depressed patients with normal blood pressure who did not take sleeping pills and the control group.

11.5.3 Treatment

Treatment for depression includes antidepressants, ECT, and modified ECT, physical therapy, and psychotherapy. Clinically, it mainly relies on antidepressants, which can effectively relieve depressive mood and accompanying anxiety, tension, and somatic symptoms, with an effective rate of about 60–80%. Although antidepressant maintenance may prevent the recurrence of depression to some extent, it cannot prevent the onset of mania and may even promote the onset of mania. When the onset of mania occurs with the use of antidepressants, bipolar disorder should be treated.

Commonly used antidepressants are selective 5HT reuptake inhibitors (SSRIs), norepinephrine (NE), and 5HT dual uptake inhibitors (SNRIs), NE and specific 5HT potent antidepressants (NaSSAs), tricyclic and tetracyclic antidepressants, monoamine oxidase inhibitors (MAOI), and other antidepressants. For patients with severe negative suicidal behaviors or depressive stupor, ECT should be the first choice. For patients with depression with obvious psychosocial factors, drug therapy is often combined with psychological therapy.

The five most widely used classes of antihypertensive drugs, with the exception of beta-adrenergic receptor blockers, are all safe for use in depression-induced hypertension. In addition, it should be noted that adverse reactions of some antidepressants, such as norepinephrine and serotonin double uptake inhibitor venlafaxine, can increase blood pressure, and should be used with caution if there is no specific indication or signs of high blood pressure have been observed [14].

11.6 Insomnia and Hypertension

Shaohong Zou

Insomnia refers to the disorder of sleep initiation and sleep maintenance, which results in the inability of sleep quality to meet individual needs. The main performance is difficult to fall asleep, sleep is not deep, easy to wake up and early wake up, after waking up to fall asleep is difficult, and performance is lack of sleep sense. Clinical observation shows that many hypertensive patients have sleep disorder, and

the fluctuation of blood pressure is related to sleep condition. On the other hand, the quality of sleep seriously affects the antihypertensive effect in patients with essential hypertension. If the sleep condition of patients with hypertension is improved, the patient's blood pressure has a significant drop phenomenon, and the target blood pressure compliance rate is also significantly increased. High blood pressure can cause insomnia, and time can raise blood pressure. They interact.

It is estimated that about one-third of adults suffer from insomnia, and between 10% and 15% of individuals present with daytime impairment. About 10–20% of individuals in primary health care settings complained significant insomnia symptoms, among which female complained insomnia more commonly than male, with a ratio of 1.44:1 [15]. The prevalence of chronic insomnia was found to be between 45% and 75% during the 1–7 years follow-up survey. Epidemiological studies confirm that 80–90% of insomnia patients are associated with other conditions, including high blood pressure. Compared with patients with normal blood pressure, the prevalence of insomnia in patients with hypertension is higher (40–60%) [16–19]. And some scholars reported that the prevalence of insomnia in women with hypertension is higher than that in men. According to the results of a 5-year follow-up survey in the city of Helsinki, the use of antihypertensive drugs increased by 57% among the population with ***frequent insomnia*** [20]. According to a data analysis conducted by Lewis et al. from 1998 to 2013, long-term insomnia can increase the risk of hypertension by 2 times [21]. Among 132 patients with chronic hypertension admitted to a hospital in Nigeria, the prevalence of insomnia was 42.4%, while that in the control group was only 17.3% [17]. The incidence of hypertension (40.1%) was significantly higher among middle-aged men with persistent difficulty in falling asleep than among those without difficulty in falling asleep (30.6%) [22]. In addition, the incidence of hypertension (42.3%) in patients with persistent sleep maintenance difficulties was significantly higher than that in patients without sleep maintenance difficulties (30.7%) [23].

11.6.1 Pathological Mechanism of Insomnia Leading to Hypertension

Three scenarios are currently considered possible. According to the psychogenictheory, due to long-term sleep disorders, recurrent mental tension, anxiety, irritability, agitation, fear and other emotional are changes. Then it can make cerebral cortex excited, restrain balance to be out of balance. Then the activity of subcortical center normally out of control and the sympathetic activity increased. And this can lead to an increase in blood pressure. The mechanism by which sleep disorders affect blood pressure is unclear. Three scenarios are currently considered possible. First, according to the psychogenictheory, due to long-term sleep disorders,recurrent mental tension, anxiety, irritability, agitation, fear and other emotional are changes. Then it can make cerebral cortex excited, restrain balance to be out of balance. Then the activity of subcortical center normally out of control and the sympathetic activity increased. And this can lead to an increase in blood pressure. Second, neurogenic theory: the nervous system

plays an important role in the regulation of blood pressure. The motor center of the medulla oblongata has the areas of compression, decompression, and sensation. Long-term insomnia may make the vascular central regulatory dysfunction, so that all levels of central distribution of vasoconstriction impulse increased or all kinds of receptor afferent vasoconstriction signal enhancement or resistance of blood vessels to the nerve medium reaction may lead to high blood pressure. The third is the maladjustment of humoral regulation: the secretion of aldosterone has the law of day and night. It is secreted more in the morning or in the awake state and less in the sleep state. Long-term insomnia makes the body in a state of wakefulness and tension, which will increase the secretion of aldosterone, cause water and sodium retention, and lead to increased blood pressure. At the same time, increased aldosterone secretion may cause increased angiotensin II secretion, resulting in vascular contraction and hypertension [24].

To treat insomnia, we should not rely solely on sedative and hypnotic drugs, but need the joint efforts of doctors and patients, close cooperation, eliminate the causes, correctly understand insomnia, and adhere to the implementation of the treatment plan. In order to improve the antihypertensive effect, improve the quality of life, patients with essential hypertension should learn self-adjusting, maintain a good mood, relieve emotional tension, avoid excessive attention to the change of blood pressure, change the bad lifestyle, control weight, quit smoking and drinking, control weight, quit smoking and drinking, Do muscle relaxation and deep breathing relaxation exercises every day, and exercise as appropriate. In order to improve the antihypertensive effect, improve the quality of life, patients with essential hypertension should learn self-regulation, maintain a good mood, relieve emotional tension, avoid paying too much attention to the change of blood pressure, change the bad lifestyle, control weight, quit smoking and drinking, every day to do muscle relaxation and deep breathing relaxation training, appropriate physical exercise.

11.7 Posttraumatic Stress Disorder and Hypertension

Shaohong Zou

PTSD is a delayed and/or prolonged response to unusually threatening or catastrophic stress events or situations that can cause diffuse distress in almost everyone (e.g., wars, natural and man-made disasters, etc.). Chronic activation of the sympathetic nervous system associated with posttraumatic stress disorder leads to changes in the structure and function of the heart, resulting in increased basal heart rate and elevated blood pressure. Patients are often accompanied by symptoms such as irritability, cold sweat, and shivering during the attack.

The sudden rise in sympathetic tension and excessive secretion of catechuamines will lead to repeated activation of platelets and release of a variety of pro-coagulant substances, as well as the release of TXA2 with strong vasoconstriction, triggering coronary spasm, causing angina, acute myocardial infarction, malignant arrhythmia, and even sudden death in the face of major psychological stress. The degree of psychological stress was negatively correlated with the density of lymphocyte

beta-adrenal receptors. When tension and fear increase, then the beta-max decreases significantly. This is manifested by increased blood pressure and increased heart rate. The mechanism of PTSD leading to hypertension is mainly related to the effect of stress on the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. It has also been confirmed that the activation of the renin-angiotensin-aldosterone system and the upregulation of angiotensin II level are also involved in the occurrence of hypertension [25, 26].

Typical symptoms of PTSD include a persistent background of *numbness* and emotional dullness, repeated reenactations of trauma in intrusive doubt (*flashbacks*) or dreams, alienation from others, in responsiveness to the environment, anhedonia, and avoidance of activities and environments that are associated with trauma. There is often a state of vegetative hyperactivity, characterized by hypervigilance, increased startle response, and insomnia. Anxiety and depression often coexist with the above symptoms and signs. Suicidal thoughts are not uncommon. Another complicating factor is excessive drinking and drug use. In the early stage of posttraumatic stress disorder, psychological treatment mainly adopts the principles and techniques of crisis intervention, focusing on providing support to help patients improve their psychological stress skills. Drug therapy is a common choice for the treatment of posttraumatic stress disorder in all stages. According to the characteristics of the patient's symptoms, the selected drugs includes: antidepressants, anti-anxiety agents, anticonvulsant drugs, lithium, etc. Antipsychotic drugs are generally not recommended unless the patient is excessively excited or violent.

In short, psychosomatic disorders generally exist in the cardiovascular department and neurology department of general hospitals. The incidence rate of depression and anxiety is as high as 20–25%, but the diagnosis and treatment situation are not optimistic. The diagnosis rate and treatment rate are very low. In fact, when cardiovascular disease and psychosomatic disorder occur at the same time, cardiologists often tend to only diagnose and treat organic cardiovascular disease and neglect the treatment of psychosomatic disorder, and only when both are treated at the same time, the clinical efficacy can be improved. Existing studies show that anxiety, depression, and other emotional disorders are closely related to hypertension, and patients with hypertension, anxiety, and depression should be paid attention to early detection, early treatment, add anti-anxiety/anti-depression drugs at the same time for psychological adjustment, eliminate psychological disorders and promote rehabilitation. Attention should also be paid to the negative effects of anti-anxiety/anti-depression on blood pressure, especially on drug-induced hypertension, so as to improve the prognosis of patients to the greatest extent.

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Cardiovascular Diseases and Hypertension

12

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Secondary hypertension caused by cardiovascular disease are mainly congenital heart disease (arterial patent ductus arteriosus, aortic sinus rupture, main pulmonary artery window), acquired heart disease (aortic regurgitation), vascular disease (aorta constriction, arteriovenous fistula, left renal vein compression syndrome), arrhythmia (complete atrioventricular block), cardiomyopathy, and end-stage heart disease. Its pathogenesis is related to its structural changes during embryonic development. There are specific signs in clinical manifestations. It can be confirmed by echocardiography, enhanced CT, MRI, and cardiac catheterization. Secondary hypertension caused by cardiovascular disease can be treated with conventional antihypertensive drugs according to the level of blood pressure. However, patients generally show poor antihypertensive effects. Considering the prognosis of patients is related to the treatment of their primary diseases, it is recommended that patients be actively treated for primary disease once they are diagnosed, so as not to delay the disease. In this chapter, we will describe the epidemiology, etiology and mechanism, pathophysiology, clinical manifestations, auxiliary examinations, diagnosis and differential diagnosis, treatment and prognosis of secondary hypertension caused by the above cardiovascular diseases.

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12.1 Aortic Constriction

Zhitao Yan

Coarctation of the aorta (COA) refers to aortic stenosis or obstruction leading to aortic blood flow disorder, which is a common manifestation of congenital cardiovascular disease, accounting for 7–10% [1], can occur alone. However, it is often associated with other congenital disorders, often associated with patent ductus arteriosus, ventricular septal defect, aortic valve malformation, mitral stenosis, atrioventricular septal defect. The disease is a relatively common congenital heart disease. The incidence rate is high in Western countries. It is reported to account for 14% of congenital heart disease. The incidence rate in the eastern countries is relatively low. It is more common in men. The ratio of male to female is 3~5.1:1 [2].

Aortic coarctation refers to the presence of hemodynamically significant stenosis in the descending thoracic aorta, which is one of the spectrum of left ventricular outflow tract obstruction. Most are thought to be related to abnormal distribution of fetal aortic blood flow. During embryonic development, any cardiovascular malformation that reduces blood flow to the aortic isthmus is prone to aortic coarctation. In 1903, Bonett divided the aortic coarctation into a pre-catheter type (infant type) and a post-catheter type or a proximal type (adult type), but the currently widely accepted typing method is to divide the present malformation into simple aortic coarctation. There are three types of aortic coarctation combined with aortic dysplasia and aortic coarctation combined with aortic arch dysplasia [3, 4].

The pathophysiological changes of aortic coarctation are mainly the increase of blood pressure in the proximal and proximal stenosis, which increases the left ventricular afterload, and causes left ventricular hypertrophy and strain, which leads to congestive heart failure. When the cerebral blood vessels are in high blood pressure for a long time, arteriosclerosis occurs, constriction of blood flow in the distal vascular vessels is reduced, and pathological changes are caused by different degrees of narrowing. In the pre-catheter type, the arterial catheter is open, and the narrowing range is wide. It can involve the aortic arch. The collateral vessels are not rich, and often combined with other intracardiac malformations. This type of symptoms is more common in neonates and infants. Most of the catheters in the posterior or proximal catheter type have closed, the narrowing range is limited, the collateral vessels are abundant, and there are few intracardiac malformations, which are more common in older children or adults. In severe cases, blood supply to the lower body and kidneys may decrease, resulting in hypoxia, oliguria, and acidosis. Some infants and young children's blood flow in the lower limbs depends partly on the supply of pulmonary arteries, so the oxygen saturation of the lower extremity blood may be lower than that of the upper limbs [3, 5, 6].

The clinical manifestations of aortic coarctation depend on the degree of narrowing of the lesion in the constricted segment, whether other cardiac vascular malformations are combined, and different age groups. Clinical symptoms are classified as symptomatic and asymptomatic aortic coarctation. Symptomatic aortic coarctation

is more common in infants, often with congestive heart failure. About half of the cases begin to show shortness of breath, heart rate, sweating, difficulty feeding, hepatomegaly, heart in the arterial catheter closure within the first month after birth. Systolic vascular murmur can be heard in the chest, back and the waist, there may be pulsation, tremor or murmur of the collateral vessels [5].

Correspondingly, asymptomatic aortic coarctation often lacks typical clinical manifestations. Upper body hypertension is found only during physical examination, femoral artery pulsation is weakened or disappeared. In a few cases, due to the decrease of blood supply to the lower part of the body, cold limbs may be cold. Walking is weak, or even intermittent. Physical examination showed normal growth and development, strong iliac artery pulsation, weakened or disappeared femoral artery pulsation, lower limb arterial pulsation delayed than upper limb artery, upper limb blood pressure was significantly higher than lower limb. Its blood pressure characteristics are mainly characterized by systolic hypertension in the right upper extremity, and upper limb blood pressure is higher than lower limbs [5].

Echocardiography is an effective means of diagnosing aortic coarctation. It can directly see the location, extent, morphology, and other cardiovascular malformations. Usually, most aortic coarctation can be correctly diagnosed. Color Doppler can detect high-speed blood flow through the narrowed part, which can be used to calculate pulmonary artery pressure, which is the basic means for noninvasive diagnosis of this disease. Echocardiography of the sternal fossa can better show the aortic arch, but it is not good for the distal end of the descending aorta and is easily missed. Cardiovascular angiography is the main method for the diagnosis of aortic coarctation. It can clearly show the location, extent, collateral circulation of the aorta and the presence or absence of arterial catheter opening, but it is an invasive examination method. Intravenous digital subtraction angiography is similar to conventional angiography in the visualization of aortic images. Combined with two-dimensional echocardiography and color Doppler examination, it can be used as an effective method to diagnose this disease. Magnetic resonance is a highly effective method for diagnosing aortic coarctation. Magnetic resonance is a noninvasive method that is widely used for preoperative diagnosis and postoperative follow-up of aortic coarctation. Dual-source and multi-slice spiral CT can be used as a first-line examination method for aortic constriction imaging. It can predict the prognosis while clarifying the diagnosis of aortic coarctation, and provide valuable information for clinicians to develop reasonable treatment plans. ECG can be expressed as left and right atrioventricular hypertrophy and myocardial strain. X-ray can indicate a severe increase in the heart and pulmonary congestion. In the elderly, the upper mediastinum can be widened, showing a double arterial lineage or a “3” sign. The esophageal swallow can be seen as an “ε” aortic notch at the aortic arch. Aortic arch dysplasia can cause narrowing of the mediastinum and a small aortic joint. The lower edge of the rib indicates that the collateral circulation is formed, which is diagnostic, but it is often not obvious in childhood [4, 7, 8].

Aortic coarctation can be clearly diagnosed based on clinical manifestations, physical examination, electrocardiogram, chest X-ray, and echocardiography. If surgery is required, magnetic resonance (MRI) or CT examinations are needed to determine aortic coarctation and collateral circulation. Cardiac catheterization is also required if hemodynamic data needs to be clarified during the course of treatment. Aortic coarctation needs to be differentiated from aortic arch interruption, aortitis, etc. [7].

The treatment of aortic coarctation is to relieve aortic stenosis and obstruction, reconstruct or restore normal blood flow to the aorta, and restore normal blood pressure and circulatory function. Once the aortic constriction is diagnosed, if the aortic lumen cross-sectional area is less than normal 50% or the pressure gradient is >50 mmHg, surgery is usually performed within 5 years of age. If symptoms such as heart failure occur, surgery should be performed as soon as possible. Surgical treatment is currently the best way to improve natural prognosis and is an important treatment for aortic coarctation. The main surgical methods include aortic constriction and end-to-end anastomosis, artificial vascular replacement, patch enlargement, left subclavian artery flap, and artificial bypass. Percutaneous catheter angioplasty plays an increasingly important role in the treatment of congenital or recurrent aortic coarctation. At present, balloon inflation and intravascular stent implantation are mainly used. It is generally believed that simple balloon dilatation has a high recurrence rate of aortic coarctation in the neonatal period. Interventional therapy for the treatment of aortic coarctation in infants and children has a recurrence rate equal to that of surgical treatment. The standard treatment for recurrence of aortic coarctation after surgery is balloon dilation. Disadvantages of interventional therapy include: (1) failure to remove arterial catheter tissue due to interventional therapy, the incidence of advanced aneurysms is higher; (2) once aneurysms appear, due to no ischemic stimulation, collateral circulation dysplasia, paraplegia of reoperation. The rate is high. With the development of interventional techniques, the improvement of interventional devices and surgical techniques, interventional therapy and surgical treatment can improve the success rate of complicated COA and improve the short-term and long-term effects of surgery. For the treatment of hypertension, conventional antihypertensive drugs can be given according to the blood pressure level, and multiple drugs are used in combination with blood pressure reduction, but the patients generally have poor antihypertensive effect. Considering the prognosis of patients is related to the treatment interventions such as surgery and intervention, it is recommended that patients be prepared for surgery once they are diagnosed, so as not to delay the disease [9, 10].

The prognosis of the disease was poor. The average survival age of the untreated patients was 35 years old, and 75% died before the age of 46. The cause of death was bacterial endocarditis or aortic endarteritis, aortic rupture, complicated left heart failure, and cerebral hemorrhage. Generally, aortic coarctation has a good effect. In most cases, blood pressure can return to normal after surgery, but some patients can still have elevated systolic or diastolic blood pressure, which lasts for a long time. Drug treatment is needed to improve target organ damage [11, 12].

12.2 Patent Ductus Arteriosus

Zhitao Yan

Patent ductus arteriosus (PDA) refers to the structure of the arterial catheter that is considered normal in the fetal circulation. It is a common congenital cardiovascular malformation. It is a common congenital cardiovascular malformation. The first phase (functional closure) was completed within 10–15 h after birth, and it was reported to be closed within 24 h. In the second phase (anatomically closed), the catheter contraction forms a cord-like residual, the arterial ligament, 80% is anatomically closed 3 months after birth, and should be completely closed anatomically after 1 year. If it continues to open, it will produce pathology. Physiological changes, known as patent ductus arteriosus, and patients with patent ductus arteriosus with large partial flow, systolic blood pressure tends to increase, while diastolic blood pressure decreases. The incidence of patent ductus arteriosus accounts for 15–21% of congenital heart disease, and about 10% of cases coexist with other cardiovascular malformations, which are common in premature infants. Women are about twice as many as men. The incidence of maternal fetus with a history of rubella increases [5, 13–15].

The fetal arterial catheter develops from the back of the sixth aortic arch, forming a physiological pathway between the fetal blood circulation aorta and the pulmonary artery. During the fetal period, the pulmonary vesicles are completely collapsed, contain no air, and have no respiratory activity. Therefore, the pulmonary vascular resistance is very large, so most of the venous blood discharged from the right ventricle cannot enter the pulmonary circulation for oxygenation. Since the pulmonary artery pressure is higher than the aorta, most of the blood entering the pulmonary artery will flow into the aorta through the arterial artery and then through the umbilical artery to reach the placenta, exchange metabolic metabolism with the maternal blood in the blastoderm, and then enter the umbilical vein into the fetal blood circulation [16, 17].

The patent ductus arteriosus is mainly caused by the left-to-right shunt through the catheter. The size of the sub-flow is related to the thickness of the catheter and the pressure difference between the main and pulmonary arteries. Since the pressure of the aorta during the systolic and diastolic phases exceeds the pulmonary artery, the blood flow through the left-to-right shunt of the patent ductus arteriosus continuously increases the blood flow of the pulmonary circulation and the left atrium, left ventricle, and ascending aorta. The heart load is aggravated. The blood output is 2–4 times normal, and 70% of the left ventricular stroke volume of some patients can enter the pulmonary artery through a large arterial catheter, leading to enlargement of the left atrium, enlargement of right ventricular hypertrophy, and even congestive heart failure. Long-term large amount of blood impacts on the pulmonary circulation, pulmonary arterioles may have reactive spasm, forming dynamic pulmonary hypertension, followed by thickening and hardening of the wall leading to obstructive pulmonary hypertension, left ventricular hypertrophy, or even failure. When the pulmonary artery pressure rises above the aortic pressure, the left-to-right shunt is

significantly reduced or stopped, and the pulmonary blood flow is reversed into the aorta and the child presents with differential purpura, the lower body is purple, and the upper limb is normal [5, 6].

The mechanism of hypertension caused by patent ductus arteriosus is mainly through the patent ductus arteriosus, and the blood in the aorta is shunted to the pulmonary artery, so that the blood circulation of the pulmonary circulation and the left atrium, the left ventricle, and the ascending aorta is significantly increased, resulting in a high row, resulting in contraction. The pressure rises and the pulse pressure increases. Some patients with patent ductus arteriosus have increased blood pressure after surgery, which is closely related to increased heart rate, increased volume of systemic blood volume, and increased cardiac output. The ductus arteriosus is closed after surgery, the left-to-right shunt disappears, and the blood discharged from the left ventricle is completely injected into the systemic circulation, causing the blood volume of the systemic circulation to suddenly increase, resulting in an increase in blood pressure; the cardiac output is increased, and the output per body is relatively fixed, to accommodate cardiac output. The increase causes the heart rate to increase as well. The thicker the catheter, the more preoperative shunt, the more obvious the increase in postoperative blood pressure [18].

The patent ductus arteriosus is different with different severity of the lesion. The mild type is asymptomatic, with severe fatigue, nausea after tiring, wheezing, chest tightness, cough, hemoptysis, etc., a few have dysplasia, and untreated patients may develop heart diseases in the late stage. In advanced stages, untreated patients may develop heart failure, significant pulmonary hypertension, and associated cyanosis, pulmonary artery or bleeding.

The second intercostal space on the left sternal border of the patient can smell loud and continuous machine-like noise, accompanied by tremors to the left upper chest and back. In infancy, with pulmonary hypertension or concomitant congestive heart failure, the pressure gradient between the aorta and the pulmonary artery changes, so that there may be no such continuous murmur, but only systolic or no significant noise. A small number of patients with pulmonary hypertension caused by right-to-left shunt may only hear diastolic snoring (relative pulmonary regurgitation) in the pulmonary valve area, and have purpura, which is more obvious in the lower body than in the upper body. The patent ductus arteriosus is thicker, and the blood flow to the pulmonary artery may cause a slight increase in pulmonary artery pressure. A small number of patients may be associated with increased vascular resistance, causing significant pulmonary hypertension, where left-to-right shunts are reduced or right-to-left shunt, purpura, and right ventricular enlargement. When the PDA has a large left-to-right flow rate, the systolic pressure tends to increase, and the diastolic blood pressure drops, even to zero point. Therefore, peripheral vascular signs such as increased pulse pressure, large pulse, enhanced carotid pulsation, and water pulse. There are capillary pulsations in the nail bed or skin; and the gunshot sound can be heard. These vascular signs all decrease with the increase of pulmonary artery pressure and disappear [17].

Two-dimensional echocardiography may show a patent ductus arteriosus. Color Doppler flow imaging can detect blood flow from the descending aorta through the

patent duct of the patent to the pulmonary artery. X-ray films showed pulmonary congestion, pulmonary artery thickening and pulsation, pulmonary artery total dry arc bulge, aortic arch shadow, and left ventricular enlargement. In nearly half of the patients, the aorta showed a local funnel-like bulge at the attachment of the arterial catheter, called the funnel sign. Electrocardiogram examination can be performed as normal, left ventricular hypertrophy, left and right ventricular hypertrophy, and right ventricular hypertrophy. Right heart catheterization revealed a higher blood oxygen content in the pulmonary arteries than in the right ventricle. Selective aortic angiography showed that the aortic arch was developed while the pulmonary artery was also developed. Sometimes, the aortic part of the aortic duct and the duct of the arterial duct were lobulated. Sometimes the proximal ascending aorta and aortic arch were dilated. The distal aortic canal is thinner [17, 19].

The PDA can be diagnosed based on typical murmurs, X-rays, electrocardiograms, and echocardiographic changes. Right heart catheterization and aortic angiography can help to confirm the diagnosis. The patent ductus arteriosus needs to be differentiated from other diseases that cause cardiac murmurs, such as high ventricular septal defect with aortic valve prolapse, aortic sinus aneurysm rupture, coronary spasm, aorticpulmonary septal defect, etc. [17, 19].

In premature infants and low-weight neonates, ibuprofen and indomethacin can be used to promote occlusion of the patent ductus arteriosus (excluding congenital defects that were once narrowed and catheter-dependent). Regardless of the size of the PDA shunt, the arterial catheter (except resting PDA) is generally closed by the hoistway method to reduce the risk of endarteritis and left heart volume overload. Once the Eisenmenger phenomenon occurs, it is strictly forbidden to close the PDA [20].

Since Portsmann first reported the success of transcatheter closure of PDA in 1967, with the continuous development of cardiac catheter technology, continuous improvement and improvement of interventional materials, transcatheter catheterization of PDA has been increasingly accepted by clinicians and family members. Portsmann, Rashkind, and Sideris occlusion devices have been used to block PDA. It has not been widely used due to complicated operation, many complications, limited indications, and high residual shunt rate. The Amplatzer mushroom umbrella PDA occluder exhibits excellent early closure with a 6 month closure rate of 98%. It can be as high as 99.7% a year. Patients who underwent PDA closure should also be prevented from developing bacterial endocarditis for at least 6 months. If residual shunt is present, lifelong prevention is required. Case report of hemolysis after rare PDA closure is provided [20].

Arterial catheter ligation, clamping, or severing sutures have lower morbidity and mortality, but are currently used less frequently. For patients with large catheter, severe pulmonary hypertension, calcification of the catheter wall, and bacterial catheterization, surgery can be performed under cardiopulmonary bypass. Some open arterial catheters can be catheter-assisted under video-assisted thoracoscopic surgery. Patients with PDA associated with other cardiovascular malformations such as ventricular septal defect, atrial septal defect, etc., may undergo either phase I surgery or staging surgery [21–23].

The prognosis of patent ductus arteriosus is generally good, many patients are asymptomatic and some have longevity. However, heart failure can occur in patients with unresectable arterial ducts, and the prognosis of patients with pulmonary hypertension and right-to-left shunt is poor. Individual patients with pulmonary artery or patent ductus arteriosus rupture can die rapidly. Severe cases of pneumonia, heart failure in infancy, long-term can lead to pulmonary hypertension, obstructive pulmonary vascular disease, and even blood flow from the pulmonary artery into the aorta (i.e., Eisenmenger syndrome), is the leading cause of death. The time to close the occluder is not clear and should be followed up frequently [24].

12.3 AortoPulmonary Window

Gulinuer Duiyimuhan

12.3.1 Definition

Aorticpulmonary windows, also known as aortopulmonaryseptal defect, is an abnormal communication, the one is semilunar valve to ascend between aorta and pulmonary artery. It's a rare congenital vascular malformation. In 1830, Elliotson first discovered and described this congenital heart disease [25], which has the lowest incidence rate of all the four types of septal defects [26]. It is about 0.1–0.2% of congenital heart disease [27, 28]. Hemodynamic changes of aorticpulmonary windows are similar to patent ductus arteriosus. Its clinical manifestation is not specific. When the partial flow rate is high, the systolic blood pressure of the patients can be increased, while diastolic pressure decreased, and pulse pressure difference increased.

12.3.2 Etiology and Pathogenesis

Generally recognizing, at 5–8 weeks of gestation, due to incomplete separation of left and right truncus cristae; primary-pulmonary septum development is arrested, so it leads to a defect between the ascending aorta and the pulmonary artery. The aorticpulmonary windows is usually located in the left posterior or posterior wall of the ascending aorta, it communicates with the adjacent right anterior outer wall of the pulmonary artery or the anterior wall of the right pulmonary artery. Defects can range in size from a few millimeters to several centimeters, generally around 2 cm, and it is usually round or oval in shape.

12.3.3 Pathophysiologic Mechanism

The defect of main pulmonary artery window is large in most patients, the left-to-right shunt is large, congestive heart failure often occurs early in life, and stunted the growth of sick children. A small number of patients have minor defects, little left-to-right shunt, and the patient can be lucky to live to adulthood.

The disease has a short natural survival, untreated people often die of intractable heart failure in infancy. Pulmonary vascular resistance continues to rise, barely survived infancy. Generally speaking, patients with a main-pulmonary arterial window developed shortly after the neonatal period, as pulmonary vascular resistance decreases, congestive heart failure will be progressive. When the pulmonary vascular resistance did not decrease, there may be no congestive heart failure or heart failure symptoms are not obvious.

12.3.4 Clinical Manifestations

The majority of mpa windows are single lesions, and it often occurs in the left side of the aorta [29]. The semilunar valves of the main and pulmonary windows were normal, the diameter of defect varies greatly, and note the aneurysmal dilatation of the larger defect. In 1979, Richardson presented the classical classification of main-pulmonary artery windows [27]. I type for proximal defects, located in the wall of the ascending aorta, near the upper part of the var. sinus; II type for the defect in the distal, located in the posterior wall of the ascending aorta, it is often near the origin of the right pulmonary artery; III type is actually a side abnormal pulmonary artery stemmed from the ascending aorta. Mori K and others redesign classification method: [30], I type and II type with the previous classification, III type is defined is given priority to, pulmonary artery completely insulation defect. In 1994, Ho et al. [31], on the basis of the original classification subdivided IV type: type in the middle.

Characteristics of blood pressure of this kind of patient: The hemodynamic changes in the main pulmonary window were similar to those in patent ductus arteriosus, and the shunt volume is mainly related to the size of the defect and pulmonary vascular resistance; small defect leads to less shunt, or asymptomatic. When the defect is large, large amount of shunt, it will cause congestive heart failure, pulmonary arterial hypertension, and early pulmonary vascular occlusion. These patients don't survive beyond infancy. Patients with high shunt volume may have elevated systolic blood pressure, diastolic blood pressure goes down, and pulse pressure differential increases.

(a) Symptoms: The defect of the main pulmonary artery window is usually larger than that of patent ductus arteriosus, the diverging part is close to the bottom of the heart, and congestive heart failure is also earlier and more severe. Those lucky enough to survive infancy often have heart palpitations, dyspnea, and repeated lung infections.
(b) Signs:
    - Physical examination revealed a precordate eminence, increased heartbeat, tremor may be felt in the upper left margin of the sternum, and in the hearing III IV/6 systolic murmurs. Because of pulmonary hypertension, the noise is rarely continuous, hyperpulmonary second tone.
    - When the defect of main pulmonary artery window is large, systolic blood pressure tends to rise when shunt volume is high, and diastolic blood pressure

goes down. Consequently, peripheral vascular signs appear: pulse pressure broadening; corrigan's pulse, quincke's sign, and traube's sign; advanced cyanosis of the lips and nail bed, and clubbed fingers.

Accessory examination

(a) Chest X-ray examination: May display the heart shadow to expand, and the left atrium and left ventricle were enlarged, increased pulmonary blood, and pulmonary segment bulges.
(b) Echocardiography: The defect between the ascending aorta and the pulmonary artery is seen, it can describe in detail the shape and location of the defect, the origin of the coronary artery and the diameter and origin of the left and right pulmonary arteries. Other concomitant deformities can be identified.
(c) Electrocardiogram: Most patients have left ventricular hypertrophy or biventricular hypertrophy, in severe cases, right ventricular hypertrophy may occur.
(d) Cardiac catheterization: If there is increased pulmonary vascular resistance, or if the person cannot be diagnosed by echocardiography, cardiac catheterization should be performed to determine blood oxygen content and pulmonary artery resistance, to further clarify the physiological status of pulmonary blood vessels. A diagnosis can be made if the cardiac catheter enters the ascending aorta or the unknown artery directly from the pulmonary artery.
(e) Ascending aortography: The pulmonary artery and ascending aorta are seen here at the same time, it shows the size and location of the defect, the relationship between the distal and proximal coronary openings and the semilunar valve and the two main arteries.

12.3.5 Diagnosis and Differential Diagnosis

Aorticpulmonary window often coexists with patent ductus arteriosus; they have the same continuous murmurs and peripheral vascular features. But the murmurs are on the low side and on the medial side, and if echocardiography indicated shunt at the root of the ascending aorta, the diagnosis of aorticpulmonary window is highly suspected. Retrograde ascending aortography demonstrates this disease. It should be distinguished from other conditions that are sufficient to cause a continuous murmur of the heart.

(a) High ventricular septal defect with aortic valve prolapsed: Aortic valve prolapse is often associated with large VSD, it leads to aortic valve insufficiency, and cause corresponding signs, clinically, a double stage murmur was heard on the left margin of the sternum. And diastole murmur is splash water sample with nonupward conduction. At present, color echocardiography has been listed in the routine examination of this kind of heart disease. In this case, aortic valve prolapse deformity and aortic backflow to the left ventricle may be demonstrated, simultaneously shunt from left ventricle to right ventricle and pulmonary artery through ventricular septal defect. Retrograde ascending aorta and left

ventricular angiography were performed for further diagnosis. The former may indicate ascending aortic contrast media flowing back into the left ventricle, the latter showed that left ventricular contrast media shunted into the right ventricle and pulmonary artery through the ventricular septal defect. So it is not difficult to make a differential diagnosis.

(b) Rupture of aortic sinusal aneurysm: The disease is not uncommon in our country, and the clinical manifestations were similar to those of patent ductus arteriosus; continuous heart murmur of the same nature can be heard. It's just the location and direction of conduction are slightly different. If color Doppler echocardiography shows aortic sinus malformation and its shunt to the ventricular and pulmonary arteries or atrial cavity can be identified, combined with retrograde ascending aortography, the diagnosis can be established.

(c) Coronary artery fistula: Such coronary artery malformations are rare, for these patients, the same continuous murmur with tremors as in patent ductus arteriosus is heard. Doppler ultrasonography can show the atrioventricular cavity in which the arterial fistula is located and communicated; retrograde ascending aortography is more likely to reveal an enlarged main branch of the coronary artery, or branch direction and fistula.

12.3.6 Treatment

Once the main pulmonary artery window is diagnosed, it should be actively treated by surgery.

1. Surgical indications:
   Once the main pulmonary artery window is diagnosed, it should be actively treated by surgery. At present, most congenital heart disease treatment centers treat main-pulmonary artery window patients with good surgical results; the death rate from surgery is close to zero [32]. As for the children with heart failure requiring medical control, efforts should be made to operate before pulmonary artery obstructive lesions appear [33]. If a small number of defects or pulmonary vascular obstructive lesions are observed, the decision whether to surgically operate should be carefully considered. Surgical closure should be contraindicated if cyanosis is evident and the defect becomes a blood outlet for pulmonary hypertension.
   Operation method:

   (a) Pure main-pulmonary window: Incisions were made through the anterior wall of the defect. The main and pulmonary arteries on both sides of the incision were closed to the leading edge of the mesh and sutured together.
   (b) Main-pulmonary window with interruption of aortic arch [34]: Interruption of the aortic arch should be addressed first, then the main-pulmonary artery window repair and plasty were performed.

(c) Main-pulmonary window with coronary artery malformation: If there is abnormal coronary artery opening, the position of the patch should be adjusted to preserve the opening of the coronary artery and separate the opening of the coronary artery into the main artery as far as possible.

2. Postoperative management:
   Intraoperative indwelling of cardiac catheter can monitor pulmonary artery pressure and blood oxygen content in the early postoperative period, and observe whether there is residual leakage or right pulmonary artery stenosis, so as to facilitate timely treatment.
3. Management of hypertension:
   The main pulmonary artery window patients generally showed increased systolic blood pressure, decreased diastolic blood pressure, and increased pulse pressure difference. Calcium channel blockers and diuretics can be selected for antihypertensive therapy.

12.3.7 Prognosis

Patients with aorticpulmonary window, especially severe patients, quickly develop refractory heart failure and have a poor prognosis. In the early stage, if the repair is performed under extracorporeal circulation via the ascending aortic incision or the anterior wall of the defect, the complications are less, the mortality is lower and the effect is satisfactory. The patient's blood pressure may drop significantly after surgery.

12.4 Aortic Regurgitation

Hong Xu

Aortic regurgitation can be caused by lesions of the aortic valve, aortic annulus, and ascending aorta. In western countries, according to the European heart VHD survey [35], degenerative lesions account for two-thirds of the potential causes of aortic insufficiency. In China, with the aging of the population, the incidence of various aortic valve diseases is gradually increasing. Other causes include infective and rheumatic endocarditis [36]. Acute severe aortic regurgitation is mainly caused by infective endocarditis and less by aortic dissection.

12.4.1 Pathogenesis

Aortic regurgitation can result from acute aortic insufficiency, which is more common in infective endocarditis, where the valve is damaged by infection and the valve is perforated, or where the valve is not completely closed due to

vegetations, or where scar and contracture form after inflammation is healed, or when the valve degenerates and prolapse. Aortic insufficiency caused by trauma is rare, and can occur after aortic stenosis dissection or valve replacement, or can be caused by non-penetrating ascending aortic tear caused by trauma. Reverse aortic dissection involving the aortic ring may also result in acute or chronic aortic insufficiency. Aortitis involving the heart valve is not uncommon, and the incidence of aortic valve insufficiency in aortitis has been reported in the literature at 7–34% [37–40].

Chronic aortic valve insufficiency is caused by lobar disease or aortic root dilation, and rheumatic valvular disease is caused by multiple rheumatic fevers in developing countries. In developed countries, aortic valve insufficiency is most often caused by dilation of the aortic root, congenital bicuspid aortic valve malformation, and calcified valvular disease.

12.4.2 Pathophysiology

The main pathophysiological changes about aortic regurgitation owe to left ventricular pressure is much lower than the aorta, a large number of blood reflux back into the left ventricle, the left ventricular diastolic load (normal backflow of left atrium and abnormal aortic regurgitation), left ventricular end-diastolic volume increases gradually, end-diastolic pressure can be normal. Because the resistance in the aorta of blood regurgitation decreased, the volume of left ventricular heart beat increased in the early systolic period, and the ejection fraction was normal. With the progress of the disease, the return flow increased, up to 80% of the cardiac volume, left ventricle further expansion, cardiac hypertrophy, left ventricular end diastolic volume and pressure significantly increased, and systolic pressure also significantly increased. When left ventricular contraction decreases, cardiac volume decreases. Cardiac volume slight reduced in early rest and cannot increase during exercise. Late left ventricular end-diastolic pressure increases, leading to increased pressure in the left atrium, pulmonary veins, and pulmonary capillaries, followed by dilation and congestion. As the aortic regurgitation was obvious, the aortic diastolic pressure decreased significantly and the coronary perfusion pressure decreased. Myocardial blood supply decreases, further weakening myocardial contractility.

When acute aortic valve insufficiency occurs, the left ventricle suddenly increases a large amount of regurgitation blood, and the cardiac volume cannot be increased correspondingly. The pressure at the end of diastolic stage of the left ventricle rapidly and significantly increases, which can cause acute left cardiac insufficiency. The increased pressure at the end of diastolic stage of the left ventricle reduces the pressure order difference between the coronary perfusion pressure and the left ventricular intraventricular pressure, leading to the myocardial ischemia under endocardium and the decreased myocardial contractility. The above factors can make the cardiac volume drop sharply, left atrium and pulmonary venous pressure rise

sharply, causing acute pulmonary edema. At this time, sympathetic nerve activity significantly increased, so that the heart rate increased, peripheral vascular resistance increased, diastolic blood pressure decreased significantly, and pulse pressure is not large.

12.4.3 Clinical Manifestation

In general, patients with aortic valve insufficiency are asymptomatic for a long time. Even with progressive ventricular dilatation, patients with aortic valve insufficiency may remain asymptomatic for decades. But when heart failure occurs, it progresses rapidly.

(a) Heart palpitations: The discomfortableness of heart beat may be the earliest chief complaint, because the left ventricle enlarge apparently, caused cardiac apical pulsation strengthened, especially in left decumbent or prone position. Palpitations may be more pronounced with emotional or physical activity causing tachycardia or premature ventricular beats. As a result of pulse pressure increasing significantly, often the body has a strong pulse feeling, especially in the head and neck.
(b) Dyspnea: Exertional dyspnea appears earliest, show cardiac reserve ability has been reduced, as the progress of the disease, sit breathing and nocturnal paroxysmal dyspnea can appear.
(c) Chest pain: Angina is less common than aortic stenosis.
(d) Syncope: Dizziness or vertigo may occur when rapid change of position occurs, and syncope is less common.
(e) Other symptoms: Fatigue, activity endurance significantly decreased, excessive sweating. Some patients with severe aortic valve insufficiency may experience sitting breathing, nocturnal paroxysmal dyspnea, nocturnal angina attacks, and pulmonary edema. Hemoptysis and embolism are rare. Late right heart failure may present with hepatic congestion, swelling, tenderness, ankle-swelling, pleural effusion, or ascites. When acute aortic valve insufficiency occurs, acute left heart failure or pulmonary edema may occur quickly due to sudden left ventricular volume loading, increased ventricular wall tension, and left ventricular dilatation.
(f) Blood pressure and related manifestations: Systolic blood pressure was normal or slightly higher, diastolic blood pressure was significantly decreased, and pulse pressure difference was significantly increased. Peripheral vascular signs may appear: pulse pulse, capillary pulsation sign, femoral artery gunshot sound, femoral artery systolic and diastolic double murmurs, Quincke pulsation sign, Mueller sign, Becker sign, Hill sign, Mayne sign, Rosenbach sign, Gerhard sign, and the up and down swing of the head heart beat frequency.

12.4.4 Examination

Clinical diagnosis is mainly based on the typical diastolic murmur and left ventricular enlargement through echocardiography. An etiological diagnosis can be made based on the history and other findings.

(a) X-ray examination: the left ventricle was significantly enlarged, and the ascending aorta and aortic node were dilated, presenting an *aortic heart*.
(b) Electrocardiogram examination: the electrocardiogram of mild aortic valve insufficiency was normal. Severe cases may have left ventricular hypertrophy and strain, electrical axis left deviation; I, aVL, V5~6 lead Q wave deepening, ST segment depression and T wave inversion; late enlargement of the left atrium also demonstrates bundle branch block.
(c) Echocardiography: echocardiography (TTE/TOE) is a key examination to describe valve anatomy, quantify aortic regurgitation, evaluate its mechanism, define aortic morphology, and judge the feasibility of aortic surgery or valve repair with valve preservation [41]. The diameter of the left ventricle and its outflow tract and the root of the ascending aorta were enlarged. The rate and amplitude of wall activity were normal or increased. Limited anterior mitral valve activity and rapid and high-frequency diastolic flapping with m-mode ultrasound are the characteristics of aortic valve insufficiency. Aortic valve thickening, vegetations, and calcification can be seen on two-dimensional echocardiography. Doppler ultrasonography demonstrates the underlying diastolic eddy beneath the aortic valve, which is very sensitive to detecting aortic valve regurgitation and determining its severity. Echocardiography is also valuable in evaluating left ventricular function in aortic valve insufficiency. It may also be helpful in determining the cause, showing a bilobed aortic valve, valve prolapse, rupture, or flail lobes, or ascending aortic dissection. Aortic valve insufficiency can be predicted by carotid flow spectra. However, diastolic regurgitation can be detected in most groups of people over 65 years old, so it is not predictive in this group of patients with aortic valve insufficiency. The sensitivity and accuracy to predict aortic valve insufficiency was 89% and 100% for increased total diastolic regurgitation and regurgitation velocity in patients under 65 years of age [42]. Echocardiography is usually an important test to determine the severity of aortic valve insufficiency. If echocardiography or CMR imaging shows one or more of the following manifestations, severe chronic aortic valve insufficiency is considered [43]: the width of the central jet is greater than or equal to 65% of the left ventricular outflow tract; the diameter of shrink flow is greater than 6 mm; total diastolic blood flow reversal in abdominal aorta; reflux fraction 50%; reflux 560 mL/stroke (combined with the patient's body size); effective counter flow area 50.3 cm^2.
(d) Radionuclide examination: radionuclide blood pool imaging showed left ventricular dilatation with increased end-diastolic volume. The left atrium can also be enlarged. Left ventricular systolic function can be measured, which is valuable for follow-up.

(e) Cardiac magnetic resonance imaging [41]: cardiac magnetic resonance imaging is required to quantify the severity of aortic valve insufficiency, measure left ventricular systolic and diastolic volumes, and assess left ventricular systolic function in patients with moderate or severe aortic valve insufficiency who are poorly assessed by echocardiography or whose outcome is uncertain. It also is required to quantify the aortic valve reflux and reflux port area.
(f) Invasive angiography: because of the use of echocardiography, invasive contrast angiography is increasingly limited in assessing chronic aortic valve insufficiency. Aortic root angiography and cardiac catheterization and measurement of left ventricular pressure are required when noninvasive examination fails to produce conclusions or results that are inconsistent with clinical findings.

12.4.5 Differential Diagnosis

1. Pulmonary insufficiency:
   The disease is often caused by pulmonary hypertension.
   At this time, the carotid pulse was normal, the second heart sound in the pulmonary valve area was hyperactive, the murmur in the left diastolic period of the sternum was enhanced when inhaling, and there was no change when making a fist forcefully. Electrocardiogram showed right atrium and right ventricular hypertrophy; X-ray examination showed pulmonary artery trunk protrusion. It is common in mitral stenosis and also in atrial septal defect.
2. Aortic sinus tumor rupture:
   The rupture of this disease often break into right heart and caused continuous murmur in left inferior margin of sternum. The murmur is similar to aortic regurgitation with systolic murmur. The patient have paroxysmal chest pain and progressive right heart function failure. Aortic angiography and echocardiography can be used in diagnosis.
3. Coronary arteriovenous fistula:
   Continuous murmurs are common, but diastolic murmurs, or their diastolic components, may be heard in the aortic valve region. However, electrocardiogram and X-ray examination were mostly normal. Aortography showed communication between the aorta and the coronary sinus, right atrium, ventricle, or pulmonary artery trunk.

12.4.6 Disease Stage

The 2014 American heart association/American college of cardiology valvular guidelines consider factors such as the severity of valvular disease, symptoms, ventricular volume response or pressure overload due to the disease, effects on pulmonary and systemic circulation, and changes in heart rhythm. Chronic aortic valve insufficiency is staged [44].

- Stage A: All aortic valve closure is not risk, but the current without aortic valve closure or only a trace of aortic valve closure is. The patients also posess the following problems: the vane aortic malformation (or other congenital valvular abnormalities), aortic valve calcification, aortic sinus or ascending aortic disease, a history of rheumatic fever or known rheumatic heart disease, or infective endocarditis.
- Stage B: Patients with progressive aortic valve insufficiency have mild or moderate left ventricular systolic function and normal or mild left ventricular volume enlargement.
- Stage C: Asymptomatic patients with severe aortic valve insufficiency were identified by echocardiography, cardiac magnetic resonance imaging, or cardiac catheterization. C1: LVEF is normal (50%) and LVESD is mildly to moderately increased (50 mm), which is the decompensation period of chronic aortic valve insufficiency. C2: LVEF less than 50%, or severe increase in LVESD (greater than 50 mm or index LVESD greater than 25 mm/m^2 according to body surface area).
- Stage D: Symptomatic patients with severe aortic valve insufficiency. LVEF may be normal, mild to moderate (40–50%), or severe (less than 40%). Moderate to heavy increases in LVESD (>40–50 mm).

12.4.7 Treatment

The treatment principle is to reduce the load on the heart, prevent and cure infection and rheumatism activity; active treatment of heart failure, angina pectoris; suitable for early surgical treatment; symptomatic support therapy.

Medication:

(a) Patients with mild diseases should mainly protect themselves, such as restricting physical activity and sodium and water intake. Active prevention of infection, tooth extraction and other surgery to be done with the appropriate application of antibiotics.
(b) Patients with rheumatic heart disease need prevent rheumatism activity, and need active treatment once rheumatism activity.
(c) Routine vasodilatation is not recommended for patients with chronic asymptomatic aortic valve insufficiency and normal left ventricular function. When left heart failure occurs, ACEI, sodium nitroprusside and other vasodilators should be actively applied together with cardiotonic drugs and diuretics.
(d) For symptomatic patients with severe disease and significant cardiac enlargement with moderate to severe insufficiency, surgical treatment as soon as possible after a period of intensive drug therapy is recommended, including aortic valve replacement and aortic valve ring repair. Treatment including diuretics, angiotensin

converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers, mineralocorticoid receptor antagonist, and digoxin treating heart failure.

(e) For symptomatic patients who are not suitable for the operation because of severe aortic regurgitation and systolic heart failure due to other pathogeny must be given treatment including diuretics angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, beta blockers and mineralocorticoid receptor antagonist and digoxin.

(f) If the patient cannot undergo surgery due to left ventricular systolic function impairment of asymptomatic patients with severe aortic valve closed due to the coexistence disease, recommend the use of angiotensin converting enzyme inhibitors or angiotensin II receptor blockers.

(g) Take a supplement of water, electrolytes, vitamins, or albumin.

12.4.7.1 Treatment of Hypertension

Aortic valve closure insufficiency and patients with higher systolic blood pressure, can choose vasodilator such as angiotensin converting enzyme inhibitors, angiotensin receptor II block, or two hydrogen pyridine class calcium channel blockers such as nifedipine to dilate blood vessels to improve myocardial remodeling, and beta blockers in this case is not so effective, because the heart rate slows and the accompanying each cardiac output increase may prompt systolic blood pressure to rise [44].

12.4.7.2 Recommendations for Physical Activity and Exercise [44]

For mild or moderate asymptomatic aortic valve insufficiency patients, if the left ventricular end diastolic diameter is normal (55 mm) or slightly increased, they can participate in all sports.

For patients with partial aortic valve insufficiency with moderate increase in left ventricular end-diastolic diameter (60–65 mm), if the exercise load test at least up to the competition level neither causes symptoms nor leads to ventricular arrhythmias, they can participate in low and moderate static exercise and all dynamic exercise.

If patients have asymptomatic nonspecific ventricular tachycardia during resting or exercise, they can only participate in low-intensity competitive sports.

Asymptomatic patients with severe aortic valve insufficiency whose left ventricular end-diastolic diameter is greater than 65 mm, and asymptomatic patients with mild or moderate aortic valve insufficiency (no matter what the left ventricular end-diastolic diameter is) should not participate in competitive sports.

Patients with aortic insufficiency due to significant dilation of the ascending aorta (>45 mm, normal 35 mm) can only participate in low-intensity competitive sports. This recommendation does not apply to patients with marfan's syndrome.

12.4.7.3 Surgical Treatment

Artificial valve replacement is the main treatment for aortic valve insufficiency. The guidelines indicate indications for aortic valve surgical intervention as follows:

(a) Symptomatic patients with severe aortic valve insufficiency regardless of left ventricular systolic function.
(b) Evidence of left ventricular systolic dysfunction with ejection fraction less than 50% in asymptomatic patients with severe chronic aortic valve insufficiency.
(c) The LVEF of asymptomatic patients with severe aortic valve insufficiency was normal (50%), but the end-systolic diameter was greater than 50 mm.
(d) Asymptomatic LVEF with severe aortic valve insufficiency was normal (50%), but progressive severe left ventricular dilatation (left ventricular end-diastolic diameter >65 mm) was observed in patients with low surgical risk.
(e) Patients with severe aortic valve insufficiency underwent cardiac surgery due to other indications.
(f) Patients with moderate aortic valve insufficiency are undergoing other cardiac procedures. It should be administered before the onset of symptoms of heart failure.

At the same time of medical treatment, should pay attention to grasp the timing of surgery. For asymptomatic patients with severe aortic valve insufficiency with normal left ventricular function (LVEF 50% and LVESD 50 mm), aortic valve surgery is not recommended, and regular examination should be conducted every 6 months. Surgical treatment should be considered in case of symptoms related to aortic valve insufficiency, left heart insufficiency or obvious cardiac enlargement.

1. Valvular repair: Rarely used, aortic regurgitation is usually not completely eliminated.

   For aortic valve vegetation or perforation in infective endocarditis only; Aortic valve and annulus tear. Aortic insufficiency due to aortic ring dilation caused by ascending aortic aneurysm may be treated by ring constriction.
2. Artificial valve replacement: Valve replacement is recommended for rheumatic and most other causes of aortic valve insufficiency. Both mechanical and biological valves can be used. Surgical risk and late mortality depend on the development of aortic valve insufficiency and the state of cardiac function at the time of surgery. In patients with significantly enlarged heart and long-term left heart insufficiency, the mortality rate is about 10% during operation and about 5% in late stage each year. Nevertheless, because of the poor prognosis of drug therapy, surgical treatment should be considered even in patients with left heart failure. Mechanical valve life as long as 70 years, biological valve life of about 15 years. Warfarin sodium should be taken after the operation.
3. In patients with congenital heart disease caused by aortic insufficiency due to aortic single lobe lesions, and the other two lobes of the aortic valve were basically normal, the diseased aortic lobes were replaced by pulmonary autograft.

Treatment of acute aortic valve insufficiency: Severe acute aortic valve insufficiency rapidly leads to acute left cardiac insufficiency, pulmonary edema, and

hypotension, and is highly fatal. In order to save the patient's life, we should adopt operation as early as possible while taking active medical treatment. Preoperatively, positive inotropic drugs such as dopamine or dobutamine, and/or vasodilators such as nitroprusside should be given intravenously to maintain cardiac function and blood pressure.

12.4.8 Prognosis

Acute severe aortic valve insufficiency often leads to death from left heart failure without timely surgical treatment. Patients with chronic aortic valve insufficiency may be asymptomatic for a long time. The 5-year survival rate of severe patients after medical treatment after diagnosis was 75%, and the condition rapidly deteriorated after the onset of symptoms, and the 2-year fatality rate of patients with severe left heart failure was 50%. The prognosis of the patients after surgery was significantly improved, and the blood pressure could be restored to normal.

12.5 Arteriosclerosis and Hypertension

Hong Wang

Arteriosclerosis refers to a noninflammatory, degenerative, and proliferative lesion that occurs in the large artery (i.e., the aorta, the innominate artery, the common carotid artery, the subclavian artery, the vertebral artery, and the common total iliac artery), resulting in thickening, hardening, loss of elasticity, and reduction of the lumen in the tube wall. Studies have shown that arteriosclerosis is divided into three species, namely atherosclerosis, arterial middle calcification/sclerosis, and fine arteriosclerosis. And large artery arteriosclerosis is mainly atherosclerosis. Large artery arteriosclerosis is mainly atherosclerosis, and closely related to isolated systolic hypertension (ISH) in clinic. Since 1999 WHO/ISH the guidelines for the treatment of hypertension have defined ISH as systolic pressure (SBP) $\geq$140 mmHg and diastolic pressure (DBP) <90 mmHg hypertension, which is currently used in research.

12.5.1 Epidemiology

Early large-scale ISH findings came from Framingham Heart Research. According to the findings of the Framingham Heart Study, ISH is defined as systolic blood pressure $\geq$160 mmHg and diastolic blood pressure <95 or 90 mmHg, then the prevalence of ISH in men aged $\geq$65 years in the United States was 18% and 30% in women. The 1999–2010 NHANES survey showed that the prevalence of adult ISH was 9.4%, 8.9% for men, 9.9% for women, 29.4% for age more than 60 years, 6.0% for 40–59 years, and 1.8% for 18–39 years [45]. ISH is the most common type of

hypertension in the elderly, accounting for 60–70% of elderly hypertension [46], and 80–90% of people with hypertension older than 70 years [47]. Meta-analysis of hypertension epidemiological data from 11 countries found that the prevalence of ISH in the elderly varies greatly depending on the survey method, survey time, selection criteria, and population structure, ranging from between 1–2% and 41%. Regardless of the difference in prevalence, the study showed that the incidence of systolic hypertension was significantly increased with age. In 1991, China's hypertension survey was 950,356. If DBP <90 mmHg is used as the standard, the prevalence of ISH was 1.25%. In 1998, the Syst-china study in China surveyed the average prevalence of ISH in the elderly population aged 60–89 years was 8%; 60–69 years old was 6%, 70–79 years old was 12%, and 80-year-old was 19%. China Hypertension League has conducted a survey of 950,000 people in China. The result is that ISH is the most common in the elderly, accounting for 86.6% of the elderly hypertension (the diastolic blood pressure <90 mmHg is the standard), or 78.7% (the diastolic blood pressure is <95 mmHg as the standard). At present, there are more than 80 million elderly hypertensive patients in China, accounting for the first place in the world.

Increased systolic blood pressure significantly increased the risk of stroke, coronary heart disease, and end-stage renal disease [46]. Prospective studies have shown that ISH can increase the risk of coronary heart disease by 34%, cerebrovascular disease by 33%, and heart failure by 26% [48]. A 11-year study of multicenter follow-up showed that ISH was independently associated with all death, nonfatal cardiovascular events [49]. Meta-analyses including 123 study showed that systolic pressure decreased by 10 mmHg, cardiac events, coronary heart disease, stroke, heart failure, and total death decreased by 20%, 17%, 17%, 18% and 13%, respectively [50].

A few young people can also behave as ISH, but the pathogenesis of ISH in young people is different from that of the elderly and has not yet been fully elucidated. This group had a higher pulse pressure differential and lower wave reflection than the age-matched group with normal blood pressure and an elevated systolic and diastolic blood pressure. It is concluded that increased heart rate, enlarged arm pulse pressure, and aortic stiffness are the causes of middle-aged ISH. Since a large proportion of young ISH patients, especially male patients, show *pseudo hypertension,* some experts suggest that it is necessary to measure the central arterial pressure for young ISH patients. Many studies have shown that there is no significant statistical difference in the risk of cardiovascular events between these patients and those with normal blood pressure. But recently Yano [51] studies have included 15,868 men and 11,213 women in the Chicago Heart Society test program, aged 18–49 years (an average of 34 years). ISH is defined as a systolic pressure of 140 mmHg or higher and a diastolic pressure of less than 90 mmHg. The results showed that during the follow-up of the average 31 years, men at risk of cardiovascular death in the high systolic pressure group increased by 23% compared with the normal blood pressure group, and 55% increased in women.

12.5.2 Etiology

The etiology and pathogenesis of arteriosclerosis have not been fully elucidated. It is currently believed that the occurrence and development of arteriosclerosis is the result of the interaction between acquired risk factors and congenital genetic factors. The main risk factors for arteriosclerosis are heredity, age, sex, high cholesterol, high blood pressure, and smoking. In addition, factors such as obesity, diabetes, lack of exercise, nervousness, advanced age, and family history are also closely related to aortic sclerosis. Modern studies have shown that chronic infectious diseases can also increase the likelihood of atherosclerosis. Lipid metabolism disorder, vascular endothelial injury, and platelet adhesion aggregation are the main conditions for the formation of aortic sclerosis. Generally, lipids and complex carbohydrates accumulate, fibrous tissue hyperplasia and calcareous deposition form plaques, gradually degenerating the middle layer of the artery, secondary plaque hemorrhage, plaque rupture, and local thrombosis. Because the appearance of the lesion is yellow atheroma, it is called atherosclerosis. The plaque gradually enlarges, making the arterial lumen progressively narrow and hard, causing structural and functional changes in tissues and organs.

The effect of arteriosclerosis on blood pressure is mainly manifested in two aspects, that is, the effect on the blood flow in the lumen and the function of the vessel wall. The main effect on intraluminal blood flow is related organ ischemia, such as renal ischemia. The most important function of the kidney, sodium drainage, is weakened, resulting in sodium and water retention. In addition, the activation of the renal ischemic renin-angiotensin-aldosterone system can lead to elevated blood pressure. And impact on the function of blood vessel wall is mainly endothelial damage and a series of secretion of vasoactive substances, resulting in thickening of the intima, smooth muscle cell proliferation, arterial remodeling, relative, or absolute reduction of the middle elastic fibers of the aorta, reduction of elasticity of the aorta and compliance attenuation, etc., eventually leads to an abnormality in the buffering capacity of the arterial blood vessels to the flowing blood, causing an increase in blood pressure.

The central arterial pressure of young ISH patients is normal, and the increase of radial artery pressure is caused by the excessive amplification of central arterial pressure waves [52].

12.5.3 Pathogenesis

Epidemiological survey results show that elderly people are the main population of arteriosclerosis, while systolic hypertension is also high in the elderly, suggesting that there is a close correlation between senile, aortic sclerosis, and isolated systolic hypertension. The possible mechanisms are as follows:

(a) Changes of blood vessels:
With age, the vitreous degeneration occurs in the middle layer of the arterial blood vessels, while the progressive enlargement of the aortic atherosclerosis

thickens the arterial wall, increases the vessel wall/cavity ratio, and increases vascular resistance. The initiation of aortic sclerosis is endothelial injury. It can produce a large number of vasoconstrictors, leading to vasoconstriction. Further development of arteriosclerosis can lead to elastic fiber rupture, increased calcium content, and deposition of collagen material on the wall, leading to further decline in arterial compliance. Intravascular hypertension further increases the stiffness of the arteries, making systolic blood pressure more pronounced than diastolic blood pressure.

(b) Decreased baroreceptor sensitivity:
In the elderly, baroreceptors located in the carotid sinus and aortic arch decrease sensitivity with age, reducing the body's ability to buffer blood pressure fluctuations. The reduced sensitivity of baroreceptors leads to the prone to orthostatic hypotension in the elderly. Since plasma norepinephrine has an increased blood pressure responsiveness with respect to age, the afferent branch of baroreflex is intact; therefore, the main reason for the change in sensitivity is the abnormality of the efferent branch. Atherosclerosis of the carotid artery and aortic arch is the cause of impaired baroreceptors, and abnormal reflexes promote the elevation of blood pressure in the elderly and are related to the variation of blood pressure.

(c) Changes in sympathetic nervous system reactivity:
Studies have shown that aging has a significant impact on the sympathetic nervous system, with decreased inactivation and clearance of norepinephrine. Plasma norepinephrine levels increase with age. At 80 years of age, plasma norepinephrine can reach 410 pg/mL, twice as much as that at 10 years of age. The plasma levels of catecholamine in patients with hypertension were higher than those with normal blood pressure. In contrast, the responsiveness of the heart and blood vessels to adrenergic receptors decreased with age in the elderly. The poor response to beta 1 agonists in the elderly and no change in beta 2 agonists, and the poor response to beta 1 antagonists in the elderly compared to the young, are mainly due to the post receptor mechanism. In some vascular beds and kidneys, there is also a decrease in beta 2 receptor-mediated vasodilation. In addition, vasodilatation in the elderly is less responsive to acetylcholine.

(d) Changes of renal function:
Glomerular filtration rate (GFR) decreased with age. In patients with aortic sclerosis, blood flow to the renal vessels decreases, leading to renal parenchymal ischemia and decreased GFR, leading to sodium and water retention. Patients with aortic sclerosis are often accompanied by renal atherosclerosis and renal vascular stenosis, which can easily be followed by renal vascular hypertension.

(e) Insulin resistance:
Hypertensive patients with no diabetes and normal weight have similar plasma basal insulin and C-peptide levels to normal subjects, but the response to glucose intake and mixed diet is significantly enhanced. Insulin-induced glucose uptake is reduced in hypertensive patients, and insulin clearance is low, but

there is no change in glucose production in the liver. Elderly hypertensive patients, especially obese patients, are clearly insulin resistant. In elderly hypertensive patients, the level of calcium in the adipocytes is increased, and the calcium channel blocker nitrendipine can normalize intracellular calcium levels and insulin reactivity. Therefore, in the elderly, changes in insulin reactivity and/or metabolism are associated with hypertension.

(f) Impaired endothelial function:
The endothelial function of hypertensive patients is found to be impaired by injection of the endothelium-dependent vasodilator acetylcholine, but the role in the pathogenesis of hypertension is still unclear.

(g) Obesity:
Muscle tissue decreases with age, while the adipose tissue increases and the body mass index increases. The increase in body mass index is weakly correlated with the occurrence of hypertension in the elderly.

(h) Decreased exercise:
Although the study of exercise blood pressure in the elderly showed an increase in vascular resistance and average arterial pressure in exercise, the systolic blood pressure of the subjects decreased by 14 mmHg after endurance training in the elderly with an average age of 71.5 years. A number of studies have found that systolic blood pressure drops significantly after a large amount of exercise training, so with the increase of age, the decrease of exercise can increase the level of systolic pressure.

(i) The pathogenesis of systolic hypertension (ISHy) in young people:
The pathogenesis of ISHy is different from that of systolic hypertension (ISHe) in the elderly, and has not yet been fully elucidated. This group of people has a larger pulse pressure difference and lower wave reflection. Studies have suggested that increased stroke volume and aortic sclerosis are the cause of ISHy. In addition, ISHy may be due to progressive pulse pressure amplification (PPA) of the upper arm artery, which makes the cuff blood pressure higher than the aortic systolic pressure. There were also great differences in other hemodynamic manifestations among patients with ISHe and ISHy. It was found that the pulse pressure of aortic and radial artery in ISHy patients was enlarged greatly, and the central artery pulse pressure is 10–15 mmHg smaller than the outer circumference. But for older people over the age of 60, the difference is about 5 mmHg. In addition, some young ISH patients, especially taller males, often exhibit “pseudo-systolic hypertension.”

12.5.4 Clinical Manifestations

The manifestations of arteriosclerosis are mainly determined by vascular lesions and the degree of ischemia of the affected organs. For patients with early arteriosclerosis, most patients develop asymptomatic concealment. For patients with intermediate arteriosclerosis, there may be clinical symptoms such as palpitations, chest pain, chest tightness, headache, dizziness, cold limbs, limbs ache, claudication,

decreased vision, memory loss, insomnia, and multiple dreams. Different patients may have different symptoms.

In patients with isolated systolic hypertension, those with mild or moderate systolic blood pressure are often asymptomatic. Patients with severe hypertension may have symptoms such as dizziness, vertigo, palpitation, and fatigue. In severe cases, heart failure may also occur.

(a) Changes in blood pressure:
The incidence of circadian rhythm abnormalities in patients with simple systolic hypertension is high, and morning hypertension can occur, which significantly increases the risk of damage to the heart, brain, kidney, and other target organs. It should be noted that blood pressure is also affected by the season. The seasonal changes of mean blood pressure were mainly diastolic blood pressure in the middle-aged group and systolic blood pressure in the elderly group, especially in the elderly over 70 years old, whose systolic blood pressure still increased in winter even in the antihypertensive treatment.
(b) Changes in the heart:
Simple systolic hypertension increases left ventricular afterload and heart work, and increases collagen fiber enlargement and amyloidosis, so that cardiac hypertrophy, diastolic and systolic function is impaired, and easy to induce heart failure. Clinical manifestations of patients may be palpitation after exercise, shortness of breath, easy to get tired, severe cases of paroxysmal dyspnea at night, and cannot lie flat. The dullness of the heart may be enlarged. The heart sounds were strong and forceful, the second heart sounds were hyperactive in the aortic valve area, and sometimes the symptoms and signs of left heart failure such as galloping and wet sounds at the bottom of both lungs can be heard.

12.5.5 Auxiliary Inspection

1. Laboratory tests: Abnormal glycolipid and uric acid metabolism is often seen in blood biochemistry (blood potassium, sodium, fasting glucose, lipids, uric acid, and creatinine), blood routine, and urine analysis (urine protein, urine sugar, and urine sediment microscopic examination). If necessary, blood homocysteine, plasma renin activity, or 17 renin concentration, blood and urine aldosterone, blood and urine cortisol, blood free methoxyepinephrine and methoxynorepinephrine, blood or urine catecholamine are measured.
2. Other auxiliary inspections:
   (a) Cardiac ultrasound: Echocardiography should be performed in patients with left ventricular hypertrophy or other heart diseases to more comprehensively evaluate the cardiac anatomical structure and function and determine the treatment plan.
   (b) Vascular ultrasound: If the aorta, carotid artery, renal artery, and peripheral arterial disease are suspected, vascular ultrasound should be performed.
   (c) Kidney ultrasound: If kidney disease is suspected, kidney ultrasound should be performed.

(d) Dynamic blood pressure monitoring: Dynamic blood pressure monitoring can avoid white coat effect, identify white coat hypertension and detect hidden occult hypertension, diagnose simple nocturnal hypertension, can observe abnormal blood pressure rhythm and variation, assess antihypertensive efficacy, full time blood pressure control.
(e) Others: Adrenal ultrasound, CT or MRI, adrenal vein blood collection and sleep respiratory monitoring, etc.

12.5.6 Differential Diagnosis

Isolated systolic hypertension can be distinguished from systolic hypertension caused by other reasons, such as high dynamic circulation state or high cardiac output state, which can also lead to increased heart rate, increased peripheral blood perfusion, and increased systolic pressure. If increased systolic blood pressure is caused by physiology period under the condition of physical activity and emotional excitement, it can return to normal after rest; diseases such as hyperthyroidism, arteriovenous fistula, etc., according to medical history, physical examination, laboratory results (such as T3, T4), etc., to exclude other causes of systolic hypertension.

(a) Hyperthyroidism: Some elderly hyperthyroidism, often with systolic hypertension as the main symptoms, accompanied by fatigue, heat, sweating, hand tremor, weight loss, palpitations, tachycardia, neuroticism, high metabolic symptoms. Serum T3, T4 increased, blood cholesterol decreased, and some elderly patients with hyperthyroidism can show nonspecific manifestations such as atrial fibrillation. Blood pressure can be controlled after treatment of hyperthyroidism. The secondary hypertension of hyperthyroidism should be treated with β-blockers, and anti-thyroid drugs or thyroid surgery should be selected according to the condition.
(b) Patent ductus arteriosus: The symptoms of patent ductus arteriosus depend on the thickness of the catheter, the size of the subflow, the level of pulmonary vascular resistance, the age of the patient, and the combined intracardiac malformation. Patients with moderately sized catheters are often asymptomatic, and symptoms of decompensation of heart function such as shortness of breath and palpitations occur until intense adult activity. In patients with patent ductus arteriosus, the blood pressure can be normal, but when the flow rate is large, the systolic blood pressure tends to increase, while the diastolic blood pressure drops, even to zero, and the peripheral vascular signs appear. These vascular signs all decrease with the increase of pulmonary artery pressure and disappear. Age and echocardiography are the main points of identification.

12.5.7 Treatment

The main lesion of aortic atherosclerosis is atherosclerosis. The basic treatment is mainly anti-atherosclerosis, while the isolated systolic hypertension has special requirements for antihypertensive treatment because of its particularity.

12.5.7.1 Anti-atherosclerosis Treatment

Including non-pharmacological treatment and medical treatment, the brief is as follows:

1. Non-pharmacological treatment:
   (a) Reasonable diet: The diet is mainly based on fruits, vegetables, low-fat dairy products, whole grains rich in dietary fiber, and protein derived from plants to reduce saturated fat and cholesterol intake. Reduce sodium intake and increase potassium intake.
   (b) No smoking and passive smoking: Tobacco poisoning cardiovascular endothelial cells, impairing endothelial function, is one of the major risk factors for cardiovascular disease and cancer. Although smoking cessation does not lower blood pressure, smoking cessation can reduce the risk of cardiovascular disease.
   (c) Adhere to the right amount of exercise: Exercise can improve blood pressure levels. Exercise intensity must vary with each individual, and the maximum heart rate during exercise is often used to assess exercise intensity. High-risk patients need to be assessed before exercise.
   (d) Restricting alcohol consumption: Excessive drinking significantly increases the risk of hypertension, and restricted drinking can reduce blood pressure. People with high blood pressure are advised not to drink alcohol. In the case of drinking, daily alcohol intake should not exceed 25 g for men and 15 g for women [53].
   (e) Maintaining psychological balance: Nervous tension can activate the sympathetic nerve and raise blood pressure. Stress management should be carried out on patients with hypertension to guide them to carry out personalized cognitive behavioral interventions. When necessary, psychological therapy combined with medication is used to relieve anxiety and mental stress.
2. Lipid-lowering drugs:
   On the basis of a reasonable diet and moderate exercise, when the blood lipids are still higher than the target value, lipid-regulating drugs can be used.
   (a) Cholesterol-lowering drugs: mainly statins, including simvastatin, fluvastatin, pravastatin, atorvastatin, rosuvastatin, etc.
   (b) Drugs to reduce triglycerides: fenofibrate, gemfibrozil, etc.

(c) Cholesterol absorption inhibitor: ezetimibe, etc.
(d) Pre-protein convertase subtilisin 9 (PCSK9) monoclonal antibody: blocking the binding of PCSK9 to the LDL-C receptor to reduce baseline LDL-C levels.
(e) Chinese medicine: such as Xuezhikang, Zhibituo, etc. also have a certain lipid-lowering effect.

3. Anti-platelet adhesion and aggregation:
Prevent thrombosis and prevent the occurrence and development of vascular obstructive diseases. Commonly used drugs are: enteric-coated aspirin, clopidogrel, ticagrelor, etc.
4. Thrombolytic drugs and anticoagulant drugs:
For patients with intracarteral thrombosis leading to lumen stenosis or obstruction, thrombolytic drugs and anticoagulants, such as urokinase, recombinant tissue type fibrinogen activator and heparin, can be used.
5. Interventional therapy:
Including stenosis or occlusion of blood vessels, especially the common carotid artery, subclavian artery recanalization, re- or bypass graft surgery, etc., can restore arterial blood supply.

12.5.7.2 Treatment for Isolated Systolic Hypertension

The purpose of treatment for isolated systolic hypertension is to minimize the occurrence and death of cardiovascular and cerebrovascular complications, as well as to intervene other reversible risk factors, such as smoking, hypercholesterolemia, diabetes, and other related clinical diseases. The goal of blood pressure reduction is to reach the standard step by step under the patient's tolerable condition. After comprehensive evaluation, patients with comorbidity and frailty should individually determine the initial treatment level of blood pressure and the target value of treatment. Generally, the target value of patients' systolic blood pressure should be reduced to below 140 mmHg. For patients with diabetes mellitus, the blood pressure drops below 130 mmHg. For patients aged 65–79 years, if tolerable, target blood pressure is less than 140/90 mmHg. For patients above 80 years old, it should be reduced to <150/90 mmHg; Patients with SBP <130 mmHg and good tolerance can continue treatment without having to adjust blood pressure level [53]. The 2018 European hypertension guidelines [54] pointed out that for all the elderly, especially the elderly and frail elderly, the systolic blood pressure that can be tolerated should be controlled at 130–139 mmHg, and the diastolic blood pressure less than 80 mmHg, but the systolic blood pressure less than 130 mmHg should be avoided. The basis and premise of antihypertensive therapy is to actively improve lifestyle, and nondrug therapy combined with drug therapy can often reduce systolic hypertension more effectively.

1. Principles of drug selection and drug combination:
It is suggested that starting from low dose, especially for the aged and elderly people, the initial treatment should usually adopt a small effective treatment

dose, which can be gradually increased to a full dose as required. Give priority to the use of long-term antihypertensive drugs, in order to effectively control the 24-h blood pressure, more effective prevention of cardiovascular and cerebrovascular complications. According to the different complications of patients and drug efficacy and tolerance, individual treatment can be implemented, if necessary, combined treatment.

For patients with high risk and extremely high risk, drug therapy should be given as soon as possible after blood pressure is determined. For patients with moderate risk and low risk, other risk factors and lifestyle changes can be considered comprehensively to reduce blood pressure, and patients' requirements for treatment strategies should be solicited to achieve doctor–patient cooperation, so as to achieve good treatment results.

2. Antihypertensive drug selection:
   (a) Diuretics: Large clinical trials have confirmed that diuretics are the first choice for isolated systolic hypertension. The initial antihypertensive effect of diuretics is mainly through the elimination of sodium and diuretic to reduce the extracellular fluid and blood volume, resulting in a decrease in cardiac output. Long-term application of diuretics can reduce the concentration of sodium ions in vascular smooth muscle due to sodium excretion, and may reduce the intracellular calcium concentration through the Na-Ca exchange mechanism, so as to reduce the affinity and reactivity of vascular smooth muscle cell surface receptors to vasoconstrictor substances and enhance the sensitivity to diastolic vascular substances. Diuretics can reduce arterial wall sodium, water content and intracellular calcium concentration, thereby reducing hardening of the arteries. Diuretics are especially suitable for elderly patients with hypertension, isolated systolic hypertension or heart failure, and are also one of the basic drugs for refractory hypertension.
   (b) Calcium antagonist: Calcium antagonist mainly plays a role in dilating blood vessels and lowering blood pressure by blocking calcium channel on vascular smooth muscle cells. Clinical trials of blood pressure lowering therapy with large samples completed in China have proved that the blood pressure lowering therapy based on dihydropyridine CCB can significantly reduce the risk of stroke in patients with hypertension. It is especially suitable for elderly patients with hypertension, isolated systolic hypertension, stable angina pectoris, coronary or carotid atherosclerosis, and peripheral vascular disease.
   (c) Angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor antagonist (ARB): ACEI blocks AngII synthesis and inhibits AngII vasoconstriction; at the same time, it reduces kinins degradation, and enhances the effect of bradykinin and prostaglandins; simultaneously, prevents the degradation of Ang1–7, and enhances the effect of antagonizing AngII to achieve the purpose of reducing blood pressure to protect the target organ. ARB blocks the binding of AngII to AT1R and inhibits its vasoconstriction. It also

promotes the binding of AngII to AT2R and enhances its vasodilator effect. A large number of basic research and evidence-based medical research results show that the above two drugs have a greater reduction in systolic blood pressure than diastolic blood pressure, and these kind of drugs can improve the process of arteriosclerosis, and thus has become the first-line drug for the treatment of systolic hypertension.

(d) β-blockers: They exert antihypertensive effects by inhibiting overactive sympathetic activity, inhibiting myocardial contractility, and slowing heart rate. Beta blockers are particularly suitable for patients with high blood pressure with tachyarrhythmia, coronary heart disease, chronic heart failure, increased sympathetic activity, and high motility. Beta blockers should not be preferred in elderly hypertension without comorbidity. Some experts suggest that drug treatment by ISH should avoid beta blockers [55].

(e) α-blockers: α-blockers can safely and effectively lower blood pressure. As the main adverse reaction is postural hypotension, drug resistance is likely to occur when applied alone, so it is not suitable for elderly patients with arteriosclerosis and simple systolic hypertension. Alpha blockers are indicated for patients with hypertension and benign prostatic hyperplasia and for the treatment of patients with refractory hypertension.

(f) Others: Studies on nitrates have shown that long-acting nitrates are effective for isolated systolic hypertension and can be used as an adjuvant antihypertensive therapy.

3. Device intervention treatment

(a) Catheter-based renal denervation (RDN): Also known as transcatheter renal sympathetic nerve ablation, can be used as an alternative treatment strategy for hypertension, and is suitable for patients with intractable hypertension who fail to achieve the goal of blood pressure reduction after lifestyle adjustment and drug treatment. The results of the SPYRAL HTN-OFF MED study and the SPYRAL HTN-ON MED study indicate that RDN is safe and effective in the treatment of untreated hypertension or mild to moderate hypertension [56, 57]. However, reports on the efficacy of ISH treatment are inconsistent [58, 59]. ISH is associated with central arterial stiffness and is associated with pulse counterpulsation or increased cardiac output. Recent studies have shown that assessing arterial stiffness can screen subgroups of ISH for benefit from RDN, and ISH patients with low iPWV benefit from RDN [60].

(b) Creation of an arteriovenous fistula: A shunt path is established between the iliac arteries and veins by means of artificial iliac arteriovenous fistula (*Coupler* device is implanted into the central iliac vein) to buffer the arterial system with better compliance, thereby improving the compliance of arterial system and possibly controlling excessive blood pressure. In 2015, Lobo [61] succeeded in the treatment of refractory hypertension with the new *ROX Coupler* device. The results showed that the blood pressure of patients receiv-

ing the new therapy showed a significant continuous drop, while the complications and admission rate caused by hypertension were reduced. And the effect of Coupler implantation on patients with insignificant renal denervation (RDN) is also significant. Subsequently, Christian Ott [62] applied *ROX Coupler* to treat ISH, and the results showed that treatment of ISH was as effective as mixed hypertension. However, the theoretical basis of arteriovenous anastomosis for the treatment of refractory hypertension is still weak and clinical practice data are scarce. More studies are needed to evaluate the long-term effects of Coupler on patients' blood pressure and evaluate the safety of the device.

4. ISHy drug therapy:
   Elderly ISH, like mixed hypertension in the elderly, has a similar risk of heart failure and cardiovascular death and requires antihypertensive therapy [63]. There is much debate about whether ISHy patients should be treated with medication. Yano et al. [7] found that compared with the normal blood pressure population, cardiovascular events such as coronary heart disease were increased in patients with ISHy, which provided a basis for ISHy to conduct drug treatment. The current guidelines recommend the same recommended treatment pattern for blood pressure drugs for all ISH patients. However, some studies suggest that there is no evidence to suggest that ISHy patients need medical treatment, especially male young people under the age of 40 [64].

12.5.7.3 Treatment of Common Complications of Isolated Systolic Hypertension

Patients with isolated systolic hypertension were mostly elderly patients, and the incidence of complications was 40%, significantly higher than that of non-elderly patients (20.4%). Stroke or transient cerebral ischemia (TIA) is the main cerebrovascular complication of hypertension, and it is the primary risk of death and disability in elderly hypertensive patients in China. Antihypertensive therapy reduces the risk of stroke by 29%, and even the slightest decrease in blood pressure, often reduces the absolute risk of cardiovascular events. However, patients with isolated systolic hypertension are mostly accompanied by coronary heart disease and heart failure, especially in the elderly population, and active treatment can significantly benefit. Many patients with isolated systolic hypertension have type 2 diabetes, and the combination of the two increases the risk of heart disease, cerebrovascular disease, and peripheral vascular disease. It has been preliminarily proved that ACE inhibitors can slow down the rate of renal decline. In patients with isolated systolic hypertension with diabetes, lowering blood pressure to the lowest target level, i.e., less than 130/85 mmHg, can significantly reduce the occurrence of microvascular disease events and major vascular disease events.

12.5.8 Prognosis

Studies have proved that arteriosclerosis is closely related to isolated systolic hypertension, and the prognostic factors are not only age and blood pressure, but also other cardiovascular risk factors. Arteriosclerosis and increased systolic blood pressure can significantly increase the risk of cardiovascular events. Current research suggests that elevated systolic blood pressure is a major risk factor, rather than diastolic blood pressure, and may be a more accurate risk predictor than diastolic blood pressure. The main complications of isolated systolic hypertension are stroke and congestive heart failure. Active prevention and treatment of arteriosclerosis and control of systolic hypertension can improve the prognosis of patients.

12.6 Valsalva Sinus Tumor Bursting

Zhitao Yan

Valsalva sinus is defined as an aortic sinus enlargement between one of the annulus and the sinus. The lack of elastic sheets causes a partial weakening of the aortic wall. This results in a weakened portion of the aneurysm expansion that eventually causes rupture. It is a rare congenital aortic root disease. Aortic sinus aneurysm can be asymptomatic. Once ruptured, it will cause severe hemodynamic disorder, resulting in increased systolic blood pressure, decreased diastolic blood pressure, and increased pulse pressure difference [65–67].

Current data show that Asians have a higher incidence than whites. More than 20–40 years old, the incidence of children is very small. Male individuals are more common, four times as many as women. Most cases combined with other cardiac malformations, such as ventricular septal defect, aortic valve prolapse with insufficiency. The prognosis of aortic sinus aneurysm is poor, and the survival time after rupture is 1–3.9 years [65, 66].

Most aortic sinus tumors are congenital. During the embryonic development period, the aortic sinus tissue is incompletely developed, and there is a weak part. When the combined ventricle is absent, the right ventricular sinus adjacent to the right coronary sinus loses support, and the tumor rupture can occur under the impact of high blood flow. Studies have shown that ventricular dysplasia may be an important factor in the formation of sinus. Aortic sinus tumors caused by acquired factors are mainly found in infections (including syphilis, bacterial endocarditis), trauma and degeneration. At present, due to the weakness or lack of elastic fibers and muscle tissue in the aortic sinus wall, there is a lack of continuity between the aortic wall middle layer and the aortic valve annulus, resulting in a weak point in the base of the aortic valve sinus, postnatal aortic blood. The flow pressure gradually pushes out the weak area of the aortic valve sinus to form an aortic aneurysm-like protrusion. The aortic root is at the center of the heart, and the sinus can protrude into any of the heart chambers, mainly the right ventricle and the right atrium. The aortic sinus

aneurysm is often windy, with a rupture at the apex. The rupture of the sinus tumor occurs in the right coronary artery sinus, followed by the non-coronary valve sinus, and the left coronary sinus is rare [66, 68].

A series of pathophysiological changes caused by rupture of aortic sinus tumor, including massive shunt from aorta to heart chamber; aortic annulus enlargement, leaflet displacement or prolapse caused by insufficiency; diastolic blood pressure decreased, systolic blood pressure increased. And pulse pressure widening. The tumor protrudes into the right ventricular outflow tract and causes obstruction of blood discharge; the sinus tumor protruding out of the heart can break into the pericardial cavity and cause acute cardiac tamponade. The progression of the disease varies with the size of the breach. The larger the aortic sinus tumor is, the more the left-to-right flow is, the earlier the symptoms appear, and the faster the disease progresses. Aortic sinus aneurysms are often the most common with ventricular septal defect (about 34.6–59%), which makes the ventricular load more important. It is also often associated with aortic regurgitation, pulmonary stenosis, aortic coarctation, and patent ductus arteriosus [68].

Most patients had no significant clinical manifestations before aortic sinus aneurysm was ruptured. Most sinus tumors have a history before rupture, such as strenuous activity, trauma, and cardiac catheterization. The symptoms of rupture of the sinus tumor depend mainly on the rate of rupture, the size of the rupture, and the broken heart chamber. About one-third of patients have sudden onset of chest pain and upper abdominal pain, palpitation and shortness of breath after severe activity or trauma. About half of the patients show a slow progressive heart failure; a small number of patients may have no obvious symptoms found at the time of physical examination. Through the heart examination, it can be found that the third to fourth intercostal space of the sternum can be buckled with fine tremor, and the superficial and rough continuous murmur of level IV–V can be heard. Patients with severe heart failure have manifestations of hepatomegaly, ascites, and lower extremity edema. The main characteristics of blood pressure are increased systolic blood pressure, decreased diastolic blood pressure, and widened pulse pressure [66, 67, 69–72].

Color Doppler echocardiography can make a clear diagnosis of the location, shape, size and location, number and size of sinus tumors. It is the first choice for the diagnosis of rupture of aortic sinus aneurysm. Right heart catheterization can determine the location of the sinus tumor fracture, measure pulmonary artery pressure, calculate the partial flow and pulmonary vascular resistance. Retrograde aortic angiography and left ventricular angiography can show the location and size of the sinus tumor, whether it is associated with aortic regurgitation and its extent, and whether there are ventricular septal defects and patent ductus arteriosus. Cardiac catheterization and cardiovascular angiography are more difficult to determine when using a two-dimensional echocardiographic examination for selective application. The chest radiograph shows an enlarged heart shadow, an increased lung texture, and a visible lung dance. Electrocardiogram can be seen in left ventricular hypertrophy or with strain [70, 71, 73].

RSVA can be diagnosed based on medical history, physical signs, and related auxiliary examination results. Echocardiography can determine the location, shape, size, and number of aortic sinus tumors, the heart chamber that is broken, and the presence or absence of other cardiac malformations. It is the first choice for the diagnosis of this disease and to diagnose whether it is combined with other cardiac malformations. Ascending aorta angiography is the gold standard for the diagnosis of RSVA, which can clarify the shape, size, rupture site, and the broken heart chamber of RSVA. Right heart catheterization has important reference value for the diagnosis of RSVA and site. RSVA is mainly associated with patent ductus arteriosus, ventricular septal defect with aortic regurgitation, coronary arteriovenous fistula, etc. [65, 71, 72, 74, 75].

Surgical repair is an effective method. The principle of surgical treatment is to firmly close the rupture, restore the continuity of the middle layer of the aortic root, prevent recurrence, avoid damage to the aortic valve, and correct the malformation in the same period. Sinus tumor repair is often used, such as ventricular septal defect, which can repair aortic sinus and ventricular septal defect at the same time. If the sinus tumor is separated from the ventricular septum by a muscle bundle, it is repaired separately. For example, aortic valve prosthesis or aortic valve replacement can be performed with aortic valve prolapse and closure. In recent years, some scholars have used patent ductus arteriosus occluder (ADO) to block the successful rupture of aortic sinus tumor. However, there is currently no special occluder and it is only suitable for rupture of aortic sinus tumor without other surgical treatment of cardiovascular disease. Transcatheter RSVA occlusion is a complementary treatment for surgery. It is suitable for rupture of aortic sinus tumor without other surgical treatment of cardiovascular disease. Its short-term effect is good, and the long-term efficacy needs further study. Hypertension caused by rupture of aortic sinus aneurysm is a high blood pressure emergency, with an increase in acute systolic blood pressure, decreased diastolic blood pressure, and widened pulse pressure. The treatment can be given intravenous hypotension according to hypertensive emergencies, including intravenous drip. Preparations of sodium nitroprusside, phentolamine, etc. [66, 67, 74, 75].

The prognosis of this disease depends on the size of the breach, the shunt, the combined cardiac malformation, whether or not the endocarditis is combined, the general condition of the patient, the time of diagnosis, and the treatment method are closely related. Due to the rapid deterioration of cardiac function during rupture of aortic sinus aneurysm, the average survival time of untreated patients is only a few years, and the prognosis is poor. A small number of patients can die within a few days after the onset of illness. The long-term outcome of surgical treatment of aortic sinus aneurysms is satisfactory, with a 10-year survival rate of 90% ± 7% and a 20-year survival rate of approximately 93%. Left or aggravated aortic regurgitation is an important factor affecting the prognosis of surgery. Hypertension secondary to rupture of aortic sinus aneurysm can be cured with rupture of aortic sinus aneurysm or interventional therapy [66, 67, 74, 75].

12.7 Cardiomyopathy and Hypertension

Li Cai

Cardiomyopathy (myocardosis) is a type of primary myocardial disease that causes myocardial dysfunction in addition to heart valve disease, coronary heart disease, hypertensive heart disease, pulmonary heart disease, congenital heart disease and hyperthyroid heart disease, including dilated cardiomyopathy, hypertrophic cardiomyopathy, restricted cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and undefined cardiomyopathy [76]. The main clinical manifestations were repeated heart failure, arrhythmia, and cardiac enlargement. Patients with cardiomyopathy had a temporary increase in blood pressure, but the diastolic blood pressure did not exceed 110 mmHg, and most of them appeared in acute heart failure, and the blood pressure decreased after heart failure improved. In the late stage of the disease, blood pressure decreased and pulse pressure decreased.

12.7.1 Definition and Etiology

Cardiomyopathy is an unexplained myocardial disease. It does not include specific cardiomyopathy with a clear cause or secondary to systemic disease. It is generally believed to be related to virus infection, autoimmune reaction, heredity, drug poisoning, and metabolic abnormalities.

Dilated cardiomyopathy (DCM): It is a heterogeneous cardiomyopathy characterized by ventricular enlargement and reduced cardiac systolic function [76]. Its etiology is unknown so far. Apart from idiopathic and familial heredity, it is believed that the pathogenesis of this disease is related to persistent virus infection and autoimmune reaction in recent years. In particular, Coxsackie B virus-induced viral myocarditis eventually transformed into dilated cardiomyopathy is the most closely related. It is suggested that persistent viral infection and immune-mediated myocardial damage may be important pathogeny and pathogenesis of myocardial injury. In addition, there are many factors, such as perinatal period, alcoholism, anticancer drugs, disturbance of myocardial energy metabolism, and abnormal nerve rapid receptor, which can also cause the disease.

Hypertrophic cardiomyopathy (HCM): It is a kind of myocardial disease characterized by myocardial hypertrophy. The main manifestation is left ventricular wall thickening, usually without enlargement of left ventricular lumen. The basic feature of this disease is high incidence of cardiac hypertrophy and sudden death [77, 78]. This disease often has an obvious family history (about 1/3) and is currently considered to be an autosomal dominant genetic disease. About 60% of adult HCM patients can detect definite mutations in the pathogenic gene [79]. Others believe that abnormal catecholamine metabolism, abnormal intracellular calcium regulation, hypertension, intensive exercise, and so on can be used as factors to promote the occurrence of this disease.

Restrictive cardiomyopathy(RCM): In this kind of cardiomyopathy, myocardial interstitial fibrosis increases myocardial stiffness and leads to restrictive diastolic dysfunction, with unilateral or bilateral ventricular filling limitation and reduced diastolic capacity, and ultimately leads to heart failure [76]. Its incidence is related to geographical, ethnic, gender, and other factors, mostly in tropical and temperate regions, but there is no large-scale data statistics, only sporadic cases in China.

Arrhythmogenic right ventricular cardiomyopathy (ARVC): It is a right ventricular myocardial disease characterized by arrhythmia, heart failure, and sudden cardiac death, also known as arrhythmogenic right ventricular dysplasia, which is often occurred in teenagers. Patients often have abnormal function and structure of the right ventricle, which is characterized by the gradual replacement of the right ventricular myocardium, especially the right ventricular free wall myocardium by fat and fibrous tissue. The heredity and family background of the disease are obvious [80]. The incidence of familial diseases is about 30–50%. It is autosomal dominant inheritance. Incomplete dominant and recessive types are also reported.

12.7.2 Pathogenesis

In the early stage or compensatory period of cardiac insufficiency, patients with cardiomyopathy may have hypertension due to sympathetic excitation and increased peripheral vascular resistance. Long-term peripheral vasoconstriction can lead to organic lesion in the wall of the vessel, resulting in permanent hypertension.

12.7.3 Clinical Manifestations and Signs

Dilated cardiomyopathy: The onset of the disease is slow. At the early stage, there was no significant abnormality except for cardiac dilatation, late stage is often for heart failure. The patient has fatigue, shortness of breath after activities, paroxysmal dyspnea at night, edema, ascites and hepatomegaly, etc. In addition, there can be a variety of arrhythmias, easily combined with brain, kidney, and lung embolism, and even sudden death. During auscultation, the third and fourth heart sounds, the Gallop rhythm and the systolic murmur with incompetence of tricuspid or mitral are often heard, and moist rales are audible at the base of both lungs.

Hypertrophic cardiomyopathy: Characterized by ventricular hypertrophy, especially asymmetric hypertrophy of ventricular septum, some of which can cause ventricular outflow tract obstruction. The onset was slow, and the early manifestations were fatigue, palpitation and dyspnea after fatigue, angina pectoris is also common, and the effect of nitroglycerin is not obvious. A serious signal of the disease is syncope, and in later stages heart failure may occur, often with atrial fibrillation. The cardiac boundary can be enlarged to the left during physical examination, and the middle and late systolic ejection murmurs can be heard in the precordial area, and the splitting of second heart sounds .

Restrictive cardiomyopathy: It is more common in tropical and subtropical regions. It is characterized by endocardial myocardial fibrosis, myocardial stiffness, and ventricular diastolic filling is blocked. The onset of the disease is slow, early can have fever, fatigue, dizziness, acute qi, and other symptoms, and heart failure may occur in the late stage. Atrial fibrillation is also common, and some of them are accompanied by visceral embolism. Physical examination can be accompanied by weak heartbeat, pure heart sound, pulmonary valve area of the second heart sound hyperactivity, can be heard and diastolic galloping horse rhythm and arrhythmia.

Arrhythmogenic right ventricular cardiomyopathy: The clinical manifestations of the disease are complex and changeable. More than half of the patients have palpitations of varying degrees. One-third of the patients have syncope. Malignant cardiac events are the first symptoms in nearly one-tenth of the patients. Sudden cardiac death can occur in about half of the ARVC patients [81]. Heart failure was rare and the incidence was less than one-tenth.

Common complications of cardiomyopathy: arrhythmia, heart failure, embolism, infective endocarditis, and sudden death. Infectious endocarditis and sudden death often occur in patients with myocardial hypertrophy; embolism often occurs in patients with atrial fibrillation, prolonged immobility, diuretics, or myocardial fibrosis and decreased systolic force. Sudden death is a common fatal complication.

Cardiomyopathy with hypertension: It is common in hypertrophic cardiomyopathy. Due to the existence of compensatory mechanism, hypertension is more stubborn in the early stage of lesion, moderate to severe elevation is more common, blood pressure is not easy to control, and late is often a signal of acute heart failure.

12.7.4 Supplementary Examination

1. Echocardiography (UCG):
   (a) Dilated cardiomyopathy: UCG is an important method for diagnosis and evaluation of DCM [82, 83]. Its main manifestations are enlargement of heart chambers, often accompanied by mitral valve, tricuspid regurgitation, and pulmonary hypertension; weakening of motion of ventricular septum and posterior wall of left ventricle; decrease of left ventricular ejection fraction; mural thrombosis mostly occurs in the left ventricular apex.
   (b) Hypertrophic cardiomyopathy: Echocardiography is of great value in the diagnosis of hypertrophic cardiomyopathy, manifesting as hypertrophy of the interventricular septum and left ventricular wall, and the ratio of the two thicknesses is larger than that of normal 1.3:1. According to the clinical manifestations, combined with echocardiography and ventriculography examination often can diagnose. For patients who plan to undergo interventricular septal myocardial ablation, the location of ablation can be determined by transcoronary echocardiographic contrast echocardiography [84].

(c) Restricted cardiomyopathy: Two-dimensional echocardiography showed a severe impairment of cardiac stenosis, apical occlusion, endocardial thickening, and ventricular diastolic function.
(d) Arrhythmogenic right ventricular cardiomyopathy: Echocardiography is usually used as the screening of suspected patients. It is the best method for moderate or severe lesions. Combining with pulsed tissue Doppler technology, the accuracy of diagnosis can be improved [85].

2. Cardiac magnetic resonance imaging (CMR):
(a) Dilated cardiomyopathy: CMR plain scan and late gadolinium enhancement (LGE) technique can not only accurately detect the myocardial function of DCM, but also clearly identify the histological characteristics of myocardium (including cardiac structure, myocardial fibrosis scar, myocardial activity, etc.). It is an important detection method for the diagnosis and differentiation of cardiomyopathy. LGE + T1 mapping (qualitative) + ECV (quantitative) technique has more advantages in identifying myocardial interstitial dispersion and quantitative myocardial fibrosis, and has important value in evaluating the risk of DCM and predicting the prognosis [86, 87].
(b) Hypertrophic cardiomyopathy: Gadolinium contrast medium delayed enhancement (late gadolinium enhancement, LGE) is the most effective method to identify myocardial fibrosis. LGE is positively correlated with some risks, such as death, SCD, etc. [88, 89]. About 65% of HCM patients developed LGE, and most of them show localized or speckled enhancement in hypertrophic myocardium. The focal enhancement at the junction of ventricular septum and right ventricular free wall was the most typical.
(c) Arrhythmogenic right ventricular cardiomyopathy: Showing the expansion of the right ventricular outflow tract, the thickness of the ventricular wall, the discovery of diastolic dilation, and left and right ventricular free wall myocardial lipid infiltration, is widely used in clinical practice. CMR has been proved to be able to accurately describe various morphological and functional abnormalities in the diagnostic criteria, but it has certain limitations in the diagnosis of this disease.

3. X-ray examination:
(a) Dilated cardiomyopathy: Enlarged heart shadow, cardiothoracic ratio >0.5, bilateral pulmonary congestion and interstitial edema, pulmonary hypertension.
(b) Hypertrophic cardiomyopathy: Left ventricular enlargement may occur in the normal range, there may be pulmonary congestion, but severe pulmonary edema is rare.
(c) Restricted cardiomyopathy: Mild cardiac enlargement and partial endocardial calcification.

4. Electrocardiogram (ECG):
(a) Dilated cardiomyopathy: ST segment depression, T wave level or inversion were the main ECG examination, R-wave increased poorly, and a few of them appeared pathological Q wave.

(b) Hypertrophic cardiomyopathy: ECG changes included obvious pathological Q waves, especially inferior wall leads (II, III, aVF) and lateral wall leads (I, aVL or V4~V6); abnormal P waves; left deviation of electrical axis; leads V2~V4 T wave depth and inversion were common in patients with cardiac apical hypertrophy. All HCM patients should be monitored by ambulatory electrocardiogram for 24 h to assess the risk of ventricular arrhythmias and sudden death and help to determine the cause of palpitation or syncope [90, 91].

(c) Restrictive cardiomyopathy: ECG showed arrhythmias such as low voltage, atrial, and ventricular hypertrophy, bundle branch block, ST-T changes, and atrial fibrillation.

(d) Arrhythmogenic right ventricular cardiomyopathy: ECG features include depolarization and repolarization abnormalities [92]. The manifestations of depolarization abnormalities are as follows: (1) Incomplete right bundle branch block or complete right bundle branch block. (2) QRS wave of right thoracic lead (V1–V3) in patients without right bundle branch block is widened to more than 110 ms, which has become one of the main diagnostic criteria due to its high specificity. (3) Right thoracic leads/waves decreased, with a low incidence. (4) Epsilon wave can appear in some patients' ECG, which is formed by delayed activation of some right ventricular fibers. Epsilon wave can be recorded in 75% of patients by high magnification and correction technique. The electrocardiographic manifestations of repolarization abnormality were inverted T wave in right thoracic lead (V1–V3), which was not related to right bundle branch block. Most patients had frequent ventricular premature beats (more than 1000 beats per 24 h) accompanied by nonpersistent and/or persistent ventricular tachycardia, mostly in the form of left bundle branch block, but this was not the characteristic of ARVC.

12.7.5 Diagnosis and differential diagnosis

12.7.5.1 Diagnosis

1. Dilated cardiomyopathy: the onset of the disease is slow, most patients see a doctor when the clinical symptoms are obvious, patients often appear gasp, and even sit breathing, edema, and other congestive heart failure symptoms and signs began to be diagnosed. Embolism or sudden death can occur in some patients.

   When the patients with heart enlargement, arrhythmia and congestive heart failure are clinically seen, the possibility of this disease should be considered if ultrasonic cardiogram confirms the presence of heart enlargement and cardiac diffuse pulsatility. Diagnostic criteria: the clinical diagnostic criteria of DCM were objective evidence of ventricular enlargement and decreased myocardial systolic function: (1) left ventricular end-diastolic diameter (LVEDd) was greater

than 5.0 cm in women and 5.5 cm in men (or 117% higher than the predicted values of age and body surface area, i.e., 2 times SD + 5%); (2) LVEF <45% (Simpsons method), LVFS <25%; (3) hypertension, valvular disease, and congenital heart disease were excluded at onset; sexual or ischemic heart disease [93].

2. Hypertrophic cardiomyopathy: some patients do not have self-conscious symptoms, but due to sudden death or physical examination was found. Many patients have palpitations, chest pain, fatigue dyspnea. For patients with clinical or ECG manifestations similar to coronary heart disease, such as younger patients, with inadequate basis for the diagnosis of coronary heart disease and if it cannot be explained by other heart diseases, the possibility of this disease should be considered. The diagnosis was made in combination with electrocardiogram, echocardiography, and cardiac catheterization. If there is a positive family history (sudden death, heart enlargement, etc.), it is more helpful in the diagnosis.

   The main diagnostic criteria were as follows: (1) the thickness of left ventricular wall or/and interventricular septum was greater than that of 15 mm by echocardiography. (2) Tissue Doppler and magnetic resonance imaging (MRI) showed that the apex of the heart was thickened near the apical interventricular septum and the myocardial density or interstitial arrangement was disorder. Secondary criteria: (1) 12-lead ECG I, aVL, V4-V6 lead ST moved downward in patients under 35 years old, with deep symmetry leading to T wave. (2) Two-dimensional ultrasonic ventricular septum and left ventricular wall thickness (11–14 mm). (3) Gene screening revealed known gene mutations, or new mutation sites, linked to HCM. Exclusion criteria: (1) systemic disease, hypertension, rheumatic heart disease mitral valve disease, congenital heart disease (atrial septum, ventricular septal defect), and metabolic disease associated with myocardial hypertrophy. (2) The athlete's heart is hypertrophic. HCM criteria for clinical diagnosis: one major criteria + exclusion criteria; one main criteria + secondary criteria (3), i.e., positive gene mutations; one main criteria + exclusion criteria (2); (2) and (3) secondary criteria; (1) and (3) secondary criteria.

3. Restrictive cardiomyopathy: Fever and general burnout are the initial symptoms, and leukocytosis, especially eosinophilia, is more specific. Later, heart failure symptoms such as palpitation, dyspnea, edema, hepatomegaly, jugular vein enlargement, and ascites gradually appeared. It resembles constrictive pericarditis, which is called constrictive endocarditis. The narrow ventricular cavity, deformation and increase of eosinophils, no calcification of pericardium and calcification of intima are helpful to the diagnosis of this disease. The diagnosis of this disease is exclusive, except hypertrophic cardiomyopathy, valvular disease, pericardial disease, and congenital heart disease. It is mainly differentiated from constrictive pericarditis.

4. Arrhythmogenic right ventricular cardiomyopathy: When one of the following conditions occurs, ARVC should be clinically diagnosed: (1) palpitation and syncope in young and middle-aged patients, excluding other cardiac diseases; (2) survivors of ventricular fibrillation without a history of heart disease; (3) patients with simple right ventricular failure, excluding other diseases causing pulmonary hypertension; (4) family members have been clinically or autopsy diagnosed ARVC; (5) sudden cardiac death in family members, autopsy cannot exclude ARVC; (6) patients with confirmed DCM in relatives; (7) asymptomatic patients (especially athletes) with corresponding manifestations of ARVC in cardiac examination, through echocardiography, magnetic resonance, and other clinical diagnosis, electrocardiogram as an important auxiliary evidence.

12.7.5.2 Differential Diagnosis

1. Rheumatic heart disease: Cardiomyopathy may also have mitral or tricuspid systolic murmurs, but generally not diastolic murmurs, and more loud in heart failure, after control of heart failure, this murmur is reduced or disappeared, rheumatic heart disease is the opposite. Cardiomyopathy often has multiple chambers enlarged at the same time, unlike rheumatic heart disease, the enlargement of left atrium, left ventricle, or right ventricle is dominant. Ultrasound is helpful to distinguish.
2. Pericardial effusion: Cardiac enlargement and weakening of cardiac beat in cardiomyopathy, which must be distinguished from pericardial effusion. In cardiomyopathy, the apical pulsation shifted to the left and lower, which was consistent with the left outer edge of the glottic realm. The apical pulsatility in pericardial effusion was not obvious or was in the medial part of the left outer edge of the glottic realm. Mitral or tricuspid systolic murmur, ventricular hypertrophy, abnormal Q waves, and various complex arrhythmias all indicate cardiomyopathy. Ultrasound examination is not difficult to distinguish between the two, multivolume fluid in the pericardium level or dark areas to indicate pericardial effusion, cardiac enlargement is cardiomyopathy. It must be noted that there may also be a small amount of pericardial effusion in cardiomyopathy, but it is neither sufficient to cause cardiac tamponade nor to affect the physical signs and cardiac function of the heart; it is only the discovery of ultrasound. Systolic time interval was abnormal in cardiomyopathy and normal in pericardial disease.
3. Coronary heart disease: Middle-aged patients with onset. Coronary heart disease and cardiomyopathy must be considered in patients with enlarged heart, arrhythmia, or heart failure without other causes. High blood pressure, hyperlipidemia, or diabetes mellitus are predisposing factors. Segmental abnormalities of ventricular wall activity are helpful for the diagnosis of coronary heart disease.

12.7.6 Treatment

1. Therapeutic principles: Active treatment may lead to the primary pathogenesis of cardiomyopathy. According to the heart function, appropriate activities can be done, but must not be too tired, should rest more, and when the illness is serious should rest in bed, should have bland diet; for heart failure should control sodium and water intake. Rule of life, avoid cold and lead to the aggravation of disease.
2. Medication:
   (a) In patients with cardiomyopathy, thrombosis is easily formed on the myocardial wall, so it is necessary to prevent mural thrombosis or long-term anticoagulation therapy. (Aspirin, warfarin)
   (b) Use of drugs to control arrhythmias and correct heart failure at low doses. (β receptor blockers, non-dihydropyridine calcium antagonists, digoxin, amiodarone, dobutamine)
   (c) Angiotensin converting enzyme inhibitors (ACEI) are commonly used in the treatment of heart failure, usually with a certain amount of diuretics. Angiotensin-converting enzyme inhibitors can not only improve symptoms and correct heart failure, but also inhibit myocardial hypertrophy and reverse some pathological changes. ACEI is not recommended for HCM patients with obvious symptoms.
   (d) Medicine for improving myocardial metabolism (trimetazidine) by turn enhances the resynthesis of glycolytic ATP and improves optimizing energy metabolism of ischemic myocardium, which is helpful to improve myocardial function [94].
3. The surgical treatment
   (a) Implantation of cardioverter defibrillator (ICD): DCM patients with severe arrhythmia, life-threatening and uncontrollable medication, with mild to moderate heart failure symptoms and good prognosis in anticipation of clinical status, are advised to implant cardioverter defibrillator (ICD) to prevent sudden death [95]. ICD treatment for ARVC patients can increase the survival rate, which is the only clear and effective treatment to prevent sudden cardiac death.
   (b) Cardiac resynchronization therapy (CRT) [96]: Evidence shows that asynchrony of ventricular contraction in DCM patients leads to increased mortality of heart failure. Synchronized stimulation of left and right ventricles (CRT) by dual chamber pacemaker can correct asynchronized contraction, improve cardiac function, and hemodynamics without increasing oxygen consumption, and make the heart failure produce adaptive biochemical changes, which can improve the symptoms of patients with severe heart failure, and improve 9-min walking ability. Significantly, it improves the quality of life. Indications of CRT for severe heart failure with LVEF <35%, NYHA cardiac function grade III–IV, QRS interval >120 ms, and intraventricular conduction block.
   (c) Temporary or buried dual chamber pacing: For HCM patients with acute dyspnea, chest pain, and confirmed outflow tract pressure gradient greater

than 30 mmHg by ultrasound, dual-chamber pacing can reduce the pressure gradient. But the effect of permanent pacing is not obvious. Dual-chamber pacemakers are not recommended as the preferred option for patients with medically refractory HCM.

(d) Percutaneous transluminal septal myocardial ablation (PTSMA): The septal branch of the coronary artery is occluded by injecting absolute alcohol through a catheter, which leads to ischemia, necrosis, thinning, and contractility of the hypertrophic septal myocardium and ventricular outflow [97].

(e) Catheter ablation: Patients with ARVC cardiomyopathy with ventricular tachycardia can choose catheter ablation therapy [98], 60–80% of the patients are successful in the near future, and in the long-term follow-up of 3–5 years, the recurrence rate is as high as 50–70%, and easy to recur or form new ventricular tachycardia. Therefore, it is not the preferred treatment.

(f) Heart transplantation: It began in 1968. The 1-year survival rate was 83%, and the 5-year survival rate was more than 70%. Due to economic constraints, donor shortage, complicated operation and rejection reaction, it cannot be carried out universally. For RCM patients, heart transplantation is considered to be the most effective radical operation, and there have been successful cases [99].

(g) Myocardioplasty: Myocardioplasty, or dynamic myocardioplasty, began in 1985, with a 1-year survival rate of 83%.

(h) Partial left ventricular myocardial resection: For HCM patients, resection of the most hypertrophic part of the myocardium, relief of mechanical obstruction, repair of mitral regurgitation, can effectively reduce the pressure gradient, significantly relieve or alleviate heart failure, prolong life, is the standard effective treatment program. Partial left ventricular myocardiectomy (VRM) or Batista was performed in 1994. The 1-year survival rate was 63–82%.

(i) Artificial heart: This method reduces the volume of the left ventricular assist device and places it in the abdominal subcutaneous or thoracic cavity of patients with DCM cardiomyopathy.

12.7.7 Prognosis

Different types of cardiomyopathy have different prognosis. Most of them have poor prognosis. About 70% of patients with cardiomyopathy die within 5 years after symptoms appear. When the myocardial wall becomes thinner and the myocardial function decreases, the prognosis will deteriorate further. Of all types of cardiomyopathy, RCM has the worst prognosis, with 50% of patients dying about 2 years after diagnosis. The existence of arrhythmia makes the prognosis worse. Hypertension associated with cardiomyopathy is often a signal of acute heart failure in the early stage of compensatory mechanism. It is suggested that early treatment, especially early use of ACEI, can improve the prognosis.

12.8 Heart Transplant-Related Hypertension

Shasha Liu

Human heart transplantation began in 1967 and was accepted as a treatment for end-stage heart disease in the early 1980s. Advances in immunosuppressive therapy and graft disposal have made heart transplantation possible and led to the success and continuous development of heart-lung transplantation. Statistics from the International Society for Heart and Lung Transplantation (ISHLT) in 2018 show that 141,268 cases of heart transplantation have been completed globally by June 2017 [100]. Increased volume load after heart transplantation and the use of immunosuppressive agents after heart transplantation were associated with increased blood pressure.

12.8.1 Etiology and Pathology

The latest data show that the etiology of heart transplantation varies in different parts of the world. Among them, non-ischemic heart disease occupies the first place in adult heart transplantation. The second is ischemic cardiomyopathy. Other end-stage heart diseases requiring heart transplantation include congenital heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, re-transplantation of transplanted heart, valvular heart disease, and others [100]. Among the patients undergoing cardiac re-transplantation, 60% had coronary heart disease, 8% had primary heart failure, 7.5% had acute or superacute rejection, 7% had nonspecific heart failure, and other causes accounted for 17.5%. Eventually, heart disease of all the above reasons can lead to atrophy of myocardial fibers, fibrosis, and matrix changes in the interstitial space of myocardial tissue, which widens the cardiac chambers. Then myocardial tissue cannot maintain normal systolic and diastolic functions and does not respond to various drugs.

12.8.2 Pathogenesis of Hypertension Induced by Heart Transplantation

Elevated blood pressure after heart transplantation may be secondary to the following causes:

1. Volume overload after heart transplantation;
2. Renal insufficiency before transplantation;
3. Cyclosporin, an immunosuppressant, was used. Cyclosporin is a calcineurin inhibitor. Studies have shown that cyclosporine is an independent risk factor for hypertension after heart transplantation (HT). The mechanism of hypertension induced by calcineurin inhibitors is complex. In addition to causing systemic and renal vasoconstriction, water and sodium retention and short-term and long-term

renal insufficiency, cyclosporine A plays an important role in up-regulating angiotensin 2 receptor, activating renin-angiotensin system, directly injuring vascular endothelial cells and renal proximal convoluted tubular cells [101–104]. Most cyclosporine-related hypertension occurs one month after the administration, and about 50% of patients develop hypertension one year later, characterized by persistent elevation of blood pressure at night. Vasodilators directly acting on blood vessels, such as hydralazine, have no effect on such hypertension. The contraction of peripheral blood vessels caused by cyclosporine often depends on calcium ion. Therefore, calcium channel blockers are effective in treating hypertension caused by cyclosporine. Although cyclosporine has no effect on the renin-angiotensin system, angiotensin converting enzyme inhibitors are effective in some patients.

Indications and contraindications

1. Indications: End-stage heart disease, grade III or IV of cardiac function (NYHA); End-stage heart disease patients, who do not undergo heart transplantation, are less than 25% likely to survive for 1 year; ventricular arrhythmia, which cannot be cured by other means, is potentially fatal; coronary heart disease, recurrent angina pectoris, or EF <20% that cannot be treated with drugs, interventional cardiology and surgical procedures; congenital heart disease that cannot be corrected by routine surgery; patients with advanced valvular lesions who cannot undergo valve replacement for various reasons; heart failure after transplantation requires re-transplantation.
2. Contraindications: Pulmonary artery systolic pressure >60 mmHg, or pulmonary transvalvular pressure >15 mmHg, and/or pulmonary vascular resistance >5 Wood units; active systemic infection; severe cerebral or carotid artery diseases that cannot be cured by surgery; severe chronic obstructive pulmonary disease or severe chronic bronchitis; irreversible severe hepatic and renal insufficiency; advanced malignant tumors; severe psychosis that is difficult to cure; active peptic ulcer; patients who cannot understand the problems related to transplantation and cannot take medicine on time; HIV antibody positive; acute pulmonary embolism; heavy smokers in the past six months; patients who cannot be considered for transplantation who are over 65 years old generally; drug addicts and alcoholics.

12.8.3 Selection of Transplantation Technology

The surgical techniques of heart transplantation have been explored for nearly 30 years and have become mature. At present, there are three main surgical methods: classical method, double vena cava anastomosis, and total heart transplantation. At present, it is considered that the classical method is simple and suitable for the use of heart centers that undertake transplantation in the initial stage of establishment. However, this method retains more atrial tissues and easily leads to atrial

enlargement and distorted heart position after transplantation, which can significantly increase the incidence of right ventricular dysfunction and arrhythmia. Therefore, for skilled cardiac transplantation doctors, double vena cava anastomosis, or whole heart transplantation should be adopted as far as possible. Myocardial protection during heart transplantation is also a key measure to improve the effect of operation. At present, all kinds of myocardial protection solutions can achieve better protection effect, among which continuous low flow warm blood perfusion with oxygen is the most ideal. Aiming at ischemia-reperfusion injury after transplantation, pre-open ischemic preconditioning can improve the prognosis of ischemia-reperfusion injury after transplantation.

Postoperative complications

1. Hemorrhage and pericardial effusion: They are common complications after heart transplantation, especially those who have had a history of heart surgery. Many patients received oral warfarin anticoagulation before operation. After operation, the original enlarged heart was replaced by a normal heart, thus forming a larger pericardial cavity, which may lead to cardiac tamponade due to bleeding.
2. Pulmonary arterial torsion: Pulmonary arterial anastomotic torsion is due to inadequate anastomosis of donor and recipient pulmonary arteries. Almost all heart implants have a certain degree of clockwise turn.
3. Rejection: Hyperacute rejection is an early and fatal complication after surgery, which is rare. It usually occurs shortly after the anastomosis is completed in the operating room and the aorta is opened. Super acute rejection can be predicted by the determination of group reactive antibodies in recipient patients before heart transplantation, and determined by the positive cross-reactivity between recipient and donor. Super acute rejection is introduced by antibodies, which can occur when the circulating antibodies pre-formed by recipient patients directly confront the human leukocyte antigen (HLA) present in the endothelial cells of donor hearts. This combination of antigens and antibodies leads to thrombosis, marked arteritis, and damage to coronary endothelial cells, which constricts the coronary artery and causes severe necrosis and hemorrhage of the donor heart. The donor heart often has punctate hemorrhage and cannot be resuscitated. Acute rejection can occur at any time after transplantation, 90% within 3 months after transplantation, and 40–45% within 4 weeks.
4. Hypertension: Recent hypertension after heart transplantation may be secondary to volume overload, pre-transplantation renal insufficiency, or the use of cyclosporine. It has been reported that cyclosporine can cause side effects of hypertension in non-transplant patients such as patients with autoimmune diseases. Most cyclosporine-related hypertension occurs 1 month after the use of drugs, and about 50% of patients develop hypertension 1 year later, characterized by persistent elevation of blood pressure at night. Because hypertension is appearing in adults and children after heart transplantation, it can be assessed by 24-h ambulatory blood pressure monitoring. Hypertension after heart transplantation is characterized by circadian rhythm disorder and 24-h blood pressure overload. Diuretic therapy actively can reduce volume load, or calcium

antagonists are effective. Adjustment of living habits can help drug therapy to achieve more effective control of blood pressure.

5. Impairment of cardiac allograft function: the following factors can reduce cardiac function: (1) longer cold ischemia time, ischemia time exceeding 4 h, usually due to myocardial edema leading to decreased systolic and diastolic function; (2) improper perfusion of cold myocardial protective solution and inappropriate drainage after donor heart rebound during heart harvesting can lead to ischemic injury; (3) older donor heart (>40 years old); and (4) longer hypotension time, for high concentration of vasopressor was used to maintain donor blood pressure. The latter can lead to subendocardial ischemic injury induced by catecholamine.
6. Transplanted coronary heart disease, also known as cardiac allograft vasculopathy (CAV), is a major complication affecting the long-term survival of heart transplant patients. Unlike common coronary heart disease, transplanted coronary heart disease originates from distal arterioles and then gradually extends to proximal vessels. Lesions rarely involve major coronary artery branches located in the epicardium.
7. Right heart failure: Right heart failure is one of the main causes of death in the first five days after heart transplantation, because the recipient has chronic, relatively fixed pulmonary hypertension before transplantation. Pre-transplant hemodynamic estimates must determine which patients are likely to develop right heart failure due to pulmonary hypertension. The size or gender mismatch between donor and recipient may promote the occurrence and development of right heart failure.
8. Arrhythmia: About 50–80% of patients need temporary cardiac pacing in the early stage after heart transplantation. This is due to the stimulation of sinoatrial node and atrioventricular node by perfusion of myocardial protective fluid, long-term cold preservation, and surgical operation.
9. Renal dysfunction: Cyclosporin is toxic to the kidney. It inhibits the production of prostacyclin, enhances the role of thromboxane, and also promotes the production of vasoconstrictive endothelial cells. Then promoting the contraction of renal arterioles and glomerular ischemia can lead to acute or chronic renal dysfunction.
10. Others: Most infections occur early after operation. If the patient has fever, CT scan can help to find the source of infection and guide the treatment. Long-term use of immunosuppressive drugs can promote the occurrence of malignant tumors. The incidence of cancer is about 100 times that of the normal population. The most common malignant tumors after heart transplantation are skin cancer and cell dysplasia [100].

12.8.4 Management of Postoperative Hypertension

Drug therapy is the main choice for hypertension after heart transplantation. In general, the early occurrence of hypertension after transplantation is related to volume. Diuretics can reduce the blood pressure of heart volume load. Although diuretics are effective in lowering blood pressure in transplant patients, they are

seldom used alone. When diuretics are combined with cyclosporine A (CSA) or tacrolimus (Tac), we should be taken care to avoid relative insufficiency of patient capacity. Alpha receptor blockers, beta receptor blockers, and direct vasodilators (hydrazine) have been successfully used in heart transplant patients [104]. Conventional doses of angiotensin-converting enzyme inhibitors (ACEI) and calcium channel blockers are effective for most patients. However, it should be noted that CsA or Tac combined with ACEI or angiotensin II receptor blockers (ARB) can lead to hyperkalemia and aggravate renal insufficiency. Many dihydropyridine calcium channel blockers, such as diltiazem, verapamil, amlodipine, felodipine, and nicardipine, increased CsA concentration by 23–35%. Diltiazem is most commonly used as a calcium channel blocker to reduce blood pressure and reduce the consumption of CsA or Tac to save money. Posttransplantation hypertension may be difficult to control, and several kinds of antihypertensive drugs are needed. Felodipine has been reported to increase Tac concentration by more than 50%. Although nifedipine has no effect on the pharmacokinetics of CSA, caution should be taken when any dihydropyridine calcium channel blockers are combined with or discontinued with Tac and CSA. The denervated heart adjusts its positive muscular response to exercise mainly by circulating catecholamine levels. Beta blockers can significantly limit exercise tolerance in heart transplantation patients with overweight. High doses of beta blockers are commonly used only in patients with refractory hypertension or myocardial infarction caused by CAV. Individual patients switched CsA to Tac, and lowering the dosage of CsA or corticosteroids helped to control blood pressure.

12.8.5 Prognosis

Current studies have shown that the survival rate of children after heart transplantation is better than that of adults. The average survival time of children is 16.5 years and that of adults is 10.8 years. One year after transplantation, the survival rate was about 85–90%. The 5-year survival rate was 65–70%. Non-ischemic and ischemic cardiomyopathy had the highest 1-year survival rate after heart transplantation, followed by valvular disease, congenital heart disease and heart re-transplantation. Among them, congenital heart disease has the highest long-term survival rate. Secondly, the older the recipient, the lower the long-term survival rate; And the older the donor, the higher the mortality rate after transplantation. The survival rate of female recipients after transplantation was significantly higher than that of male recipients. Extracorporeal membrane lung (ECMO) survival during transplantation is reduced, especially in the first few months after transplantation. The causes of death after transplantation include transplant organ failure, non-cytomegalovirus (CMV) infection and multiple organ failure. The death rate due to transplant organ failure was the highest within 30 days after transplantation. The death rate due to infection complications occurred in the first year after transplantation. The death rate of malignant tumors, graft vasculopathy, and renal failure increased with the increase of transplantation time [100].

12.9 Complete Atrioventricular Block

Zuoreguli Aibaidula

Complete atrioventricular (AV) block is defined as interruption in the transmission of the cardiac impulse from the atria to the ventricles due to an anatomical or functional impairment in the AV conduction system. This is the highest atrioventricular block. The block area may be located in the atrioventricular node, His bundle branch system. Clinically, some patients may be asymptomatic, but most patients have palpitation, obvious activity, often accompanied by dizziness, fatigue, chest tightness, shortness of breath, such as ventricular rate is too slow, can occur dark, or even syncope, and amaurosis may occur. Due to the increase of ventricular diastolic filling and cardiac volume, systolic blood pressure and pulse pressure are often observed clinically.

12.9.1 Epidemiology

Complete atrioventricular block can be divided into congenital and acquired. Congenital atrioventricular block was first described in 1901 by Morquio, who also noted a familial occurrence and an association with Stokes–Adams attacks and death. The presence of fetal bradycardia (40–80 bpm) as a manifestation of CHB was first noted in 1921. The incidence of congenital complete atrioventricular block in the general population varies between 1 in 15,000 and 1 in 22,000 live-born infants, the majority of which are autoimmune mediated. Acquired complete atrioventricular block might be a complication of surgical repair, infection, neoplasm, or other rare occurrences; it can occur later in childhood or adolescence spontaneously.

12.9.2 Etiology

1. Acute myocardial ischemia or necrosis: Complete atrioventricular block is common in patients with coronary heart disease, especially in patients over 50 years old. The incidence of complete atrioventricular block in acute myocardial infarction was 1.8–8% [105].
2. Focal or diffuse acute myocardial inflammation: Viral myocarditis leading to third-degree atrioventricular block is not uncommon, usually temporary, but occasionally can also be the initial manifestation and cause of sudden death in patients with acute myocarditis [106].
3. Conduction system or myocardial degeneration: degeneration caused by unknown fibrosis of conduction system, cardiomyopathy, myocardial amyloidosis, mitral or aortic valve calcification, and tumor compression. For dilated cardiomyopathy, 15% had complete atrioventricular block [107].
4. Injurious lesions: Most of them are conduction system damage or surrounding tissue edema caused by surgery.
5. Toxic effects of digitalis, quinidine and chloroquine.

6. Functional changes of conduction system: elevated vagal nerve tension, hypoxia, electrolyte disturbance (hyperkalemia, hypokalemia) and hyperthyroidism, etc.
7. Congenital heart conduction system defect: such as congenital endocardial cushion defect, giant atrial, ventricular septal defect and macrovascular malposition [106, 108].

12.9.3 Pathogenesis and Pathophysiology

The mechanism of complete atrioventricular block is that the pathological absolute refractory period of the atrioventricular junction area is extremely prolonged, which occupies the whole cardiac cycle. All atrial excitations fall within the absolute refractory period of the atrioventricular junction, which prevents all atrial excitations from being transmitted to the ventricle. The ventricle is controlled by the atrioventricular junction area or pacing point, forming the atrioventricular junction area escape rhythm or ventricular escape rhythm, or the atrioventricular conduction system due to surgical injury or congenital malformation and the occurrence of complete atrioventricular block [109].

Complete atrioventricular block leads to hypertension mainly due to the increase of ventricular diastolic filling and cardiac volume, which leads to the increase of systolic blood pressure, pulse pressure and peripheral vascular signs.

12.9.4 Clinical Manifestations and Complications

1. Clinical manifestations: complete atrioventricular block is more common in patients over 50 years old, and complete atrioventricular block is more common in young patients temporarily. More men are affected than women. The symptoms and hemodynamic changes of complete atrioventricular block depend on the degree of ventricular rate deceleration, myocardial lesions, and functional status.
   (a) Congenital complete atrioventricular block: When complete atrioventricular block occurs, the time-dependent relationship between atrium and ventricle is separated, and the auxiliary pump function of atrium to ventricular contraction is lost, resulting in a decrease in cardiac output. In congenital complete atrioventricular block, the ventricular rhythm point is usually above the bifurcation of the atrioventricular bundle, the ventricular rate is faster, and can increase with physical activity. Myocardial function is good, cardiac output is easy to increase, so these patients often have no obvious symptoms [110].
   (b) Acquired complete atrioventricular block: Most patients with acquired complete atrioventricular block are asymptomatic at rest or have palpitations. Palpitations, dizziness, fatigue, chest tightness, and shortness of breath may occur during physical activity. If the ventricular rate is too slow, especially if the heart has obvious ischemia or other pathological changes at the same

time, or is complicated by extensive acute myocardial infarction or severe acute myocarditis, the symptoms may be more severe. Heart failure or shock may occur, or because of insufficient cerebral blood supply, slow reaction or confusion may occur, and then develop into syncope (the incidence can be up to 60%) and Aspen syndrome. With the increase of diastolic ventricular filling and stroke volume, there may be widening of pulse pressure difference and mild to moderate cardiac enlargement [111, 112].

(c) Clinical manifestations of complete atrioventricular block in acute myocardial infarction: The degree of hemodynamic disturbance in acute myocardial infarction depends on the location of infarction, the rate of conduction block, the location of ventricular pacing point, and ventricular rate. Inferior wall infarction complicated with third-degree atrioventricular block, such as the gradual development of first-degree or second-degree ventricular block, with ventricular rate not too slow, cannot cause clinical deterioration. On the contrary, hypotension, shock, and severe left ventricular failure may occur in most anterior wall infarctions with third-degree atrioventricular block. Complete atrioventricular block caused by acute myocardial infarction is mostly temporary, and only a few patients never recover after infarction [113, 114].

2. Signs: The heart rate is only 30–40 beats per minute. Congenital third-degree AVB heart rate can reach 0–60 beats per minute, the first heart sound intensity varies. The audible fourth heart sound (S4) and the special *firing sound* are the results of phase change during atrioventricular contraction.
3. Characteristics of hypertension: Due to the increase of ventricular diastolic filling volume and cardiac volume, the patients' systolic blood pressure and pulse pressure increase, and the occurrence of water pulse and femoral artery gunshot sound.
4. Complications
   (a) Syncope: According to statistics, 19% of the patients had cardiogenic syncope.
   (b) Adams–Stokes syndrome: Complete atrioventricular block patients are more prone to this disease, especially those with ventricular rate below 35–40 beats/min, long intervals of ventricular beats, or no escape beats at low pacing points. As a result of the marked reduction of cardiac output, blood pressure decreases and cerebral cortical dysfunction caused by the failure to maintain the minimum blood flow in brain tissue occurs.
   (c) Sudden cardiac death: 20–30% of sudden cardiac death is slow arrhythmia or cardiac arrest.
   (d) Heart failure: Complete atrioventricular block causes a significant decrease in cardiac output due to the loss of atrioventricular sequential contraction; coupled with the original cardiac basis, it is easy to induce heart failure.
   (e) Cerebral embolism: Complete atrioventricular block can lead to blood flow disorder, which is easy to form mural thrombosis. Once it falls off, it will form cerebral embolism.

12.9.5 Supplementary Examination

ECG examination: The characteristics of typical complete atrioventricular block are as follows: (1) Atrial (P) and ventricular (QRS) are respectively excited and unrelated, showing complete atrioventricular segregation. The P-R interval was not fixed and the atrial rate was faster than the ventricular rate. (2) Atrial rhythm can be sinus rhythm, atrial tachycardia, atrial flutter, or atrial fibrillation. (3) Ventricular rhythm can be atrioventricular junctional escape rhythm (QRS wave is normal), ventricular rate 40–60 beats/min or ventricular escape rhythm (QRS broad deformity), ventricular rate 20–40 beats/min. Ordinary or irregular ventricular rhythm.

12.9.6 Differential Diagnosis

1. Complete atrioventricular dissociation: Similar to complete atrioventricular block, both showed atrioventricular separation, regular P-P interval, regular R-R interval, and no fixed relationship between P-R. The distinguishing points between the two are as follows: (1) The ventricular rate of complete atrioventricular dissociation was higher than that of atrial rate (QRS wave was more than P wave), and the ventricular rate was generally faster than that of 60 beats/min. The room rate was higher than the ventricular rate (P wave was more than QRS wave), and the ventricular rate was slower, generally less than 60 beats/min. (2) The QRS wave of complete atrioventricular dissociation is mostly supraventricular (normal), and the width of QRS wave of complete atrioventricular block is abnormal [115].
2. In complete atrioventricular dissociation, interference and block coexist: When the ventricular rate is between 60 and 100 times/min, the p-wave occurring in the middle diastole cannot capture the ventricle. The complete atrioventricular disjunction caused by the coexistence of two factors can be considered. atrioventricular dissociation.

12.9.7 Treatment

Objective and principle: Complete atrioventricular block is a serious and dangerous arrhythmia, which must be treated promptly and actively. On the one hand, actively seek for the causes and treat the causes, such as timely control of various infectious diseases, correction of electrolyte disorders, treatment of digitalis drug poisoning, myocarditis, cardiomyopathy, and other primary diseases; on the other hand, The principal therapeutic decision at the time of diagnosis involves the need for pacemaker placement [116–120].

12.9.8 Prognosis

Prognosis of complete atrioventricular block depend on the nature and severity of disease, whether the combined cardiac insufficiency and response to treatment.

Temporary third-degree AVB can often restore sinus rhythm within 1–2 weeks after effective treatment of etiology. The prognosis of third-degree AVB with QRS wave broadening and slow frequency is poor. It is often seen in diffuse myocardial lesions or extensive anterior myocardial infarction. It is easy to cause frequent attacks of AS syndrome, poor response to treatment, and sudden death. Long-term third degree AVB can cause cardiac hypertrophy and heart failure. Congenital third-degree AVB usually has a good prognosis if there are no other serious congenital malformations. With the wide application of artificial cardiac pacing, the prognosis of complete atrioventricular block has been greatly improved.

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Obstructive Sleep Apnea and Hypertension

13

Xiaoguang Yao, Mei Li, Ling Yao, and Liang Shao

13.1 Sleep Apnea Syndrome and Hypertension

Mei Li

Sleep disordered breathing (SDB) is a common disorder characterized by complete or partial obstruction of the upper airway during sleep and apnea caused by decreased central drive of breathing, which leads to chronic intermittent hypoxia, carbon dioxide retention, repeated micro-awakening, abnormal sleep structure, daytime sleepiness, memory decline, and group of syndromes causing autonomic nervous dysfunction [1]. They can be divided into obstructive sleep apnea (OSA), central sleep apnea (CSA), and sleep-related hypoventilation.

13.1.1 Epidemiology

13.1.1.1 Prevalence

Many population-based case studies in the United States, Australia, and Europe point out that OSA prevalence varies among adults according to different definitions of OSA (measurement methods, snoring criteria, and truncation values of AHI). Apnea hypopnea index (AHI) was greater than five events per hour. The estimated prevalence of OSA in North America was 20–30% in males and 10–15% in females [2, 3]. If a more stringent definition is used, that is, AHI is greater than or equal to five events

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per hour and patients report at least one symptom of sleep disorder (such as daytime sleepiness), or AHI is greater than or equal to 15 events per hour, the estimated OSA prevalence is about 15% in men and 5% in women [2–4]. OSA is more common in African Americans under 35 years of age (independent of weight) than in white people of the same age group [5, 6]. Although the risk of obesity and related craniofacial anatomical abnormalities is low in Asians, the prevalence of OSA is similar to that in Americans [4, 7]. In some populations, the prevalence of OSA has increased significantly, for example, in patients undergoing weight loss surgery (estimated at 70–80%) [8] or in patients with transient ischemic attack or stroke (estimated at 60–70%) [9]. Other disease-specific populations found to increase the incidence of OSA include heart failure [10], coronary heart disease, arrhythmia, type 2 diabetes mellitus, and polycystic ovarian disease [11, 12]. OSA is more common in men, 2–3 times more common than in women, but it narrows in menopausal women [13–15].

13.1.1.2 Relevant Risk Factors

The clinical risk factors of OSA include aging, male, obesity, craniofacial morphology, or abnormal upper airway soft tissue. Other risk factors identified in some studies include smoking, nasal congestion, menopause, and family history. Some medical conditions also increase the incidence of OSA, such as pregnancy, end-stage renal disease, congestive heart failure, chronic lung disease, posttraumatic stress disorder, and stroke.

1. Obesity:
   With the increase of BMI and related indicators (such as neck circumference, waist-hip ratio) in both men and women, the prevalence of OSA increased gradually [3.14]. In a prospective study, nearly 700 adults were followed up longitudinally for 4 years and found that 10% weight gain increased the risk of new OSA to six times [16]. A population study involving more than 1000 adults who underwent polysomnography revealed that 11% of normal-weight men, 21% of overweight men (BMI 25–30 kg/m^2), and 63% of obese men (BMI > 30 kg/m^2) had moderate to severe OSA (AHI > 15) [14]. The same trend exists in adult women: 3% normal weight women, 9% overweight women, and 22% obese women have OSA. A retrospective cohort study included 184 obese individuals with hypoxemia at awake and found a prevalence of 80% for OSA (AHI > 5) [17]. A study using data modeling from a prospective North American cohort study and the National Health and Nutrition Examination Survey (NHANES) database found that OSA prevalence estimates increased from 1990 to 2010 in all age groups and BMI categories studied, with an increase of up to 50% in some cases [3].
2. Age and gender:
   The prevalence of OSA increased from the early adulthood to the age of 50–60, and then stabilized [14, 18]. OSA is more common in men than in women, which is 2–3 times more common, but in menopausal women, the gap narrows [13–15].

3. Upper airway anatomy abnormality:
   Both craniofacial abnormalities and upper airway soft tissue abnormalities may increase the likelihood of developing OSA or OSA [13]. These factors are most recognized in Asian patients whose obesity is not very significant [19]. Such abnormalities are, for example, abnormal maxillary size or short mandible, wide craniofacial base, tonsil hypertrophy, and adenoid hypertrophy.
4. Long-term heavy smoking:
   Smoking seems to increase the risk of OSA or at least aggravate existing symptoms. A study shows that the likelihood of OSA in current smokers is nearly three times that of former smokers or never smokers [20] family history.
5. Family history:
   OSA patients often report a family history of snoring or OSA. Although this may be due to the presence of common obesity-related behavioral factors, it may also be due to the presence of craniofacial structures and other genetic susceptibility to OSA [21]. It has been suggested that about a quarter of patients with OSA have a genetic basis [22].
6. Long-term heavy drinking and/or taking sedative hypnotics:
   Although a variety of substances and drugs (including alcohol, benzodiazepines and anesthetics) may aggravate OSA, its causal relationship has not been confirmed [23].
7. Other related diseases:
   including neuroendocrine diseases, such as hypothyroidism, acromegaly, hypopituitarism, amyloid, peripheral nerve palsy, myasthenia gravis, cerebrovascular disease, etc.

13.1.1.3 Complications

SDB is closely associated with several of the most important chronic diseases, including cancer, cardiovascular disease, heart failure, hypertension, diabetes, stroke, and COPD. In these disease states, the prevalence of SDB/OSA varies, with COPD of 3–66% and congestive heart failure (HF) and stroke of approximately 75%. SDB is also associated with the development and severity of these diseases.

1. Heart failure
   The overall prevalence of obstructive and central sleep apnea varies from 47% to 81% in the population with heart failure, which may be attributed to different demographic criteria (age, sex, and race), risk factors (obesity and comorbidity), AHI truncation values, and heart failure incidence [17].
2. Hypertension
   Detailed below.
3. Diabetes
   OSA is thought as “metabolic syndrome.” More and more evidences show that OSA is associated with metabolic abnormalities such as dyslipidemia, hypertension, hyperuricemia, insulin resistance, impaired glucose tolerance, and type 2 diabetes mellitus. The prevalence of diabetes mellitus in OSA patients is much higher than that in snoring patients. With the increase of OSA severity, blood

sugar control becomes worse. OSA is an independent risk factor for diabetes mellitus [24, 25]. The findings of 3 prospective US cohorts (Nurses' Health Study(NHS;2002–2012), Nurses' Health Study II (NHSII;1995–2013), and Health Professionals Follow-Up Study(HPFS;1996–2012)) comprising participants free of diabetes, cardiovascular disease, or cancer at baseline indicate a bidirectional correlation between diabetes and OSA. OSA is associated with 37% of diabetes risk, independent of demographics, lifestyle, comorbidity, and anthropometric factors. In contrast, the risk of developing OSA in diabetic patients is also moderately increased. After adjusting for obesity, it is found that diabetic patients treated with insulin, especially women, have a 43% higher risk of developing OSA [26].

4. Stroke
   There is sufficient evidence that 50–70% of stroke patients have sleep-related breathing disorders. Among them, 90% of stroke patients have severe neurological impairment, long hospitalization and rehabilitation time, stroke recurrence, and mortality increase [27, 28]. And studies have shown that obstructive sleep apnea syndrome is mainly associated with increased risk of ischemic stroke [29, 30].
5. Chronic Obstructive Pulmonary Disease (COPD)
   COPD-OSA Overlap Syndrome, which implies that both disorders occurring together. Overlap syndrome is uncommon in the general population and inpatients (range: 1.0–3.6%), but in patients diagnosed with OSA (range: 7.6–55.7%) or COPD (range: 2.9–65.9%), it is highly popular. Patients with overlap syndrome have greater nocturnal oxygen desaturation (NOD) than those with OSA alone (showed as lower capillary peripheral oxygen saturation oxygen saturation (SpO2) and longer sleep time with SpO2<90% (T90)) moreover, the quality of sleep is even worse [31, 32].

13.1.2 Diagnosis and Differential Diagnosis

At present, there is no unified diagnostic and grading standard at home and abroad, and there are different opinions on the definition of adult OSA.

1. Early detection of high-risk patients:
   Clinically, should be highly vigilant if patients suffer from sleep apnea at the same time, or whether their cardiovascular diseases are related to sleep apnea: (1) refractory hypertension, or circadian rhythm of blood pressure is non-dipper or reverse dipper; (2) repeated angina pectoris occurs at night and severe myocardial ischemia is difficult to alleviate; (3) night-time refractory arrhythmias are serious, complex, and difficult to correct, mainly slow arrhythmias or fast–slow alternating arrhythmias; (4) intractable congestive heart failure; (5) incomplete daytime hypoxemia or polycythemia, increased blood viscosity; (6) increased insulin resistance and uncontrollable diabetes mellitus.
2. Screening diagnostic apparatus examination:

Most of them are portable, most of them are combined with PSG monitoring indicators, such as simple SaO2 monitoring, nasal and nasal airflow + SaO2 monitoring, nasal and nasal airflow + snoring + SaO2 monitoring + chest and abdomen movement, etc., mainly suitable for lack of PSG monitoring at the grassroots level. Some mild patients who are unable to be examined in the sleep monitoring room due to changes in the sleeping environment or too many leads may be used to exclude OSA or to initially screen OSA, as well as for pre- and posttreatment comparisons and patient follow-up.

3. Polysomnography (PSG):
   (1) Polysomnography is commonly used to diagnose sleep disorders and is the gold standard for the diagnosis of OSA. By recording dual lead electroencephalography (EEG), dual lead electrooculogram (EOG), mandibular electromyography (EMG), electrocardiogram, oral and nasal respiratory flow, chest and abdomen respiratory movement, SaO2, position, snoring and sputum muscular EMG and other physiological indicators, to understand the sleep phase, respiratory and blood oxygen conditions, with or without frequent physical activity, comprehensive assessment of the presence and nature of OSA and extent.

   It is generally believed that OSA can be diagnosed in adults with AHI (>5 times per hour) and ESS (Epworth sleepiness score) (>9 points) during 7 h of sleep. According to blood oxygen saturation (SaO2) and apnea hypopnea index (AHI), the severity of sleep apnea was classified as mild 5 times per hour (<AHI < 15 times per hour), moderate 15 times per hour (<AHI < 30 times per hour), and severe AHI (>30 times per hour).

   (2) Diagnostic criteria: According to medical history, signs and PSG monitoring results, there are typical nocturnal snoring, irregular breathing, and excessive daytime sleepiness in clinic. PSG monitoring indicates that sleep apnea and hypopnea recur more than 30 times during 7 h of sleep every night, or AHI is greater than or equal to 5 times per hour, which can be diagnosed as sleep apnea syndrome.

   (3) Grading: OSA is classified into mild, moderate, and severe according to AHI and nocturnal oxygen saturation, with AHI as the main criterion and the lowest SaO2 as the reference (Table 13.1).

   Clinical indications of PSG: (1) Patients with OSA-related signs or symptoms, such as sleep snoring, obesity, daytime sleepiness, and abnormal nasopharyngeal and oral anatomy; (2) Other clinical symptoms and signs support sleep apnea disorders, such as night asthma, pulmonary, or neuromuscular disorders affecting sleep; (3) unexplained daytime hypoxemia or polycythemia; (4) unexplained arrhythmia, night angina pectoris, morning hyperten-

Table 13.1 Grading of OSA

Main criteria	Mild	Moderate	Severe
AHI (events/h)	5–15	15–30	>30
$LaSO_2$ (%)	85–89	80–84	<80

sion, and pulmonary hypertension; (5) monitoring the degree of hypoxia during night sleep to provide objective basis for oxygen therapy; (6) recognizing that obvious cognitive impairment, nocturnal urine and brain and urinary system disease degree is not parallel; (7) to evaluate the therapeutic effect of various treatment methods on OSA.

4. Home sleep apnea testing.
   In general, home sleep apnea testing (HSAT) devices are classified as Type III or Type IV instruments depending on the number and type of leads used. HSAT devices typically do not include EEG, EMG, or eye movement monitoring, and these monitoring are used to identify if sleep is still awake. PSG identifies the severity of sleep-disordered breathing based on real sleep time, while HSAT is based on the estimated severity of the monitoring time (e.g., respiratory event index, REI). Conventional leads used by HSAT also do not detect hypopnea associated with cortical arousal. Due to these limitations, HSAT may underestimate the severity of OSA.

   Both PSG and HSAT can be used for adult diagnosis of OSA, but HSAT is slightly less sensitive than PSG. For adult patients with uncomplicated symptomatic signs and high suspicion of moderate-to-severe OSA, it is recommended to use adequate HSAT for PSG or device technology (highly recommended). If the technically adequate HSAT test results are negative, it is recommended to use PSG instead of the second night of HSAT review (strongly recommended). If HSAT technology is not sufficient, PSG is recommended to diagnose symptomatic patients.

   Due to the high price and complicated implementation of the laboratory PSG examination, its clinical application is limited. To a certain extent, PSG is expected to be replaced by HSAT. If the family management path is implemented, the HSAT is more cost effective. However, HSAT is not recommended for the diagnosis of suspicious OSA patients with concomitant disease (strongly not recommended).
5. Evaluation of lethargy: It includes two parts: subjective evaluation and objective evaluation.
   Subjective assessment of lethargy (Epworth sleepiness scale [33], Berlin questionnaire [34], STOP-Bang [35], NOOSA [36]).

   The objective assessment of lethargy is primarily assessed by daytime sleepiness in suspicious patients. A multiple sleep latency test (MSIT) is commonly used, which is an examination method for objectively determining the degree of daytime sleepiness by allowing the patient to perform a series of short sleeps during the day. Test every 2 h, each time lasting 30 min, calculate the average latency of patients falling asleep and the number of abnormal rapid eye movement sleep, sleep latency <5 min is lethargy, 5–10 min is suspicious sleepiness, >10 min is normal.
6. Other laboratory examinations, including erythrocyte count, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin concentration, arterial blood gas analysis, fasting lipid, blood sugar, X-ray chest film, X-ray projection measurement (determination of upper airway obstruction plane), electrocardiogram, cardiac ultrasound, etc.

Differential diagnosis

1. Primary snoring: There were almost no respiratory obstruction attacks, no sleep rupture or impaired daytime function. The critical value of apnea-hypopnea index was <5 apnea/hypopnea events [37] during hourly sleep.
2. Upper airway resistance syndrome (UARS): UARS is characterized by increased respiration during sleep, can lead to sleep disruption, and is suspected of being overly sleepy, fatigued, and sleep disrupted during the day. This condition first appeared in adults with excessive daytime sleepiness and increased wakefulness. The UARS criteria are the presence of lethargy (Epworth Sleep Scale [ESS] ≥ 10) and/or fatigue (Modified Fatigue Impact Scale [MFIS] ≥ 38), and apnea/hypopnea index (AHI) ≤ 5 and respiratory disorder index (RDI) > 5 events/h of sleep and/or more than 30% of total sleep time (TST) [38].
3. Obesity hypoventilation syndrome: Obesity hypoventilation syndrome describes the relationship between obesity and the development of chronic daytime alveolar hypoventilation. The syndrome results from a complex interaction between sleep-disordered breathing, decreased respiratory drive, and obesity-related respiratory damage, and is associated with significant morbidity and mortality. Treatments that reverse these abnormalities improve daytime respiration, including available treatment options such as positive pressure therapy, weight loss, and medication management [39].

13.1.3 Pathogenesis

The pathogenesis of OSAS is still not fully understood. Its clinical manifestations are generally attributed to upper airway obstruction, hypoventilation, and sleep division; pharyngeal muscle collapse is the main cause of poor breathing and pause during sleep. Despite the continued forced breathing of the body to compensate, the blocked pharyngeal airways still interfere with effective ventilation, causing apnea and hypopnea.

1. Anatomical features
   (1) reduced ventilatory motor impulse output will reduce upper airway muscle activity, especially muscles that are strenuous [40, 41]. A study investigating respiratory muscle activity at the onset of sleep showed that when the EEG waveform was dominated by θ (light sleep) rather than α (awakening), the activity of the respiratory muscles and upper respiratory tract muscles changed less [42]; (2) changes in airway caliber and compliance—with sleep, accompanied by decreased pharyngeal caliber, increased upper airway resistance [43], and increased upper airway compliance [44]. A significant increase in upper airway resistance results in increased airflow turbulence, limited inspiratory flow, and soft tissue and upper airway soft tissue vibration [45, 46]; (3) lower airway alveolar surfactant changes, in recent years, the study will only focus on the upper airway changes deep into the lower airway changes, studies have shown that the level of alveolar surfactant protein in patients with OSA is reduced [47, 48].

2. Enhanced autonomic nervous activity
   Human and animal experimental studies have shown increased efferent sympathetic activity during seizure pause using microneurography.
3. Inflammatory factors
   Inflammation may cause stenosis of the upper airway, reflexes in the upper airway, upper airway collapse, and pharyngeal respiratory muscle function disorders. These processes may aggravate upper airway obstruction during sleep and form a vicious circle. Patients with OSAS have local upper airway inflammation and systemic inflammatory response. Among them, neutrophils and bradykinin and vasoactive intestinal peptide, neutral endopeptidase, bradykinin, and substance P may be associated with local inflammation of the upper airway, while some proinflammatory mediators such as CRP, TNF-a IL-1, IL-6, leptin, active oxidized family, and adhesion molecules may be associated with systemic inflammation. But the specific mechanism is still under further study.
4. Genetic factors
   Studies of first-degree relatives of twins and OSAS patients have shown that OSAS has family aggregation. A cohort study of the family showed that genetic factors have an effect on ventilation drive and anatomical features. Studies on children's OSAS have confirmed that some genetically related diseases, such as Down syndrome, horse syndrome, etc., affect the structure of the airways, muscle tone, muscle control, etc., which are prone to OSAS. Genetic factors also play an important role in central ventilatory control of OSAS. In some cases, related mutations are the main cause of abnormal ventilation control in the central nervous system. Animal and human experiments have shown that chromosome 8q22 contains three carbonic anhydrase isomerase genes: CA1, CA2, and CA3. The role of carbonic anhydrase is to regulate respiratory control. The action of carbonic anhydrase inhibitors is a latent therapeutic effect in respiratory instability, including periodic breathing and apnea during sleep.
5. Fluid-endocrine factors: OSAS is more common in men, postmenopausal women, acromegaly, hypothyroidism, which suggests that OSAS may be related to the regulation of endocrine hormones. There was a significant difference in the incidence of OSAS symptoms in women before and after menopause, probably because progesterone played a role before menopause, and androgen excess was associated with OSAS, and the mechanism was unclear. However, hemodialysis patients who use testosterone to stimulate erythropoiesis do not cause or cause an increase in OSAS, and the relationship between them remains to be further studied.
6. Obesity
   Obesity is also an important risk factor for OSAS. About 60–90% of adult OSAS patients are overweight. When BMI > 29 kg/m^2, the ratio of relative risk will be >10. Concentric fat distribution (abdomen and neck) is at greater risk. The effect of obesity on the structural load of upper airway during sleep is mainly due to the accumulation of fat in the airway wall occupying the pharyngeal volume. At the same time, the accumulation of fat in the abdomen pushes the diaphragm upward, reducing lung volume, especially reducing functional residual air. This effect

reduces the longitudinal traction of the lower respiratory tract to the main bronchus and upper airway during inhalation, and indirectly increases the compliance of the pharyngeal wall. Moreover, the infiltration of adipose tissue by the upper airway dilator in obese patients may reduce the contractile function of the upper airway dilator.

Hypopnea is the main cause of respiratory disorders. The pharyngeal collapse of OSAS patients is usually later than that of tongue, uvula, soft palate, or other components of these tissues. The pharyngeal airway (from nasal septum to epiglottis) lacks bone and is not rigid enough, so its opening mainly depends on muscle activity. The main abnormality in OSAS patients is the anatomical pharyngeal airway stenosis due to obesity, bone and soft tissue structure. This can also lead to increased airflow resistance and intra-pharyngeal negative pressure during inhalation in the awakened state. The mechanical receptor located in the larynx reacts to this negative pressure, causing an increase in the activity of the pharyngeal dilator, thus maintaining airway opening when awake. However, during sleep, the compensatory activity of the neuromuscular is reduced or disappeared, resulting in a decrease in the activity of the pharyngeal enlargement muscle, which eventually leads to stenosis of the pharyngeal cavity and complete collapse of the rupture. In the subsequent dyspnea or hypopnea, hypoxia and hypercapnia stimulate ventilatory function, causing wakefulness, thereby terminating apnea.

13.2 The Relationship Between OSA and Hypertension: Correlation or Causation

Liang Shao

Both obstructive sleep apnea (OSA) and hypertension (HTN) affect about 20–30% of general population worldwide and have been proposed to be causally related to nonfatal and fatal coronary events [49, 50]. From 1980s to now, several large population studies, including cross-sectional or longitudinal ones, have been performed on the relation between sleep disordered breathing and blood pressure (BP) changes, whose results have largely confirmed the positive "dose–response" relationship between OSA and HTN. It is commonly believed that more than half of patients with severe OSA are hypertensive. Therefore, the prevalence of OSA in subjects with hypertension is as high as 30–50%. Compared with general population, moderate to severe OSA increases the risk of hypertension by 1.5–3.2 folds [51–54].

OSA might be one of the most common secondary hypertension. Some studies do indeed support a causal role of OSA on the appearance of HTN. Animal experiments explain that intermittent hypoxia can have a significant effect on BP, and BP fails to return to normal after the release of hypoxia [55–57]. Though, meta-analyses have shown that the effects of continuous positive airway pressure (CPAP) treatment on hypertensive patients with OSA are very limited (about 3 mmHg), they mainly focus on the reduction of nocturnal BP, while SBP and DBP in daytime

remain unchanged [58]. However, the prevalence of OSA in refractory HTN is even higher, about 64–83%, especially in male patients. CPAP therapy for refractory HTN with OSA can achieve better BP lowering effects compared with general HTN patients [59–61].

13.2.1 Common Risk Factors (Shown in Fig. 13.1)

13.2.1.1 Obesity

HTN and OSA are each very strongly associated with obesity. Among the risk factors for OSA, obesity is probably the most important. The prevalence of obesity in both OSA and HTN is about 70% [62, 63]. The prevalence of moderate to severe OSA is threefold higher in the highest quartile of body mass index (BMI), relative to the lowest [52]. Greater BMI is associated with narrowing of the pharyngea, decreased regulatory function of the pharyngeal muscles, and decreased lung volume (especially in the recumbent position). Being overweight or obese can significantly increase the risk of OSA and HTN. Without obesity, there is no statistically significant relationship, however, between OSA and HTN. Therefore, it is no doubt that weight loss could reduce both BP and apnea and hypopnea index (AHI) in hypertensive subjects with OSA [64–66].

13.2.1.2 Gender

OSA is more common in men than in women. The male-to-female ratio for OSA prevalence ranges between 2:1 and 4:1, and this phenomenon also exists in hypertensive subjects [67, 68]. Cano-Pumarega et al. reveal the association between moderate and severe OSA, and the incidence of more severe forms of HTN (SBP ≥160 mmHg and/or DBP ≥100 mmHg) occurring in men (OR = 2.54 [95% CI, 1.09–5.95], P = 0.032) but not in women [69]. Otherwise, Huang et al. analyzed data from Nurses' Health Study (NHS), NHS-II (age 48–93 years), and from Health Professionals Follow-up Study (age 65–101 years) and observed that prevalence of OSA in men and women are 3.8% and 6.4%, respectively, and OSA is more closely associated with HTN in women than in men [70].

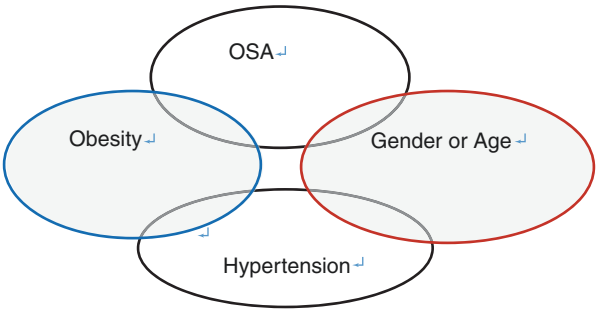

Fig. 13.1 Common risk factors of OSA and hypertension

13.2.1.3 Age

OSA (AHI > 10 times/h) in the elderly (65–99 years old) men and women can reach about 70% and 56%, respectively and the prevalence is about 2–3 times higher than that in the middle-aged population, whereas severe OSA is relatively rare [71, 72]. There are also differences in the effects of OSA on BP in different age groups. In the middle-aged population, OSA has a greater effect on nocturnal BP, especially DBP levels [73]. On the contrary, isolated systolic HTN, which is more common in the elderly, is not associated with OSA in any age groups. OSA in the elderly may be less severe than in the middle age, and may not be associated with the same increase in mortality and morbidity [71]. It remains to be clarified whether OSA in the elderly is a different condition from that observed in the middle-aged population.

13.2.2 Pathophysiologic Links Between OSA and HTN

During the sleep asset, BP shows a trend of decrease at the beginning of apnea, whereas gradually increases with the extension of apnea, and reaches the peak at the time of respiratory recovery, and then gradually decreases. Nonetheless, this acute change in BP is associated with changes in heart rate, nerves, and hemodynamics at the time. This process includes intermittent hypoxia, sleep fragmentation, and mechanical stress resulted from increased intrathoracic pressure, which can cause fluctuations in BP through the following mechanisms. Ultimately, this condition progress accelerates the developing of HTN.

13.2.2.1 Sympathetic Overactivity

The sympathetic nervous system is the highlight in the pathogenesis of OSA-related HTN. It has been proposed that intermittent hypoxia, repeated arousal, and dynamic changes in intrathoracic pressure are associated with increased sympathetic activity [74, 75]. The techniques used in studies to assess sympathetic nervous activity include direct recordings of muscle sympathetic nerve activity, and measurements of catecholamine levels [76, 77]. Even if sleep-related respiratory events disappear diurnally after awaking, individuals with OSA exhibit high levels of sympathetic nerve activity, which means that BP oscillation in OSA condition may not terminate immediately as evidenced in recent studies [78]. There is ample evidence from randomized controlled trials proving that treatment of OSA with CPAP reduces sympathetic nervous system activity [79–81].

13.2.2.2 Elevation of Circulating Aldosterone Levels

Aldosterone elevates BP through inducing sodium and water retention and fibrillation of cardiovascular and renal system. In addition, sodium and water redistribution during sleep is considered the main factor for occurrence of OSA in condition of elevated aldosterone [82]. Prevalence of OSA in HTN subjects with elevated aldosterone is as high as 77.3% [83], and severity of OSA is in positive association with aldosterone levels [84]. Calhoun et al. assessed risk of having OSA in population using Berlin questionnaire and observed that prevalence of primary

aldosteronism is twofold higher in those with higher risk for OSA than in those with lower risk (36% vs. 19%). Barcelo et al. reported that OSA subjects with and without metabolic syndrome have higher levels of aldosterone than in those without OSA and 12 month CPAP therapy lowered their aldosterone levels significantly than baseline [85], whereas Svatikova et al. failed to observe this condition in 40 OSA subjects and healthy volunteers without cardiovascular complications [86]. This inconsistency might be attributable to the fact that the relationship between OSA and aldosterone is affected by disease duration and severity.

13.2.2.3 Vascular Factors

Chronic intermittent hypoxia stimulates the secretion of inflammatory factors, increases products of oxidative stress, and decreases secretion of endothelium-derived relaxing factors and thus increases vascular resistance [87]. There is also co-relationship between OSA severity and biomarkers of vascular endothelial function. In addition, oxidative stress induces endothelium dysfunction, indicating the presence of atherosclerosis [88]. Tagetti et al. observed that AHI is negatively associated with vascular stiffness ($r = -0.367$), suggesting that it is one of the factors to elevate BP in OSA [89]. Furthermore, hypoxia induced factor resulted from respiratory events participates in BP regulation through inducing malfunction of internal carotid sinus [90]. CPAP therapy improves the systemic inflammatory levels of OSA, whereas its interruption worsens the endothelial malfunction, systolic and diastolic blood pressure, and heart rate [80, 91].

13.2.3 Identification of OSA in Hypertension

Although polysomnography (PSG), the ***gold standard*** for the diagnosis of OSA, has been widely used in clinical setting, its applicability is limited by the complexity of operation and analysis, expensiveness, and time consuming. Accordingly, in recent years, portable monitors have developed as a reasonable substitute for in-laboratory PSG, considering its high diagnostic value and comfort [92]. For consolidating comprehension and memorization, a four-step screening process is proposed for HTN population with suspected OSA, as shown in Table 13.2.

Table 13.2 Clinical clues for the screening of OSA

Assessment scale	STOP-Bang, Berlin Questionnaire, Epworth Sleepiness Scale.
Biomarkers	Hemoglobin, red blood cell count, [HCO_3^-](blood gas analysis).
Clinical prediction	Snore, excessive sleepiness, fatigue, nocturia. Microgenia, neck circumference > 40 cm, cyanosis, chest deformity, lower limbedema; a non-dipping pattern.
Diseases combined	Hypertension related diseases: diabetes, renal disease, hypothyroidism, stroke, primary aldosteronism. Other diseases: rhinitis, tonsil hypertrophy, neuromuscular disease.

13.2.3.1 Assessment Scale

Although screening tools such as the Berlin questionnaire (BQ), STOP-Bang questionnaire, STOP questionnaire (STOP), and Epworth sleepiness scale (ESS) are frequently used worldwide for OSA in general population, the findings regarding their diagnostic accuracy are controversial. Compared with the BQ, STOP, and ESS, the STOP-Bang is a more accurate tool (assessed by sensitivity and specificity) for detecting mild, moderate, and severe OSA [93]. Unfortunately, there is no accepted specific questionnaires for HTN with suspected OSA, whereas these screening tools still provide some valuable help.

13.2.3.2 Biomarkers

Complete blood count provides clinical manifestation or clues to the diagnosis of OSA, such as elevated hemoglobin and erythrocytes [94, 95]. Increased serum [HCO_3^-] in arterial blood gas analysis resulted from nocturnal carbon dioxide retention may partly reflect the severity of OSA [96]. Although some studies have found relationships between some serum biomarkers, such as inflammatory, special proteins and enzymes, and the severity of OSA, whereas unsatisfied sensitivity, specificity, and poor repeatability are still main disadvantages of these biomarkers [48, 97–99].

13.2.3.3 Clinical Prediction

Individuals at higher risk for OSA can be identified by considering demographic characteristics as well as body measurements and bed partner observations, including obesity, neck circumference (>40 cm), snoring, breathing pauses witnessed by a bed partner, sleepiness, fatigue, morning headaches, impaired concentration, dyspnea, restless sleep, nocturia, diaphoresis, peripheral cyanosis, and leg edema. It is well established that OSA promotes BP surges during sleep and non-dipping BP patterns. Therefore, it is feasible to use of 24-h ambulatory BP monitoring (ABPM) for the screening of moderate-to-severe OSA among HTN patients during their treatment. A non-dipping pattern (especially reverse dipping pattern), increased nocturnal BP variety, and morning BP surges may represent as good markers for diagnosing OSA from ABPM [100, 101].

13.2.3.4 Diseases Combined

Given the higher prevalence of OSA among individuals with HTN related diseases, such as diabetes mellitus, stroke, renal disease, and primary aldosteronism, it is necessary to conduct OSA screening in HTN subjects with above-mentioned conditions. Meanwhile, findings frequently noted on examination of the upper airway including posterior lateral wall narrowing, enlarged tonsils, tongue, and/or uvula, low-lying soft palate, rhinitis, and retrognathia also provide clinical clues for OSA, whereas with no sufficient evidence that these morphological changes are related to the severity of OSA [102]. Meanwhile, lower end-expiratory lung volume, as occurs in the setting of pulmonary disease, increases the tendency of the upper airway to collapse. Cardiopulmonary disease, impairing diaphragm, and interstitial lung diseases also should be noted [103].

13.3 Diagnosis of OSA-Related Hypertension

Xiaoguang Yao

Hypertension which is caused by or coexist with obstructive sleep apnea (OSA) is referred to as "OSA-related hypertension." Therefore, the diagnosis of the disease needs to meet two conditions: (1) obstructive sleep apnea, (2) hypertension.

1. Diagnosis of OSA.
   Although there many methods for clinical evaluation and diagnosis of OSA, such as symptoms and signs, nasopharyngoscopy, imaging examination under drug-induced sleep, Epworth sleepiness scale (ESS), STOP-Bang scale, polysomnography PSG, esophageal pressure test, home sleep apnea testing (HSAT), but the gold standard for OSA diagnosis is polysomnography (PSG) monitoring. See Sect. 1.2, *Diagnosis of OSA* in Sect. 1 of this chapter for detailed methods.
2. Hypertension is defined as a systolic blood pressure (SBP) ≥140 mmHg and/or a diastolic blood pressure (DBP) ≥90 mmHg in the absence of antihypertensive drugs. For the patient who has a history of hypertension and is currently using antihypertensive drugs should still be diagnosed as hypertension even the follow-up blood pressure is less than 140/90 mmHg [104].

13.4 OSA Treatment

OSA can cause multiple organ damage and is a veritable systemic disease. All patients with OSA should be approached as a chronic disease requiring longterm, multidisciplinary treatment according to the patient's condition [105]. There are behavioral, medical and surgical options for the treatment of OSA.

13.4.1 First, Behavioral Treatment

1. Weight loss. It is recommended that all overweight patients (BMI ≥ 23 kg/m^2) should be encouraged to lose weight; obese patients can be divided into nonsurgical treatment and surgical treatment according to different methods of weight loss.
2. Quit smoking, abstain from alcohol, use sedative hypnotic drugs with caution, as well as other drugs that can cause or aggravate OSA.
3. Positional therapy [106], including lateral sleep, properly raise the bedside; for patients with mild OSA, postural therapy can be used as an initial treatment. Which is simple, effective in mild OSA. For some patients with poor tolerance or less effect, postural therapy does not affect other subsequent treatments.
4. Avoid overwork during day time and avoid sleep deprivation.

13.4.2 Second, Surgical Treatment

Surgery is the basic method for the treatment of OSA. The purpose of surgical treatment is to reduce and eliminate airway obstruction and prevent airway soft tissue collapse. The choice of surgical method depends on the location of the airway obstruction, the severity, whether there is morbid obesity and general condition. The commonly used surgical methods are as follows.

1. **Tonsillectomy, adenoidectomy.** This type of surgery is only used in children with a history of tonsillary and adenoid hyperplasia before puberty. Generally, it is effective in the short-term after surgery. With the development of puberty, the tongue and soft diaphragm muscles can still recur after development.
2. **Nasal surgery.** Nasal septum angioplasty, nasal polyps or turbinate resection can be used to relieve symptoms due to nasal obstruction, nasal polyps, or turbinate hypertrophy.
3. **Tongueplasty.** By tongue hypertrophy, giant tongue disease, tongue root shift, tongue base tonsil enlargement, it is feasible to form a tongue.
4. **Uvulopalatopharyngoplasty (UPPP).** The operation is to remove the posterior margin of the soft palate and the loose pharyngeal wall mucosa, and the pharyngeal wall mucosa is stretched and sutured forward to relieve the soft palate and oropharyngeal airway obstruction, but cannot relieve the hypopharynx. The airway of the department is blocked, so you must choose the indications.
5. **Tracheostomy.** Tracheostomy is a permanent tracheotomy that was the only effective treatment in the 1970s. However, there are a series of problems in tracheostomy: lifelong cumbersome care, infection, loss of language ability, declining quality of life, work ability and social interaction difficulties, etc.; have been rarely used.
6. **Orthognathic surgery.** Since the 1970s, the technique of orthognathic surgery for the treatment of dental and maxillofacial deformities has become more and more mature. The application of orthognathic surgery to OSAHS for oropharyngeal and hypopharyngeal airway obstruction caused by jaw deformity has become one of the effective methods. There are four commonly used methods.
   (a) Mandibular advancement: This type of surgery can alleviate OSAHS caused by mandibular dysplasia and mandibular retraction. As the mandible moves forward, the genioglossus and its muscles move forward accordingly, and the tongue root is moved forward, thereby expanding the pharyngeal airway. Mandibular advancement is usually performed with bilateral mandibular sagittal splitting.
   (b) Anterior migration: This type of surgery is suitable for OSAHS without significant hernia retraction. Surgery is to preserve the lower edge of the lower jaw, and the osteotomy in the ankle is like a “drawer-like” with the genioglossus being pulled forward. The osteotomy block is rotated by 90° to fix it.
   (c) Anterior iliac crest, sublingual muscle mass cut suspension: This type of surgery is to remove all the sublingual muscles at the large angle of the hyoid bone and hyoid bone. The hyoid bone is also moved forward and upward,

and then suspended from the mandible with the autologous fascia. This type of surgery has great advantages in enlarging the oropharynx and hypopharyngeal cavity. It does not change the relationship and does not require intermaxillary fixation. It can be used as a separate operation or as an auxiliary surgery for other operations.

(d) Bi-maxillary migration, anterior migration, and lingual migration: This type of surgery includes standard maxillary LeFort I osteotomy and mandibular sagittal split osteotomy to advance the upper and lower jaws. At the same time, the ankle osteotomy was performed, and the hyoid muscles were cut and suspended. This type of surgery not only fully advances the upper and lower jaws, but also improves the airway, and the shape and relationship are improved. Because the surgery is so extensive, it is necessary to strictly control the surgical indications, especially to identify central sleep apnea syndrome, and mixed sleep apnea syndrome, because these two types of syndrome cannot be cured by surgery alone. For elderly patients, severe obesity, and patients with systemic organ dysfunction, the risk of surgery is very high, so it should be very cautious.

13.4.3 Third, Drug Treatment

1. **There is currently no recognized effective treatment for OSA.** But a randomized, controlled, double-blind trial of the latest study showed that combination of 80 mg of tomoxetine and 5 mg of ocybutynin improved the severity of OSA (apnea hypopnea index, primary endpoint) and genioglossus reaction (secondary endpoint) [107].
2. **Antihypertensive treatment.** Single antihypertensive drug treatment of OSA-related hypertension patients was followed up for 6 weeks, compared with other antihypertensive drugs; losartan treatment group 24 h blood pressure decreased slightly, but the difference was not statistically significant [108]. In hydrochlorothiazide and nebivolol groups, the nebivolol group had a lower blood pressure than the hydrochlorothiazide group [109]. However, the results aren't exactly consistent. Of the 94 hypertensive patients, 55% had OSA. However, after treatment with a regimen of 30-days hydrochlorothiazide 25 mg plus enalapril (20 mg BID) or losartan (50 mg BID) no difference of 24-hour mean blood pressure and arterial stiffness was observed between patients with and without OSA [110].
3. **Others.** Such as nerve respiratory stimulant Angong progesterone, etc., is also one of the auxiliary treatment methods.

13.4.4 Fourth, Device Treatment

1. **Nasal continuous positive airway pressure (nCPAP)**
   This method is currently the most effective nonsurgical treatment for OSAHS. CPAP is like an airway dilator in the upper airway, which can prevent the passive collapse of soft tissue during inhalation and stimulate the mechanical

receptor of the genioglossus muscle to increase the airway tension. It can be used alone as a therapy or in combination with surgery, but the main problem at present is that patients generally have poor compliance and are difficult to adhere to for a long time.

2. **Oral appliances (OA)** [111]
   Oral appliance (OA) has become an alternative to continuous positive airway pressure (CPAP) in the treatment of obstructive sleep apnea (OSA). The most commonly used OA reduces upper respiratory tract collapse by advancing the mandible (OAm). There is strong evidence that OAm improves OSA in most patients, including some with more serious diseases. However, OAm is not effective for all, and about one-third of patients have no therapeutic effect. OAm is generally well tolerated, although short-term adverse reactions are common in adapted environments. It is true that there will be dental changes during the growing period, but these changes are largely subclinical and do not preclude continued use. In recent years, remotely controlled mandibular locators have the potential to identify treatment responders and the level of treatment progress required for single-night titration of polysomnography. Now we can use small embedded temperature sensor data recorder to objectively monitor the compliance of OAm, and will strengthen clinical practice and research. These technologies will further improve the efficacy and effectiveness of OAm in the treatment of OSA.
3. **Oxygen inhalation.**

13.4.5 Fifth, New Treatment

Recent years, there are some new noninvasive treatment, including nonsurgical oral pressure therapy and improved oral appliances; New surgical treatments include low-temperature plasma radiofrequency ablation, hernia implantation, electrical stimulation of upper airway muscles or nerves.

1. Nasal expiratory positive airway pressure (EPAP)
   Compared with the sham-treated group, the use of nasal EPAP significantly reduced AHI in patients with mild to severe OSA, improved daytime sleepiness in subjects, and was highly compliant [112]. EPAP is not as effective for patients with obstructed nose. Side effects found in clinical trials include difficulty breathing, difficulty falling asleep or waking up, dry mouth, nasal congestion, headache, difficulty in wearing or removing, and anxiety [113].
2. Upper-airway stimulation device
   Sensing lead detects respiratory movements in the fourth intercostal space. Stimulation lead stimulates the hypoglossal nerve, causing the genioglossus to contract and expand the airway [114]. Both objective and subjective effects were significantly improved.
3. Oral pressure therapy (OPT) system
   OPT is composed of two parts, one of them is the nightstand console unit containing the vacuum pump and saliva reservoir. Another part is the mouthpiece. OPT provides a vacuum negative pressure to the mouth, which promotes the soft

palate to move forward, thereby stabilizing the posterior airway to serve as a therapeutic effect, and the tolerance rate is high [115].

4. Nasal insufflation

NI is a heated, humidified air that provides a high flow rate into the open nasal cannula to increase pharyngeal pressure. Studies have shown similar adherence to CPAP (observed for 2 weeks) and may be recommended as a treatment for patients with mild to moderate OSA. However, the efficacy has yet to be verified [116].

13.5 Obstructive Sleep Apnea and Special Types of Hypertension

Ling Yao

Although the proportion of obstructive sleep apnea (OSA) combined with special types hypertension is not high, the absolute number is still quite large. Some special types of hypertension, such as primary aldosteronism (PA), hypothyroidism-related hypertension, gestational hypertension, perimenopausal hypertension, and chronic kidney disease-related hypertension can be cured or alleviated by surgery or medicine. Moreover, OSA can also be cured or alleviated by surgery or continuous positive airway pressure (CPAP) treatment. Therefore, early diagnosis and treatment can significantly improve the cure rate and prevent the progress of the diseases.

13.5.1 Obstructive Sleep Apnea and Primary Aldosteronism

13.5.1.1 Epidemiology

PA and OSA were the most common secondary causes and coexisting diseases of hypertension among hypertensive patients. Both higher blood pressure level and target organ damage are more pronounced in patients with PA and OSA [117]. OSA was accounting for 24.7%, PA was accounting for 5.8%, and OSA + PA accounts for 4.9% patients among secondary causes and coexisting diseases [118].

13.5.1.2 Pathophysiological Mechanism

Sympathetic and renin-angiotensin-aldosterone system activation secondary to repeated intermittent nocturnal hypoxia in OSA patients may increase aldosterone level, water and sodium retention and blood volume and then lead to high blood pressure. On the contrary, elevated aldosterone levels in PA patients may lead to water and sodium retention, thus redistributing fluid during supine sleep and accumulating fluid in the neck, which resulting in increased neck circumference and upper airway resistance. All of these may contribute to the development of OSA.

13.5.1.3 Relevant Studies

The level of aldosterone in patients with resistant hypertension complicated with OSA was higher, which was positively correlated with the severity of OSA [84]. CPAP treatment can reduce the level of aldosterone in patients with hypertension

and OSA [119]. Spironolactone reduces severity of OSA in patients with resistant hypertension [120]. The treatment of PA has a positive effect on OSA. Following the guidelines of the Management of Primary Aldosteronism, PA screening should be performed in patients with hypertension and OSA [121]. Renin-angiotensin (RAS) system can be activated by OSA, which increasing aldosterone level and renin activity. So, PA screening for patients with hypertension complicated with OSA should not rely on ARR value completely. For patients whose ARR value is less than cut-off point, we should pay attention to avoid missed diagnosis [122].

13.5.2 OSA and Hypothyroidism-Related Hypertension

13.5.2.1 Epidemiology

Both OSA and hypothyroidism are the causes of secondary hypertension. The incidence of OSA increased in hypothyroidism patients is 25–35% [123, 124]. OSA patients presented higher hypothyroidism and subclinical hypothyroidism prevalence [125], which correlated with the severity of OSA [126]. OSA and hypothyroidism comorbidity is approximately 1.2–12.77% [127].

13.5.2.2 Pathophysiological Mechanism

OSA may be a causative risk factor for hypothyroidism and vice versa. Frequent hypoventilation and apnea during sleep in OSA patients lead to carbon dioxide retention and intermittent hypoxia, which can cause hypothalamic-pituitary axis disorders and decreased thyroid function, including decreased serum free thyroxine(FT-4) secretion and increased thyroid hormone(TSH) secretion. Hypoxia leads to gastrointestinal blood stasis and mucosal edema, which reduces the absorption of iodine in the intestine, thus inhibiting the secretion of FT4. In addition, nocturnal intermittent hypoxia can increase cortisol levels, thereby feedback inhibition of hypothalamus-pituitary-thyroid axis, reduce thyroid hormones, and aggravate severity of hypothyroidism. Conversely, lower thyroxine levels in patients with hypothyroidism lead to tissue edema in tongue and throat, persistent contraction of swallowing muscles, and the deposition of mucoproteins in the upper airway causing upper airway obstruction, which aggravates the development of OSA. Increased sympathetic nerve activity caused by intermittent hypoxemia and hypercapnia at night would lead to oxidative stress, augment of inflammation and prethrombotic factors, endothelial dysfunction, and elevated TSH levels. Together, these factors give rise to increased peripheral vascular resistance and arterial stiffness, finally result in high blood pressure.

13.5.2.3 Relevant Studies

Studies have confirmed that CPAP can reduce TSH levels in OSA patients [128] and replacement therapy with thyroxin can improve thyroid hormone level and alleviate clinical symptoms of OSA in patients with hypothyroidism and OSA [129]. Owing to OSA and hypothyroidism have similar symptomatology, such as obesity, fatigue, decreased libido, depressed mood, impaired concentration, snoring, and witnessed apneas. The overlap in clinical presentation creates a significant risk for misdiagnosis.

So, physicians should be alert for hypothyroidism comorbidity in OSA, and suspected subjects with OSA should be screened for hypothyroidism considering early diagnosis and treatment could reduce the risk of potential cardiovascular complications.

13.5.3 OSA and Hypertensive Disorders of Pregnancy

13.5.3.1 Epidemiology

The detection rate of OSA of pregnancy was 3.6–8.3% [130]. Even in early pregnancy, the incidence of nocturnal hypoxic breathing events increased by about 10.5% [131]. Pregnant women with OSA have an increased risk of gestational hypertension, preeclampsia, and eclampsia [132]. Pregnant hypertension has been proved to be the main cause of maternal and infant morbidity and mortality.

13.5.3.2 Pathophysiological Mechanism

Hormonal, physiological, and physical changes in pregnant women, such as pregnancy weight gain, pregnancy-related nasopharyngeal edema, decreased lung function reserve capacity, and increased sleep arousal, may lead to changes in sleep patterns and sleep quality, thereby increasing the risk of sleep-related breathing disorders or previous sleep apnea. Pregnancy OSA patients with hypertension may be associated with increased the risk of cardiovascular disease and increased risk of adverse pregnancy outcomes via inflammation, oxidative stress, and endothelial dysfunction, leading to adverse pregnancy outcomes and increased risk of long-term cardiovascular disease.

13.5.3.3 Relevant Studies

Nasal continuous positive airway pressure (nCPAP) has been proved to be an effective treatment for OSA, and nCPAP also has been proved to be safe and effective for OSA patients of pregnancy [133, 134]. For OSA patients of pregnancy, nCPAP can decrease maternal blood pressure, risk and severity of preeclampsia, and prolong fetal intrauterine time to improve neonatal outcomes without impairing maternal health [135].

13.5.4 OSA and Perimenopausal Hypertension

13.5.4.1 Epidemiology

The risk of OSA in perimenopausal and postmenopausal women is higher than premenopausal women. The prevalence of hypertension in perimenopausal and postmenopausal OSA patients is increased (56.9%), and blood pressure level is higher than premenopausal women [136].

13.5.4.2 Pathophysiological Mechanism

Owing to the cardiovascular protective effects of estrogen, vascular damage in premenopausal women caused by OSA can be offset to some extent by estrogen. However, the risk of OSA increased due to the increase of age and the change of estrogen level in perimenopausal and postmenopausal women, such as decreased dilatory muscle activity of upper airway, fat redistribution, and changes in sleep structure caused by estrogen deficiency. Thus, OSA may lead to blood pressure elevated, risk of atherosclerosis increased. Moreover, OSA is an independent risk factor of perimenopausal and postmenopausal hypertension.

13.5.4.3 Relevant Studies

Perimenopausal and postmenopausal women should pay attention to the screening of OSA and hypertension, early diagnosis and treatment, so as to reduce the risk of cardiovascular disease. However, it is still controversial whether hormone replacement therapy can reduce OSA severity and blood pressure in patients with OSA and hypertension [137–139].

13.5.5 OSA and Chronic Kidney Disease-Related Hypertension

13.5.5.1 Epidemiology

There is a bidirectional relationship between OSA and chronic kidney disease (CKD). CKD increases the risk of OSA, while OSA accelerates the progression of CKD [140]. The incidence of CKD and end-stage renal disease (ESRD) in OSA increased. Studies have shown that the prevalence of OSA in ESRD is much higher: from 50% to 70% [141]. The prevalence of CKD in OSA is 9.1–18% [142, 143].

13.5.5.2 Pathophysiological Mechanism

Repeated apnea and intermittent nocturnal hypoxia in patients with OSA promote systemic inflammatory response and endothelial dysfunction, the rise in sympathetic tone and activation of the renin-angiotensin system, cause renal vasoconstriction, tubulointerstitial injury and glomerulosclerosis, and promote the progress of CKD. The risk of CKD increases with the duration and frequency of hypoxia. Conversely, the decrease of glomerular filtration rate and the retention of water and sodium in CKD patients can cause upper respiratory edema and airway collapse, induce, and aggravate OSA. Uremia is also an important cause of OSA. Both OSA and chronic kidney disease lead to elevated blood pressure. OSA, CKD, and hypertension share common pathogenic relationships, including water and sodium retention, renin-angiotensin-aldosterone overactivation, endothelial dysfunction, inflammation, oxidative stress, and proteinuria. The common pathophysiology drives all the three diseases together, which can lead to a significant increase in the risk of cardiovascular disease.

13.5.5.3 Relevant Studies

CPAP is currently recognized as the most effective treatment of OSA, and to a certain extent, it may reduce blood pressure, improve renal function, and slow down the progress of CKD. In addition, nocturnal hemodialysis in patients with ESRD can help to delay uremia, improvement in OSA, and control blood pressure [144]. Because of the lack of typical symptoms of OSA patients such as snoring, apnea, and daytime sleepiness due to chronic fatigue, kidney disease itself, or drug effects, the detection rate of OSA in CKD and ESRD patients is lower [140, 145]. Therefore, patients with CKD and ESRD should be alert to whether OSA complications occur, and some measures need to be taken to early screen and treat OSA in order to alleviate end-organ damage.

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Connective Tissue Disease and Hypertension

14

Jing Hong and Yue Ma

14.1 Systemic Lupus Erythematosus

Jing Hong

Systemic lupus erythematosus (SLE) is an autoimmune-mediated, diffuse connective tissue disease characterized by immune inflammation [1]. The presence of multiple autoantibodies and multisystem involvement represented by antinuclear antibodies in serum are the two major clinical features of SLE. The cause is unknown and may be related to genetic, sex hormones, environment, infection, drugs, immune abnormalities, and other factors. The prevalence of hypertension in SLE is significantly higher than that in the general population, mainly secondary to connective tissue disease (CTD) vascular lesions. This chapter focuses on the relationship between SLE and hypertension.

14.1.1 Epidemiology

Lupus erythematosus originated from the translation of *Latin.* In 1828, the French dermatologist Biett described a patient with irregular facial erythema on his face, which was named ***lupus erythematosus***. At the beginning of the twentieth century, American doctor Osler proposed the term systemic lupus erythematosus.

According to a survey conducted by the World Health Organization in Australia, Japan, New Zealand, and the USA, the prevalence of hypertension in adults is 8–18%, and the prevalence of hypertension in people over 20 years old in China is

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9.1%, and in various CTDs (connective tissue diseases). The prevalence of hypertension in patients was 45% for SLE and 68% for children with SLE [2, 3]. Peking Union Medical College Hospital data statistics reports SLE with hypertension of up to 34.7%. The annual incidence of SLE varies with region, race, gender, and age. Women are significantly more ill than men, and the ratio of gestational age to males is 1:5 to 1:10. The prevalence of hypertension in patients with SLE is significantly higher than that in the general population, mainly secondary to CTD vascular lesions.

14.1.2 Etiology and Pathogenesis

The etiology of SLE may be caused by internal and external factors to stimulate individuals with genetic susceptibility, leading to the onset of the body's immune system disorder. The pathogenesis of SLE is not fully understood. A large number of studies have shown that SLE may be related to endocrine, immune abnormalities, infection, and other factors [4]. The current study found that HLA class II genes are more related to SLE than H class I genes, while HLA-II is more involved in the production of certain autoantibodies.

Although genetic factors determine the predisposition to SLE, internal and external stimuli can cause disease and may change the severity of the disease. Exogenous stimuli such as infection (bacteria and virus) destroy the body's own immune tolerance through molecular modeling, super-antigen mechanism, and autoreactive B-cell polyclonal activation. Ultraviolet rays can cause inflammation, tissue damage, and deformation of their own tissue components. The drug causes its own tissue components to become alleles. Endogenous stimulating factors such as estrogen promote anti-DNA antibody formation, aggravating clinical symptoms of lupus. Stress can stimulate neuroendocrine and affect immune cell function. The above-mentioned multifactor interaction leads to disorder of the immune system of the body. An important feature is that various autoantibodies such as antinuclear antibodies can be produced, and autoantibodies and antigens form immune complexes and deposits on the blood vessel wall of tissues and organs and activate the complement system. Vasculitis is the common immunopathological basis for multiple tissue and organ damage in SLE. Some people think that this immune complex disease may be the main mechanism for the occurrence and development of SLE.

14.1.3 Mechanisms of Connective Tissue Disease with Hypertension

The pathogenesis of CTD with hypertension is multifaceted, mainly involving the kidney and secondary renal hypertension, and many other factors are also involved, such as long-term use of glucocorticoids, hypoproteinemia, and sodium retention. The central nervous system is involved in blood pressure regulation disorders, obesity, and certain autoantibodies. Kidney is an important organ regulating blood

pressure, mainly through the renin-angiotensin-aldosterone system (RAS) to control blood volume and peripheral vascular resistance to regulate blood pressure and water and electrolyte balance, to maintain a constant body environment. Kidney involvement causes high blood pressure, while SLE is prone to lupus kidney (see Sect. 5.3 for details).

14.1.3.1 Pathology and Pathophysiology

The pathological changes in SLE are connective tissue mucin-like edema, fibrin degeneration, and necrotic vasculitis.

1. Histopathological changes in the skin: Epidermal atrophy, basal cell liquefaction degeneration, increased phlegm cells in the upper part of the dermis, collagen fiber edema, and fibrin-like degeneration, surrounded by lymphocytes, a few plasma cells, and tissue cells in the blood vessels and skin appendages. Often there are inflammatory changes in the blood vessels.
2. Muscle: The striated muscle is often involved. The connective tissue between the muscle bundle and the muscle bundle is characterized by small fibrin-like degeneration, infiltration of peripheral lymphocytes and plasma cells, and sometimes muscle fiber atrophy or hyaline degeneration.
3. Kidney: The glomerulus is involved first, followed by renal tubular lesions, mainly fibrin-like degeneration or focal necrosis of the glomerular capillary wall, with transparent thrombus and hematoxylin, or capillary basal membrane Thick, severe diffuse thickening, forming so-called "wire loop" damage, deposition of DNA, anti-DNA antibodies, complement and fibrin. In addition to glomerular devascularization, the number of cells can also increase, mainly due to mesangial cell proliferation, often focal. The glomerular wall epithelial cells can proliferate to form a crescent. In advanced cases, glomerular fibrous tissue increased, vascular occlusion, and even fibrosis due to adhesion to the wall of the capsule.
4. Heart: Fibrin-like degeneration in the pericardial connective tissue with infiltration of lymphocytes, plasma cells, histiocytes, and fibroblasts. Myocarditis changes similar to striated muscle. Endocarditis is a focal fibrin-like degeneration of the connective tissue of the endocardium, followed by lymphocyte and fibroblast proliferation and fibrogenesis, which occurs repeatedly, forming a sacral endocarditis involving the valve and nipple. The muscle can affect the function of the valve, and the mitral valve has the highest damage rate. It has been called Libman–Sacks syndrome.
5. Lungs: Vasculitis and perivascular inflammation at the beginning, and later interstitial and parenchymal, fibrin-like degeneration, necrosis and transparency of interstitial alveolar walls and capillaries, accompanied by lymphocyte and plasma cell infiltration.
6. Nervous system: Infiltration of endothelial cells and lymphocytes in small blood vessels and capillaries, extensive microthrombus, and localized softening lesions. Recently, immunoglobulins and complement immune complexes have been

found on the choroid plexus, and DNA and anti-DNA complexes can be found in the cerebrospinal fluid.
7. Spleen: Visible thickening of the envelope fiber, follicular hyperplasia, increased plasma cells in the red pulp, special fibrosis in the central artery, surrounded by thick and dense concentric collagen fiber hardening ring, called ***onion spleen***.

14.1.4 Clinical Manifestations and Complications

The clinical manifestations are complex and diverse. Most of them are insidious onset. Most of them are women of childbearing age. They only involve 1–2 systems at the beginning. Some patients also involve multiple systems when they are sick, and even manifest as lupus crisis.

1. Skin and mucous membrane manifestations: Skin changes are more common, and the erythema with butterfly-shaped distribution on the bridge of the nose and the cheeks is a characteristic change of SLE; skin damage of SLE includes light sensitivity, hair loss, palmar and nail erythema, discoid erythema, nodular erythema, panniculitis, reticular bluish, Raynaud's phenomenon, etc. Oral mucosal ulcers are common. Symmetrical polyarticular pain, swelling, usually does not cause bone destruction.
2. Bone and joint performance: More than 90% of cases have multiple joint pain or arthritis, and severe joint deformities may occur.
3. Fever and fatigue are common systemic symptoms of SLE.
4. Kidney: Common kidney involvement is a major factor affecting long-term prognosis. Urine routine examination found renal involvement, pathological changes seen by renal biopsy can be divided into: (1) normal or little change; (2) mesangial glomerulonephritis; (3) focal proliferative glomerulonephritis; (4) diffuse proliferative glomerulonephritis; and (5) membranous glomerulonephritis. Clinical manifestations are nephritis or nephrotic syndrome. In addition to a large amount of proteinuria, there may be more red blood cells and casts in the urine, impaired renal function, and high blood pressure (see Sect. 5.3 for details).
5. Cardiovascular system: SLE heart involvement includes pericarditis, myocarditis, endocarditis, and coronary artery disease, about 50–89% of patients have cardiac symptoms, pericarditis is a common form of SLE heart involvement, and hypertension is common in SLE, one of the main manifestations of cardiovascular disease. Patients often show mild to moderate elevation of blood pressure, but when combined with lupus renal hypertension, blood pressure is often moderately severe, and antihypertensive treatment is poor.
6. Lung performance: Pleuritis is the most common clinical manifestation of the lungs in SLE, manifested by cough, chest pain, and difficulty breathing. About one-third of patients have pleural effusions, often small to medium (400–1000 mL), with very few pleural effusions, either unilateral or bilateral, often exudative. Invasive pulmonary lesions, including acute lupus pneumonia and chronic pulmonary interstitial lesions, are rare clinically. Other rare lung

manifestations include pulmonary hypertension, pulmonary embolism, alveolar hemorrhage, pneumothorax, and contracture of the lungs.

7. Neuropsychiatric system: Also known as neuropsychiatric lupus. Mild people only have migraine, personality changes, memory loss, or mild cognitive impairment; severe cases can be manifested as cerebrovascular accidents, coma, status epilepticus, etc.
8. Digestive system performance: About 40% of cases have gastrointestinal symptoms, common loss of appetite, difficulty swallowing, nausea, vomiting, abdominal pain, diarrhea, ascites, and blood in the stool. Liver disease is indicated when the measured value of transaminase (such as ALT, AST, γ-GT, AKP, bilirubin, etc.) is higher than twice the normal value.
9. Hematopoietic system performance: Common anemia and/or leukopenia and/or thrombocytopenia; anemia may be chronic disease anemia or renal anemia. Severe anemia in the short term is often caused by autoimmune hemolysis, and some patients are accompanied by lymphadenopathy and/or splenomegaly in the early stage of the disease or during the active period of the disease.
10. Endocrine system performance: Most patients with SLE have increased estrogen and decreased androgen. Female patients have irregular menstruation (reduced or increased menstruation); SLE patients have thyroid diseases such as hyperthyroidism, hypothyroidism, immune thyroiditis, and parathyroidism. Hyperthyroidism is associated with an increased incidence of Jaccoud's arthritis in SLE; a small number of SLE patients have renal tubular acidosis, high renin or aldosteronism-induced hyperkalemia or high-secretion complications of vasopressin.
11. Eye, ENT performance: SLE patients may have clinical manifestations of Sjogren's syndrome. In addition, patients with SLE may have a spotted rash, ophthalmoplegia, or paralysis; the incidence of conjunctivitis is 10%, iritis is 1–2% (more common in children); choroid or (and) retinal vasculitis, blood vessel embolism, optic nerve and/or retrobulbar neuritis can lead to retinal pigment epithelial uplift, exfoliation, macular degeneration, optic nerve fiber cell-like changes, resulting in decreased or even blind vision; auditory organ involvement in SLE is rare, occasional serous otitis media, vestibule inflammation, and auditory nerve involvement lead to reports of tinnitus and deafness.
12. Several special cases of lupus are listed in Table 14.1.

14.1.5 Laboratory Inspection

1. Blood routine examination: There may be anemia, leukopenia, and thrombocytopenia.
2. Urine routine: Urine analysis can show proteinuria, hematuria, and cells and granular casts when the kidney is involved. Urinary microalbumin can respond to changes in glomerular function in early stage, and the extent of glomerular damage is affected. Urinary β2 microglobulin is important for early glomerular damage.

Table 14.1 Several special cases of lupus

Several special cases of lupus	Age of onset	Fever	Joint pain/ myalgia	Rash/ cutaneous lesion	Pleuritis/ seritis	Kidney, central nervous system damage	Rheumatoid factor	Abnormal blood	ANA, anti-histone antibody and anti-SS-DNA antibody, anti-SSB antibody and other immune indicators
Drug-induced lupus syndrome		Exist		Exist	Exist	Rarely	Positive	Exist	Positive
Late-onset lupus	Over 50 years old	Rarely	Exist		Exist				Positive
Occult lupus		Exist				Exist	Positive		
Systemic lupus erythematosus in children	Adolescent onset	Exist	Exist	Exist	Exist	Exist		Exist	Positive
SLE and pregnancy	The pregnancy rate of SLE patients is the same as that of the normal population. The prognosis of the fetus and mother is related to disease activity, past pregnancy, antiphospholipid antibodies, and anti-SSA/SSB antibodies								

3. ESR increases: Erythrocyte sedimentation rate increases during SLE activity, while remission period can be reduced to normal.
4. Serum protein: Albumin decreased, α2 and gamma globulin increased, fibrinogen increased, and cold globulin and condensed agglutinin increased. Immunoglobulin monitoring showed that the blood IgG, IgA, and IgM increased during the active phase, especially in IgG, and the increase in inactive cases was not obvious or increased. In patients with large amounts of proteinuria and long duration, IgG levels in the blood can be reduced.
5. Rheumatoid factor: About 20–40% of cases are positive.
6. Syphilis serology: There may be a 2–15% false-positive reaction.
7. Antiphospholipid antibodies: Antiphospholipid antibodies are a group of antibodies that react with a variety of antigenic substances containing phospholipid structures, including anticardiolipin antibodies, anti-phosphatidylserine antibodies, anti-phosphatidylinositol antibodies, anti-phosphatidyl antibodies, and five kinds of anti-phosphatidylglycerol antibodies. Currently commonly used anticardiolipin antibodies are representative of antiphospholipid antibodies.
8. Lupus cells (LE): Itargraves first discovered LE in the bone marrow in 1948, and Haserick found LE cells from peripheral blood in 1949. Miecher demonstrated that the erythema LE factor is an antinuclear factor. About 40–70% of patients with active SLE have positive LE cells. The cells can be found in about 10% of other diseases such as scleroderma and rheumatoid arthritis. In addition, chronic active hepatitis and drug eruptions such as procainamide and hydralazine can also be positive.
9. Antinuclear antibody (ANA): A group of autoantibodies to nucleic acids and nuclear proteins in the nucleus or cytoplasm. ANA is positive in about 80–95% of cases in SLE. Common ANA are anti-deoxyribonucleic acid (DNA) antibody, anti-deoxyribonucleic acid nuclear protein (DNP) and histone antibody, anti-nucleosome antibody (AnuA), and nuclear antigen (ENA) antibodies.
10. Lupus belt test (LBT): The application of direct immunofluorescent antibody technology to detect skin immunofluorescence bands or lupus belt, that is, a localized immunoglobulin deposition zone can be seen at the dermal–epithelial junction, and the positive rate of skin lesions is 92%.
11. Determination of cellular immune function: Including lymphocytes, T-cell subsets, and natural killer cells (NK).
12. Serum complement is reduced in about 75% to 90% of patients with SLE, especially in the active phase, with C3 and C4, but not in other connective tissue diseases such as dermatomyositis, scleroderma, and rheumatoid arthritis.
13. Circulating immune complex: Serum CIC increased during the active phase.
14. Capillary fluoroscopy: A variety of microcirculatory disorders can be seen in the nails of the SLE and the microcirculation of the tip of the tongue. The manifestations are: (1) increased microvascular vasospasm, poor microvascular tension; (2) microvascular disorders; and (3) exudation and hemorrhage around the microvessels.

14.1.6 Pathological Diagnosis

1. The basic pathological changes of SLE:
   (a) Connective tissue fibrin-like degeneration: caused by the deposition of connective tissue by eosinophils composed of immune complexes and fibrin.
   (b) Mucoid edema occurs in the connective tissue matrix.
   (c) Vascular lesions include mild vascular disease (degeneration or hyperplasia of the vessel wall), embolic angiopathy (caused by inflammation and antiphospholipid antibodies), and vasculitis (inflammation of the vessel wall, necrosis).
2. Characteristic pathological changes in tissue damage: Can be examined by ***hematoxylin***, skin pathology and lupus phenomenon, lymph node disease, kidney pathology, etc. SLE kidney pathology type I: normal or minimal changes; type II: mesangial glomerulonephritis, system membrane hyperplasia, and immune complex deposition; type III: focal proliferative glomerulonephritis, mesangial cells, endothelial cell proliferation, immune complex deposition along the capillaries, but the affected glomerulus is less than 50%; type IV: diffuse proliferative glomerulonephritis, involving more than 50% of glomeruli, cell hyperplasia significantly forming crescent; type V: membranous glomerulonephritis, deposition of subcutaneous immunoglobulin particles; type VI: sclerosing glomerulonephritis. The crescent fibers and the blood vessels are hardened.

14.1.7 Diagnosis and Differential Diagnosis

1. Diagnosis
   The etiology of SLE is unknown, and the clinical manifestations often involve multiple tissues and organs. The condition is complicated, especially in the early stage, atypical, or even no clinical manifestations, and the diagnosis is difficult. China's clinical use of the American College of Rheumatology (ARA) in 1997 again revised classification criteria [5], a total of 11:
   (a) Erythema on the cheeks
   (b) Discoid lupus
   (c) Light sensitive
   (d) Oral ulcer
   (e) Nonerosive arthritis
   (f) Pleurisy or pericarditis
   (g) Proteinuria (>0.5 g/day) or urinary cell cast
   (h) Seizures or psychosis, except for drugs or known metabolic disorders
   (i) Hemolytic anemia or leukopenia, or lymphopenia, or thrombocytopenia
   (j) Anti-dsDNA antibody positive, or anti-Sm antibody positive, or antiphospholipid antibody positive (including anticardiolipin antibody, or lupus anticoagulant, or at least 6 months of syphilis serum test false positive each have a positive)

(k) Antinuclear antibody titer is abnormal. Antinuclear antibody titer abnormalities at any time and without drug-induced lupus

Among the 11 items of this classification standard, 4 and 4 or more, after the exclusion of infection, tumor, and other connective tissue diseases, SLE can be diagnosed. Its sensitivity and specificity were 95% and 85%, respectively. For some special types of SLE such as hemolytic anemia, thrombocytopenic purpura, lymphadenopathy, nephrotic syndrome, arthritis, and urticaria vasculitis as the first symptom or prominent manifestation of SLE should be more diagnostic alert [6].

2. Differential diagnosis (Table 14.2):

14.1.7.1 Therapy

Because there are many subgroups of SLE, the severity of the disease is different. Individualized treatment plans should be developed according to the condition of each patient and the previous treatment, and the risk/effect ratio should be compared to control the SLE. Drugs used to treat SLE have varying degrees of toxicity, and the most appropriate drug type, dosage, and course of treatment must be sought in controlling disease activity and drug toxicity. Severe patients should be treated with medication, and maintenance treatment should be given after the disease is controlled.

Table 14.2 Differential diagnosis

Identifying diseases	SLE	Rheumatoid arthritis	Polymyositis/ dermatomyositis	Nodular polyarteritis	Mixed connective tissue disease
Fever		Low heat	Irregular low heat	Exist	Exist
Joint involvement	Exist	Exist	No	Big joint swelling and pain	Exist
Morning stiffness	Exist	Exist	No		No
Rash	Exist	No	Exist	Subcutaneous nodules	Exist
Renal lesion	Exist	No	No	Hypertension	No
Respiratory system changes		Exist			Exist
Muscle pain	Exist	No	Severe	Exist	Exist
Hair loss	Exist	No	Exist	No	Exist
Blood vessel	Small blood vessel			Medium size artery	
ANA		Positive		Positive	High and low spot type
Anti-UIRNP					High titer
Reynolds phenomenon					Exist

Mild Cases

If you only have rash, hypothermia, or joint symptoms, you only need to use non-steroidal anti-inflammatory drugs. However, such drugs can sometimes damage liver cells, reduce glomerular filtration rate, and increase serum creatinine and should be used with caution in patients with kidney disease. If it is not effective, thalidomide 100~150 mg/day can be used, and the maintenance amount is 25~50 mg/day. Chloroquine 250~500 mg/day or hydroxychloroquine 400 mg/day and tripterygium preparation, small doses of glucocorticoids such as prednisone 15~20 mg/day can also be used.

Severe Cases

1. Glucocorticoids: The current drug of choice for the treatment of severe autoimmune diseases can significantly inhibit the inflammatory response, inhibit the neutrophil to the inflammation site, and inhibit the phagocytic function of neutrophils and monocytes and the release of various enzymes. It has antiproliferative and immunosuppressive effects, has direct cytotoxic effect on lymphocytes, and can also adjust various cytokine levels and inhibit antigen–antibody reaction. Adaptation:
   (a) Acute or subacute attack, moderate fever or high fever, joint pain and/or lesions quickly involving the serosa, heart, lung, liver, kidney, hematopoietic organs, and other organ organizers.
   (b) Chronic diseases such as those with clear progressive visceral damage.
2. Immunosuppressive drugs: Glucocorticoid combined with immunosuppressive agents for the treatment of SLE; regardless of the rate of progression of renal failure or by mortality, the effect is significantly better than those with corticosteroid alone. Adaptation:
   (a) Glucocorticoid alone is not effective.
   (b) Cannot be tolerated by long-term treatment with large amounts of glucocorticoids.
   (c) Effective control of SLE such as lupus nephritis.
   (d) Lupus crisis.
   (e) After the acute symptoms are controlled, in order to further reduce the amount of hormone maintenance or gradually reduce the hormone.
3. Immunopotentiator: Restores low cellular immunity to normal, such as levamisole, thymosin, transfer factor, and the like. The literature indicates that the addition of immunosuppressive agents is of great significance in relieving and controlling the severity and development of diseases and prolonging the survival of patients.
4. High-dose intravenous infusion of immunoglobulin: Suitable for lupus crisis, hormone, or immunosuppressive therapy, combined with severe systemic infection and SLE patients with pregnancy with antiphospholipid antibody syndrome.
5. Plasmapheresis: The principle is to remove specific autoantibodies, immune complexes, and nonspecific inflammatory mediators involved in tissue damage such as complement, C-reactive protein, fibrinogen, and improve mononuclear-

macrophage system clearance. The ability of the complex, due to its short-lived effect, still needs to be treated with hormones and immunosuppressive agents.
6. Dialysis therapy and kidney transplantation: Cases of advanced renal damage with renal failure, such as general conditions, can be performed by hemodialysis or peritoneal dialysis, remove blood urea nitrogen and other harmful substances to improve azotemia and other conditions.
7. Hematopoietic stem cell transplantation: Patients selected as a strict standard: (1) Life-threatening, type III or IX glomerulonephritis with anti-cyclophosphamide, uncontrolled vasculitis (lung, heart, brain), hemoptysis relying on blood transfusion. (2) Conventional treatment includes high doses of glucocorticoids and cytotoxic drugs for 3 months. (3) All organs have sufficient function to tolerate adverse reactions caused by the entire transplantation process.
8. Ischemic osteonecrosis: Early patients should try to reduce the amount of glucocorticoids, protect the joints from all kinds of gravity, and try bone marrow decompression.
9. Traditional Chinese medicine therapy.

Treatment of Secondary Hypertension

SLE secondary hypertension must be highly valued. Hypertension in most patients with SLE is caused by kidney involvement. The presence of high blood pressure is more likely to cause kidney involvement or suggest aggravation of kidney disease. It is necessary to remove the factors that cause high blood pressure as much as possible and actively control the primary disease. In addition, high blood pressure will aggravate the primary disease, especially the kidney damage. Therefore, the control of hypertension is an essential measure to treat the primary disease and prolong the survival of patients. Anyone with SLE hypertension should be treated actively.

The principle of treating SLE secondary hypertension is roughly the same as that of treating essential hypertension, with the aim of maintaining the patient's blood pressure at 139/89 mmHg or below by various measures. In 2018, the European Society of Hypertension, a European Society of Cardiology, determined the risk of hypertension according to the classification of hypertension, risk factors for cardiovascular disease and target organ damage or related diseases, and adopted different antihypertensive factors according to the degree of risk. Principles and methods of treatment for patients with secondary hypertension with connective tissue disease [7].

1. Patients should regularly assess blood pressure at each visit, at least once a year.
2. If the patient's blood pressure rises (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg) should be closely observed, provide lifestyle recommendations, emphasize non-pharmacological treatments, limit sodium intake, control alcohol consumption, control weight and other cardiovascular risk factors are the basic treatment of SLE secondary hypertension, and are also an important method to prevent the occurrence of hypertension.

3. If the above measures are taken and blood pressure is maintained at a systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg, antihypertensive medication is considered.

Drug selection should consider other risk factors and/or associated diseases of the patient. Low-dose thiazide diuretics are effective first-line drugs, but many patients require a combination of drugs to achieve the target blood pressure. Angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II receptor blockers are recommended (ARB); beta blockers may aggravate the Raynaud's phenomenon in some patients; those who are intolerant to thiazide diuretics may be replaced with calcium antagonists. Some patients use three antihypertensive drugs, including diuretics. Blood pressure cannot be controlled in the normal range, suggesting that the prognosis is not good, and must be treated according to refractory hypertension, so that blood pressure is controlled at an ideal level.

4. Blood pressure was observed every 3 months. The ideal target blood pressure should be controlled at systolic blood pressure < 130 mmHg and diastolic blood pressure < 80 mmHg.

In short, the high blood pressure secondary to SLE is caused by kidney factors, so it is appropriate to choose angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, and calcium antagonist, and to adjust diuretic reasonably for refractory hypertension. And try not to use drugs that are harmful to the kidneys.

14.2 Systemic Sclerosis and Hypertension

Yue Ma

Systemic sclerosis (SSc) is a systemic autoimmune disease that is characterized by limited or diffuse skin thickening, hardening, and shrinking for the final feature and can affect multiple organs, blood vessels, heart, lungs, kidneys, gastrointestinal tract, and other systems. A variety of specific autoantibodies can be found in the serum of patients with this disease. According to the extent of skin lesions, SSc is divided into two subtypes: restricted and diffuse. Symmetrical skin thickening in restricted systemic sclerosis and is limited to distal limbs and face, often a characteristic of CREST syndrome, that is, subcutaneous calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasis. The prognosis of localized skin scleroderma is relatively good, but some patients may have pulmonary hypertension or biliary cirrhosis after many years. The other type is diffuse SSc, characterized by rapidly developing symmetrical skin thickening of the limbs, face, and trunk. The lesions are easily affected by the kidneys and other internal organs and can be expressed as small amounts of proteinuria, mild to moderate hypertension, and chronic kidneys dysfunction. A small number of patients have scleroderma renal crisis, malignant hypertension with acute renal failure, and, if not treated in time, often died of heart failure and uremia within a few weeks.

14.2.1 Relationship with Hypertension

The pathogenesis of systemic sclerosis is not well understood. Immune activation, vascular injury, and excessive synthesis of extracellular matrix lead to excessive deposition of collagen fibers that play an important role in disease progression. The pathogenesis of hypertension caused by SSc is multifaceted, mainly involving kidney and secondary renal hypertension, and many other factors also play a role, such as long-term use of glucocorticoids, hypoproteinemia caused by sodium retention such as central nervous system involvement, blood pressure regulation disorders, obesity, and certain autoantibodies. It has been reported that 45% of patients with SSc have renal involvement, 80% of biopsies have renal vascular involvement, and 42.5% die of renal failure and malignant hypertension. When renal vasculitis occurs, renal blood flow decreases due to stenosis of the lumen and ischemic. Renal vascular wall tension is reduced, stimulating glomerular arterial wall baroreceptors, increases renin release, and then increases blood pressure through the RAS system. Once the blood pressure rises, it will affect the kidney function, further aggravate the kidney disease, increase the blood pressure, and form a vicious circle. Usually occurs after systemic sclerosing kidney involvement, usually with persistent moderate to severe hypertension, individual patients due to systemic sclerosis kidney crisis (SRC). Moderate and severe hypertension, which is characterized by sudden onset of symptoms, is often accompanied by acute damage such as fundus hemorrhage and hypertensive encephalopathy. The classic manifestation of SRC is the rapid onset of accelerated hypertension and acute kidney injury (AKI). However, up to 10% of patients with SSc SRC maintain normal blood pressure. Since SRC does not have a widely accepted and validated definition, it is reasonable to consider SRC for any SSc patient with elevated blood pressure and/or serum creatinine. Normal blood pressure SRC is usually difficult to diagnose, and kidney biopsy is the only way to ensure a correct diagnosis [8].

14.2.2 Diagnosis and Treatment

Diagnosis: The commonly used classification of SSc is the American College of Rheumatology classification criteria [9]:

1. The main criteria:
   Proximal scleroderma, that is, the skin of the finger and metacarpophalangeal joint or any part of the metatarsophalangeal joint has a symmetrical thickening, tightening, and infiltration. The above changes in the skin can affect all limbs, face, neck, and torso.
2. Secondary criteria:
   (a) Finger end hardening, hard skin change is limited to fingers only.
   (b) There is a swelling scar on the fingertip or a lack of finger pad, and the fingertip has atrophy or finger pad tissue atrophy due to ischemia.
   (c) There is fibrosis at the bottom of both lungs. There is a network texture or nodular density increase on the bottom of the lungs of the standard chest

X-ray film. It can be diffuse spot or honeycomb-like change, and it is clear that it is not the original caused by diseases that occur in the lungs.

Any secondary indicator with a primary indicator or greater than or equal to 2 can diagnose SSc.

Treatment: A review from the lancet summarizes treatment approaches. Interstitial lung disease: Early recognition is key, stabilization of lung function is the preferred outcome, oral or monthly pulse cyclophosphamide is supported by two RCTs, followed by MMF or azathioprine MMF is increasingly used as the first-line drug and is supported by SLS-II. HSCT might be considered in patients who have failed immunosuppression but should be done in expert centers.

Digital vasculopathy: Multidisciplinary approach ideal for Raynaud's phenomenon; CCBs are the initial choice for Raynaud's phenomenon; fluoxetine and ARBs are additional therapies; phosphodiesterase-5 inhibitors are widely used for digital ulcers. Intravenous epoprostenol therapy for digital is chaemia and severe Raynaud's phenomenon.

Cardiac: It is important to identify hemodynamically significant disease; systolic dysfunction requires ACE inhibitors, diastolic dysfunction needs diuresis. Consider immunosuppression if evidence of myocarditis. Consider ICD for low ejection fraction, ventricular arrhythmia.

Pulmonary arterial hypertension: Early recognition is important; many targeted therapies are available, including endothelin receptor antagonists, epoprostenol analogues, and phosphodiesterase-5 inhibitors. Initial or sequential combination therapies might be advantageous.

Renal: Glucocorticoids can precipitate scleroderma renal crisis so maintain dose at less than 10–15 mg/day in early disease. ACE inhibitors are the initial choice of therapy for scleroderma renal crisis. No evidence to support prophylactic use of ACE inhibitors.

Skin or musculoskeletal: Methotrexate is effective in early diffuse cutaneous systemic sclerosis (supported by two RCTs) and is the choice for inflammatory arthritis, MMF is effective in case series; supported by post-hoc analysis in SLS-II; low-dose prednisone (10–15 mg/day) used for tendon friction rubs; biologics used in case series for resistant arthritis and supported by a phase 2 study.

Gastrointestinal: All patients should have antireflux treatment with a PPI or H2 blocker and antacids; midgut disease might lead to bacterial overgrowth that responds to antibiotics; prokinetics and dietary adjustment might benefit abdominal distension; enteral or parenteral nutrition should be considered in case of refractory weight loss; anorectal disease needs specialist management.

There is no cure for SSc, and its treatment is mainly for the treatment of hard skin, Raynaud's phenomenon, and combined kidney, gastrointestinal, heart, lung and other organ diseases. A multicenter randomized trial (SCOT study) in the USA showed reduced treatment-related mortality for HSCT with selection of appropriate patients and experienced centers, thus confirming the feasibility of this approach in selected cases with a poor prognosis. Patient selection is crucial, and HSCT should be considered in patients with underlying interstitial lung disease or involvement of other internal organs and who have not improved or have worsened with conventional immunosuppressive agents [10].

The following key treatment methods are introduced to the treatment of hypertension:

1. The goal of antihypertensive therapy is through nondrug and/or drug treatments: blood pressure should be controlled below 140/90 mmHg. If you have diabetes, blood pressure should be controlled below 130/80 mmHg. If the urine protein level is greater than 1 g/day, the blood pressure should be reduced to below 125/75 mmHg. If the urine protein is below 1 g/day, the blood pressure should be below 130/80 mmHg.
2. Antihypertensive drugs: Because hypertension is secondary to SSc kidney damage and RAS is activated, angiotensin-converting enzyme inhibitor (ACEI) antihypertensive therapy is preferred. If the blood pressure cannot meet the standard, it can be combined with CCB, diuretics, etc. For SSc kidney crisis, mostly malignant hypertension, blood pressure control is most important in SSc kidney crisis. If intensive treatment is given before irreversible vascular injury, and hypertension is controlled, 55–70% of patients with renal crisis can be stable, and even renal function can be alleviated. ACEI is recommended as the first choice. Compared with other antihypertensive drugs, ACEI has antihypertensive effect, improves survival rate, and protects renal function. It can also improve skin sclerosis and Raynaud's sign in some patients. The role of angiotensin-converting enzyme (ACE) inhibitors in blocking or even reversing the pathology of SRC can be attributed to two effects: (1) Interruption of the renin-angiotensin system in a disease state is known to have high levels of renin, thereby reducing angiotensin II-induced vasoconstriction. (2) It interferes with the degradation of bradykinin, resulting in beneficial renal vasodilation [1]. Preliminary studies suggest that ACEI can also improve the prognosis of patients with normotensive systemic sclerosis and kidney crisis. Premise the use of short-acting ACEI to control blood pressure, and strive to reduce blood pressure to the normal range within 72 h; ACEI dose can be adjusted every 6–12 h. If you use ACEI to its maximum dose within 48 hours, blood pressure can not be reduced to normal, you can consider adding CCB and clonidine and other drugs. Excessive blood pressure and hypovolemia should be avoided as it can further reduce renal perfusion. Parenteral antihypertensive drugs (such as intravenous sodium nitroprusside) should be avoided as much as possible. If necessary, central venous pressure or pulmonary wedge pressure should be monitored to observe changes in hemodynamics. It is worth noting that even if the blood pressure control is normal, the serum creatinine of some patients may continue to increase at a rate of 44.2–88.4 μmol/L until the peak of serum creatinine after 3–4 days. Therefore, unlike other cases of using ACEI, even if the renal function is further deteriorated, the use of ACEI should be adhered to for the SSc kidney crisis. Although some patients have started dialysis treatment, the use of ACEI helps to control hyperreninemia, so that patients still have the opportunity to partially restore kidney function. Studies have shown that patients with renal involvement with the use of ACEI have a 1-year survival of 76%, 5 years 65%; those who do not use ACEI have a survival of 1-year survival of 15%, 5 years 10%. Therefore, high blood pressure in patients with clinical manifestations of SSc advocates the use of

ACEI. Regarding the use of ACEI in the prevention of scleroderma kidney crisis, especially in patients with early diffuse cutaneous systemic sclerosis or anti-RNA polymerase III antibody-positive patients, although this is not currently recommended, the debate is fierce. Although it is not recommended at this time, the debate is fierce [10]. More than 50% of patients requiring renal replacement therapy during an acute episode of SRC can restore adequate renal function to stop dialysis within 12–18 months. There have been reports of beneficial applications of selective endothelin A receptor antagonists or nonselective endothelin A receptor antagonists [8]. Recent articles indicate that activation of the complement system may be involved in SRC, and C5 inhibitors may become effective therapeutic agents for SRC [11, 12].

3. Disease monitoring: Systemic sclerosis damage, which is usually treated when the symptoms are not obvious at the beginning of the disease, is usually reversible and is more dangerous when the patient develops diffuse skin lesions. Therefore, in patients with rapidly progressive skin sclerosis, the condition should be closely monitored during the first 5 years, as most kidney lesions occur in this period. Blood pressure, serum creatinine level, and urinary protein should be measured frequently every 3–6 months. If there is a new increase in serum creatinine concentration or a new appearance of urinary protein greater than 500 mg/day, there may be a possibility of renal crisis. Follow-up should be strengthened. And check plasma renin activity, if the plasma renin level is elevated, even if the patient's blood pressure is within the normal range, ACEI should be treated. Anti-RNA polymerase III-positive antibody predicts scleroderma kidney crisis: approximately 25% of positive cases develop scleroderma kidney crisis [3, 4]. Even if SRC is diagnosed and treated in a timely manner, 45–55% of patients may develop end-stage renal disease (ESRD). For these patients, kidney transplantation is a reasonable choice and may be more sustainable than chronic dialysis and provides a survival advantage. It has been reported that recurrence of SRC is very rare (less than 5%) in allografts transplanted. The choice and dosage of immunosuppressive agents is a further concern for SSC patients [8].

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Metabolic Disorder-Related Hypertension

15

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15.1 Diabetes, Diabetic Kidney Disease, and Hypertension

Yanying Guo

15.1.1 Epidemiology

15.1.1.1 Prevalence of Diabetes

The epidemiological survey of diabetes in China shows that the prevalence of diabetes is increasing year by year, and China has become the largest country in the world in terms of diabetes, with type 2 diabetes mellitus (T2DM) accounting for the majority (over 90%) of diabetes patients. In 2010, the Chinese Center for Disease Control and Prevention (CDC) and the Endocrinology Branch of the Chinese Medical Association investigated the prevalence of DM in people aged 18 years and above in China, showing that the prevalence of diabetes was 9.7% [1]. According to the latest research report in 2013, the prevalence of DM in Chinese population over 20 years of age is as high as 11.6%, and the pre-diabetes prevalence rate has reached 50.1% [2].

15.1.1.2 Prevalence of Diabetic Kidney Disease

Diabetic kidney disease (DKD) refers to chronic kidney disease (CKD) caused by diabetes. DKD is one of the common chronic microvascular complications of DM.

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20~40% of diabetic patients are reported abroad. At present, there is still a lack of national DKD epidemiological survey data. It has been reported that the prevalence of DKD in type 2 diabetes patients in China is 10~40% [3]. DKD is mainly seen in male patients with longer duration of diabetes, more severe illness, long-term hyperglycemia, and those with high blood pressure or smoking. Compared with diabetic patients who did not have DKD, DKD patients had higher mortality and most of the deaths were due to cardiovascular events [4]. Early diagnosis, prevention, and delay of the occurrence and development of DKD are of great significance in reducing the occurrence of macrovascular events, improving patient survival rate and improving quality of life.

15.1.2 Natural History

15.1.2.1 Natural History of DM

It is important to understand the natural history of DM and the pathophysiology that causes it. In the natural history of T2DM, insulin resistance prompts β-cell to secrete extra insulin, which initially increases insulin levels [5]. However, an increased insulin secretion actually represents relative insulin deficiency, as β-cell function begins to decline in the early stages of T2DM. Progressive β-cell dysfunction is necessary and sufficient for the development and progression of DM. In DM, insulin secretion levels are no longer synchronized with insulin resistance, and β-cell function has decreased significantly. According to UKPDS, DM is not clinically diagnosed until 10 years later, when β-cell function may be reduced by more than 50% [6].

15.1.2.2 Natural History of DKD

The natural history of DKD is constantly changing, and most DKD patients are not classically advanced from glomerular ultrafiltration to persistent proteinuria with hypertension and decreased GFR [7]. As the history of DKD changes, its clinical manifestations are also changing.

Studies have shown that compared with 1988–1994, the incidence of proteinuria in adult DKD patients decreased from 21 to 16% in 2009–2014, the incidence of low eGFR (<60 mL/min/1.73 m^2) increased from 9 to 14%, and the incidence of severe eGFR reduction (<30 mL/min/1.73 m^2) increased from 1 to 3%. In patients with advanced DKD, multiple renal complications will occur, compared with other CKD. In DKD patients with anemia, mineral bone metabolism abnormalities occur earlier [8].

15.1.3 Mechanisms

15.1.3.1 Risk Factors for DKD

The occurrence of DKD is the result of synergistic accumulation of multiple risk factors.

Risk factors for DKD in the existing evidence include DM-related diseases including DM course, substandard blood glucose, and diabetic retinal complications; renal function includes glomerular hyperfiltration; cardiovascular risk factors

include advanced age, hypertension, lipid metabolism disorders, obesity, and uric acid. Therefore, in addition to the detection of blood glucose level, patients with DM with normal renal function and no proteinuria should monitor the levels of urinary protein, renal function, cardiovascular disease-related risk factors (such as TG, HDL-C, etc.), and uric acid on a long-term and regular basis and have regular fundus examinations to comprehensively assess the risk of DKD.

Risk factors for DKD in the available evidence include DM related to DM course, hypoglycemia, and diabetic retinal complications; renal function related to glomerular hyperfiltration; cardiovascular risk factors including advanced age, hypertension, lipid metabolism disorders, obesity, and elevated uric acid. Therefore, in addition to detecting blood glucose levels, DM patients with normal renal function and no proteinuria should be monitored for long-term and regular monitoring of urinary protein, renal function, cardiovascular disease-related risk factors (such as TG, HDL-C, etc.), uric acid levels, and regular fundus. Check and comprehensively assess the risk of DKD.

15.1.3.2 Mechanism of DKD Increasing Blood Pressure

Hypertension, diabetes, and renal dysfunction are closely related. Hypertension is a common complication of DKD lesions. The mechanisms of DKD elevation of blood pressure mainly include overactivity of the sympathetic nervous system (SNS), activation of the renin-angiotensin-aldosterone system (RAAS), endothelial dysfunction, impaired insulin-mediated vasodilation, abnormal immune responses, and inflammation.

Insulin Resistance (IR) and Hyperinsulinemia

More and more studies have shown that the adverse effects of insulin resistance on the balance of kidney and water-sodium metabolism play an important role in the pathogenesis of hypertension [9]. The main mechanisms include: (1) promote water and sodium retention: water and sodium retention is an important link in the pathological process of hypertension, insulin affects ions transport inside and outside the cell membrane, mainly by improving the expression of sodium transport channels, strengthening the sodium reabsorption in the distal convoluted tubule, thereby reducing the excretion of sodium. Secondly, insulin can indirectly promote sodium reabsorption in renal tubules by activating SNS and RAAS, resulting in increased sodium retention and extracellular fluid volume and elevated blood pressure [10]. Concurrently, uric acid and sodium have similar metabolic pathways in kidney, and water and sodium retention also leads to a decrease in uric acid excretion, and hyperuricemia is very common in patients with hypertension, further becoming one of the contributing factors in the pathogenesis of hypertension [11]. (2) Endothelial cell-dependent vasodilatation is impaired: insulin reduces the synthesis of prostaglandin and prostacyclin in vascular endothelial cells, stimulates the synthesis and secretion of endothelin by aortic endothelial cells to constrict blood vessels, with the effect of enhancing blood pressure level and promoting the proliferation of smooth muscle and myocardial cells, leading to cardiovascular remodeling; insulin as a growth factor can stimulate small arteriole smooth muscle cell proliferation and subintimal migration, arterial wall thickening, atherosclerosis, and elevated blood pressure [12]. Insulin can increase plasminogen activator inhibitor l (PAI.1), which

leads to changing of cell membrane mobility being limited, and the state of high coagulation increases blood flow resistance, thereby raising blood pressure. (3) SNS dysfunction: insulin resistance activates adrenergic α-receptors and contracts blood vessels; hyperinsulinemia stimulates sympathetic nerve activity and increases renin excretion [13]. When the renin-angiotensin system is activated, causing an increase in substances such as catecholamines in the blood, resulting in increase in cardiac output and peripheral vascular resistance [14]. (4) Influencing the transport of calcium ions inside and outside the cell membrane: insulin resistance decreases the activity of Ca^{2+}ATPase and Na^{+}-K^{+}ATPase on the cell membrane, increasing the concentration of calcium (Ca^{2+}) and sodium (Na^{+}) in vascular smooth muscle cells, resulting in vasoconstriction or spasm, which increases the peripheral vascular resistance and increases the sensitivity of the resistance vessels to the pressurized substance, causing an increase in blood pressure (especially diastolic blood pressure). (5) Insulin causes obesity by stimulating fat synthesis, leading to obesity and hypertension associated with type 2 diabetes [15].

Hyperglycemia Status

The mechanism of hyperglycemia-induced hypertension is as follows: (1) hyperglycemia promotes the reabsorption of glucose in the proximal convoluted tubules, accompanied by sodium reabsorption, increases sodium capacity in the body (about 10%), and increases extracellular fluid volume which leads to hypertension. (2) Hyperglycemia rises plasma osmotic pressure, which leads to increased blood volume [16]. (3) Blood sugar and electrolyte are similar and can increase the crystal osmotic pressure in blood, so as to increase blood volume, resulting in increased peripheral vascular resistance. (4) Hyperglycemia non-enzymatic irreversible glycosylation products form an Amadori product and a Schjf base, which are then rearranged to produce an irreversible polymer glycation end product (advanced glycation end products, AGEs). AGEs bind to the AGE receptor (receptor of advanced glycation end products, RAGE), resulting in increased cell proliferation and affecting cytokine gene transcription, promoting smooth muscle cell migration, proliferation, and increasing the contents of monocyte chemoattractant protein-1 (MCP-1), c-jull, and e-fos; enhancing the activity of p38MAPK, AP-1, and MAPK in smooth muscle cells [17]. At the same time, AGEs can also stimulate the secretion of many cytokines, such as platelet-derived growth factor (PDGF), insulin-like growth factor, etc., stimulate smooth muscle cell proliferation, cause the occurrence and development of atherosclerosis [18]. (5) The glucose perfusion in the blood vessel wall can increase vascular smooth muscle responsiveness to sympathetic nerves, causing vasoconstriction and elevated blood pressure. (6) Blood sugar symptoms stimulate the activation of oxidative stress, leading to an increase in the number of superoxide anions, so that nitrous oxide is inactivated, and then vascular endothelial damaged, vascular dilatation function reduced, and ultimately promote the occurrence and development of hypertension [19].

Inappropriate Activation of RAAS

The main components of the classical RAS pathway are angiotensin-converting enzyme (ACE), angiotensin II (Ang-II), and Ang-II receptor (AT receptor). ACE is the speed limit enzyme of RAAS, which stimulates angiotensin I transform into

angiotensin II, thereby regulating vascular tension and maintaining stable blood pressure. It has been confirmed that angiotensin II in the RAS system can directly or indirectly activate a pro-inflammatory cytokines and promote insulin sensitivity down-regulation, leading to oxidative stress, inflammation, and insulin resistance, and its activity is abnormally involved in the onset of diabetes [20, 21].

Obesity and increased visceral fat are key pathogenic factors for the coexistence of diabetes and hypertension. Chronic low-grade inflammation and oxidative stress in adipose tissue leads to increased production of angiotensinogen (AGT) and AngII, resulting in tissue RAAS activation. Furthermore, overexpression of AGT in white adipose tissue leads to an increase in blood pressure. Therefore, AGT and AngII have local and systemic effects on blood pressure regulation. AngII exerts many of its deleterious effects by activating the AngII type 1 receptor (AT1R). Activation of AT1R in non-adrenal tissue results in a variety of intracellular events, including the production of oxygen free radicals, which leads to the downregulation of insulin sensitivity, ultimately leading to endothelial dysfunction, insulin resistance, and hypertension.

Sympathetic Excitation

Under normal circumstances, vascular baroreceptors sense changes in blood pressure and maintain blood pressure by regulating sympathetic and/or parasympathetic activity. (1) Many studies have confirmed that the sensitivity of baroreceptors is reduced under IR and hyperinsulinemia, leading to the occurrence of hypertension. (2) IR and hyperinsulinemia excite the sympathetic nerves, activate the RAAS system, increase ATII, directly cause vasoconstriction through ATRl, or interfere with the insulin/P13K/Akt signaling pathway, leading to IR and accelerating the occurrence of hypertension. At the same time, increased sympathetic activity causes vasoconstriction, and skeletal muscle blood flow is reduced, which makes sugar utilization impaired and promotes IR. (3) Cardiac autonomic neuropathy is very common in diabetic patients. Hyperinsulinemia causes imbalance of nocturnal sympathetic–vagal nerve balance, which is characterized by decreased vagal activity, increased sympathetic activity, and dysfunction of blood pressure circadian rhythm, resulting in "non-dipping" changes [22, 23]. (4) A large number of studies have shown that the sympathetic system (SNS) activity of obese people is enhanced, and the sympathetic nervous system activity of central obese people is higher than that of peripheral obesity, and the sympathetic nerve activity of obese hypertensive patients is higher. Obesity-induced SNS activation is associated with a variety of factors, including hyperinsulinemia, elevated free fatty acid concentrations, impaired baroreceptors, chemoreceptor activation due to sleep apnea syndrome, and release of adipokines (leptin, melanocortin, tumor necrosis factor, interleukin-6, etc.) [24].

Vascular Endothelial Cell Dysfunction

VEC (vascular endothelial cell) is a kind of flat monolayer cells covering the whole vascular wall. While there are changes in blood pressure, inflammatory signals, and circulating hormone level, the endothelial cells can make regulatory response, and synthesize and secrete a variety of vascular active substances and growth factors,

such as NO, prostacyclin, endothelin, angiotensin II, thromboxane regulatory protein, heparin, human tissue-type plasminogen activator, vascular von Willebrand factor, adhesion molecules, and cytokines. The interaction among these factors can maintain vasomotor state and effectively regulate the inflammatory response and coagulation state, etc. [25]. Insulin resistance, hyperglycemia, and inflammatory responses in adipose tissue are also involved in endothelial injury. After the endothelial cell function is impaired, it will lead to dysfunction in secretion of active substances, which may result in the increase of AngII with inflammatory effect, thereby further exacerbating the endothelial injury and producing oxidized lipoprotein, which is the key element of endothelial injury; the vascular barrier function is impaired, the intercellular space is enlarged, and the permeability is increased, so the macromolecular substances and inflammatory cells can enter the vascular wall, thus promoting the occurrence of atherosclerosis. The dysfunction in reception and transmission of information are mainly manifested in the dysfunction of receptors in endothelial cells. The disorders in hemodynamic regulation mentioned above serve as the basis for the formation of atherosclerosis and hypertension.

Renal Sodium Transporters

Renal tubular epithelial sodium channel (ENaC) plays a key role in maintaining sodium balance and hypertension [26]. The mutations of ENaCβ subunits are often involved in the hypertension, which may lead to the increased sodium reabsorption in renal tubules, thereby leading to hypertension syndrome [27]. Animal models have shown that obesity will increase the expression of ENaC in the kidney, thereby leading to sodium retention and obesity-related hypertension. It has also been proved that insulin can increase ENaC activity [28]. In addition, some studies have also suggested that there is a positive correlation between blood glucose level and the density of ENaC subunits [29].

Others

Genetic susceptibility, abnormal lipid metabolism, signal transduction system with stable energy dynamics (e.g., neuropeptide Y, peptide YY), obstructive sleep apnea hypopnea syndrome, parathyroid and thyroid hypertension factors, etc. are also involved in the pathophysiology of hypertension in DKD patients.

15.1.4 Pathological Features of DKD

The occurrence and development of DKD is mainly caused by the increase of blood glucose, leading to advanced glycation end products, growth factors, hemodynamics, and hormone changes; these changes result in glomerular hyperfiltration, glomerular hypertension, and renal hypertrophy, which is manifested clinically as albuminuria and hypertension. The pathological basis of DKD is the structural changes of the kidney, including glomeruli, tubules, blood vessels, and stroma. The pathological manifestations depend on whether the patient is complicated with hypertension, the type of DM, the length of the course of disease, and whether it is

complicated with renal vascular disease or recurrent chronic infection, the severity of the disease determines the prognosis of DKD patients. Although the renal pathological changes of type 1 and type 2 DM are very similar, the former is more typical, and the latter is more diverse. Renal pathological features including deposition (in primarily the mesangium) of extracellular matrix, glomerular basement membrane thickening, and tubular atrophy ultimately result in interstitial fibrosis and glomerulosclerosis [30].

15.1.5 DKD Screening

15.1.5.1 Urinary Albumin

Random urine determination of UACR is recommended to reflect the amount of urinary albumin. Random urinary UACR ≥ 30 mg/g indicates increased urinary albumin excretion, which means albuminuria. Confirmation of albuminuria requires two increased urinary albumin excretion measurements of repeated examination (three times) of UACR in 3–6 months, excluding other factors such as infection. Clinically, UACR 30~300 mg/g is defined as microalbuminuria, and UACR > 300 mg/g is defined as macroalbuminuria. The determination of UACR is affected by many factors such as infection, fever, hyperglycemia, high blood pressure, heart failure, strenuous exercise within 24 h, menstruation, etc., these factors should be taken into account in the analysis of the results. When albuminuria is used as a basis for diagnosis, it is necessary to make a comprehensive judgment, repeated testing, and long-term follow-up of eGFR and to exclude other causes of albuminuria.

15.1.5.2 eGFR

Glomerular filtration rate [31] (glomerular filtration rate, GFR) is the main index to reflect renal function. EGFR is generally used instead of direct determination of GFR. It is worth noting that not all diabetic patients with decreased eGFR have increased urinary albumin excretion. The results of cross-sectional survey showed that there was no abnormal urinary albumin excretion in some diabetic patients, but there was already a decrease in eGFR [31, 32]. The common parameters used to calculate eGFR include age, sex, and serum creatinine concentration; it is recommended to use CKD-EPI formula or MDRD formula. When eGFR < 60 mL/min/1.73 m^2, eGFR can be diagnosed as decreased, but the value of eGFR may fluctuate; when there is a decrease, it should be reexamined to determine the stage of DKD.

15.1.5.3 Other Indexes

Serum urea nitrogen, creatinine, endogenous creatinine clearance rate, serum cystatin C, double renal radionuclide renal scanning (ECT).

15.1.5.4 Biomarkers

At present, DKD biomarkers mainly include glomeruli, renal tubular injury, interstitial fibrosis, inflammatory injury, and other related markers. It has been found that

MRC1, PLD4, MGP, SCN7A, STRA6, and SMOC2 can also be used as markers of renal fibrosis and tubule injury in DKD.

15.1.6 DKD Staging

After DKD is confirmed, the severity of renal function damage should be further determined according to eGFR (Table 15.1) [3, 33].

15.1.7 Diagnosis of DKA

Pathological biopsy is the golden standard for the diagnosis of DKD. The typical renal morphological changes of DKD included thickening of glomerular basement membrane, widening of mesangial matrix, glomerulosclerosis, and loss of podocytes. Other characteristics are thickening of renal tubular basement membrane, atrophy of renal tubules, increase of apoptosis, inflammatory infiltration of renal stroma, renal interstitial fibrosis, sparse perivascular capillaries, and vitreous degeneration in and out of the wall of glomerular arterioles, in particular, the hyaline degeneration of the bulbar arterioles [7, 34].

In 2010, the Research Committee of the Society of Renal Pathology proposed the DKD pathological grading criteria for the first time, which is applicable in both type 1 and type 2 diabetes mellitus. According to the changes of light microscope, electron microscope, and immunofluorescence staining of renal tissue, the glomerular damage and renal tubular/renal vascular injury were classified, graded, and scored, respectively. Glomerular injury was divided into four grades: Class I: glomerular basement membrane thickening; Class II: mesangial hyperplasia, mild (IIa) or severe (IIb); Class III: more than one glomerulus with nodular sclerosis (Kimmelstiel-Wilson nodule, K ≤ W nodule); Class IV: diffuse glomerulosclerosis. Renal tubulointerstitial fibrosis, renal tubular atrophy, and interstitial inflammation were scored, and renal vascular injury was scored according to the degree of vascular hyaline degeneration and macrovascular sclerosis [3, 35].

Table 15.1 Stages of diabetic kidney disease

Stage	Kidney damage	eGFR (mL/min/1.73 m^2)
1	+	≥90
2	+	60–89
3a	+ or −	45–59
3b	+ or −	30–44
4	+ or −	15–29
5	+ or −	<15 (or dialysis)

Remarks: kidney damage: mainly refers to albuminuria (urinary albumin/creatinine ≥ 30 mg/g), also includes hematuria, other urine sediment abnormalities, and imaging or pathological abnormalities; eGFR: predicts glomerular filtration rate

15.1.7.1 Clinical Diagnosis

DKD is usually diagnosed on the basis of diabetic retinopathy. However, according to the 2018 (ADA) guidelines of the American Diabetes Association, diabetic retinopathy is concordant with T2DN in only about 60–65% of cases. Therefore, the absence of retinopathy in DM patients does not generate a negative predictive value for the diagnosis of diabetic nephropathy. In addition, ADA also pointed out that proteinuria in patients before 5 years or after 25 years duration of type 1 diabetes mellitus (T1DM) indicates the existence of non-diabetic nephropathy (NDRD). Therefore, for patients with long course of T1DM (>25 years) with proteinuria, should be alert to DM combined with NDRD. In addition, up to 25% of patients with DM and diminished kidney function have little or no proteinuria. At present, some scholars call this disease normal proteinuria diabetic nephropathy, but whether it can be used as a disease diagnosis remains to be studied.

15.1.7.2 Early Diagnosis Index

The early diagnosis of diabetic nephropathy mainly includes four categories: (1) glomerular injury index, (2) renal tubular injury index, (3) oxidative stress and inflammatory markers, and (4) other diagnostic indicators. The results of the latest study by the Joslin Diabetes Center suggest that serum TNF receptor levels are a powerful predictive biomarker for progressive decline in GFR.

15.1.8 Treatment

15.1.8.1 Treatment of DKD

2019 Chinese Clinical Practice Guideline of Diabetic Kidney Disease pointed out that the prevention of DKD was divided into three stages. The first stage is to prevent the occurrence of DKD, including early screening, lifestyle changes, and blood glucose and blood pressure control. The second stage is early treatment, patients with DKD who have decreased albuminuria or eGFR, and comprehensive treatment (such as optimization of hypoglycemic, antihypertensive, rational use of ACEI/ARB, etc.) to reduce or delay the occurrence of ESRD. The third stage is a comprehensive treatment for advanced DKD, including renal replacement therapy for ESRD, prevention of ESRD-related complications, reduction of cardiovascular events and mortality, improvement of quality of life, and longevity.

15.1.9 Non-drug Therapy

It mainly includes control of protein intake, blood glucose, blood pressure, correction of dyslipidemia, correct use of diuretics, smoking cessation, salt intake restriction, and appropriate exercise, and recommended DKD patients limit salt intake to less than 6 g/day. For patients with hyperkalemia, there is also a need to limit potassium intake. Patients being overweight or obese DKD should maintain their normal weight (BMI < 24 kg/m^2). Smoking is a risk factor for proteinuria and renal function

progression in DKD patients. Studies had showed that in DM patients, smokers are 4.5 times more likely to develop proteinuria than non-smokers. Quitting or reducing smoking is an important measure for preventing or controlling the progression of DKD in DM patients. In addition, patients with DKD should avoid excessive dietary protein intake, which should not exceed 1.3 g/kg/day, and the protein source should be based on high-quality animal protein. An intake of 0.8 g/kg/day for a DKD patient with a GFR < 30·30 mL/min/1.73 m^2 is suitable. If the protein intake is ≤0.6 g/kg body weight, the compound α-keto acid preparation should be supplemented.

15.1.10 Drug Therapy

15.1.10.1 Blood Pressure Control

Currently, for DKD blood pressure control, guidelines and consensus control objectives are different. *2019 Chinese Clinical Practice Guideline of Diabetic Kidney Disease* pointed out that for patients with DKD, especially albuminuria, blood pressure should be controlled below 130/80 mmHg, but diastolic blood pressure should not be lower than 70 mmHg, and diastolic blood pressure should not be lower in elderly patients. At 60 mmHg, ACEI or ARBs are preferred for antihypertensive drugs. ACEI or ARB has the effect of controlling blood pressure, reducing proteinuria and delaying the progression of renal function in diabetic nephropathy. It is the most clinically proven drug in the treatment of DKD and is recommended as the first-line drug for the treatment of DKD. Patients with DKD or diabetes with hypertension are preferred to use one of them. When they are intolerable, they should be replaced by another. Serum creatinine and potassium levels should be monitored during use. When the antihypertensive effect of ACEI or ARB is not ideal, a combination of a calcium antagonist, a thiazide or a loop diuretic, a beta blocker or the like can be used. Multiple clinical studies and meta-analyses have shown that combined use of ACEI and ARB does not improve renal endpoint outcomes and cardiovascular events compared with ACEI or ARB alone, but rather increases adverse events (hyperkalemia, acute incidence of kidney damage, irritating dry cough, etc.) [36–38]. Therefore, the combined use of ACEI and ARB drugs is not recommended.

15.1.10.2 Blood Glucose Control

Blood glucose control should follow the individualization principle. For most patients, glycosylated hemoglobin was recommended to be below 7% without hypoglycemia. However, for elderly and end-stage renal disease patients, the control target of HbA1c should be appropriately relaxed to no more than 7–9%. It should be noted that when the patient is complicated with anemia, metabolic acidosis, etc., it will interfere with the measurement results of glycated hemoglobin. For patients with diabetic nephropathy, hypoglycemic drugs should be selected according to the eGFR level. Patients with renal insufficiency may prefer hypoglycemic agents that are excreted from the kidneys. Patients with severe renal insufficiency

should be treated with insulin. Currently, hypoglycemic drugs mainly include antihyperglycemic drugs including biguanides, sulfonylureas, glinides, α-glucosidase inhibitors, thiazolidinediones, and dipeptidyl peptidase IV (DPP-4) inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, and insulin.

15.1.10.3 Albuminuria Control

In addition to antihypertensive effects, ACEI and ARB can also reduce thyroid capillary hydrostatic pressure, improve glomerular basement membrane permeability, reduce protein filtration, and reduce glomerular system and have the ability of membrane cells to uptake and scavenge macromolecular substances. The US DKD guidelines recommend ACEI and ARB as the first choice for early DN to reduce proteinuria and protect kidney function. For DM patients with normal blood pressure and large amount of proteinuria, ACEI or ARB should be applied as soon as possible, if microalbuminuria is present, it is also recommended.

15.1.10.4 Blood Lipid Control

It was recommended to lower LDL-C as the primary target for extrem risk patients, the LDL-C level is less than 55 mg/dL. Extrem risk factors include progressive ASCVD unstable angina after achieving an LDL-C <70 mg/dL or established clinical cardiovascular disease in patients with DM, CKD 3/4, or history of premature ASCVD (<55 male, <65 female). For very high risk patients, who with established or recent hospitalization for ACS, coronary, carotid, peripheral vascular disease, HeFH, diabetes or CKD 3/4 with one or more risk factor(s), the LDL-C level is less than 70 mg/dL. For high risk patients, who have more than 2 risk factors and 10-year risk >10% or CHD risk equivalentc, including diabetes or CKD 3/4 with no other risk factors, the LDL-C level is less than 100 mg/dL [39]. The treatment of hyperlipidemia with high cholesterol is the preferred statin lipid-lowering drug, which can not only effectively lower cholesterol levels but also improve vascular endothelial function through anti-inflammatory and immune regulation and at the same time inhibit mesangial cell proliferation and cells. Exogenous matrix production and expression of plasminogen activator inhibitors reduce renal pathology and delay glomerular sclerosis. Beta drugs are mainly used in patients with elevated TG, based on drug treatment, combined with diet therapy.

15.1.10.5 Alternative Treatment of ESRD

Dialysis should be actively prepared when the general GFR is reduced to 15–20 mL/min or serum creatinine level exceeds 442 μmol/L. The dialysis methods include peritoneal dialysis and hemodialysis. Kidney transplantation or pancreas–kidney transplantation is feasible in patients with conditional diabetes.

15.1.11 New Treatment

Some new formulations are expected to be used in the treatment of DKD, such as protein kinase C inhibitors, selective tyrosine kinase 1 and tyrosine kinase 2

inhibitors, anti-inflammatory and anti-fibrotic agents, and selective endothelin A receptor antagonism, a highly selective non-steroidal mineralocorticoid receptor antagonist. However, none of the preparations completed Phase III clinical trials and could be used for DKD treatment without passing.

New hypoglycemic agents: In recent years, research on new types of hypoglycemic agents in the treatment of diabetic nephropathy has gradually increased, including SGLT-2 inhibitors (EMPA-REG, CANVAS study, dapagliflozin Phase III clinical post hoc analysis), GLP-1 receptor agonist (LEADER study), DPP-4 inhibitor (SAVOR TIMI-53 study kidney disease results, TECOS study kidney disease results, MARLINA study), etc., which also provide more evidence for the treatment of diabetic nephropathy.

SGLT-2 inhibitor: SGLT-2 inhibitor is a new type of hypoglycemic drugs for type 2 diabetes; in addition to hypoglycemic, it also has the benefit of reducing blood pressure, losing weight, and dropping uric acid. However, the publication of the results of the large-scale cardiovascular evaluation trial EMPA-REG OUTCOME [40] opened the way for the treatment and prevention of cardiovascular diseases with hypoglycemic drugs. The study in 2016 published that the SGLT2 inhibitor empagliflozin was associated with delayed progression of renal disease. There were also fewer clinically relevant renal events or worsening of kidney disease compared with placebo (progression to high albuminuria, doubling of creatinine levels, initiation of renal replacement therapy, or death from renal disease) and comprehensive benefits [41]. Subsequently, the CREDENC research shows that the existing evidence base for canagliflozin and other SGLT2 inhibitors in patients with normal or mildly impaired renal function supports a potential benefit for these therapies on renal and cardiovascular outcomes in patients with impaired kidney function [42]. The result shows that compared with placebo, the renal composite endpoint was reduced in patients treated with canagliflozin (elevated creatinine, end-stage renal disease, and renal death). In addition, the annual decrease rate of eGFR was lower in the canagliflozin group than in the placebo group (discrepancy 1.2 mL/min/1.73 m^2/year, 95% CI 1.0–1.4 mL/min/1.73 m^2). Albuminuria was significantly reduced (Patients treated with Canagliflozin had an 18%, 95% CI 16–20, reduction in albuminuria during follow-up.), and there was no increase in adverse events [43]. A Phase III clinical postmortem analysis of dapagliflozin showed that the ratio of urinary microalbumin to urinary creatinine was significantly decreased in patients with type 2 diabetes mellitus and stage 3 diabetic nephropathy.

Renal benefits and possibility mechanisms of SGLT-2 inhibitors include preventing nephron ultrafiltration, decreasing extracellular fluid volume dilation and increased atrial natriuretic peptide levels, reducing sodium reabsorption; restoring to normal of the feedback mechanism of the tube ball. Reducing proteinuria: the potential side effects of SGLT-2 inhibitors include changes in urine volume and electrolytes in patients, urinary/genital tract infections, diabetic ketosis, and amputation/toe amputation. People at high risk should be aware of the risks associated with their use.

Pancreatin drugs: In 2017, the LEADER cardiovascular outcome trial showed that in addition to Liraglutide benefitting the cardiovascular system, renal outcomes

in patients with type 2 diabetes were significantly improved. The AWARD 7 trials was published in 2018 [44]. An evaluation of the efficacy and safety of dulaglutide in patients with moderate to severe diabetic nephropathy (Stage 3–4) showed that for patients with high levels of proteinuria, the kidney benefit was even more pronounced. TECOS and MARLINA studies showed that DPP-4 inhibitors did not significantly improve renal function but showed a trend of benefit.

15.2 Hyperuricemia and Hypertension

Jianwen Zhao

Hyperuricemia is a metabolic disease caused by the disturbance of purine metabolism. Clinically, it is divided into primary and secondary hyperuricemia. The former is mainly caused by congenital abnormal purine metabolism, which is related to hypertension. But the latter is caused by some systemic diseases or drugs. A small part of patients with hyperuricemia have gout, which is characterized by the clinical symptoms and positive signs of the acute arthritis, gout kidney, gouty tophus and so on. Hyperuricemia is related to multiple risk factors that lead to hypertension including obesity, excessive alcohol intake, and insulin resistance. Moreover, it causes hypertension by the interaction with the risk factors or by alone. This chapter focuses on the correlation between hyperuricemia and hypertension, and the rational drug usage in clinical practice.

15.2.1 Pathogenesis of Hyperuricemia

Uric acid is the end product of purine metabolism that is decomposing the nucleic acids and other purine compounds of cell metabolism and the purine of food by enzymes. In human body, 80% of the uric acid is derived from the nucleic acids and other purine compound decomposed from protein by the uric acid synthetase of liver; 20% of the uric acid is derived from the food full of purine or nucleic acid, including animal viscera, beer, and seafood. Though there are two ways for purine entering the human body, oral intake and biosynthesis, the amount of biosynthesis is significantly higher than oral ingestion. About two thirds of the uric acid is excreted through the kidneys, and the rest is excreted by the digestive tract. Uric acid is filtered by glomerulus, and then reabsorbed, secreted, reabsorbed after secreted though proximal renal tubules; the unabsorbed part is excreted from the urine. Uric acid at physiological concentrations exists in the form of soluble urate and has a strong antioxidant effect. Normally, the production and excretion of uric acid in the body are balanced, and the factors that lead to excessive uric acid and/or reduced excretion can cause hyperuricemia.

Commonly, uric acid increases with age, especially in women after menopause. The level of serum uric acid is affected by multiple factors such as race, eating habits, region, age, and body surface area. Internationally, the diagnostic criteria of

hyperuricemia is defined as follows: under normal purine diet, two fasting uric acid levels in different day: male >420 μmol/L, female >360 μmol/L. Hyperuricemia can be classified into primary and secondary types. Primary hyperuricemia is a congenital uric acid metabolic disturbance without other acquired diseases, presenting with increased serum uric acid levels or uric acid deposition. Secondary hyperuricemia is an increased serum uric acid levels secondary to any hereditary or acquired pathological process.

15.2.2 Possible Correlation Mechanism of Hyperuricemia Affecting Hypertension

With the improvement of people's living standards, the morbidity of hyperuricemia is also increased year by year [45]. Currently, multiple studies have shown that hyperuricemia may be an independent risk factor for cardiovascular diseases. Hyperuricemia is closely related to the occurrence, development, and mortality of hypertension [46]. The incidence of hyperuricemia is also closely related to secondary hypertension [47]. Initially, it was attributed to the contraction of renal vessels, causing reduced uric acid excretion. With in-depth studies, it has been recognized in recent years that elevated serum uric acid is an independent risk factor for hypertension. In 2018, the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) updated the guidelines for hypertension management, and for the first time, uric acid was included as a cardiovascular risk factor for the patients with hypertension [48]. Olivetti cardiac study indicates that basic uric acid level is the strongest independent predictor for the occurrence of hypertension. Hyperuricemia is an independent risk factor for the occurrence of atherosclerosis in patients with hypertension [49]. Previous studies demonstrated that it is easy to form uric acid crystals and deposit in the collecting ducts of nephron with the increase of serum uric acid level, causing renal tubular obstruction, renal interstitial inflammation, and fibrosis. Hyperuricemia can also cause renal diseases by multiple mechanisms such as inducing cellular oxidative stress, mitochondrial dysfunction, endothelial dysfunction caused by inflammatory response, and activation of renin-angiotensin system (RAS), vascular smooth muscle cell proliferation, and interstitial cell infiltration, thus influencing the occurrence and development of hypertension.

15.2.3 Pathogenesis of Hypertension with Hyperuricemia

Hypertension can cause the damage of target organs and then cause the pathological changes of great vessels and capillaries, especially for the damage of renal capillaries. The damage of kidney is mainly for the small arterioles, especially for efferent arteriole, which narrows or even occludes the renal tubular, causing hemorrhage of the renal parenchyma, glomerular fibrosis, and decrease of urate excretion of the renal tubules, and then decreasing the uric acid excretion and increasing the blood

uric acid level. At the same time, the damage of renal capillaries leads to glomerulosclerosis and hypoxia of local tissues, which increases the production of lactic acid. Lactic acid competitively inhibits the excretion of uric acid by the renal tubules and increases the substrate adenine and hypoxanthine during the formation of uric acid, and then increases the synthesis of uric acid, ultimately causing an increase of serum uric acid. In addition, high concentration of urate can deposit in renal tubules and interstitium, stimulate renin secretion, increase blood pressure, and aggravate the damage of renal function. The two are cause and effect each other, forming a vicious circle and influence the development of lesions.

15.2.4 Treatments of Hyperuricemia

Once a patient is diagnosed as hyperuricemia and gout definitely, we should perform immediately mission and lifestyle interventions for the patient. Patients with hyperuricemia require comprehensive and long-term management and should be immediately educated and provided lifestyle interventions. According to the level of blood uric acid and the combined clinical symptoms or signs, the time of drug initiation treatment is determined, and the corresponding treatment goal is formulated and hierarchical management is performed.

The management of patients with hyperuricemia: (1) popularizing common knowledge related to hyperuricemia; (2) providing health guidance on diet and exercise to formulate individualized lifestyle intervention; (3) screening and preventing the gout and complications; (4) cooperating with specialists to formulate treatment strategies and try to avoid using the drugs increasing the uric acid level of blood and/or urine; and (5) long-term control of drug treatment is necessary. The blood uric acid should be continued to meet the standard, patients receiving drug treatment must accept healthy lifestyle interventions at the same time.

15.2.4.1 Urate-Lowering Therapy

Drug therapy is performed when the effect of non-drug intervention on hyperuricemia is not good. The treatment strategies should be individualized, stratified, up to standard, long-term management, and gradually adjust the dose to avoid excessive fluctuation of serum uric acid level in short term which can induce acute gout. Clinically, the common uric-acid-lowering drugs inhibit uric acid synthesis and promote uric acid excretion. Selecting the drugs should base on the etiology, complications, and the function of liver and kidney [50, 51].

15.2.4.2 Treatment of Alkalinizing Urine

Patients accepting uric-acid-lowering drugs (especially uricosuric drug) and patients with uratic kidney stones are recommended to maintain the pH value of urine at 6.2–6.9 to increase the solubility of uric acid in urine. Excessive urinary pH increases the risk of stone formation such as calcium phosphate and calcium carbonate.

15.2.4.3 Drug Treatment of Acute Gout

The aim of the treatment of acute gout is to quickly control the symptoms of arthritis. In the acute stage, patients should rest in bed, raise affected limbs, and perform local cold compress. Drugs should be given as early as possible to control acute attack, the earlier the treatment, the effect is better. Colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line drugs for the treatment of acute arthritis. When the above drugs are taboo or have poor effects, glucocorticoids can be chosen to control inflammation. Acute episodes involve 1–2 of large joints, the systemic treatment is poor, and intra-articular injection of short-acting glucocorticoid may be considered to avoid short-term reuse.

15.2.4.4 Antihypertensive Strategy of Hyperuricemia Combined with Hypertension

For most patients with asymptomatic hyperuricemia, the risk–benefit analysis cannot confirm the necessity anti-hyperuricemia medication is necessity. The estimated risks should be weighed against the potential benefits and risks of drug treatment because primary hyperuricemia usually persists indefinitely. Due to the possible significant adverse reactions of urate-lowering therapy, the therapy of decreasing uric acid is not recommended for the patients with asymptomatic hyperuricemia [52]. For the patients with hypertension accompanied by hyperuricemia, the usage of anti-hypertensive drugs is slightly different from the patients with simple hypertension. A large number of clinical data show that multiple anti-hypertensive drugs can influence the production and excretion of uric acid, causing the increase of blood uric acid concentration, induce or aggravate hyperuricemia, thereby inducing gout, producing urinary calculi, urate nephropathy, aggravating the disease; hence, it is particularly important to choose reasonable treatment drugs.

ESH/ESC hypertension management guidelines in 2018 emphasized that antihypertensive treatment strategies should be selected based on indications and contraindications. The guide mentions that gout is the absolute contraindication of thiazide diuretics, and hyperuricemia is the cautious indication of thiazide diuretics. Urate retention induced by diuretics was dose-dependent [53]. Patients with hypertension combined with hyperuricemia should avoid using thiazide diuretics and loop diuretics singly. Diuretics can directly facilitate the reabsorption of uric acid by proximal renal tubules, and the volume deficit caused by diuretics can indirectly facilitate the reabsorption of uric acid by proximal renal tubules [54]. Angiotensin-converting enzyme inhibitors combined with thiazide diuretics can inhibit uric acid transporter and reduce the level of serum uric acid in patients with hypertension accompanied with hyperuricemia or gout.

15.3 Hyperhomocysteinemia

Hongmei Wang

Homocysteine (HCY), a sulfur-containing amino acid, is an important intermediate in the metabolism of methionine and cysteine. Elevated HCY level in the body will

damage vascular endothelial cells, cause proliferation of vascular smooth muscle cells, affect coagulation and fibrinolysis system, and significantly increase the risk of coronary heart disease, peripheral vascular disease, and cerebrovascular disease.

15.3.1 The Metabolism of HCY In Vivo

Under normal circumstances, HCY can be catabolized in the body, and its concentration is maintained at a low level. Its two main metabolic pathways in the body are:

1. Methylation pathway: methionine metabolic cycle, HCY accepts methyl group provided by methylenetetrahydrofolate reductase catalyzing 5,10-methy lenetetrahydrofolate, via methionine synthase, methionine is re-synthesized, and vitamin B12 as a cofactor of methionine synthetase involves in its metabolic cycle.
2. Sulfonyl transfer pathway: about half of HCY and serine form cystathionine under the action of cystathionine beta synthase (CBS), which in turn converts to cysteine, a process that requires cofactor vitamin B6 [55].

In the process of HCY metabolism, any factor that can cause abnormalities of various enzymes and cofactors can release HCY into the extracellular fluid to form hyperhomocysteinemia. Reduction of folic acid, vitamin B12, or vitamin B6 for any reason (e.g., the body's absorption and metabolic disorders, smoking, drinking, mental and psychological factors, kidney failure, liver disease, contraceptives, and other diseases and drugs) will seriously affect the activity of HCY metabolic enzymes, which causes the above two metabolic pathway disorders, and an increase in HCY level.

Studies have shown that genetic variation and abnormal gene expression play an important role in the metabolism of HCY [56]. 5,10-Methylenetetrahydrofolate reductase (MTHFR) is the most important key enzyme affecting HCY metabolism. The abnormal regulation of MTHFR gene leads to abnormal methylation pathway of HCY and an increase in HCY content and consequently more hereditary diseases [57]. MTHFR gene C677T mutation can decrease the activity of MTHFR, hinder the conversion of HCY to S-adenosylmethionine, cause hyperhomocysteinemia and cytotoxicity, damage vascular endothelial cells, and ultimately increase coronary heart disease and stroke, and the risk of cardiovascular and cerebrovascular diseases.

15.3.2 The Hazard of Hyperhomocysteinemia

Homocysteinemia refers to an increase in free and protein-bound HCY in plasma or serum. According to the degree of HCY elevation, hyperhomocysteinemia was classified as mild (16–30 μmol/L), moderate (31~100 μmol/L), and severe (>100 μmol/L) [57–60].

The increase of HCY will cause multiple system damage to the body. Its pathogenic mechanism is mainly to damage the vascular endothelium, cause the

proliferation of vascular smooth muscle cells, which in turn affects the body's coagulation function and fibrinolysis mechanism.

The pathogenic mechanism has the following aspects:

1. Damage to vascular endothelial cells by oxidative stress reaction, which reduces vasodilation function [58], causing increased resistance of peripheral blood vessels and increased blood pressure.
2. Stimulate the proliferation of vascular smooth muscle cells, making the degree of atherosclerosis more serious, resulting in decreased arterial elasticity and increased stiffness [59], causing an increase in systolic blood pressure.
3. The increase of HCY content can promote lipid deposition on the blood vessel wall, reduce the compliance of the blood vessel wall, damage the blood vessels, and induce vascular remodeling [60, 61].
4. Promote platelet adhesion and aggregation, thereby destroying the mechanism of coagulation and fibrinolysis, and causing thrombosis [62].

15.3.2.1 HCY and Cerebrovascular Disease

In recent years, the incidence of acute cerebrovascular disease has increased year by year, and it has become one of the major diseases that cause human death. At present, relevant studies have confirmed that hyperhomocysteinemia is associated with the development of cerebrovascular disease, and patients with hyperhomocysteinemia are more likely to develop atherosclerosis and thrombosis than the control group. And the time of emergence is earlier, which leads to a significant increase in the incidence of cerebrovascular events such as stroke, cerebral infarction, and cerebral hemorrhage.

HCY has a close relationship with cerebral infarction. Recent studies have shown that HCY is one of the risk factors for cerebral infarction [63]. The HCY value of the study group is higher than that of the control group. Moreover, the mean value of HCY in patients with cerebral infarction in the study group was higher than normal value. HCY is a reactive vascular injury amino acid, and its rise in expression level can independently predict the occurrence of arteriosclerotic disease, damage vascular endothelial cells, promote the proliferation of vascular smooth muscle cells, and affect coagulation function and fibrinolysis mechanism, leading to thrombosis [64, 65]. Studies have shown that the HCY level of elderly patients with cerebral infarction is significantly higher than the control group, and the infarct size has a certain correlation with the concentration of HCY in the plasma. In the acute phase, the plasma HCY level is the highest, which indicates the level of HCY and cerebral infarction is closely related [66]. Another study showed that the level of HCY in plasma of patients with acute cerebral infarction was significantly higher than that of healthy control group, and its level gradually increased with the severity of the disease [67].

In addition, studies have shown that [68] the increase of blood HCY content is a risk factor for cerebral small vessel disease (cSVD), cSVD is a kind of insidious cerebrovascular disease, and its pathological changes mainly involve small brain blood vessels (artery of 30–300 μm in diameter). It is closely related

to dementia, risk of death, and cognitive dysfunction in the elderly [69]. High HCY can damage small blood vessels, leading to white matter degeneration or asymptomatic cerebral infarction, which are the most important causes of cognitive impairment [70]. Some scholars have found that HCY promotes the appearance of white matter damage symptoms and is closely related to the degree of disease [71].

15.3.2.2 HCY and Coronary Heart Disease

Coronary atherosclerotic heart disease (CHD) refers to myocardial ischemia and hypoxic heart disease caused by coronary atherosclerotic lesions which can result in stenosis or occlusion of lumen. It is one of the major diseases affecting human health, with mortality ranking first among all heart diseases [72].

Previous studies have found that hypertension, diabetes, hyperlipidemia, and smoking are the main risk factors for coronary heart disease. However, recent studies have shown that high blood HCY is an independent risk factor for coronary heart disease, and can independently predict the risk and prognosis of coronary heart disease, especially myocardial infarction (MI). High HCY damages vascular endothelial cells, causing proliferation of smooth muscle cells, thereby impairing the coagulation system, promoting the production of oxidized low-density lipoprotein and vascular calcification, leading to the occurrence and development of coronary heart disease [73]. Some studies [74] confirmed that HCY level is directly proportional to the incidence of cardiovascular and cerebrovascular events, and high HCY is a risk factor for coronary heart disease. The study pointed out that early intervention of HCY level can effectively reduce the incidence of cardiovascular events, so HCY level should be monitored and tracked in the middle-aged and elderly population, especially in patients with cardiovascular and cerebrovascular diseases. Early intervention can reduce the risk of coronary heart disease. Another study [75] pointed out that HCY level was positively correlated with the risk of cardiovascular accidents. An increase of 3 μmol/L of HCY will cause the elevation of the risk of cardiovascular adverse events by approximately 8% [76]. HCY has become an important indicator for clinical prevention and control of cardiovascular diseases. The study showed that HCY is positively correlated with the severity of coronary artery disease and has a high predictive value in the risk assessment of coronary heart disease. Regular monitoring of the level of HCY can provide a reliable basis for clinical diagnosis and treatment of coronary heart disease.

15.3.2.3 HCY and Diabetes

Diabetes mellitus (DM) is a chronic disorder of glucose metabolism which can cause a variety of complications. A large number of studies have found that [77] the increase of HCY concentration will not only increase the patient's insulin resistance, but also the levels of urea nitrogen and serum creatinine in diabetic patients. HCY not only is a risk factor for diabetes but also aggravates the occurrence and development of chronic complications of diabetic patients [78]. In patients with DM, high blood HCY can damage large blood vessels and microvessels, heart, brain, kidneys, and lower limbs, causing increased blood pressure, elevated uric

acid, and impaired renal function [79]. The latest study [80] has showed that high HCY has a certain correlation with the occurrence of diabetic nephropathy. Studies have shown that HCY in DM group and pure DM group are higher than healthy control group, suggesting that hyperhomocysteinemia is associated with the occurrence and development of type 2 diabetic nephropathy. Other studies have shown that [81] HCY level is a risk factor for diabetic retinopathy, monitoring HCY level has a certain guiding significance for the diagnosis and treatment of diabetic retinopathy.

15.3.2.4 HCY and Hypertension

Clinical data [82] show that nearly 75% of hypertensive patients in China are accompanied by elevated blood HCY level. We refer to essential hypertension with blood HCY level > 10 μmol/L as H-type hypertension. Previous studies have confirmed that when blood HCY exceeds 18 μmol/L, the risk of hypertension will increase by three times; when HCY increase by 5 μmol/L, and systolic and diastolic blood pressure will increase by 0.5 mmHg and 0.7 mmHg, respectively [83].

What is the causal relationship between elevated plasma HCY level and risk of hypertension? A cohort study (3913 subjects with normal blood pressure, and mean age at 50) [84] showed that after adjusting for potential confounders, the risk of hypertension increased with increasing HCY level (second and first quartile array: OR = 1.262, 95% CI: 1.155–1.378; third and first quartile array: OR = 1.458, 95% CI: 1.335–1.593; fourth and first quartile array: OR = 1.520, 95% CI: 1.388–1.664), suggesting that elevated plasma HCY level can be used as predictors of hypertension.

At present, the mechanism of hypertension caused by high HCY is mainly as follows:

1. *Through oxidation pathway, it can cause endothelial damage and vascular pathological hypertrophy, and blood pressure increasing:*
   When the HCY plasma concentration is >20 μmol/L, the case fatality rate increases by approximately 35%. In Hordaland Homocysteine's studies, the investigators included 16,000 subjects aged between 40 and 67 years who have no history of hypertension, diabetes, or coronary heart disease, they confirmed that plasma HCY concentration is positively correlated with blood pressure. Malinow and Sutton-Tyrrell also found that vascular dysfunction, including vascular endothelial damage and vascular wall hypertrophy, is a characteristic manifestation of HCY-hypertension and a possible formation mechanism of H-type hypertension [85, 86].

   HCY can activate MMPs and cause collagen to dissolve, resulting in hypertrophy of the vessel wall. A recent model experiment of rat with hyperhomocysteinemia [87] has showed that mice with hyper-homocysteinemia have low hydrogen sulfide level and CSE level. In another study of model experiment of rat with high-HCY, Distrutti [88] reported that hyperhomocysteinemia can reduce the production of nitric oxide in hepatic vascular sinusal endothelial cells, leading to contraction of hepatic stellate cells. It is suggested that portal hyper-

tension caused by the hyperhomocysteinemia may be a result of the combination action of HCY and hydrogen sulfide.

In summary, hyperhomocysteinemia not only impairs the vascular endothelial function through oxidative stress but also participates in the occurrence of hypertension through the metabolism of CSE/hydrogen sulfide.

2. *Direct cause of increase in blood pressure:*
Currently, studies have shown that hyperhomocysteinemia is positively correlated with pulse wave, and pulse wave increase is a characteristic manifestation of hypertension disease. Vyssoulis et al. [89] found that plasma HCY concentration is positively correlated with pulse wave velocity of carotid-femoral artery (stiffness index) after adjustment of age, mean blood pressure, arterial occlusion degree, and glomerular filtration rate ($P = 0.0016$).
3. *Activate metalloproteinases, degrade proteins and elastin, increase blood calcium, cause pathological hyperplasia of vascular endothelium, destroy the integrity of blood vessels and blood vessel walls, lead to increase of blood pressure:*
Studies have shown that [90] HCY can induce angiotensin 1 (AT1) receptor production, resulting in the generation of matrix metalloproteinase-9 (MMP-9) and synthetic collagen. Laggner et al. [91] found that hydrogen sulfide can inhibit angiotensin activity of vascular endothelial cells. Therefore, when HCY is increasing, the production of hydrogen sulfide is decreased, and the activity of angiotensin will increase; therefore, upregulating the concentration of angiotensin II will lead to the occurrence of hypertension disease.

Abnormal regulation of intracellular calcium concentration plays an important role in hypertension. Acute calcium overloading of vascular smooth muscle cells further increase peripheral vascular resistance, resulting in excessive vasoconstriction and increase of blood pressure. Related studies [92] have shown that increased blood calcium concentration promotes collagen production and its deposition in the vessel wall and impairs the integrity of blood vessel and vessel wall structures; calcium channel antagonists can block extracellular matrix (ECM) collagen synthesis. In hyper-homocysteinemia, collagen substances can be altered by peroxidation and deposited in ECM. Studies also have shown that HCY can cause ECM hyperplasia by inducing intracellular calcium release, while disrupting the structural integrity of arterial and arteriolar walls, leading to stiffness and fibrosis of blood vessels. Therefore, abnormal regulation of intracellular calcium plays an important role in the process of blood pressure increasing caused by high homocysteinemia.

Recent studies [93] have found that HCY level is closely related to stratification of hypertension risk criteria. As HCY level increases, the risk of hypertension also increases; detection of blood HCY level has a judging value for the risk of patient's cardio-cerebrovascular disease. It is conducive to the diagnosis, treatment, and management of patients with hypertension. Another study [94] found that HCY levels in H-type hypertension group were higher than those in the control group ($P < 0.05$); 24-h systolic blood pressure variability, 24-h diastolic blood pressure variability, daytime systolic blood pressure variability, daytime variability, nighttime systolic pressure variability, and nighttime dia-

stolic pressure variability were positively correlated with HCY ($P < 0.05$); 24-h ambulatory blood pressure variability in H-type hypertensive patients is increased; and 24-h ambulatory blood pressure variability is positively correlated with HCY.

15.3.2.5 HCY and Other Diseases

Recent studies have shown that the detriment caused by HCY to the body is not only manifested in cardiovascular disease but also found that HCY increased in the blood tests of patients with liver disease and kidney disease.

In normal circumstances, HCY in plasma is mainly metabolized in the liver. The damage of parenchymal hepatic cells can cause HCY metabolic disturbance and increase of the content of HCY. Conversely, high HCY can lead to liver fat cell degeneration [95]. Sette et al. [96] have found that plasma HCY level is associated with severity and activity of liver diseases such as chronic hepatitis.

High HCY is closely related to kidney diseases such as nephrotic syndrome and chronic renal failure. A cohort study [97], 3602 subjects included, explored the effect of increased HCY level on renal function decline and chronic kidney disease (CKD) incidence in natural population and employed the Cox proportional hazard model to estimate the hazard ratio of CKD between the normal control group and homocysteine increased group; the result suggested that the annual glomerular filtration rate decreased by 25% (0.90 ± 0.16 mL/min/1.37 m^2) in patients with high HCY level. The study suggested that increase of HCY in serum is associated with accelerated renal function decline.

Another study [98] explored the relationship between HCY level in plasma in early pregnancy and gestational hypertension (GH), preeclampsia (PE), and its severity and found that high HCY in early pregnancy is an independent risk factor for severe PE. The study included 147 cases of confirmed pre-eclampsia, 147 cases of confirmed GH, and 4418 normal pregnant women control group. It was found that the HCY level in serum of the severe PE group were significantly higher than those in the control group (median: 8.50 mol/L and 7.33 mol/L, $P < 0.001$); after adjusting for potential confounding factors, the logistic regression analysis indicated that the adjusted odds ratio (AORs) of HCY of patients with severe PE was 1.12 (95% CI 1.06–1.20).

The study [99] found that compared with the normal control group, the proportion of patients with hyper-homocysteinemia (≥15 mmol/L) in the cognitive dysfunction group was higher than that of normal control group; serum HCY concentration was negatively correlated with MMSE-DS scores ($r = -0.150$, $P = 0.037$) after adjusting for age, gender, and education level. The incidence rate of cognitive dysfunction was high in the high HCY group ($P = 0.014$); it is suggested that lowering HCY level has a protective effect on cognitive dysfunction in the elderly.

In summary, increased HCY is a risk factor for the occurrence and development of diseases such as hypertension, cardio-cerebrovascular diseases, diabetes and its complications, vascular dementia, and hypertension in pregnancy. The detection of

HCY in plasma and the control of high HCY are beneficial to prevent the occurrence of these diseases and control the development of the disease.

15.3.3 Treatment of Hyperhomocysteinemia

15.3.3.1 Improving the Lifestyle

1. Reduce and control weight. Exercise properly every day to keep the weight in the normal range.
2. Reasonable dietary structure: The principle of reasonable dietary should be to maintain a balanced diet while limiting total calories, reduce sodium intake, supply calcium and potassium salts, and reduce fat intake.

   HCY is an amino acid synthesized by the body's protein metabolism, and a low-fat diet rich in fruits and vegetables can lower the level of HCY in blood. Studies found that B-vitamins such as folic acid in meat, seafood, and green leafy vegetables can reduce HCY level.
3. Quit smoking and limit drinking.
4. Relieve mental stress and maintain a psychological balance

15.3.3.2 Drug Treatment

1. Vitamins: When vitamin B6, folic acid, and vitamin B12 are insufficient, the activity of metabolic enzyme of HCY is declined, which will cause hyperhomocysteinemia. Therefore, supplementing B-vitamins can reduce the content of HCY in the blood. Serum HCY concentrations were negatively correlated with serum folic acid ($r = -0.234$, $P = 0.001$) [99]. Studies [100] also confirmed that folic acid, vitamin B6, and vitamin B12 combined treatment of ischemic cerebrovascular disease has an effect on reducing HCY.
2. Betaine: The active ingredient of betaine is trimethylglycine, which has a methyl donor function, and it participates in the regeneration and circulation of methionine with HCY as a substrate. Studies have shown that betaine is effective in the treatment of HCY caused by cystathionine-β-synthase and vitamin B6 deficiency, but it is ineffective in the treatment of patients with renal failure and high HCY [101].
3. N-acetylcysteine: It is acted as an antioxidant and scavenges oxygen free radicals. Ventura et al. [102] have showed that N-acetylcysteine may increase the excretion of free HCY from the urine, thereby decreasing the HCY concentration.

15.3.3.3 Gene Therapy

Genetic factors are one of the most important mechanisms for the formation of hyper-homocysteinemia. Gene therapy may be a more feasible method for high HCY caused by cofactors and metabolic enzyme deficiency. Currently, it is still at the experimental research stage, and it still need further research for effective prevention and treatment of HCY [103].

15.3.4 Outlook

At present, many scholars are studying the relationship between HCY and various diseases, the outcome after treatment. In addition to standardized treatment of various diseases, try to adjust the diet structure and supplement appropriate amount of folic acid and B-vitamins for treatment, and pay attention to the individual differences, but extensive clinical data to further validate the effectiveness of this strategy is still required. In the current health checkups, improving the detection of HCY level can be used as an indicator not only for evaluating risk factors of related diseases but also for early prevention and treatment of arteriosclerosis and risk assessment of cardio-cerebrovascular diseases.

15.4 Porphyria

Shanshan Liu

Porphyria is a group of diseases caused by deficiency of enzymes in the heme synthesis pathway leading to increased generation of porphyrin and its precursor, α-aminolevulinic acid (ALA) and porphobilinogen (PBG). Most of them are hereditary diseases, presenting as photoallergic dermatitis, abdominal pain, neuropsychiatric disorder, and acute intermittent porphyria. One of the most common types, AIP, can be associated with elevated blood pressure during acute episodes.

15.4.1 Summary

Porphyrin is the intermediate metabolite of heme biosynthesis. Bone marrow and liver are vital organs for the synthesis of porphyrin with glycine and succinate CoA as raw materials, under a series of special enzyme catalysis by porphyrin precursor and porphyrin synthesis stage, which finally combine with iron chelate to form heme from delta–amino–gamma–ketone pentanoic acid (ALA) in the synthesis of hemoglobin which requires the participation of seven special enzymes. Enzyme defects occur in each step of the process; all can cause accumulation of porphyrin in the organs and its precursor material. According to the enzyme defects, porphyria can be classified into seven types: delayed skin porphyria, protoporphyria, congenital erythropoiesis porphyria, acute intermittent porphyria, ALA dehydratase-deficient porphyria, mixed porphyria, and hereditary fecal porphyria. Clinical skin allergy symptoms of light as the main performance of late-onset porphyrin disease (PCT), protoporphyrin (EPP), and neurological symptoms as the main performance of acute intermittent type porphyrin disease (AIP) three types of the most common type of acute intermittent porphyrin disease onset can cause high blood pressure, is the key point of this section, the rest are outside it is

important to note that the hybrid porphyrin disease hereditary coproporphyrin disease with acute intermittent type porphyrin disease, also can cause high blood pressure.

15.4.2 Acute Intermittent Porphyria

15.4.2.1 Epidemiology

Acute intermittent porphyria was first reported in 1911, which is a porphyrin disease and is one of the more common type in different regions having different incidence of morbidity in 0.15~1/estimated one million people [104] have statistics the latest European countries each year from sexual porphyrin disease cases ratio is about 0.13 one million/a genetic defect distribution in men and women are equal, but adults has obvious clinical symptoms for women more reports of clinical manifestation in children is limited, compared with adults, most of the reports of pediatric cases are male·[105].

15.4.2.2 Pathogenesis

Acute intermittent porphyria is located on chromosome 11q24, the allele of porphyrinogen deaminase mutation and follow autosomal dominant inheritance, epithelial membrane and red blood cells in patients with liver cell lymphatic skin porphyrinogen former deaminase activity was only 50% of the normal, but only about 10% of patients with clinical symptoms, the rest is recessive enzyme defect causes porphyrinogen former into urinary porphyrins original way blocked, at the same time cause feedback inhibition is abate boosting the ALA synthase, causing porphyrinogen former and ALA synthesis, accumulate in the body. Studies have shown that porphyrins and ALA have toxic effects on the nervous system, with ALA as the main agent. It is a strong stimulant of inhibitory neurotransmitter gamma-aminobutyric acid. Both patients with hereditary tyrosinemia and those with severe deficiency of ALA dehydrase had excessive accumulation of ALA, and their neurological symptoms were similar to this disease. Heme synthesis defects in the nervous system, in vitro cell culture experiments, showed that inhibition of heme synthesis can cause severe cell degeneration, heme can inhibit the nervous system symptoms of the disease, most heterozygous gene carriers lack symptoms, but some factors can promote the pathogenesis.

15.4.2.3 Hypertension Mechanism

Due to the partial lack of uroporphyrinogen I synthetase, the biosynthesis of heme is blocked, the feedback inhibition is weakened, and the activity of aminoketone synthetase is enhanced, which results in the decrease of the conversion of porphyrinogen (PBG) to uroporphyrinogen and the increase of PBG. PBG excess can affects the central peripheral and autonomic nervous system, neural endocrine disorders, causing increased blood pressure. At the same time, it can be combined with renal function damage, thus initiating a series of mechanisms of renal

insufficiency and renal substantive hypertension and further aggravating hypertension.

15.4.2.4 Clinical Features

Acute intermittent porphyria usually occurs at the age of 30~40 years, and most of the patients without clinical symptoms are acute onset. The symptoms can last for several months, with fewer episodes once in a lifetime and more than 2~3 times a year, and the onset can last for many years without symptoms.

Most of the acute cases have the symptom of abdominal pain, accompanied by mild mental symptoms, and serious plant nerve dysfunction syndrome may be accompanied by peripheral neuropathy and central nervous symptoms, such as convulsions and epilepsy in a coma. Some of the common causes of death in obese patients are drinking, smoking, hunger, infection, mental stimulation, estrogen menses injury some drugs, etc. as shown in Table 15.2.

Abdominal pain is a common symptom, associated with visceral autonomic neuropathy caused by gastrointestinal cramps in abdominal pain site; for more severe cramping, it may radiate to the back and external genitalia, not with abdominal muscle tension, and peritoneal irritation seizures lasts for several hours to several days, often associated with nausea and vomiting constipation. X-ray examination (flat) showed intestinal gas or liquid gas, easy to be misdiagnosed as intestinal obstruction.

Peripheral nerves may develop axonal degeneration, which mainly involves the motor system, presenting as muscle weakness, more upper limbs than lower limbs, and even respiratory paralysis leading to respiratory failure. Some patients are accompanied by limb pain, fatigue, hypoesthesia, and other similar manifestations of peripheral neuritis.

Symptoms of autonomic nervous disorder include elevated blood pressure, fluctuation of blood pressure, tachycardia, postural hypotension, etc., which are easily misdiagnosed as pheochromocytoma. The incidence of hypertension is 36~55%; the disease can appear as chronic renal insufficiency, and the blood pressure continues to rise.

Central nervous system involvement causes psychiatric symptoms, which may include personality changes, psychosis, depression, hallucinations, anxiety, mania, etc. A small number of patients present with seizures as the chief complaint. The onset of EEG (electroencephalogram) can be changed, and there are symptoms of remission after they return to normal.

Table 15.2 Drugs that may induce episodes of acute intermittent porphyria, mixed porphyria, coproporphyria

Drug induced	Barbiturates, carbomax, sulfamethoxazole, danazol, phenytoin sodium, ergotamine
Drugs that may be induced	Alkylating agent, chloroquine, diazepam, clonidine, etomidate, hydralazine, calcium antagonist, ketamine, methyldopa, nicosalmide

Skin involvement is manifested as erythema, herpes, and even canker after exposure to light. Scar left after scab, causing deformity and pigmentation. Oral mucous membrane can have red spot, the tooth assumes palm red. At the same time can be complicated with eye damage such as conjunctivitis.

15.4.2.5 Lab Examination

1. Blood routine: Normal in intermission, acute attack can be due to slightly increased white blood cells.
2. Urine routine: The urine is dark brown or normal at the onset. When urine is acidified or exposed to sunlight, the colorless porphyrins in the urine turn the urine into brown or oxidize into bilirubin, and the urine is red or brownish red. A large number of porphyrin precursors were excreted in the urine of the patient, and the porphyria was more than ALA. The porphyria was excreted at 20 g~200 g/day (normal <2 mg/day), which was roughly related to the clinical symptoms. The porphyrin content in feces was normal or slightly increased.
3. PBG assay: PBG is a precursor of heme biosynthesis pathway, and a urine level of 20–200 mg/L during symptom onset can be diagnosed (normal urine PBG reference range: <2 mg/L) [106].
4. Blood biochemical test: Commonly associated with hyponatremia and mild increase in urea nitrogen, associated with vomiting and dehydration, and may also be associated with the imbalance of antidiuretic hormone secretion.
5. Electroencephalogram (EEG): Abnormal during the onset, presenting diffuse nonspecific slow wave manifestations.

15.4.2.6 Diagnosis and Differentiation

Acute intermittent porphyria has a specific triad of acute onset, including acute abdominal pain, neuropsychiatric symptoms, and brown-red urine. Some patients have no clinical symptoms and are found abnormal only on biochemical examination. The diagnosis of recurrent abdominal pain, mental and neurological symptoms, often accompanied by increased blood pressure, and the presence of large amounts of porphyrin and ALA in urine is not difficult to establish. A history of exacerbation following the administration of barbiturates, aminopyrine, or sulfonamides is helpful in the diagnosis of acute intermittent porphyria.

Differential diagnosis: Acute attack of abdominal pain should be identified with acute abdominal surgery, such as ulcer disease, biliary gallbladder disease and appendicitis. Patients with nervous and mental symptoms should be differentiated from hysteria, abdominal epilepsy, radiculitis and psychosis. Patients with intermittent hypertension should be differentiated from pheochromocytoma and anxiety.

15.4.2.7 Treatment

The treatment of acute intermittent porphyria is to remove the triggers (such as avoiding hunger, drinking, mental stimulation, etc.), control the infection, and avoid the use of drugs that induce the disease, especially barbiturates and sulfonamides. The main treatment measures include the following aspects:

1. General treatment: Eat high carbohydrate food, acute phase attack, and menstrual cycle-related patients, can be prevented or treated with contraceptives.
2. Supportive treatment: Glucose can inhibit the activity of ALA synthase in liver and reduce the excretion of ALA and porphyrinogen in urine. During the acute episode, 10% glucose injection was given intravenous infusion, lasting for 24 h, which can alleviate the symptoms in some patients. Pay attention to correct electrolyte disturbances.
3. Control of abdominal pain: Available morphine, should avoid the use of induced drugs. Phenothiazines can be used for the treatment of vomiting symptoms, and lactulose can be used for the treatment of constipation [107].
4. Heme therapy: If the patient's symptoms do not improve within 24 h, heme therapy can be used. The application of 3~4 mg/kg day, once in every 12 h, a uniform intravenous infusion, continuously for 3~4 days, can quickly and effectively control the moderate acute attack. Acute renal failure may occur as a result of rapid, high-dose infusion.
5. Treatment of seizures: Epilepsy is a rare complication that can be induced by the effects of low sodium, low magnesium, and porphyrins on glial cells themselves. Correction of electrolyte disturbance and control of hypertension can control seizures [107].
6. Control of hypertension: Beta blockers are preferred to control blood pressure and heart rate in patients with hypertension and tachycardia. Clonidine for chronic porphyria progression leading to chronic renal insufficiency and substantial hypertension, and it is generally difficult to reduce blood pressure. The beta blocker drugs can be added to the maximum tolerance according to the condition, or the advantages and disadvantages can be weighed in combination with antihypertensive therapy [107, 108].

15.4.2.8 Prognosis

Acute intermittent porphyria tends to decrease with age and has a good prognosis. In the past 20 years, the death rate in the acute stage of this disease has been significantly reduced, and the causes of death are mostly respiratory paralysis and malignant arrhythmia. Neuropsychiatric symptoms were reversible in most patients after prompt treatment, but there were a few patients with varying degrees of residual. Avoiding the use of drugs such as barbiturates, which may induce acute episodes, is the most effective preventive measure. Porphyrin-induced hypertension usually has a good prognosis, but chronic renal insufficiency caused by porphyrin-induced renal parenchymal hypertension has a poor prognosis.

15.5 Fabry Disease

Tai Huang

Fabry disease is a rare lysosomal storage disease (LSD), related to the mutation of α-Gal A (a lysosomal enzyme) gene in Xq_{22} [109]. Until now, the incidence of Fabry

patients is not clear, and the reported incidence rate in male neonates is about 1/40,000 to 1/117,000 [110, 111].

15.5.1 Pathogenesis

As a result of the mutation in the α-Gal A gene, part or all of enzyme activity is lost, which leads to the accumulation of its metabolic substrate, globotriaosylceramide (GL-3), and related sphingolipids in various organs and tissues of the human body, such as heart, kidney, pancreas, skin, nerve, and lungs, eventually causing a series of organ lesions. Since GL-3 and other metabolites are deposited in various tissues and organs from birth, clinical symptoms often occur from childhood to adolescence, and gradually aggravate with the progression of the course of disease [110, 111].

Hypertension in Fabry patients may be associated with renal damage and Fabry-related vascular diseases. In renal vessels, GL-3 mainly accumulates in endothelial cells, vascular smooth muscle cells, and adventitia cells of renal arteries, arterioles, and capillaries. In glomeruli, GL-3 mainly accumulates in glomerular epithelial cells and endothelial cells, and there is also a little accumulation of GL-3 in glomerular mesangial cells. In renal tubules, GL-3 mainly accumulates in distal tubular epithelial cells, including Henle's loop and collecting tubule, especially in interlaced cells (intercalated cells), but less in proximal tubular epithelial cells [112]. The accumulation of GL-3 enlarged the secondary lysosomes and formed multilayer thin slices and threaded corpuscles. The cells were filled with lipids in vacuoles, and the structure and function of the cells were lost. The glomerular visceral epithelial cells were fused and damaged in the early stage after destruction, and then the basement membrane was in direct contact with and adhered to the parietal epithelial cells, resulting in repair reaction under the action of polypeptide growth factor and cytokine, and the basement membrane thickened or showed two tracks, mesangial cells and macrophages activate and proliferate, mesangial hyperplasia, extracellular matrix increase, capillary loop collapse, and glomerulosclerosis. The accumulation of GL-3 in renal tubular epithelial cells also leads to focal tubular atrophy, interstitial fibrosis, loss of upstream glomerular function, compensatory hypertrophy of other glomeruli, ultrafiltration, and focal segmental glomerulosclerosis. The accumulation of GL-3 in renal blood vessels makes endothelial cells necrotic, smooth muscle proliferation, interstitial fibrosis, vascular wall thickening, renal ischemic changes caused by vascular occlusion, and also participates in the formation of glomerulosclerosis. Some studies have shown that hypertension occurs only when renal function declines in patients with Fabry disease. Only 1/3 of Fabry patients suffer from hypertension, and half of them develop chronic renal insufficiency. In addition, in 65% of hypertensive Fabry patients, hypertension did not occur until long after the onset or

onset of chronic renal insufficiency or end-stage renal disease. This suggests that hypertension is more likely to be primary or secondary to diagnosed kidney disease. In patients with Fabry disease, GL3 accumulation in renal vessels can cause hyperreninemic hypertension [113]. The accumulation of GL3 in peripheral arteries, causing peripheral vascular sclerosis and so on, can also lead to elevated blood pressure [114].

15.5.2 Clinical Manifestations

Fabry disease is often with multi-organ, multi-system involvement, with skin, eyes, ears, heart, kidney, nervous system, and gastrointestinal tract symptoms. The clinical phenotype of male patients is more serious than that of female patients [110, 111, 115–126].

(a) **Face:** Most of the male patients showed characteristic facial features at the age of 12~14 years, such as supraorbital ridge protruding, frontal protuberance, and lip thickening.
(b) **Nervous system:** Peripheral neuropathy has the clinical characteristics of small fiber neuropathy. (1) Neuralgia occurs in about 72% of the patients, which is one of the early and more common symptoms in childhood. The degree of pain in most patients may be alleviated after puberty, which is characterized by limb pain at the distal end of the lower extremity, characterized by chronic or intermittent seizures. It is often described as an unbearable burning sensation in the soles and palms of the feet and radiates to the proximal extremities and occasionally to the abdomen. Pain attacks are often exacerbated by weather changes, fever, mental tension, and physical exercise. (2) Low sweating or non-sweating is one of the early and common clinical symptoms, which can be accompanied by low fever, a few of which can be manifested as hyperhidrosis. Serious autonomic nerve damage can lead to blood pressure regulation disorder and syncope. (3) A small number of patients present with cranial nerve damage, such as sensorineural deafness and so on. The manifestations of central nervous system are generally early apoplexy, transient ischemic attack (TIA) or ischemic stroke, such as hemiplegia, hemianopia, vertigo, ataxia, and dysarthria. The posterior circulation involvement is more common and the prognosis is poor. Nonspecific symptoms include inattention, headache, cognitive impairment, and so on.
(c) **Cutaneous angiokeratomas:** It is common in classical patients and is characterized by small, raised red spots on the skin, mostly in the “bath and sitting” area (genitals, scrotum, buttocks, and inner thighs), as well as in the back, perimouth, or other parts of the body. The number and distribution of angiokeratomas can increase with the progression of the disease.
(d) **Eye:** Most patients may have ocular involvement, mainly manifested as conjunctival vascular tortuosity, corneal vortex opacity, posterior lens capsule opacification, and retinal vascular tortuosity, and in severe cases can lead to visual impairment or even loss.

(e) **Gastrointestinal tract:** It is one of the common symptoms, most of them are diarrhea, nausea, vomiting, abdominal distension, spastic abdominal pain, gastrointestinal malabsorption, and constipation, which occur after eating.
(f) **Kidney:** Early manifestations of urinary concentration dysfunction contain increased nocturnal urine, polyuria, and enuresis. With the progression, proteinuria can occur and even reach the level of nephrotic syndrome and renal function involvement. Generally end-stage renal failure may occur at the age of 30 years. In addition, there can also be hematuria, renal tubular acidosis, and other manifestations.
(g) **Heart:** It is the late manifestations of the disease, common in hypertrophic cardiomyopathy (mainly left ventricular hypertrophy), conduction block, cardiac valvular disease, left atrial enlargement, and tachyarrhythmia, and severe symptoms can lead to heart failure and myocardial infarction. Heart involvement may be the only symptom in some male patients.
(h) **Respiratory system:** It is manifested as chronic bronchitis, dyspnea, wheezing, and other obstructive pulmonary dysfunction, smoking can be aggravated.
(i) **Skeletal system:** Osteoporosis is more common in young and adult patients, mostly in the lumbar vertebrae and femoral neck.
(j) **Mental illness:** It is characterized by depression and anxiety commonly.

Because the deposition of GL-3 is a gradual process, the clinical manifestations of Fabry disease vary with age [110].

According to the clinical manifestations, Fabry disease is usually divided into two types: (1) Classical type: the activity of α-Gal A in patients is significantly decreased or even completely deleted. Brain, kidney, heart, peripheral nerve, and other multi-system are involved; (2) Delayed type (further divided into *kidney type* and *heart type*): patients with partial decrease in enzyme activity, often limited to

Table 15.3 Clinical manifestations of various types of Fabry disease [110]

Clinical manifestations	Classical type	Kidney type	Heart type
Age of onset	4–8 years old	>25 years old	>40 years old
Average life span	41 years old	Unknown	>60 years old
Angiokeratoma	Yes	Yes or no	No
Limb sensory abnormality	Yes	Yes or no	No
Low sweating or non-sweating	Yes	Yes or no	No
Corneal and lens opacity fundus vascular tortuosity	Yes	Yes or no	No
Cardiac involvement	Left ventricular hypertrophy, myocardial ischemia	Left ventricular hypertrophy	Left ventricular hypertrophy, cardiomyopathy
Cerebrovascular involvement	Transient ischemic attack (TIA), cerebral stroke	Unknown	No
Renal involvement	Proteinuria, renal failure	Proteinuria, renal failure	Microalbuminuria
α-Cal A activity	<5%	>5%	>5%

heart or kidney involvement. The vast majority of male patients and a very small number of female patients are classical type, and the majority of female patients are delayed type (Table 15.3) [110].

15.5.3 Laboratory Examination [114]

(a) **Assay of α-Gal-A enzyme activity:** The demonstration of a deficient activity of a-galactosidase activity in plasma or leukocytes is the reference laboratory method which should systematically be used to confirm the clinical diagnosis of Fabry disease in males in whom the result will be conclusive. However, the enzyme activity of about 30% of female patients can be in the normal range, so the diagnosis of female patients cannot be based solely on enzyme activity. In addition, the establishment of the method using dried blood spots to detect the activity of α-Gal A in peripheral blood is helpful to the screening of high-risk population and the investigation of family members.

(b) **Globotriaosylceramide measurement:** It has been found that the detection of GL3 in blood and urine can be used as a biochemical diagnostic index of Fabry disease. The GL3 in blood and urine of male patients with Fabry disease is significantly higher than that of healthy people, and the GL3 of blood and urine in some female patients is higher than that of healthy people. The sensitivity of globotriaosylceramide measurement was higher than that of enzyme activity detection. In addition, the results showed that the sensitivity of plasma lyso-GL3 was higher than that of blood and urine GL3, especially in female patients with Fabry disease.

(c) **Pathological examination:** It is helpful for the diagnosis of Fabry disease (samples were taken from kidneys, skin, myocardium, or nerve tissue). It is the characteristic pathological manifestation of Fabry disease that the corresponding change of tissue cell vacuole can be seen under the light microscope, and the cytoplasm of the corresponding histocytes (such as glomerular podocytes, tubular epithelial cells, vascular endothelial cells and smooth muscle cells, cardiomyocytes, nerve bundle cells, and sweat glands of the skin) was filled with osmium-like "medullary body" under electron microscope.

(d) **Gene detection:** It is a gold index for diagnosis, especially for female heterozygotes without pathological examination. Peripheral blood DNA or RNA can be extracted, or hair follicle DNA can be extracted for GLA gene detection.

The diagnosis should be combined with clinical manifestations, laboratory examination, and family history and rely on enzyme examination and gene detection.

15.5.4 Differential Diagnosis [114]

Pain symptoms should be differentiated from growth pain, juvenile rheumatoid arthritis, Raynaud syndrome, sensory neuropathy caused by other causes, erythematous limb pain, and so on. Digestive tract symptoms should be differentiated from gastroenteritis,

dyspepsia, irritable bowel syndrome, and so on. Cutaneous angiokeratomas should be differentiated from Henoch-Schonlein purpura or other rashes. Proteinuria and renal insufficiency need to be differentiated from primary glomerulonephritis or other secondary glomerular diseases. Patients with heart involvement need to be distinguished from hypertrophic cardiomyopathy, arrhythmia, and cardiac insufficiency caused by other causes. Patients with brain involvement need to be distinguished from early-onset stroke and leukoencephalopathy caused by other factors. Corneal opacity should be differentiated from corneal opacity caused by amiodarone and chloroquine.

15.5.5 Treatment

The treatment of Fabry disease includes disease-specific treatment and non-specific treatment. The ideal treatment regimen is a combination of specific and non-specific treatment, with regular follow-up by experienced physicians involved in a wide range of professions.

(a) **Treatment of hypertension:** ACEI, ARB, and CCB are used in the treatment of hypertension. In patients with kidney disease, the target blood pressure of treat-

Table 15.4 Non-specific treatment of Fabry disease [114]

Limb pain	
Chronic pain	Avoiding overwork or exposure to inducing factors
Pain crisis	Carbamazepine, oxcarbazepine, gabapentin, topiramate
Digestive tract symptom	Eat less and eat more, methoxyclopramin, H2 receptor blocker, gastrointestinal motility drug
Kidney disease	
Proteinuria	ACEI, ARB
End-stage renal failure	Blood or peritoneal dialysis, kidney transplantation
Myocardial disease	
Angina	β-Receptor blocker, CCB, nitrate ester preparation
Heart failure	Diuretic, ACEI/ARB, β- receptor blocker
Atrial and ventricular tachycardia	Antiarrhythmic drugs, anticoagulation
High-degree atrioventricular block slow-fast syndrome	Permanent pacemaker
Nervous system diseases	
Ischemic stroke or TIA	Secondary preventive stroke drugs recommended in Chinese stroke guidelines [128]
Hearing loss	Hearing aid
Cutaneous angiokeratomas	There is generally no need for special treatment, and laser therapy may be considered if requested by the patient
Lung disease	
Cough, airway obstruction	Smoking cessation, bronchodilators
Depression, anxiety	Psychotherapy is recommended and, if necessary, antipsychoactive drugs

ment is 130/80 mmHg. Both ACEI and ARB play a good role in the progression of renal disease [127].

(b) **Non-specific treatment:** Non-specific treatment is mainly for the treatment of organ involvement. All non-specific treatment comes from clinical experience, rather than randomized controlled studies (Table 15.4).

(c) **Specific therapy:** Enzyme replacement therapy, in which α-Gal A was synthesized by gene recombination technique in vitro, was used to treat Fabry disease by replacing the defect in vivo. The results of several randomized controlled and open extended clinical trials showed that recombinant human α-Gal A replacement therapy could reduce intracellular GL3 deposition, which can effectively alleviate limb pain and gastrointestinal symptoms, improve myocardial hypertrophy, and stabilize the renal function in patients with Fabry disease, thus improve the quality of life and prognosis [114].

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Hematological System Diseases

16

Lin Wang, Amin Shi, and Nuerguli Maimaiti

16.1 Polycythemia Vera

Lin Wang

Polycythemia vera (PV) is a clonal myeloproliferative disease characterized by erythrocytosis. This is pathologically characterized by the simultaneous proliferation of erythroid, granulocyte, and megakaryocytes in bone marrow. The count and the capacity of erythrocyte are significantly increased in clinical characteristics, accompanied by neutrophils and thrombocytosis, and a series of symptoms and signs caused by multiple blood and hyperviscosity. PV is often accompanied by splenomegaly. The onset of PV is insidious, in which the progress is slow and various transformations can occur in the late stage. Approximately half of the patients develop hypertension, usually with elevated systolic blood pressure.

16.1.1 Epidemic Characteristics

The incidence of PV is estimated at 1.9–2.6/100,000 per year, slightly higher in men than in women (2.8/100,000 per year vs. 1.3/100,000 per year), and is particularly prevalent among Ashkenazi Jews [1, 2]. The incidence rate increases with age. Among the 1545 patients analyzed by International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT), the median age of PV diagnosis was 61 years (18–95 years) [3].

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16.1.2 Etiology and Pathogenesis

The etiology of PV is unknown. Exposure to certain mutants, such as ionizing radiation and benzene, is considered a risk factor. Recent studies have shown that PV is closely related to JAK2 gene mutation, and jak2-mediated signal transduction plays an important role in promoting or regulating cell proliferation. In multiple studies, V617F mutation of JAK2 exon 14 was found in 95–97% of PV patients, and mutation of JAK2 exon 12 was found in about 3% of PV patients, which may lead to transitional expression of bcl-xl, a protein generated by red line progenitor cells through the jak-stat signaling pathway [2, 4–6]. The upregulation of bcl-xl or bcl-2 antiapoptotic proteins is an important mechanism to maintain the survival of red line progenitor cells. It has been proved that the phosphorylation of tyrosine kinase after JAK2 gene mutation promotes the overreaction of erythroid clones to cytokines and induces the proliferation of erythroid cells in mice. Normally activated JAK2 is the EPO—the EPO receptor pathway controls erythroid cell differentiation and apoptosis. The mutation leads to the spontaneous growth of PV erythroid clones without relying on EPO [6–11].

The pathogenesis of hypertension caused by PV: The number and capacity of erythrocytes are significantly increased in polycythemia vera due to abnormal proliferation of erythrocytes in bone marrow. The capacity and viscosity of blood are increased, so that the systolic blood pressure increases because of the increase in peripheral resistance, which is the main reason for rising blood pressure.

16.1.3 Pathology

PV lesions mainly involve bone marrow, spleen, and liver. The structure of bone marrow is almost normal. The erythroid hyperplasia is extremely obvious, and the granulocyte and megakaryocyte cell lines often proliferate at the same time or one of them proliferates, and some patients have erythroid hyperplasia alone. The immature erythrocytes are island-like hyperplasia near the sinus. The immature granulocytes in each stage diffuse hyperplasia around the trabecular and perivascular, and the megakaryocytes proliferate in the inter-trabecular region. The proliferating cells in the bone marrow are highly atypia and the sinusoidal expansion is significant. Iron storage cells in bone marrow and iron particles were significantly reduced, and about 80% of patients had negative iron staining. Fibroblasts and blood vessels proliferated obviously in the later stage of the disease, and big red blood cell hematopoietic islands appeared together with immature granulocytes and heterogeneous megakaryocytes. The reticular fiber staining indicates that the reticular fibers are highly proliferative, indicating that the bone marrow will be transformed or combined with the bone marrow fibrosis.

At early stage of disease, spleen sinus significantly dilated and hyperemia, the count of erythrocytes is increased, and accompanied by a small amount of immature erythrocytes. Three lines of hematopoietic cells can appear in the spleen at the late stage of the disease, which is similar to myeloid metaplasia. Several researchers

believe that splenomegaly is caused by spleen congestion due to the accumulation of mature erythrocytes and platelets in the spleen. Dilatation of the hepatic sinuses occurs in the enlarged liver, with cellular components similar to the splenic sinuses. Myeloidosis can also occur in the liver at the late stage of the disease.

The above-mentioned pathological changes of liver and spleen are also the pathological basis of portal hypertension and frequent upper gastrointestinal bleeding. If there is thrombosis in the larger blood vessels, the infarct can occur in the corresponding organs; others usually have no obvious pathological changes.

16.1.4 Clinical Manifestations

PV often develops insidiously, and some cases are found by routine blood cell tests. The symptoms are classified into the following groups:

1. Neurological symptoms: The symptoms include headache, fatigue, dizziness, and hyperhidrosis, which are associated with increased blood viscosity, thrombocytosis, and lacunar cerebral infarction.
2. Aquagenic pruritus is usually the chief complaint of PV patients and is described as "intolerable" by 15% of patients with this symptom. The symptom appears approximately 3 years before PV diagnosis on average and is the basis of suspected PV diagnosis in 15% of patients. The most common symptom areas are chest, back, medial arm, and ventral leg. Polyplasmic manifestations: accounts for 60%, such as conjunctival congestion, blush, purple lip, dark red tongue, and varicose blood vessels [12].
3. Erythromelalgia: Erythromelalgia or burning pain in the feet or hands accompanied by erythema, pallor, or cyanosis in the presence of palpable pulses is seen in 29% of patients with PV [13].
4. Thrombosis: Venous thrombosis and arterial thrombosis complications were found in 7 and 16% of PV patients, respectively, with the most common brain involvement, presenting as transient ischemic attack or cerebral infarction, and a few patients complicated with limb arterial thrombosis [3]. It has been reported that thrombosis of hepatic vein or inferior vena cava occurs in Budd–Chiari syndrome; PV is one of the important causes of this syndrome, accounting for about 10% [14]. In rare cases, blood clots form in the heart cavity, leading to refractory heart failure.
5. Polyplasmic manifestations: Accounts for 60%, such as conjunctival congestion, blush, purple lip, dark red tongue, and varicose blood vessels.
6. Hemorrhage: Accounts for about 40% of the total; there are often gingival bleeding, epistaxis, skin ecchymosis, and gastrointestinal bleeding, and a few patients can be complicated by intracranial hemorrhage [15].
7. Hepatosplenomegaly: Hepatomegaly accounts for about 24%, and splenomegaly accounts for about 87%. The liver is usually mild to moderately enlarged, while the spleen can be swollen and stretched to the pelvis with advanced fibrosis. Some patients may have discomfort or pain due to swelling of the liver and spleen.

8. Hypertension: According to relevant statistics, about 78% of patients with PV have elevated blood pressure. About half of patients with general polycythemia have high blood pressure, mostly mild to moderate, mainly with elevated systolic blood pressure.
9. Hyperuricemia: Hyperuricemia is common in PV patients, some of whom have gout attacks in clinical practice.

16.1.5 Laboratory Inspection

16.1.5.1 Hemogram

1. Erythrocyte: Erythrocyte count >6 × 10^{12}/L, hemoglobin >180 g/L, hematocrit >50%, which are the hemographic characteristics of PV patients. If accompanied by repeated gastrointestinal bleeding and/or multiple venous bleeding treatments, low-pigmented microcytic anemia can be caused by iron deficiency, with saturation of serum iron, ferritin, and transferrin decreasing. In the late stage, combined with myelofibrosis and extramedullary hematopoiesis, the life span of erythrocyte was shortened, and the erythrocyte and hemoglobin gradually decreased from elevation to anemia. The increase of plasma volume caused by erythrocyte stasis in megaspleen and portal hypertension can lead to dilutional anemia. When complicated with extramedullary hematopoiesis, teardrop red blood cells, abnormal red blood cells with uneven coloration, and nucleated red blood cells can be found in peripheral blood smears.
2. Leukocyte: Leukocyte in peripheral blood increased in more than 80% of patients, usually up to (10–30) × 10^{9}/L. There were also a few neutrophils, late granulocytes, and a slight increase of basophils. In the late stage of myelofibrosis, the number of promyelocytes increased further, and even a small amount of primordial or promyelocytes appeared.
3. Platelet: More than 40% of patients had more platelets in peripheral blood. Giant platelets could be seen in blood smears. Some patients had abnormal platelet function, such as decreased aggregation and adhesion. The platelet life is still normal. In the late stage with myelofibrosis, platelets gradually decrease until thrombocytopenia.

16.1.5.2 Bone Marrow

Bone marrow aspiration smears showed active proliferation or obvious activity, mainly erythroid proliferation, often accompanied by granular and megakaryocyte proliferation. The proportion of cells in each stage was normal. Iron staining showed that both intracellular iron and extracellular iron are reduced or even disappear. Bone marrow biopsy revealed the aforementioned pathological changes.

16.1.5.3 Erythrocyte Volume

The erythrocyte volume measured by radionuclide labeling increased significantly (male >36 mL/kg, female >32 mL/kg). Erythrocyte volume measurement is an important index for the diagnosis of erythrocytosis. It has high repeatability, and the

error range is only ±5%. When complicated with portal hypertension, the increase of plasma volume may result in the false appearance of normal erythrocytic count, hemoglobin concentration and hematocrit. In addition, similar phenomenon may occur when iron is deficient. At this time, the detection of erythrocyte volume can be confirmed.

16.1.5.4 Others

1. Hemorheological examination showed that the blood viscosity was significantly increased and that the sedimentation rate was slowed down. The coagulation and fibrinolysis indexes were mostly normal. The release of vitamin B12 from granulocytes increased in about 40% of patients, so the level of serum vitamin B12 increased and that of folic acid often decreased. The levels of serum uric acid and lactate dehydrogenase increased. Blood gas analysis showed normal oxygen saturation. Serum EPO levels are often reduced.
2. Karyotype analysis of bone marrow chromosomes: about 30–40% of patients have acquired abnormalities, but no marker chromosomes. Trisomy 8 and 9 were the most common, among them, while the others were 20q-, llq-, and 13q-. Abnormalities such as 5q- and 7q- may also occur after chemotherapy, radiotherapy, or progression of the disease. The prognosis of patients with chromosomal abnormalities at diagnosis is poor [16, 17].
3. Echocardiography: About 77% of patients with PV have aortic or mitral valve lesions, such as valve thickening and vegetation, which is one of the pathological bases of thromboembolic complications.

16.1.6 Diagnosis and Differential Diagnosis

16.1.6.1 Diagnosis

The diagnostic criteria proposed by the WHO in 2016 [18]:

1. Main criteria:
   (a) Hb >185 g/L (male) or >165 g/L (female).
   Or male hematocrit >49%, female hematocrit >48%.
   Or increased red blood cell volume (RCM): >25% of the average normal predictive value.
   (b) Bone marrow biopsy showed age-adjusted three-line hematocytosis (full myelin hyperplasia), that is, significant erythroid, granulocyte, and megakaryocytic proliferation accompanied by pleomorphic, mature megakaryocytes (different sizes).
   (c) JAK2 V617F(+) or other functionally identical mutations such as JAK2 exon 12 mutation.
2. Secondary criteria:
   (a) Serum EPO is lower than the normal reference range.
   It can be diagnosed by meeting the three main criteria, or the first two major and minor criteria.

If Hb >185 g/L (male) or 165 g/L (female), HCT >52% (male) or 48% (female), JAK2 gene mutation is positive, and serum EPO is lower than the normal reference range, which met PV diagnostic criteria.

16.1.6.2 Differential Diagnosis

PV must be differentiated from secondary and relative polycythemia.

PV must be differentiated from secondary and relativistic polycythemia. Secondary erythrocytosis is caused by long-term and chronic hypoxia resulting in increased EPO, which stimulates the overreaction of bone marrow erythroid system, and can also be caused by EPO tumors. Relative erythrocytosis, also known as benign or pseudocytosis, is caused by reduced plasma volume, hence not true erythrocytosis. The three types of erythrocytosis are identified in Table 16.1.

PV also needs to be differentiated from other myeloproliferative diseases. In a small number of patients, the blood in the second and even the third line of the blood is significantly higher than normal, but none of them meet the criteria for diagnosis of PV or essential thrombocythemia (FT) or chronic myelogenous leukemia (CML). If one of the significantly increased ones involves red blood cells, it needs to be differentiated from PV. In principle, the diagnostic criteria for PV should be closely

Table 16.1 Identification of three types of polycythemia

	Polycythemia vera	Secondary polycythemia	Relative polycythemia
Pathogen	Unknown	Tissue hypoxia or abnormal EPO increased	Blood concentration
Skin and mucous membranes	Dark red	Common Cyanosis	No Cyanosis
Splenomegaly	More common	Rare	No
Hypertension	Common	No	No
Volume of erythrocytes	↑	↑	Normal
Volume of plasma	Normal or ↓	Normal or ↓	↓
Arterial oxygen saturation	Normal	Normal or ↓	Normal
White blood cell count	↑	Normal	Normal
Platelets count	↑	Normal	Normal
Neutrophil alkaline phosphatase concentration	↑	Normal	Normal
Bone marrow smear	Simultaneous proliferation of erythroid, granulocyte and megakaryocytes	Erythroid hyperplasia	Normal
EPO	↓or normal	↑	Normal
Serum vitamin B12	↑	Normal	Normal
EPO-free BFU-E growth	(+)	(−)	(−)

followed. If it is not met, it should be diagnosed as "myeloproliferative disease." Usually there is no need for treatment, and regular follow-up until the diagnosis is confirmed.

PV can be converted into myelofibrosis at later stage of disease. If patients visit a doctor at this stage, it can be misdiagnosed as primary myelofibrosis. The identification is mainly based on careful medical history. There is no other effective method.

16.1.7 Treatment

The goal of treatment is to reduce the risk of thrombosis and bleeding, to eliminate various symptoms and signs caused by erythrocytosis, to reduce the risk of transformation into myelofibrosis and acute leukemia and to reduce red blood cell capacity <0.55 [19].

1. First-line therapy
   (a) Prevention of thrombosis: Because embolism is the main cause of death in patients with PV, thrombosis prevention should be performed in patients diagnosed. Oral low-dose aspirin (100 mg/day) is preferred. Based on the evidence from the ECLAP study, it is recommended that patients with no specific contraindications should use low-dose aspirin [20].
   (b) Symptomatic treatment [21]: Venous bloodletting and myelosuppressive agents are often ineffective for skin itching. Since hot water bathing can aggravate skin itching, patients should be advised to reduce the frequency of baths or avoid bathing with overheated water. Aspirin and Cyproheptadine have a certain effect, but antihistamines do not. IFNα also plays a role, but with slower effect. Symptoms are usually relieved after controlling hemogram by chemotherapy and radiotherapy. Recent studies have shown that JAK2 inhibitors and mammalian rapamycin target protein inhibitors (mTOR inhibitors) are effective against refractory pruritus.
   (c) Venous bloodletting: Weekly bloodlets two to three times, each time 200~400 mL, until the hematocrit <0.45. This treatment can quickly relieve symptoms and reduce red blood cell volume, but cannot reduce the increase of white blood cells and thrombocytosis, nor can it alleviate the intractable skin rash and gout attack. Those who have heart or cerebrovascular disease or history of thrombosis should be careful in bloodletting. It should be no more than 200~300 mL each time, up to two times a week. To prevent thrombosis after bloodletting, low molecular dextran 500 mL should be infused intravenously after bloodletting, and ensure adequate intake. Erythrocyte monoharvesting can rapidly reduce HCT in a short period of time and can be used if necessary. Repeated venous bloodletting treatment may have associated symptoms and signs of iron deficiency, but generally no iron supplementation.

The treatment had the lowest proportion of leukemia conversion (1.5%) and secondary solid tumors and the least adverse reactions, and the median survival time was 12.6 years, similar to other treatments. However, the incidence of thromboembolic complications in the first 3 years of treatment alone was higher, and more patients were associated with myelofibrosis. It must be emphasized that even in patients who have only had bloodletting, their leukemia conversion is lower than other therapies, but it is still significantly higher than the matched normal population. The current consensus is that young patients with stable disease (<50 years old) and those who have no previous history of thrombosis are more suitable for bloodletting therapy and supplemented with low-dose aspirin.

(d) Decellular therapy: High-risk patients should receive decellular therapy. The patients who could not tolerate or needed frequent venous bloodletting, the patients with symptoms or progressive splenomegaemia, the patients with serious disease-related symptoms, PLT 1500×10^9/L and the patients with progressive increased leukocyte count (leukocyte count $>15\times10^9$/L) were all the patients treated with decellular therapy.

Hydroxylurea (HU) is most commonly used in Europe and America. The dose is 1.5~2 g/day. The blood level can reach the normal range within a few weeks, and then it is maintained at 0.5~1 g/day. The efficacy of HU is short-lived, and it often rebounds quickly after stopping the drug, so continuous medication is necessary. Once myelosuppression occurs, it can be recovered from days to weeks after stopping the drug. Acute leukemia occurred in 5.4% of patients treated with HU for a long time, although higher than venous bleeding, but the safety is relatively good. The occurrence of bone marrow fibrosis and mortality in HU is similar to that of venous bloodletting, and the thromboembolic complications are significantly reduced, only 6%. Therefore, HU often combines with venous bleeding to learn from each other.

For patients with ineffective treatment of HU, cyclophosphamide, busulfan, chlorambucil, (melphalan), and alkylating agents can be used.

The use of recombinant interferon alpha (IFNα) in the treatment of PV has a good effect [22]. It inhibits the proliferation of abnormally cloned hematopoietic progenitor cells and bone marrow fibroblasts, antagonizes platelet-derived growth factor (PDGF) and metastatic growth factor (TGF-β) to alleviate abnormal hematopoiesis and myelofibrosis. Because of the slow onset of IFNα, it should be used after the hemogram is obviously improved, as a long-term maintenance treatment. It can also be applied at the same time as other treatments to exert a superimposed effect. The dose of IFNα is 3 million U to 5 million U/time, three times a week, and the course of treatment is at least 6–12 months. IFNα also relieves intractable skin itching and is not associated with cytopenia. The conversion rate of long-term leukemia is lower than that of chemotherapy.

2. Second-line treatment: About 25% of patients are resistant or intolerant to hydroxyurea, and 20–30% of patients are intolerant to interferon. These patients can be treated with second-line therapy [23].
   (a) Radionuclide therapy: 32P is most commonly used, which inhibits hematopoiesis by releasing beta-rays to prevent nuclear division of bone marrow hematopoietic cells. After the first intravenous injection of 3~5 mCi, the hemogram returned to normal in 4 weeks, and the liver and spleen decreased. After 12–16 weeks, the second dose was 2~3 mCi. If the hemogram is not corrected, the second dose should be increased by 25%. A small number of patients need to be administered for the third time, but the total dose should not exceed 15 mCi within 1 year. 32P can also be administered orally, but the dose should be increased by 25%, divided into two times, 1 week apart. The remission rate of 32P treatment is 75~85%, the effect can last for 6 months to several years, and the thromboembolic concurrency can be significantly reduced. Its shortcomings is that the dose is difficult to control, too much dose can cause bone marrow suppression, too little dose is ineffective. In addition, the incidence of acute leukemia and solid tumor after treatment is significantly higher than that of venous bloodletting, especially the incidence of long-term acute leukemia is as high as 10–15%, mostly occurring 2–8 years after treatment. If chemotherapy is used after treatment, the incidence of acute leukemia is higher. In view of the above reasons, 32P is currently only used for elderly patients who need frequent bloodletting, long-term application of myelosuppressive drugs, and liver and kidney function. The median survival of the 32P treatment was 10.9 years.
   (b) Ruxolitinib [24]: In an international, randomized, open-label, multicenter phase III clinical trial, relying on venous bloodletting for PV patients with splenomegaly was randomized to receive Ruxolitinib (110 cases, starting dose 20 mg/day) or standard treatment (112 cases, physicians choose hydroxyurea, interferon, anagrelide, lenalidomide, thalidomide, or no treatment according to the situation), After 32 weeks of treatment, for Ruxolitinib group and standard treatment group, the HCT control rate (HCT <45%) was 60% and 20%, spleen volume reduced by 35% was 38% and 1%, complete hematologic remission rate was 24% and 9%, symptoms reduced by 50% were 49% and 5%, respectively. Based on this result, in December 2014, Ruxolitinib was approved by the FDA for the treatment of PV patients with poor or intolerable hydroxyurea. The recommended starting dose is 20 mg/day. Dosage adjustment is not performed for the first 4 weeks of treatment. The interval between dose adjustments should not be less than 2 weeks, and the maximum dose should not exceed 50 mg/day.

   The most common hematologic adverse effects of Ruxolitinib are grade 3/4 anemia, thrombocytopenia, and neutropenia, but rarely lead to treatment interruption. If peripheral blood PLT $<50 \times 10^9$/L or neutrophil absolute value $<0.5 \times 10^9$/L, and HGB <80 g/L, the treatment should be discontinued. The drug should be gradually reduced within 7–10 days. Avoid sudden

withdrawal. It is recommended to add prednisone (20–30 mg/day) during the withdrawal.

3. Antihypertensive treatment
   As the primary disease is controlled, hypertension can be ameliorated. Patients with elevated blood pressure may use vasodilators, calcium channel blockers, and vasoconvertase inhibitors to reduce blood pressure but diuretics are prohibited to avoid the decrease of blood volume and further increase of blood viscosity leading to thrombosis. At the same time, an anticoagulant is used in combination to prevent thrombosis.
4. Other treatments
   (a) In PV patients with marked increase in platelets, if hydroxyurea is ineffective, anagrelide can be used at a dose of 24 mg/day, which works within 1 week, with a response rate of 75%, but with adverse reactions such as headache, palpitations, diarrhea, and liquid retention.
   (b) In late-stage PV combined with myelofibrosis, which is the stage of PV failure, patients often have spleen, anemia, leukocytopenia, and thrombocytopenia, and the treatment is very difficult. Radiotherapy in the spleen area has been confirmed to be ineffective, and splenectomy can achieve temporary relief. Since the general condition of the patient is usually poor at this time, and the complications are many, the mortality rate is as high as 25%. Therefore, it should be carried out cautiously and fully prepared before surgery. Patients with severe anemia who need regular blood transfusions may also be treated with androgens. Iron supplementation should be cautious when iron deficiency occurs, which can promote the rapid increase of red blood cells in the short term and aggravate the condition.
   (c) Patients with PV have complications with surgical diseases, including tooth extraction, postoperative complications up to 47%, most of which are hemorrhagic or thromboembolic complications; the risk is greater. Preoperative venous bloodletting and hematocyte replacement before surgery are recommended. The blood level is obviously improved, and then the surgery is performed.

16.1.8 Prognosis

Most of PV is slow to develop, but the prognosis is poor. The average survival time of nontreated patients is about 18 months. According to relevant statistics, the median life expectancy of untreated patients is 1.5 years. After various treatments, the median survival period can reach 10–15 years. The hypertension caused by PV improves with the improvement of PV conditions.

The first cause of death of PV is thromboembolic complications, accounting for 30–40%, myocardial infarction accounted for 50%, stroke accounted for 31.5%, venous thrombosis accounted for 18.5%, and other causes of death were acute leukemia (19%), solid tumor (5%), and bleeding (5%). The remaining cases died of advanced bone marrow failure, including myelofibrosis, most of which were due to neutrophil deficiency, death from infection, followed by thrombocytopenia and death from visceral hemorrhage. PV can be converted to other myeloproliferative

diseases and/or acute leukemia during the course of the disease, and in some cases, there can be multiple transformations. Individual cases are converted to chronic lymphocytic leukemia. Those who are converted to acute leukemia have poor therapeutic effects and usually die within a few months.

As the primary disease is controlled, hypertension in PV patients can be improved. Patients with elevated blood pressure may use vasodilators, calcium channel blockers, and vasoconvertase inhibitors to reduce blood pressure, but diuretics are prohibited from reducing blood volume-induced thrombosis.

16.2 Anemia

Amin Shi

Anemia is a common clinical symptom, which can be caused by different reasons or diseases. Anemia can be a primary cause of hematopoietic organ disease or a concomitant symptom of some systemic diseases. Anemia can cause elevated blood pressure by itself, or it can coexist with hypertension as two manifestations of a disease, which requires careful identification and vigilance against the possibility of some systemic diseases.

16.2.1 Definition and Diagnostic Criteria

1. **Definition:** Anemia refers to a syndrome in which the erythrocyte volume of the human peripheral blood decreases below the lower limit of the normal range and insufficient oxygen is transported to the tissues. The concentration of hemoglobin in the peripheral blood per unit volume, RBC count, and/or hematocrit are lower than the normal standards of the same age, sex, and region.
2. **Diagnostic Criteria:** Becase the red blood cell volume measurement is complex, often in clinical hemoglobin (HB) concentration of red blood cell (RBC) count and/or hematocrit (HCT) to replace, but mainly by the hemoglobin concentration is the most important, it is generally believed in the sea areas in China, adult male HB <120 g/L, RBC <4.5 × 10^{12}/L, and/or HCT <42% and adult female HB <110 g/L, RBC <4.0 × 10^{12}/L, and/or HCT <37%, can be diagnosed with anemia. In foreign countries, it is generally based on the diagnostic criteria established by WHO in 1972, that is, in the sea level area, the diagnosis of anemia is made when the HB level is lower than the following levels: 110 g/L for children aged 6 months to less than 6 years; 120 g/L for children aged 6–14 years; 130 g/L for adult males; 120 g/L for adult females (130 g/L for postmenopausal women); and 110 g/L for pregnant women [25].

   The hemoglobin concentration of infants, children, and pregnant women is lower than that of adults, and the normal hemoglobin value of residents living in plateau areas is higher than that of residents living at sea level. Meanwhile, attention should be paid to the fact that when the plasma volume increases, the blood is diluted and the hemoglobin concentration decreases, which is easily misdiagnosed as anemia.

In dehydration or decreased circulating blood volume, anemia can be masked by increased hemoglobin concentration due to blood concentration.

16.2.2 Pathogenesis

1. **Physiological changes of human red blood cells**
   Red blood cells are derived from hematopoietic stem cells in the bone marrow. Under the influence of hematopoietic microenvironment (protein, erythropoietin, iron, folic acid, vitamin B12, etc.), hematopoietic stem cells first differentiate into erythroid oriented progenitor cells, and after multiple proliferation and differentiation, they become mature erythrocytes. After many proliferation differentiation, become mature red blood cells with the average life expectancy of 90–120 days. Aging red blood cells are destroyed by phagocytosis in the mononuclear macrophage system. About the same amount of red blood cells (1/120 or 0.8% of the whole body) are destroyed and born every day.
2. **Pathogenesis of Anemia**
   (a) Abnormal erythropoiesis anemia (hematopoietic stem progenitor cells, hematopoietic dysregulation, and hematopoietic raw materials lack or use disorder): Hematopoietic stem cell damage or the bone marrow microenvironment defect of congenital abnormal erythropoiesis anemia, Aplastic anemia are of ineffective hematopoiesis, and form of refractory anemia characterized by malignant clone hematopoietic system disease, such as myelodysplastic syndrome [26]. Myelopathic anemia resulting from myelofibrosis or infiltration of abnormal cells (such as leukemia or metastatic cancer). During the proliferation and differentiation of erythroid progenitor cells, folic acid and vitamin B12 are important coenzymes for the synthesis of cell DNA. If there is a lack of folic acid and vitamin B12, it can cause the stagnation of nuclear division, forming megaloblastic erythrocytes with unbalanced nuclear and plasma development, leading to megaloblastic anemia. The synthesis of hemoglobin began from early young red blood cells, iron first synthesis is blood red element and protoporphyrin, later is blood red element and globin synthesis of hemoglobin, iron deficiency or iron metabolic disorders can result in iron deficiency anemia, iron bead young cell anemia and chronic anemia, porphyrin metabolic disorders, can cause porphyrin disease, globin synthesis disorders can result in hemoglobin disorders and globin generation barrier anemia (Mediterranean anemia).
   (b) Erythrocyte destruction anemia: Hemolytic anemia occurs when certain external factors (including physicochemical infection or immunity) or erythrocyte internal factors (membrane defect, enzyme defect, abnormal hemoglobin structure, etc.) shorten the life span of erythrocytes and cause too much damage, which exceeds the compensation ability of bone marrow hematopoiesis.
   (c) Hemorrhagic anemia: Excessive loss of red blood cells, acute and chronic hemorrhagic anemia, including bleeding from ulcer disease, bronchiectasis, hemoptysis, hemorrhoids, and traumatic blood loss [26].

(d) Secondary anemia: Secondary anemia caused by various chronic diseases and systemic diseases (such as renal failure, liver disease, endocrine disease, gastrointestinal disease, etc.), such as renal insufficiency, pituitary or hypothyroidism, liver disease, etc., can be caused by insufficient erythropoietin and lead to anemia. Neoplastic diseases or certain viral infections can induce negative hematopoietic regulatory factors and inhibit hematopoiesis, leading to anemia [26].

In short, the pathogenesis of anemia is relatively complex and diverse. The same type of anemia may coexist with different pathogenesis. In aplastic anemia, in addition to bone marrow hematopoietic stem cell injury and microenvironmental defects, there are cellular immune mechanism factors. Certain tumor (be like lymphoma) besides encroach marrow outside still can cause autoimmune anemia.

3. **Anemia and Hypertension**

Anemia and hypertension concerns are complex. Anemia itself can cause hypertension. Primary lesions leading to anemia may be associated with hypertension, and anemia related drugs may cause high blood pressure.

(a) Anemia itself can cause elevated blood pressure: mainly occurs when anemia is compensated. First, when associated with anemia caused by hemodynamic changes, increased cardiac output, heart rate differential pressure of arteries and veins increases, leads to increase in systolic blood pressure second, anemia, when blood flow to the heart muscle of oxygen sensitive organs such as brain, and in the kidney, caused renal hypoxia ischemia, activation of the RAS system that can lead to high blood pressure, renal vasoconstriction. In addition, the higher incidence of hypertension in children with chronic hemolytic anemia (such as sickle cell anemia) may be associated with increased erythropoietin (EPO), increased blood viscosity, renal endothelin abnormalities, or other renal tubular sodium transport defects in chronic anemia [27].

(b) Secondary anemia, as one of the manifestations of some systemic diseases, may be associated with hypertension, common diseases listed below (Table 16.2), common in clinical renal disease lead to anemia and high blood pressure for see, mainly because the kidney is the important viscera of erythropoietin, regulate the production of the red blood cells, anemia and high blood pressure, kidney disease become easily happened.

(c) Some drugs used to treat anemia can raise blood pressure, drugs such as glucocorticoid cyclosporine erythropoietin can cause drug-induced hypertension.

16.2.3 Classify

There are a variety of classification methods of anemia, commonly used according to the red blood cell morphology, hemoglobin concentration, anemia etiology and pathophysiology and bone marrow proliferation or not and classification.

Table 16.2 Anemia associated with hypertension common diseases.

Diseases	Disease name
Connective tissue disease	Rheumatoid arthritis Systemic lupus erythematosus Vasculitis
Endocrine disease	Hyperthyroidism Hypothyroidism Pheochromocytoma
Diseases of urinary system	Diabetic nephropathy Chronic urinary tract infection A variety of causes of kidney failure
Tumor	Multiple myeloma Lymphoma Small cell lung cancer Bronchial carcinoid
Other	Severe trauma Burns Thrombotic phlebitis

Table 16.3 Cytological classification of anemia

Type	MCV (fL)	MCH (pg)	MCHC (%)	Common diseases
Macrocytic anemia	>100	>34	32~36	Megaloblastic anemia
Normocytic anemia	80~100	27~34	32~36	**Aplastic anemia**
Hemolytic anemia				
Acute hemorrhagic anemia				
Microcytic hypochromic anemia	<80	<27	<31	Iron deficiency anemia Iron granulocyte anemia Globinogenesis anemia

Red blood cell morphological classification Anemia is divided into three categories according to mean red blood cell volume (MCV), mean red blood cell hemoglobin concentration (MCHC), and mean red blood cell hemoglobin content (MCH) (Table 16.3).

1. Macrocytic anemia: MCV >l00 fL, red blood cell diameter >10 m; most of this kind of anemia is normal pigment type and belongs to this type of anemia mainly due to folic acid and/or vitamin B12 deficiency caused by megaloblastic anemia, Hemolytic anemia occurs when the number of reticulocytes increases, Anemia of liver disease and hypothyroidism.
2. Normocytic anemia: MCV between 80 and l00 fL; most of this kind of anemia is normal pigment type, a few can have low pigment type and belongs to this kind of anemia mainly due to aplastic anemia, hemolytic anemia, acute hemorrhagic anemia, hypersplenism, and chronic renal failure caused by anemia.

Table 16.4 Classification criteria of anemia severity [25]

Hemoglobin concentration	<30 g/L	30~59 g/L	60~90 g/L	90~110 g/L
Red blood cell	$<1 \times 10^{12}$/L	$(1\sim2) \times 10^{12}$/L	$(2\sim3) \times 10^{12}$/L	$(3\sim4) \times 10^{12}$/L
Severity of anemia	Extremely severe	Severe	Moderate	Mild

3. Microcytic hypochromic anemia: MCV <80 fL, MCHC<31%; iron deficiency anemia, aplastic anemia (thalassemia), iron granule anemia, and some chronic anemia belong to this type of anemia.
   (a) Anemia was divided into mild, moderate, severe, and extremely severe anemia according to the concentration of hemoglobin and the number of red blood cells (Table 16.4).
   (b) According to the classification of the etiology and pathogenesis of anemia, anemia can be divided into the following categories: decreased erythropoiesis, including the lack of hematopoietic raw materials (iron folic acid, vitamin B12, etc.), and bone marrow diseases that affect the production of red blood cells; excessive destruction of red blood cells, anemia due to excessive destruction of red blood cells and insufficient compensatory capacity in the body; and hemorrhagic anemia.
   (c) According to the classification of bone marrow hyperplasia, anemia can be divided into hyperplastic anemia, including iron deficiency anemia, hemorrhagic anemia, and hemolytic anemia; dysplasia such as aplastic anemia.

   Clinical applications often combine several methods; erythrocyte morphological taxonomy can provide clues to the diagnosis of anemia, especially for iron deficiency anemia and megaloblyte anemia. Hemoglobin concentration has a certain practical value, can help determine the severity of anemia. However, according to the classification of etiology and pathogenesis, anemia caused by a variety of factors or with complicated mechanism cannot be classified, and it needs to be analyzed according to different conditions, such as chronic system diseases (cirrhosis, uremia).

16.2.4 Pathophysiology

1. The pathophysiological basis of anemia is a decrease in hemoglobin, the ability of the blood to carry oxygen is reduced, hypoxia changes in body tissues and organs, the body give play to the role of the corresponding compensation, such as pulse frequency increased faster heart beat with a breathing accelerate erythropoietin increase and a decreased hemoglobin affinity with oxygen, make more blood flow to the lack of oxygen sensitive organs such as brain heart [1]. The body's compensation for anemia includes a reduction in oxygen consumption, which is sometimes greater than normal due to the overload of the lungs and heart during anemia. Others, reduce the affinity between hemoglobin and oxygen: when anemia occurs, the production of 2,3-diphosphoglycerate (2,3-DPG) in red blood cells is increased, the PH value in red blood cells is increased, and the oxygen released in tissues is increased, so as to reduce hypoxia of tissues.

Redistribution of blood oxygen in tissues: blood flow is mainly to organs sensitive to hypoxia (such as heart and brain muscles) and is decreased in skin mucosa and kidney. With the increase of cardiac output, there were hemodynamic changes such as increased heart rate and pulse pressure difference. Respiratory hyperplasia: The increased production of erythropoietin by the kidney is up to 1000 times of normal and bone marrow hyperplasia is up to six to ten times of normal. These compensatory effects, coupled with inadequate oxygen supply, result in a range of clinical manifestations.

Anemia symptoms and severity depend on the causes of anemia and the primary disease, the rate of anemia occurred, the degree of anemia, body compensatory ability and the ability to adapt to oxygen in addition, also with the patient's age, with or without basic diseases such as cardiovascular disease and cerebrovascular disease and cardiovascular system of compensatory capacity if anemia occurred more rapidly, blood volume decreased significantly, older patients, with cardiopulmonary disease, clinical symptoms can be serious if the anemia is slow, the body has enough time to compensate, even more severe (Hb <60 g/L), the symptoms of anemia can be lighter.

2. Anemia itself can cause elevated blood pressure: mainly occurs when anemia is compensated. First, when associated with anemia caused by hemodynamic changes, increased cardiac output, heart rate differential pressure of arteries and veins increases, leads to increase in systolic blood pressure. When anaemia occurs, blood can flow to the heart, brain, muscle and other organs sensitive to hypoxia, and decrease in the kidney, cause renal hypoxia, ischemia, activation of RAS system so that renal vasoconstriction can cause blood pressure rise. In addition, chronic anemia with erythropoietin increased, the blood viscosity increases, also can cause high blood pressure.

   Secondary anemia, as one of the manifestations of some systemic diseases, may be complicated with hypertension. Anemia and hypertension caused by renal diseases are common. This type of anemia is mainly caused by a decrease in EPO due to impaired renal function, resulting in anemia. Anemia also causes renal hypoxia, ischemia, activation of the RAS system makes renal vasoconstriction can cause high blood pressure, high blood pressure in turn worsen kidney.

   Medications for anemia can raise blood pressure, and medications such as glucocorticoids, cyclosporins, and erythropoietin can lead to drug-induced hypertension.

16.2.5 Clinical Manifestations

The clinical manifestations of anemia are associated with five factors which is the etiology of anemia (including the related diseases that cause anemia), the degree to which anemia leads to a decrease in oxygen-carrying capacity of blood, the degree to which blood volume drops during anemia, the rate of anemia, and the ability of the blood circulation and respiratory system to compensate for and tolerate anemia.

1. General manifestation: fatigue, fatigue is the most common and earliest symptom of anemia. Severe anemia can appear low thermal and basal metabolic rate increased pale skin and mucosa is the main sign of anemia, must pay attention to the temperature of the environment factors such as personal skin pigment and subcutaneous tissue water content will affect the color of skin to observe the nail bed palpebral conjunctiva of oral mucosa and tongue is more reliable.
2. The most common symptoms of cardiovascular system are palpitation, shortness of breath and hypertension. Patients often have a fast heart rate (more than 100 beats per minute) and a very strong heartbeat. Blood pressure increased, mainly systolic blood pressure increased, accompanied by increased pulse pressure (more than 50 mmHg). Severe anemia can appear angina, heart failure, physical examination may have heart enlargement, apex or bottom of the heart appear gentle systolic murmur, lower limb edema. ECG showed ST segment decrease, T wave flatness or inversion. These symptoms and signs disappear after anemia is corrected.
3. Central Nervous System: Headache, dizziness, dizziness, tinnitus, memory loss, inattention, and lethargy are common symptoms. Patients with severe anemia may experience syncope. Elderly patients may have confusion and mental abnormalities. Vitamin B12 deficiency can lead to limb numbness and sensory disorders.
4. Digestive System: Anorexia, abdominal distension, nausea, and other symptoms are more common; atrophy of tongue and mastoid process can be seen in nutritional anemia; jaundice and splenomegaly can be seen in hemolytic anemia.
5. Urogenital System: Anemia when the renal vasoconstriction and renal hypoxia can appear mild proteinuria and urine concentration function decline, the performance of nocturnal polyuria. Sexual desire changes and menstrual disorders were also common in women.
6. Others: Dry skin, dry hair, slow wound healing. Fundus pallor and retinal hemorrhage are rare.

16.2.6 Diagnosis

Diagnosis of anemia involves understanding the extent, type, and cause of anemia. The etiology diagnosis of anemia is the most important, only to find out the cause, can be reasonable and effective treatment of anemia.

1. Collect Medical History: Detailed questions should be asked about present and past history, family history, nutrition history, menstrual and reproductive history, and risk factor exposure. The history of present illness is an examination of the timing, speed, severity, complications, possible triggers, and response to intervention of anemia occured. The past history may provide clues to the cause of the disease. Family history provides the genetic background for anemia. Nutritional history, menstrual history and reproductive history are of auxiliary diagnostic value for anemia and hemorrhagic anemia caused by deficiency of

iron, folate or vitamin B12. A history of risk factor exposure is important for the diagnosis of anemia associated with hematopoietic tissue damage and infection [25]. It mainly includes acute or chronic bleeding, diarrhea, black stool, soy sauce urine menorrhagia, nutrition condition, history of exposure to chemical poisons, radioactive substances, or special drugs; Anemia in the family; A history of chronic inflammation, infection, liver and kidney disorders, connective tissue disease, and malignancies.

2. Physical Examination: Based on the general performance for anemia and influence on the system, carefully with general physical examination, should pay special attention to skin sclera for yellow dye, presence of bleeder skin and mucosa, liver and spleen enlargement and, lymph node, heart murmur, The anal finger examination has bloot. Flat or sunken nails are common in iron-deficiency anemia. Atrophy of the lingual papilla and deep sensory disturbance of the nervous system are seen in vitamin B12 deficiency.
3. Laboratory Examination: Laboratory examination is the main basis for the diagnosis of anemia, and it should be conducted from simple to difficult, including blood examination, bone marrow examination, and laboratory examination for the pathogenesis of anemia.
   (a) **Blood**: It mainly includes routine blood tests such as peripheral blood smear count and erythrocyte count.

   Routine Blood Tests: Hemoglobin and red blood cell count are reliable indicators for the determination of anemia. Cytological classification based on the mean red blood cell volume (MCV) calculated from the hemoglobin concentration red blood cell count and the hematocrit (MCH) and the mean red blood cell hemoglobin concentration (MCHC) is helpful for the diagnosis and classification of anemia.

   Peripheral Blood Smears: Peripheral blood smears can observe the changes in the number and morphology of red blood cells, white blood cells, and platelets, whether there are abnormal cells and malaria parasites, etc., which can provide diagnostic clues for the nature and type of anemia, and should be paid enough attention to, such as the size of red blood cells and the enlargement of the central pale staining area in iron deficiency anemia. Spherocytosis is seen in hereditary spherocytosis. Erythrocyte basophilic stipulation occurs in lead poisoning; target erythrocytes are found in globin-producing anemia. Lacrimal erythrocytes are seen in myelofibrosis. Rouleau was found in multiple myeloma. The possibility of microangiopathologic hemolysis is often suggested by various erythrocytes or fragments of erythrocytes. The occurrence of late and young red blood cells suggests that the proliferation of red blood cells is accelerated or anemia caused by myelopathy or hematopoiesis.

   Reticulocyte Count: It can help understand the proliferation of red blood cells and, as early indicators of anemia after treatment efficacy, should be as a routine examination in patients with anemia of normal adults reticulocyte accounted for 0.2~1.5% in the peripheral blood increased reticulocyte in hemolytic anemia after massive bleeding or after effective treatment, reticulocyte reduce in aplastic anemia.

(b) Bone Marrow Examination: Bone marrow smear classification reflects the degree of proliferation of bone marrow cells, cell composition ratio, and morphological changes, bone marrow biopsy reflects the degree of structural proliferation of bone marrow hematopoietic tissue cell composition and morphological changes [25]. Any unexplained anemia should be treated with bone marrow puncture, if necessary should also be treated with bone marrow biopsy. Examination of bone marrow specimens should first visually observe whether the bone marrow granule is rich, whether the fat droplets are too much. Under a microscope to observe the nucleated cell hyperplasia, proportion of each series of cell count, and presence of abnormal cells or parasites. Bone marrow examination results should be combined with outine blood and clinical manifestations for a correct diagnosis, sometimes needs a bone marrow biopsy or histochemical staining and chromosome examination.

(c) Etiological Examination: Etiological examination items were selected according to patients' different conditions, including routine urine biochemical immunology fecal occult blood and parasite eggs examination, various special hemolysis tests, X-ray examination, gastroscopy, histopathology, and nuclide examination.

16.2.7 Treatment

The treatment of anemia and hypertension is mainly aimed at the symptoms of anemia and hypertension. While improving the symptoms of anemia, appropriate antihypertensive drugs should be selected for antihypertensive therapy to actively clarify the causes of anemia and hypertension.

1. Symptomatic Treatment: Treatment is mainly to relieve severe anemia in patients with fatal effects, improve symptoms of anemia, improve patient hemoglobin content, improve the symptoms of oxygen in the body, to find the reason that anemia and high blood pressure and treatment time, such as blood transfusion, blood transfusion can quickly relieve or correction of anemia, anemia is symptomatic treatment of the main measures in acute blood loss, blood transfusion can quickly restore blood volume and correction of anemia of chronic anemia have obvious symptoms in hypoxia, blood transfusion can make its ease symptoms. However, over a long term, a large number of blood transfusions may cause iron overload and appear secondary blood disease, therefore for some chronic refractory anemia should try to use a small amount of multiple transfusions in order to reduce blood transfusion on the cardiovascular system load and the transfusion reaction caused by repeated blood transfusion, should try to use red blood cells composition blood transfusion due to blood transfusion may be serious transfusion reaction increase hepatitis, malaria, syphilis, and AIDS chance of infection, therefore, must strictly grasp the indications of blood transfusion anemia with bleeding or infection, should according to the specific situation at the same time be bleeding or anti-infection treatment [25].

2. Etiological Treatment: Eliminating the cause of anemia is the first principle in treating anemia. The nature of the cause of anemia determines the therapeutic effect of anemia. There are three main treatments for anemia, depending on the cause: drugs, splenectomy, and bone marrow transplantation.
   (a) **Medication for Anemia**: Different medications are used for different causes of anemia. Therefore, it is necessary to understand the pharmacological properties and effects of various drugs and strictly grasp the indications. Before the cause of anemia is clear, medicines should not be taken casually, otherwise can make the situation complicates, cause the difficulty on diagnosis, and delay treatment. The following drugs are commonly used to treat anemia:

   Iron agent: Commonly used ferrous preparation, such as ferrous succinate, ferrous fumarate, ferrous gluconate, etc., is only effective for iron deficiency anemia, and it is not suitable for long-term application of iron agent for non-iron deficiency anemia.

   Folic acid and vitamin B12: Only for the deficiency of these two vitamins of megaloblastic anemia. Hemolytic anemia occurs because the need of folic acid is increased, also can compensatory folic acid.

   Glucocorticoid: The good curative effect to the autoimmune hemolytic anemia, may also be used for hemorrhage tendency of the patient.

   Androgen: Commonly used is a synthetic derivative of testosterone, long-term application (>3–6 months) can make aplastic anemia reduce some of the chronic refractory anemia which also has a certain effect, the application process to monitor the liver function, or add the use of hepatoprotective drugs.

   Cyclosporine-A: An immunosuppressant commonly used in organ transplantation. In recent years, it has been used in the treatment of aplastic anemia and has achieved good results. Some people have tried it in myelodysplastic syndrome and paroxysmal sleep hemoglobinuria.

   Erythropoietin: A recombinant human EPO gene that corrects renal anemia and is often used in conjunction with hemodialysis. It can also be used for anemia of chronic diseases, improve the hemoglobin level, and improve the quality of life of patients, but long-term application can cause increased blood pressure.

   (b) **Splenectomy**: The spleen is the main site of destruction of red blood cells and is also involved in the production of antibodies. Splenectomy can reduce red blood cell destruction and anemia in patients with hereditary spherocytosis and hypersplenism. Splenectomy is also effective in patients with autoimmune hemolytic anemia who cannot maintain the therapeutic effect with glucocorticoid.

   (c) **Bone Marrow Transplantation**: Bone marrow transplantation is mainly used for severe aplastic anemia and some severe aplastic anemia. Bone marrow transplantation requires high technical conditions, and the patient is no more than 45 years old, so donors with HLA matching are needed. Moreover,

the high medical cost limits the wide application of bone marrow transplantation, and it is difficult to carry out generally at present.

3. Treatment of Anemia with Hypertension
   (a) First, treatment should be targeted at basic diseases. Blood pressure caused by anemia itself can be decreased after anemia is corrected.
   (b) Anemia and hypertension caused by systemic diseases should be treated on the premise of primary disease. Meanwhile, the selection principle of correct anemia and anti-hypertensive therapy for anti-hypertensive drugs depends on the specific primary disease. For example, alpha-receptor blockers are preferred for hypertension caused by pheochromocytoma. Beta blockers are preferred for hypertension caused by hyperthyroidism. Hypertension caused by renal failure should be carefully treated with ACEI or ARB class antihypertensive drugs, calcium antagonist diuretics can be selected; Diuretics should be avoided in patients with severe burn injuries, where blood volume is often inadequate, and blood viscosity in multiple myeloma is often significantly elevated.
   (c) For hypertension caused by anemia drugs, EPO is the first-line treatment for renal anemia recommended by domestic and foreign guidelines. Long-term use of EPO is usually associated with elevated blood pressure, but there is no need to stop or discontinue erythropoietin treatment because of high blood pressure, except for uncontrolled hypertension. The Japanese guidelines recommend that mild elevated blood pressure caused by EPO should be considered a response to improve anemia rather than an adverse reaction. Patients' HB level should be closely monitored, and EPO dosage should be adjusted according to the appropriate HB target value, so as to ensure that patients with CKD can use EP0 reasonably, so as to achieve the goal of correcting anemia and effectively control the fluctuation of blood pressure [28].

16.2.8 Prognosis

The prognosis of anemia depends on the cause. Dystrophic anemia and hemorrhagic anemia have good prognosis. Except for tumors, secondary anemia has good prognosis. Systemic diseases with anemia have poor prognosis. Hypertension caused by anemia itself can be recovered after correction of anemia, but if combined with hypertensive heart disease, blood pressure control is relatively difficult and may require long-term drug treatment.

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Hypertensive Diseases in Female and Pregnancy

17

Delian Zhang, Xiaotong Wang, Jiao Qu, Yuanyuan Li, Tian Shi, and Weiwei Zhang

Due to the special physical, psychological, and genetic characteristics of women, especially the different secretion and metabolism of endocrine hormones in their lifetime, the changes of blood pressure in women are different from those in men. Epidemiological data show that women's blood pressure fluctuates with the menstrual cycle and changes with age. Studies have shown that hormones play an important role in maintaining blood pressure stability and the occurrence of hypertension in women. The main types of female hypertension include pregnancy-induced hypertension, perimenopausal hypertension, premenstrual tension syndrome hypertension, contraceptive-related hypertension, and polycystic ovary syndrome-related hypertension. The mechanism of elevated blood pressure caused by these diseases is different from that of the general population, and the epidemic characteristics are also different. Therefore, special methods should be adopted in the diagnosis, treatment, prevention, and control.

17.1 Premenstrual Syndrome and Hypertension

Xiaotong Wang

17.1.1 Introduction

Premenstrual disorders (PMDs), including both premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), is characterized by a constellation of both somatic and psychological symptoms occurring during the luteal phase of a woman's menstrual cycle (7–14 days before menstruation). The incidence of the

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disease is high. More than half of menstruating women experience at least some premenstrual symptoms of varying severity, with 20–30% of women affected by moderate to severe symptoms and 3–8% of women meeting diagnostic criteria for PMDD [1]. The clinical symptoms of PMS are complicated. The main symptoms are irritability, insomnia, tension, headache, breast pain, facial edema, etc. Some women may have a paroxysmal rise in blood pressure. Usually, these symptoms can be predicted and disappear before or after the onset of menstrual cramps. As multiple symptoms affect the quality of life of patients, it is becoming a hot spot in today's women's health study.

17.1.2 Prevalence

The number of women experiencing PMS is entirely dependent on the rigor of the definition of the menstrual syndrome. This syndrome affects all age groups; however, the most common age group is 25–45 years. The incidence of this syndrome in Europe has been reported to be 41%, 83% in Africa, 46% in Asia, and 61% in South America [2]. A meta-analysis of 17 studies showed that the pooled prevalence of PMS was 47.8% (95% CI: 32.6–62.9). The lowest and highest prevalence was reported in France 12% (95% CI: 11–13) and Iran 98% (95% CI: 97–100), respectively [3]. Also, according to another meta-analysis of epidemiology worldwide fluctuates between 10 and 98%. The prevalence of PMS/PMDD and the frequency and severity of the symptoms have their characteristics in Chinese women. Among the study group, the incidence of PMDD was 2.1% and PMS was 21.1% [4]. Although some experts claim that almost all menstruating women experience PMS, a newer and more neutral view suggests that only a small percentage (2–5%) of women have severe PMS and are separated from the discomfort caused by menstruation [5].

Besides, PMS has recently been identified as a risk factor for high blood pressure. The results of a prospective study showed that before 40 years of age, women with PMS had a threefold higher risk of developing hypertension compared with women without PMS [6].

17.1.3 Etiology and Pathogenesis

The etiology of PMS is unclear. The results suggest that the etiology of PMS is diverse, including genetic factors, family inheritance, effects and changes in sex hormones, neurotransmitters and central nervous system, environmental factors, depression, migraine, and lack of social and emotional support, which can affect the development and intensity of symptoms.

1. RAAS activation—Sodium-water retention

   Weight gain and sodium salt increase occur in many PMS patients. During the normal menstrual cycle, the secretion of aldosterone in the luteal phase is

increased. Among women with premenstrual tension syndrome, the aldosterone excretion is increased and the concentration of angiotensin II in the plasma is also increased. Therefore, it is considered that this premenstrual symptom may be a manifestation of transient high aldosterone. The increase in aldosterone may be caused by the direct action of estrogen on the kidney or indirectly on the angiotensin-aldosterone system. The increase in aldosterone leads to sodium retention and the leakage of capillary water from the body, resulting in the retention of systemic water. Progesterone can promote the excretion of sodium and water in the distal renal tubules. When it is reduced, it directly leads to the retention of water and sodium, resulting in signs of weight gain and blood pressure. This is the main pathophysiological basis of hypertension in women with PMS [6, 7].

2. Role of sex hormone
   (a) Progesterone

   Since the 1980s, the factors that cause PMS symptoms have been thought to be progesterone, which is produced by the corpus luteum. However, a large number of studies have failed to provide evidence that excessive or insufficient progesterone is the cause of PMS. In many studies, serum progesterone levels in women with PMS did not show any significant differences compared to the control group. At the same time, a series of randomized, double-blind, placebo-controlled trials (RCTs) failed to demonstrate the effectiveness of progesterone supplementation. The metabolites of progesterone (and corticosterone) are psychoactive and have produced sedative in animals for nearly a century, but these effects are not mediated through classical progesterone receptors. According to this evidence, the researchers hypothesized that progesterone metabolites might promote emotional and physiological symptoms of PMS by regulating different receptor mechanisms [8].

   (b) Prolactinoma (PRL)

   Prolactin has a certain role in regulating osmotic pressure. In 1974, some scholars suggested that the increase of prolactin might be the cause of PMS, because women with a series of premenstrual symptoms had higher plasma prolactin levels in the whole menstrual cycle than the control group. The retention of body fluid leads to local subcutaneous edema, which causes breast swelling, and treatment with bromocriptine can work. However, many scholars hold the opposite opinion, because patients with hyperprolactinemia have no symptoms similar to premenstrual tension syndrome, and there is no significant difference in plasma prolactin concentrations in symptomatic women compared with the control group. Besides, the regulation of osmotic pressure by PRL is more significant in animals than in humans. It is also possible that PRL only acts on the mammary gland, affecting the balance of local osmotic pressure, causing breast enlargement and tenderness. In short, the PRL increase doctrine still lacks reliable and strong evidence [8].

3. Neuronal-neuroendocrine system imbalance
   (a) γ-amino butyric acid

   In the ovaries and brain, progesterone is metabolized to form potent neuroactive steroids, 3-hydroxy-5-progesterone-20-1 (pregnenolone or ALLO) and 3-hydroxy-5-progesterone-20-1 (progesterone). These metabolites play an active allosteric regulatory role in the brain GABA neurotransmitter system. Studies have shown that ALLO plays an important physiological regulatory role in altering the sensitivity of $GABA_A$ receptors to GABA by binding to $GABA_A$ receptors. Decreased expression and binding of $GABA_A$ receptors, as well as the decoupling of receptors by antianxiety modulators, leads to an increase in anxiety. Studies in rodents have shown that both acute and long-term exposure and withdrawal from ALLO are associated with increased α-4 γ-2 and δ subunits of the $GABA_A$ receptor [8]. This $GABA_A$ plasticity subsequently leads to a temporary decrease in sensitivity to GABA and GABA agonists and enhances anxiety-like behavioral changes.

   (b) Serotonin

   The role of 5-HT in premenstrual syndrome is supported by a variety of evidence. PMS symptoms overlap with symptoms associated with reduced 5-HT delivery [8]. These symptoms include depression, mood swings, irritability, self-deprecation, poor impulse control, sleep disturbances, anxiety, aggression, decreased pain thresholds, a desire for carbohydrates, and difficulty concentrating. Through the tryptophan load test (50mg/kg), it was found that the content of 5-HT in whole blood of patients in both groups was fixed increased in the follicular stage and middle luteal stage, and continued to increase in the control group until the late luteal stage and early menstruation, but decreased in PMS patients. It indicates that the 5-HT nervous system of PMS patients is defective before menstruation, resulting in variation in response to stimulation. Besides, the reduced uptake of 5-HT by platelets decreased activity of platelet monoamine oxidase (MAO) have been shown to occur during the luteal phase of the menstrual cycle [8]. On the other hand, 5-HT metabolism is also regulated to some extent by ovarian sex steroids (estrogen and progesterone), which are also involved in the uptake, metabolism, binding, and transport of serotonin. Finally, drugs that increase 5-HT neurotransmission is effective for the treatment of PMS.

   (c) β-endorphin

   Preliminary studies have shown that nearly 40% of women with premenstrual syndrome have a significant decrease in circulating plasma levels of β-endorphin. Endorphin can inhibit the secretion of pituitary gonadotropin. When the endorphin inhibitor naloxone acts on the endorphin receptor, it can change the secretion of the luteinizing hormone (LH). Changes in the action of endorphins can affect mental and neurological factors, manifested as premenstrual tension. Endorphin inhibits the biogenic amine system and reduces the release of norepinephrine and dopamine, resulting in fatigue and depression. If the inhibition of endorphins is suddenly removed, can be accompanied by excessive sensitivity, irritability, and aversion to everything.

Endorphin inhibit prostaglandin E during the luteal phase, causing water retention and reduced muscle activity [8].

(d) Cranial nerve reflex

Neuroimaging studies of hormone-mediated changes in the menstrual cycle, as well as comparisons between PMDs and asymptomatic controls, can provide valuable information on potential neurophysiological abnormalities in PMS and PMDD. For example, early positron emission tomography (PET) studies have shown that cerebral blood flow in the anterior frontal cortex is weakened by pharmacological ovarian suppression and subsequently returned to normal with estrogen or progesterone replacement therapy. In a study using functional magnetic resonance imaging researchers found that women with PMDD were inferior to the control group at suppressing false responses to negative emotional vocabulary. The control subjects showed the anterior medial frontal cortex(OFC) is more activity in the late luteal phase than in the follicular phase, while in the lateral forehead cortex, insular cortex, and posterior cingulate cortex showed less active. However, PMDD subjects showed more activity in the tonsils of the late luteal than in the follicular phase, while showing less activity in OFC. This is explained as the reduction of impulse control by top-down adjustment of the limbic system by the prefrontal lobe. In another study, researchers hoped to map brain dysfunction associated with negative emotional states in PMDD. PET plus [18F] fluorodeoxyglucose was used to assess regional brain metabolism in the menstrual cycle of PMDD patients and asymptomatic participants. Women with PMDD have increased cerebellar activity from the follicular phase to the late luteal phase, which is associated with mood deterioration. Increased activity was mainly confined to the cerebellar region, previously described as marginal cerebellum [8].

4. Plasma Leptin

Leptin is a hormone produced by fat cells and has many functions. For example, it regulates food intake and body mass index (BMI), increases energy expenditure, and acts on the hypothalamic-pituitary-gonadal axis to induce serotonin metabolism. Leptin may be associated with premenstrual syndrome because it acts on the hypothalamus, which regulates mood. Besides, leptin also regulates follicle stimulating hormone and luteinizing hormone. Leptin interfere with the production of estradiol in vitro, and when the levels of plasma estrogen and progesterone are higher, the symptoms of PMS are more serious [9].

5. Chronic inflammation

The immune system plays an important role in many aspects of female reproductive function, including follicular supplementation, ovulation, implantation, and endometrial repair. Premenopausal women with plasma and endometrial inflammatory factors c-reactive protein (CRP), interleukin (IL)-6, IL-1b, tumor necrosis factor-a, and other inflammatory factors increased after ovulation, with the highest rise during menstruation [10]. The magnitude of the cyclic change in immune markers is measurable among women; changes in immune function promote chronic systemic inflammation, which is possible, directly contributing

to the expression of premenstrual symptoms. Extensive research has linked chronic inflammation to mental and physical illnesses, which share common characteristics with premenstrual syndrome, including depression, anxiety, migraine, and irritable bowel syndrome. To date, few studies have directly evaluated the relationship between inflammation and premenstrual symptoms or premenstrual syndrome, but the results are very consistent. Puder et al. (2006) reported that CRP levels in 15 healthy women were positively correlated with the severity of symptoms and most strongly associated with mood and pain symptoms [11]. In a recent study of 277 young women, emotional and physiological premenstrual symptom scores were positively correlated with levels of several inflammatory factors including IL-2, IL-4, IL-10, IL-12, and interferon [12]. Patients with the premenstrual syndrome had more than twice as much IL-12 and interferon levels as the control group, even after adjusting for weight, smoking, and other risk factors for premenstrual syndrome.

6. Psychological and spiritual factors

Due to the extensive and unrelated characteristics of PMS symptoms, the use of placebo or receiving mental and psychological treatment has a good effect, and the psychological and mental factors have a dynamic relationship with the severity of PMS, so the psychological etiology theory is formed. An interesting hypothesis assumes that premenstrual syndrome is the failure result of reproductive in the current cycle; therefore, it leads to an increase in desires and jealousy, which in turn increases the chances of the next ovulation fertilization [2]. The female ovulation pleasure syndrome hypothesis refers to the improvement of female ovulation birth opportunities and believes that women will experience more positive physiological and behavioral states during ovulation, such as happiness, relaxation, and sexual desire. When these positive states stop before menstruation and turn into irritability, depression, anxiety, and exhaustion, they lead to a decrease in physical, mental, and intellectual pleasure, and are characterized by premenstrual syndrome. Some patients have prominent mental symptoms, and emotional symptoms often aggravate the original symptoms. The reason is also related to women's emotions, personality, and psychology. Studies have shown that mood has a greater impact on premenstrual syndrome. When the patient is emotionally stressed, the symptoms will be aggravated, while the tension will directly increase the secretion of aldosterone, resulting in water, sodium retention and edema. In addition to emotions, women's personality traits are also an important factor leading to premenstrual syndrome. Many psychological tests found that emotional instability and neurotic personality characteristics are closely related to the occurrence of premenstrual syndrome, especially in the Eysenck personality questionnaire, neurotic segregation, susceptible to premenstrual syndrome. Related studies suggest that personality is related to the fixed pattern of the brain affecting the activity of the hypothalamus, which in turn affects the activity of the hypothalamic-pituitary-ovarian axis and changes in estrogen secretion, so adverse personality characteristics may affect the premen-

strual syndrome severity. The SAS (Anxiety Self-Assessment Scale) and TAS (Toronto Autism Disorder Scale) tests for women of childbearing age found that women with excessive psychological stress and anxiety were prone to premenstrual syndrome and psychological counseling, emotional adjustment, and seeking family support helps contribute to the improvement of premenstrual syndrome and the mechanism is mainly considered as the endocrine disorders caused by psychological stress.

7. Genetic influence

   Therefore, the family history of a genetic disease is considered to be a useful predictor of premenstrual syndrome. The current inheritance of premenstrual symptoms has been widely accepted and plays an important role in the expression of PMS symptoms. In 1971, studies showed that mothers and daughters had a strong correlation with premenstrual tension, and they had many similarities in the subgroup of premenstrual syndrome. When the mother had symptoms such as anxiety, fatigue, and irritability, 69.8% of the daughters had similar symptoms, and 62.5% of the daughters of asymptomatic mothers had no symptoms [2]. Family history of depression and PMDD are risk factors for PMDD [13].

8. Nutrition and Lifestyle (Risk Factor)

   (a) Vitamin B deficiency

   Vitamin B6 deficiency has been considered as a factor in the pathogenesis of this disease, but current studies have shown that patients' clinical response to treatment varies widely, so it is not possible to determine its pathogenic status. However, at least treat with vitamin B6 can promote excessive estrogen clearance, enhance brain monoamine biosynthesis and regulate behavior and mood.

   (b) Alcohol

   A systematic review and meta-analysis showed that alcohol consumption was associated with a modest increase in the risk of PMS, a growth that was more pronounced among alcoholics. During the menstrual cycle, drinking alcohol may increase the risk of premenstrual syndrome by altering the levels of sex steroids and gonadotropins. Besides, alcohol consumption affects the activity of serotonin and γ-aminobutyric acid (GABA), while women with changes in serotonin and GABA systems may be more sensitive to alcohol [14].

   In summary, although the cause of PMS is still not clear, through researches in recent years, PMS may be caused by estrogen, progesterone, and/or their metabolites in corpus luteum. Due to their periodic changes, they affect the function of certain regions of the brain through the mediation of the neural mediators (which include β-endorphin, serotonin, and even γ-aminobutyric acid, the adrenergic nervous system). Forms a neuroendocrine disorder that produces numerous symptoms involving multiple systems. The level of ovarian steroid hormones in peripheral blood is still the normal range in PMT patients, but it does not reflect the level in the central nervous system. Its effect on the central nervous system is still different from that of healthy women. This may satisfactorily explain the multifactor and heterogeneous barriers of PMS.

17.1.4 PMS and Hypertension May Have a Common Physiological Mechanism

(a) Renin-angiotensin-aldosterone system

Emerging data suggest that several potential pathways for hypertension can also, lead to PMS. For example, renin-angiotensin-aldosterone system dysfunction can lead to hypertension by altering sodium balance, blood volume, and regulation of arterial contraction. Progesterone and estrogen directly affect RAAS function, possibly affecting aldosterone secretion in premenopausal women alone RAAS dysfunction also appears to be associated with premenstrual edema, including bloating, swelling of the extremities, and breast tenderness. Besides, drugs that work on RAAS, including diuretics (such as spironolactone) and some progestogens with anti-aldosterone properties (such as drospirenone), are effective treatments for many female premenstrual syndrome-related physical and emotional symptoms [6, 7].

(b) Obesity

Obesity increases the risk of hypertension by negatively affecting the function of renin-angiotensin-aldosterone and promoting chronic inflammation through other mechanisms. Obesity has been associated with premenstrual syndrome, which may be related to its inflammatory response [6].

(c) Inflammatory component

On the other hand, the psychological manifestations of the syndrome may further increase the surge in inflammatory burden, although limited data suggest that inappropriate overproduction of nitric oxide, an effective vasodilator and anti-inflammatory endothelial-derived factor, may also play pathogenesis. These PMS-related processes also involve cardiovascular disease and may therefore increase the cardiovascular risk of these women. An increase in the burden of inflammation is considered to be the cornerstone of the atherogenesis process and is associated with early subclinical atherosclerosis, while depression and anxiety disorders are also considered early atherosclerosis and cardiovascular potential risk factors. Also, short-term challenges of inflammation or emotional distress have been shown to cause acute changes in arteriosclerosis, central and peripheral blood dynamics [6, 7, 10, 12].

(d) Dietary factors

Moreover, some dietary factors related to hypertension, including calcium, potassium, and vitamin intake may also play a role in the development of PMS [6, 7].

17.1.5 Clinical Symptoms

More than 200 different symptoms have been identified in PMS patients, concentrated in physical symptoms, mental symptoms, and behavioral changes. There are many symptoms of premenstrual syndrome, but not all of them are present in each patient. However, the appearance of symptoms and the relationship with the

menstruation disappearance is fixed and is the characteristic of this disease. The duration of the disease varies, and patients with severe symptoms need to be treated for a long time. About 40% of patients have a duration of 1–5 years, and 10% can last for more than 10 years [8, 15]. According to a prospective investigation in 1992, the most common symptoms of PMS in terms of mood and behavior were fatigue (insensitivity), irritability, bloating and swelling of the limbs, anxiety/tension, breast tenderness, emotional instability, depression, craving for certain foods, hemorrhoids, increased appetite, excessive sensitivity, edema, irritability, easy crying, solitude, headache, forgetfulness, gastrointestinal symptoms, inattention, hot flashes, heart palpitations, and dizziness. The relevant meta-analysis showed that the three most significant symptoms of PMS were irritability, nervousness, and restlessness. These exact symptoms and their severity vary from person to person. Most women with premenstrual syndrome experience only a small number of problems [15].

In a recent study, a set of criteria has been used to diagnose premenstrual anxiety disorder (PMDD). The standard is based on at least five symptoms, including one of four core psychological symptoms (selected from 17 physical and psychological symptoms), with severe premenstrual symptoms and mild or disappeared symptoms after menstruation. These 17 symptoms are depression, despair or guilt, anxiety/tension, mood swings, irritability/continuous anger, loss of interest, lack of concentration, fatigue, craving for food or increased appetite, sleep disturbance, feeling out of control or overwhelming, poor coordination, headache, pain, swelling/weight gain, cramps, and breast tenderness [16, 17]. Symptoms must be linked to the luteal phase, starting at some time after ovulation, ending at the end of menstruation, and asymptomatic intervals before the next ovulation. Typical symptoms often begin 1 week before menstruation, gradually worsening, until the last 2–3 days before menstruation is the most serious, and suddenly disappear after menstruation. Some patients have a longer time to resolve symptoms and gradually reduce it, and they continue to disappear until 3–4 days after the start of menstruation.

1. Somatic symptoms

   It is characterized by headache, breast tenderness, small abdominal distension, constipation, and decreased motor coordination. Some people gain weight and have edema in 2–3 days before menstruation. The most common physical symptom of premenstrual syndrome is bloating (90% of women with this condition), breast pain and headache are also common, with a prevalence of over 50%.

2. Mental symptoms

   Different degrees of fatigue, irritability, and depression can appear as early as 10–14 days before menstruation, with sleepiness, unwilling to work or study, or even crying or anger without reason. Serious people are reluctant to pay attention to family and friends, and are bedridden in isolation. The most common psychiatric symptom of premenstrual syndrome is severe fatigue, with an incidence of more than 90%; depression, mood swings (80%), and increased appetite (70%).

3. Behavior change

   Mainly manifested in the lack of concentration, forgetfulness (50%) in the premenstrual period, judgment difficulties, uncoordinated actions, and therefore troubled to affect the work, prone to criminal behavior or suicidal intentions.

4. Hypertension characteristics

   Premenstrual syndrome hypertension is secondary hypertension closely related to women's menstrual cycle. Prospective studies by Elizabeth R. et al. show that premenstrual syndrome is considered to be the outpost of future risk of hypertension, consistent with moderate to women with severe premenstrual syndrome criteria who have a 40% higher risk of developing hypertension in the next 20 years than those with few menstrual symptoms [6].

   (a) Diastolic blood pressure is elevated in young lady experiencing PMS.

   Because menstrual cycles are often irregular in patients with premenstrual syndrome, monitoring of ambulatory blood pressure can improve the detection rate of premenstrual syndrome hypertension. The clinical observation of blood pressure characteristics is more common with periodic episodes of mild to moderate blood pressure, and most increase in diastolic blood pressure, accompanied by other symptoms of PMS [18].

   (b) PMS may affect arterial stiffness and BP monthly variability.

   A cross-sectional study by Kimon S. et al. showed that women with premenstrual syndrome had a periodic increase in aortic sclerosis at different stages of the menstrual cycle, manifested by an increase in neck-femoral pressure and pulse pressure. These fluctuations are associated with simultaneous changes in blood pressure, an increase in inflammatory status, and the severity of psychosomatic PMS-related symptoms. Compared with women without the premenstrual syndrome, premenstrual syndrome women have more obvious monthly fluctuations in arteriosclerosis, central and peripheral blood pressure [19].

17.1.6 Diagnosis

1. Tools for diagnosis [20]

   (a) The Daily Record of Severity of Problems (DRSP): is a validated instrument that is used prospectively across a menstrual cycle to tracking 11 symptoms and the associated levels of severity and impairment.

   (b) The Premenstrual Symptoms Screening Tool (PSST): is a validated screening instrument which includes a list of premenstrual symptoms and a 4-point rating for each symptom to identify the level of impairment of the symptom.

   (c) A variety of older screening tools: Premenstrual Record of Impact and Severity of Menstruation (PRISM), the Calendar of Premenstrual Experiences (COPE), the Daily Symptom Report (DSR), and visual analog scales.

2. Diagnosis

   Although there is no universal diagnostic protocol for the diagnosis of premenstrual syndrome, the following two definitions have been widely used in research projects.

   (a) National Institute of Mental Health:

   A comparative study of the 5–10 days before the start of menstruation and the 6-day interval. To be diagnosed with premenstrual syndrome, the intensity of the symptoms must be increased by at least 30% within 6 days before menstruation. Furthermore, this symptom must be proven to last for at least two consecutive cycles.

   (b) The University of California, San Diego, defines:

   It requires emotional and physical symptoms in the first 5 days of each of the three consecutive cycles, and does not result in the current period of the ovulation period (4–13 days). In this definition, emotional symptoms include depression, snarl, irritability, anxiety, confusion, and discomfort. Physical symptoms include breast tenderness, bloating, headache, and swelling of the hands and feet.

3. Identification [21]

   (a) Psychotic disorder: First of all, we must pay attention to the symptoms of periodicity, if neglect of the symptoms and the characteristics of premenstrual symptoms, PMS is easy to be confused with the usual mental anxiety and depression, the latter in the three stages of the menstrual cycle (follicular phase, ovulation phase, and luteal phase) have the same symptoms and lack of regularity in severity. Therefore, patients considered to be PMS concurrently with mental disorders should be first diagnosed by psychiatric experts, and treated as PMS after excluding mental illness.

   (b) Periodically exacerbated chronic disease: Idiopathic and periodic is unexplained edema that occurs in women. It is characterized by periodic swelling and anxious mood, which indicates an imbalance of water and electrolyte (increased aldosterone secretion). The basis for identification with PMS is that it can develop symptoms throughout the menstrual cycle, and the symptoms worsen before menstruation. Excessive diuretics may aggravate the symptoms, and it is advisable to turn to medical treatment.

   (c) Tumor of the breast: Additionally, if the nodules of the breast should be differentiated from breast tumors, the premature tensioned nodules are mostly bilateral or multiple or diffuse, varying with the menstrual cycle.

   (d) Others: Furthermore, other physiological conditions that may better explain the condition must be ruled out. Many physical conditions deteriorate during menstruation, the process known as menstrual amplification effect. These physiological conditions may cause the patient to be considered to have premenstrual syndrome, and these potential physiological disorders may be other problems at this time. A key feature is that these physiological conditions may also occur outside the luteal phase.

17.1.7 Treatment

Because the etiology and pathogenesis of PMS are still unclear, there is still a lack of specific and standardized treatment methods, mainly symptomatic treatment. Therefore, first of all, clarify the main aspects of symptoms, and treatment should be given to the symptoms varied from the person, including the following aspects.

1. Lifestyle modifications

   Lifestyle changes may improve certain symptoms in affected women, but are often insufficient for patients with severe symptoms. Patients should be encouraged to try to change their lifestyles while completing the expected symptom tracking. Improvements in lifestyle patterns, including adjustments to living conditions, proper diet and nutrition, proper physical exercise, quitting smoking, limiting salt, sugar and coffee intake, and eating more fiber foods, have been widely used to treat PMS. Typically, exercise is considered an effective lifestyle change in the treatment of PMS/PMDD, and it was previously supported by the American College of Obstetrics and Gynecology (ACOG) [1]. In the general population, exercise has been shown to alleviate the symptoms of patients with PMS, such as depression, fatigue, bloating, and constipation, thus supporting the hypothesis that exercise can improve the symptoms of patients with premenstrual syndrome or premenstrual anxiety. Studies have shown that high-intensity aerobic exercise can significantly alleviate premenstrual symptoms compared with placebo and low-intensity aerobic exercise, but lacks relevant systematic evaluation. Following a healthy lifestyle can alleviate some symptoms of premenstrual syndrome. Studies have shown that changes in eating habits have a certain effect on specific symptoms: by increasing the intake of carbohydrates or other foods rich in tryptophan can relieve emotional symptoms, limiting sodium intake can reduce abdominal distension, water retention, breast swelling and pain, reducing the intake of theophylline (coffee, tea, cola, chocolate) to reduce breast discomfort and supplementation of soy isoflavones may reduce sputum and Edema [1, 22].
2. Cognitive behavioral therapy (CBT)

   The effect of biofeedback-supported relaxation training in the treatment of PMS has become a hot topic in the research of nondrug therapy for PMS, and cognitive behavioral therapy is the focus of research. CBT is of benefit in the treatment of women with severe premenstrual syndrome and premenstrual discomfort and has also been shown to be a successful complementary therapy for SSRIs [1]. Biofeedback enables PMS patients to learn to relax the response technology, so that PMS patients can respond to stressors well, thus effectively reducing or controlling emotions. Sleep disorders in PMS patients are common, from insomnia to lethargy, using sleep schedules to develop consistent sleep and wakefulness time, which helps to improve sleep disorders. Psychologists use biofeedback-supported relaxation training to treat patients with PMS and found that patients' blood pressure can be significantly reduced, and PMS patients have elevated blood endorphin concentrations under stress, thus improving the emotional symptoms of PMS patients. A

recent meta-analysis of the effects of psychosocial interventions on the severity of PMS showed that the combined effects of 11 psychosocial interventions had statistical significance on the severity of the premenstrual syndrome. The severity of pre-symptoms was significantly lower than that of the control group [23].

3. Medications
   A. Hormonal Treatment:
      (a) Oral Contraceptives (OCs): Hormone therapy can be treated with progesterone in a variety of ways. However, the synthetic progesterone used in more oral contraceptives currently does not resist the symptoms of sodium and water retention caused by estrogen. Many women complain of weight gain and swelling after use, which is also an important reason why oral contraceptives are not easily used. The new generation of contraceptives researched and developed in recent years not only prevents pregnancy but also has many noncontraceptive benefits that can alleviate the symptoms of patients with premenstrual syndrome [8, 22]. Chinese researchers Ligang Chen et al. observed the effects of two one-way oral contraceptives, Yasmin and Marvelon, on premenstrual syndrome in women of childbearing age, and found that both oral contraceptives had a certain improvement effect on PMS. Yasmin has a more significant improvement effect on PMS than Marelon, which is related to the anti-mineral corticosteroid effect of the drug. The improvement effect on PMS is more significant, which is related to the anti-mineral corticosteroid effect of the drug. The most economical drug with fewer side effects is oral medroxyprogesterone. The usage is from the 16th day of the menstrual cycle with daily oral medroxyprogesterone 6 mg for a total of 10 days. The drug is a synthetic 19-norsteroids with androgenic and antiestrogenic and progesterone properties. By blocking the estrogen receptors in the breast and eliminating the periodic changes in the breast, it can effectively reduce breast tenderness and can dissipate breast nodules or reduce nodule volume. Side effects are mainly acne caused by its androgenic properties, and may increase the risk of venous thrombosis (VTE) formation [1]. Therefore, when starting any OCs treatment, the clinician should obtain a detailed medical history, conduct a risk assessment and consult the patient appropriately about the risks, benefits, and alternatives.
      (b) Danazol: is a synthetic steroid with both androgenic and antiandrogenic properties that can effectively treat PMS/PMDD mood and physical symptoms. However, the dose of danazol must be high enough (200–400 mg/day) to inhibit ovulation and reduce the symptoms of PMDD. Due to its androgenic properties, danazol does have significant side effects such as hirsutism, acne, and body weight increase, which makes it less popular in treating premenstrual syndrome/premenstrual anxiety [1].
      (c) Spironolactone: Due to lack of experiments, it is confirmed that there is indeed fluid retention in the PMS patient, so it is not necessary to immediately give a diuretic. If symptoms do not improve after reducing salt intake, improve symptoms after supplementation of calcium and

magnesium minerals, or increase body weight in the luteal phase >2500 g, then give spironolactone (Antisophetamine) 25 mg, 4 times a day, and take on days 18–26 of the cycle. Spironolactone is a potassium-sparing diuretic that antagonizes aldosterone. It has low potassium excretion and does not require potassium supplementation, and is less prone to dependence. This medicine not only reduces swelling and weight, but also relieves mental symptoms, including lethargy, sleepiness, depression, and sadness. In a double-blind, crossover study, Wang et al. studied the effect of taking 100 mg of spironolactone in the luteal phase and noted improvements in physical symptoms: swelling, craving for food, breast tenderness, and emotional symptoms (irritability and depression). Patients receiving spironolactone should be regularly monitored for electrolytes to assess hyperkalemia. The use of this drug has a special effect on PMDs with hypertension. The combination of snail ketone and ethinyl estradiol in oral contraceptives has a significant effect on body weight and blood lipid levels. It can also alleviate symptoms associated with menstruation (such as negative effects and water retention), which are common with other combined oral contraceptives [23].

(d) Gonadotropin Releasing Hormone (GnRH) Agonists: GnRH agonists are effective means of inhibiting ovarian ovulation and periodic hormone production. Numerous randomized controlled trials have shown that GnRH agonists do attenuate the body and certain emotional symptoms of PMDD patients [1]. A meta-analysis reported that the odds ratio of GnRH agonists to improve PMS symptoms was 8.66 [24]. However, patients with premenstrual depression did not improve their depressive symptoms after receiving GnRH agonist treatment [8]. Considering the long-term use of GnRH agonists (such as Leuprorelin Acetate) may lead to a risk of estrogen reduction, it is recommended to provide supplemental treatment to patients in the form of estrogen and progesterone when needed to prevent endometrial hyperplasia. Estrogen helps to alleviate emotional and vasomotor symptoms caused by menopause and helps prevent dangerous effects on bone and heart health. However, the use of progesterone in the addition of the formulation may result in the recurrence of PMS/PMDD. In this case, a levonorgestrel-releasing intrauterine device can be considered. Although GnRH agonists are effective drugs for the treatment of PMS/PMDD, they should be used as third-line therapy and the course of treatment should not exceed 3–6 months [1, 22].

B. Selective Serotonin Reuptake Inhibitors (SSRIs): It can be used to treat severe premenstrual syndrome. Based on reliable evidence, the most effective treatment for PMDD is SSRIs. A decrease in serotonin transporter receptors in PMS/PMDD patients results in abnormal serotonin transmission. Serotonin regulation has been shown to improve a variety of symptoms, including psychological: anxiety, depression, and irritability, as well as physical: bloating, breast tenderness, and appetite changes [1]. In 2013, Cochrane reviewed 31 randomized controlled trials of SSRIs treatment of premenstrual syndrome and concluded that these drugs are more effective than placebo in reducing

symptoms of premenstrual syndrome, whether taken during the luteal phase or continued [1]. Therefore, SSRIs are recommended as first-line treatment. Three SSRIs are commonly used to treat PMDD: fluoxetine, sertraline, and paroxetine. Citalopram, isophthalopram, and fluvoxamine have also proven to be effective drugs for the treatment of PMS/PMDD in various trials. The most widely studied of these drugs is fluoxetine (Prozac) at a dose of 20–60 mg/day. There are four administration strategies for SSRIs in the treatment of PMS/PMDD: (1) continuous administration, (2) intermittent administration, (3) semi-intermittent administration, and (4) symptomatic seizure administration [1]. A systematic review of SSRI administration involves daily administration of fluoxetine, sertraline, paroxetine, citalopram, and fluvoxamine during the full menstrual cycle (continuous cycle), as well as during the washout period (intermittent administration), sertraline and citalopram were administered daily, and the authors noted that continuous and intermittent schedules have similar effects. Another meta-analysis showed that continuous administration was more effective than intermittent administration [24]. Common side effects of SSRIs include insomnia, drowsiness, fatigue, nausea, nervousness, headache, mild tremors, and sexual dysfunction. The current study focuses on the use of low doses during the luteal phase to reduce side effects [22].

C. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs): There are few studies used to evaluate the efficacy of PMS/PMDD treatment. In a randomized, controlled trial, venlafaxine responded quickly to a better response than placebo [1, 8].

D. Anxiolytics: Data suggest that taking alprazolam during the luteal phase may reduce anxiety, tension, or irritability in patients with PMDD [1, 22]. However, benzodiazepines have a sedative effect and may be abused. Because of this, coupled with lower therapeutic effects, benzodiazepines are considered to be second-line treatments and are recommended for use only during the luteal phase to avoid abuse [1].

E. Nonsteroidal anti-inflammatory drugs (NSAIDs): NSAIDs (such as mefenamic acid and naproxen) are traditional drugs for the treatment of primary dysmenorrhea and menorrhagia. RCT has found that nonsteroidal anti-inflammatory drugs are beneficial for alleviating a range of premenstrual symptoms compared with the placebo. Currently, ibuprofen has been used in PMS [22].

F. Bromocriptine: For breast tenderness with hyperprolactinemia, 1.25–2.5 rng of bromocriptine is given orally twice a day after the menstrual cycle, and the symptoms disappear in 90% of patients.

G. Supplements and Herbal Treatments

(a) Calcium supplements: Recent evidence suggests that premenstrual syndrome may be associated with disorders of calcium homeostasis and dysregulation of parathyroid hormone. Calcium supplementation has been shown to relieve many PMS symptoms such as irritability, depression, anxiety, social withdrawal, headache, and cramps. The study found that calcium supplements (twice a day, 600 mg each time) have been shown to reduce negative emotional and physical symptoms [1]. Calcium is effective against four core symptom factors (negative effects, water retention, food cravings, and pain) of premenstrual syndrome and 15 of the 17 symptoms [8].

(b) Vitamin supplements: Vitamin B6 regulates the relationship between the autonomic nervous system and the hypothalamic-pituitary-ovarian axis and also inhibits the synthesis of prolactin. Patients should not take more than 100 mg/day because high doses can cause peripheral neuropathy. Data on vitamin E for the treatment of PMS/PMDD symptoms are limited. Smaller studies have shown that it can treat breast pain, while daily supplementation of 400 IU of vitamin E in the luteal phase can improve emotional and physical symptoms, but more data is needed to support it as an effective treatment [1].

(c) Clonidine: It has been reported that many women have been successfully treated. At the same time, it is reported that based on taking 1 month, the symptoms of premenstrual syndrome and β-endorphin in plasma are simultaneously reduced, but there is a lack of large-scale clinical randomized controlled study.

(d) Supplementation of blood magnesium: Studies have shown that serum magnesium levels vary periodically among women of childbearing age. The levels of magnesium in red blood cells and white blood cells of women with premenstrual syndrome was lower than those of women without premenstrual syndrome; however, plasma magnesium levels did not show this pattern. Because magnesium is involved in the activity of serotonin and other neurotransmitters, as well as vasoconstriction, neuromuscular function, and cell membrane stability, magnesium may affect PMS in many ways.

(e) Herbal medicine: Herbs have recently been considered an acceptable treatment because of fewer side effects. Herbs commonly used in the treatment of PMS are cranberry, saffron, St. John's wort, black hemp, etc. A growing body of literature supports the use of Vitex agnus castus/chasteberry to alleviate PMS and PMDD symptoms [1, 25, 26]. It is superior to placebo in relieving breast filling, headache, irritability, anger, and emotional instability. There is another Chinese herbal medicine, evening primrose oil (EPO). The basic principle of usage is that the distribution of essential fatty acids in women with premenstrual syndrome is abnormal. It can be regulated by supplementing EPO. The most obvious symptom relief is breast pain [22].

4. Others:

Including supplemental manganese, zinc sulfate, tryptophan, and other trace elements. A double-blind randomized controlled trial of zinc sulfate on PMS and health-related quality of life showed zinc sulfate as a simple, inexpensive treatment with PMS improvements in symptoms related to health-related quality of life, but more research is needed to confirm these findings [27, 28]. Traditional Chinese medicine such as acupuncture, massage, medicated diet, etc., as well as other music therapy, full-spectrum glare therapy, aromatherapy, etc., showed improvements but the results of the study on the exact efficacy of these treatments have not yet been determined [22, 29].

5. Surgical Management:

   Surgical treatment of bilateral salpingectomy (BSO) should be considered the last resort of PMDD [1]. Patients should be tested through all available medical therapies before deciding on the procedure. Although the scale of the study is small, the data show that BSO has significantly improved in women who have failed conservative treatment [8]. Before excising the ovaries, GnRH agonists with estrogen supplementation should be used to assess the patient's mood and signs, but ovarian function cannot be assessed and the patient's tolerance to estrogen replacement drugs cannot be assessed. Considering the harmful effects of surgical menopause on heart and bone health in young women, patients should be treated with estrogen replacement therapy. If the uterus is preserved during surgery, progesterone replacement therapy is also required, but as mentioned earlier, it may accelerate the recurrence of PMS symptoms. In these cases, a simultaneous hysterectomy can be considered in BSO [1, 30].

17.1.8 Treatment of PMS with Hypertension

Furthermore, the link between premenstrual syndrome and hypertension can also be explained by the side effects of premenstrual syndrome drugs on blood pressure. In several studies, the researchers observed that serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants increased the risk of hypertension, and found that use when pregnancy was associated with a preeclampsia risk. In contrast, the use of selective serotonin reuptake inhibitors is often not associated with hypertension.

For patients with a definite diagnosis of premenstrual syndrome hypertension, blood pressure should be carefully monitored before menstruation, emphasizing a positive low-salt diet, generally no conventional antihypertensive medication, if necessary, consider using beta-blockers and sedatives to block the transmission of nerve impulses between the thalamus and the cerebral cortex which controls blood pressure and relieves neuropsychiatric symptoms. For patients with premenstrual syndrome with hypertension and edema, the aldosterone antagonist, spironolactone, has a very good effect.

17.1.9 Prognosis

In general, premenstrual syndrome is a stable diagnosis of disease, because women who have been susceptible to the disease for many years have experienced the same symptoms at the same intensity at the end of each menstrual cycle. The aforementioned treatments are usually effective in treating certain specific conditions. With aging, premenstrual symptoms tend to decrease in women's peri-menopause and disappear during menopause. Similarly, blood pressure also changes regularly with the menstrual cycle as the symptoms of premenstrual syndrome improve. Although

there is no case-control study on the effect of hypertension on target organ damage in premenstrual syndrome patients, the prognosis of this disease is generally good.

17.2 Peri-menopausal Period and Hypertension

Jiao Qu

Peri-menopausal period, formerly called "climacteric period," refers to the period of physiological transformation of women from the reproductive period to the old age. It is the stage in which ovarian function begins to decline to complete cessation, that is, menopausal transition period to 1 year after menopause. During this period, some women developed a series of symptoms of autonomic nervous dysfunction caused by a decrease in sex hormones, namely peri-menopausal syndrome (formerly called climacteric syndrome). There are many clinical manifestations, and about 25% of women have severe symptoms, affecting life and work, and need treatment. Peri-menopausal period not only can increase blood pressure, that is, climacteric hypertension (also known as peri-menopausal hypertension), and blood pressure during this period is often unstable, fluctuating, is one of the main symptoms in climacteric period, at the same time, changes of hormone levels during climacteric period can lead to bone loss, centripetal redistribution of fat in the body, and increase the risk of cardiovascular diseases. Therefore, this special period has become the focus of women's health. This article explores the characteristics of peri-menopausal hypertension in women. The global incidence of hypertension has remained high for many years, and it has gradually increased with age. Among them, the incidence of men before 50 years is higher than that of women, while the prevalence of hypertension and cardiovascular disease increases significantly in women over 50 years old, and the prevalence of cardiovascular disease in women is higher than men after 70 years old. This change is believed to be related to an increase in cardiovascular-related risk factors caused by the significant decrease of estrogen levels in menopause [34].

17.2.1 Epidemiology of Peri-menopausal Hypertension

In 1994, the World Health Organization (WHO) proposed a new definition of peri-menopausal period at a conference on "Advances in menopause in the 1990s": after 40 years of age, irregular menstruation begins to appear at any time in clinic, and the concentration of reproductive hormones in the body changes accordingly, until 1 year after menstruation is stopped, this period is called peri-menopausal period. According to this definition, combined with statistical data, the age of menopause of American women has increased from 48.8 to 51.0 years in the past 30 years [31]. However, there are very few large sample surveys on menopause age observation in China. According to the investigation of different age menopausal women, Chen et al.[32] found that the natural menopause age

increased gradually with the decrease of the age of the investigated women. The natural menopause age increased by 1.36 years in more than 20 years, which may be due to the different social environment experienced by women and many other factors affecting their menopause age and showing the trend of postponing [33]. Many studies [35, 36] have shown that estrogen has a strong protective effect on the cardiovascular system of postmenopausal women, which is enough to reduce the incidence of hypertension and improve blood flow in postmenopausal women, significantly reduce the incidence of myocardial infarction and stroke, and even prolong the survival of women with myocardial infarction. In addition, compared with men, women's stress caused by social environmental factors significantly affected blood pressure, even more than high salt intake.

17.2.2 The Pathogenesis of Peri-menopausal Hypertension

Elevated blood pressure in peri-menopausal period often occurs during menstrual disorders and several years after menopause. The mechanism of peri-menopausal hypertension is still unclear and may involve multiple systems, but it is mainly related to hypothalamus-pituitary-gonad dysfunction caused by ovarian dysfunction, which affects the autonomic nervous center and the various functions under its control.

1. Estrogen and hypertension: Estrogen can directly act on vascular parietal cells to maintain their functional status. The exact mechanism of estrogen dilating blood vessels and reducing blood vessel tension is not yet fully understood. It may be that (1) estrogen directly acts on estrogen receptors of vascular smooth muscle cells, producing changes in membrane potential and relaxing vascular smooth muscle; (2) estrogen increases the production of vascular smooth muscle and uterine prostacyclin; (3) estrogen increases the density of acetylcholine-activated muscarinic receptors, causing arteriosclerosis; and (4) estrogen acts on vascular smooth muscle as a result of mediation of calcium channel blockade. Once the level of estrogen in the blood is reduced, the intracellular free calcium in the vascular wall increases, causing arteriosclerosis. Estrogen also increases the activity of the sympathetic nervous system, increases the sensitivity of blood vessels to catecholamines, and increases peripheral vascular resistance and cardiac output to increase or maintain blood pressure. Estrogen affects lipid and glucose metabolism, and increases high density lipoprotein, reduces low density lipoprotein, and promotes insulin secretion, reduces insulin resistance. Estrogen can be a protective factor for female hypertensive patients through its beneficial effects on blood lipids and insulin resistance. In-depth studies have shown that estrogen may only partially antagonize its vasodilator-induced hypotensive effect by stimulating sympathetic nerve. Therefore, the total net effect of estrogen on blood vessels is to decrease blood pressure and increase blood pressure in the absence of estrogen. This effect is more obvious in postmenopausal women.

2. Androgen and hypertension: At present, it is still under discussion. Testosterone directly stimulates the synthesis and secretion of atrial natriuretic peptide in atrial and ventricular myocytes of cultured rat. A decrease in atrial natriuretic peptide caused by insufficient androgen may play a role in the occurrence and maintenance of EH. Testosterone also increases the response of the pituitary to growth hormone releasing hormone (GHRH), which is highly correlated with the increase in growth hormone (GH) after activation of the central α_2 receptor. In addition, the decrease of testosterone levels promote the expression of ventricular myosin heavy chain (MHC) B isoforms, making MHC2B chain dominant, and such patients are often associated with hypertension and cardiac hypertrophy. In conclusion, androgen may affect the occurrence and development of hypertension in many ways.
3. Progesterone and hypertension: Progesterone can act on the distal end of the renal tubule and competitively inhibit the activity of aldosterone in order to counteract the effects of sodium retention, increased blood volume, and elevated blood pressure. Progesterone also acts as a protective factor for hypertension by combating the action of glucocorticoids. Another study found that hypertension caused by oral contraceptives in women is related to the amount of progesterone in the contraceptive. Thus, the effects of progesterone on blood pressure have both positive and negative aspects.
4. Insulin resistance and hyperinsulinemia: In recent years, although studies have shown that estrogen replacement therapy has a dual effect on insulin sensitivity in postmenopausal women—moderate estrogen can improve insulin sensitivity, while high dose estrogen can aggravate insulin resistance (IR), progesterone can reduce IR; however, a large number of data suggest that postmenopausal women with sex hormone abnormalities (including estrogen reduction and hyperandrogenism) are related to insulin resistance.
5. Psychological factors: When women reach peri-menopausal period, with physiological changes, endocrine disorders, autonomic nervous dysfunction often lead to emotional instability, insomnia, irritability, etc., is also one of the important causes of menopausal hypertension.
6. Sleep apnea: Peri-menopausal women with estrogen levels that drop sharply, obstructive sleep apnea hypopnea syndrome becomes more serious, which increases blood pressure. It is an independent risk factor for postmenopausal hypertension in women [37–39].

17.2.3 Clinical Characteristics of Peri-menopausal Hypertension [40]

Elevated blood pressure is one of the most common symptoms of peri-menopausal vasomotor disorders. It can occur in patients with previous hypertension or in women with normal blood pressure. The latter is also known as menopausal hypertension (also known as menopause hypertension). Menopausal hypertension is characterized by increased systolic blood pressure, normal or slightly higher diastolic blood pressure, large fluctuations, and often no organic damage

to the heart, brain, kidneys, and fundus. Unlike essential hypertension, elevated blood pressure is often paroxysmal, and by regulating endocrine and autonomic dysfunction, blood pressure decreases with peri-menopausal symptoms. Because of the slow progress of the disease, it is often unknowingly ill, and is ignored because there is no obvious symptoms of hypertension, even when the medical examination or other diseases are found. However, the original hypertensive patients showed high blood pressure instability and wide fluctuations during this period, which became the main reason for patients to see a doctor. In the peri-menopausal period, the risk of hypertension is high due to dysfunction of vaso-motor function. However, due to the lack of large-scale epidemiological investigation, the exact incidence rate is unknown. It may be due to elevated blood pressure based on essential hypertension or menopausal high blood pressure. Generally, the systolic blood pressure is mainly increased, unstable, and fluctuating.

17.2.4 Auxiliary Examination

1. Vaginal exfoliated cell smear: About one-fourth of women have vaginal smears as early as several years before menopause, showing that estrogen levels have varying degrees of decline. Conversely, vaginal smear examination of postmenopausal women shows that there are influencers. When evaluating vaginal epithelial cells, it is necessary to consider not only the effects of estrogen activity, but also other hormones (especially progesterone and testosterone), local vaginal inflammation, and vaginal bleeding. The presence of cancer, the location of the specimen, and the difference in estrogen response to the target organ (vaginal epithelium) also affect the smear results. Therefore, in postmenopausal women should pay attention to the results of vaginal smear analysis: (1) smear is only a rough measure of estrogen status, and sometimes it may be completely misunderstood. (2) Vaginal cell images cannot predict whether a patient has menopausal symptoms and signs. (3) Smear results cannot be used as the only way to guide supplemental therapy. (4) Treatment of vaginal atrophy before smear can help determine the amount of estrogen.
2. Diagnostic curettage: Patients with postmenopausal bleeding should be treated with segmental diagnostic curettage and endometrial biopsy to exclude cervical lesions and endometrial cancer. The curettage should be taken separately in the cervix and palace and sent to biopsy, and sent to the menopausal women for menopause. Without the antagonism of progesterone, the endometrium often shows a proliferative phase, and the exogenous progesterone has a withdrawal hemorrhagic reaction, which can also be atrophic.
3. Hormone determination:
   (a) Pituitary gonadotropin: FSH > 40 U/L after menopause, LH > 30 U/L, FSH rises early, and the rising level is higher than LH. Determination of plasma FSH, LH, and estradiol levels is helpful for diagnosis. For patients who have undergone ovarian surgery after resection of the uterus, blood

E_2 < 20 pg/mL, while elevated FSH and LH suggest that ovarian function has stopped.

(b) Estrogen: The level of estradiol in normal young women does not overlap with the level of estradiol observed in postmenopausal women. Due to ovarian dysfunction, blood estradiol levels are often <20 pg/mL. The level of estrone overlaps significantly before and after menopause, so measuring estrone does not help to understand the patient's ovarian function.

(c) Androgen: The concentration of plasma androstenedione in postmenopausal women is reduced by about 50%, about 0.6 ng/mL, plasma testosterone level is slightly decreased (about 0.25 ng/mL), plasma DHEA of women aged 60–70 years old. The DHEAS average levels were reduced to below 1.8 ng/mL and below 300 ng/mL, respectively.

(d) Progesterone: Progesterone levels were significantly reduced after menopause, about 0.17 ng/mL.

4. Ultrasonography: Pelvic ultrasonography, determination of endometrial thickness to determine whether the patient has intimal hyperplasia or endometrial cancer, ovarian b-ultrasound to help identify the cause of certain pathological amenorrhea.
5. Bone density measurement: Early/double-beam light absorption measurement, radiological bone density measurement, electronic computed tomography, etc. can be used to detect early osteoporosis.

17.2.5 Diagnosis and Differential Diagnosis

17.2.5.1 Peri-menopausal Hypertension Diagnosis

1. Meet the diagnostic criteria for hypertension

   Refer to the 2013 China Guidelines for the Prevention and Treatment of Hypertension [41]:

   Under the premise of not taking antihypertensive drugs, blood pressure was measured twice a day, and the average value of blood pressure was taken twice. Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg were diagnosed as hypertension.
2. Meet the diagnostic criteria for perimenopausal syndrome

   Published in 2011 [42] "Seminar of reproductive aging stage + 10" diagnostic criteria and "obstetrics and gynecology" [43]: The period of time in a woman before and after menopause (from about age 45 to 12 months after menopause), which includes the endocrine, biological, and clinical characteristics associated with menopause that begin near menopause and end 1 year after the last menstrual period.

   According to age, menstrual changes and self-symptoms, the diagnosis is not difficult, but the symptoms of perimenopausal are not specific except episodes of hot flashes, and should be diagnosed after excluding organic diseases.

   Pay attention to the history of menstruation, marriage and childbirth, age of menopause, history of ovarian and hysterectomy, history of postmenopausal

bleeding and family history (cardiovascular disease, diabetes, cancer) and history of treatment (hormone and drugs). Whether or not menopause is extremely important. In addition, some scholars have proposed to predict menopause through menopausal predictors. Generally, the forecast can be made from the following three aspects. First, it is predicted by family inheritance: since the age of entering the menopause has a certain relationship with genetic factors, the age of menopause, grandmother, mother, and siblings can be used as predictors of grandchildren, daughters, and sisters entering the age of menopause. However, this indicator is not absolute and is susceptible to factors such as living conditions, environment, climate, social factors, drugs, diseases, etc., causing menopause to be advanced or postponed. Second, the age of menopause can be predicted from the age of menarche: most people observe that the age of menarche is negatively correlated with the age of menopause, that is, the earlier the age of menarche, the later the age of menopause (menopausal); on the contrary, the later the age of menarche, the earlier the age of menopause. Three from the menstrual disorders to see if menopause is coming.

The current history of the disease requires a detailed and comprehensive description of the symptoms of the patient, such as the frequency, duration, and accompanying symptoms of hot flashes. The different symptoms of each patient's performance should be considered in the identification of organic diseases such as hypertension, coronary heart disease, hyperthyroidism, and neurosis.

17.2.5.2 Differential Diagnosis

Many other diseases can cause symptoms and signs similar to menopause. In general, a preliminary diagnosis can be made based on their clinical manifestations. If there is no evidence of other diseases, it often indicates ovarian function and support peri-menopausal syndrome.

1. Amenorrhea: Women aged 40–50 years often have natural menopause, young women with amenorrhea can have premature ovarian failure, but must be differentiated from other non-ovarian amenorrhea, such as anorexia nervosa, hyperprolactinemia, and polycystic ovarian syndrome; these diseases have their own symptoms, although there is decreased estrogen, vasomotor symptoms are rare.
2. Vascular motor flushing: Some diseases produce flushing symptoms that are confused with hot flashes, such as hyperthyroidism, pheochromocytoma, carcinoid syndrome, diabetic neuropathy, niacin excess, tuberculosis, and other chronic infections. The skin flushing caused by the above diseases does not have the characteristics of menopause hot flashes (duration, special distribution on the body, etc.). In addition, if the patient has symptoms of skin flushing and no other menopause, she should be further tested for hormones.
3. Abnormal vaginal bleeding: 40- to 50-year-old patients have prolonged menstrual cycle and decreased menstrual flow, which is caused by degenerative ovarian function in menopause. Endometrial biopsy is not necessary, but if menstruation occurs frequently, menstruation increases, or if intermenstrual

uterine bleeding occurs, the endometrium should be examined. Endometrial biopsy and dilatation curettage are often used. After 6 months of menopause, ovarian function is recurrent with vaginal bleeding, which must be taken seriously, often associated with organic lesions. In addition, many special vulvar and vaginal lesions (such as trichomonas vaginitis, vaginal candidiasis) are similar to the vulvovaginitis caused by estrogen deficiency, often require special examination to confirm the diagnosis.

4. Coexistence of heart palpitations, dizziness, and high blood pressure: Menopausal syndrome is often accompanied by symptoms such as palpitations, dizziness and hypertension, which need to be differentiated from coronary heart disease, hypertension, and hyperthyroidism. If there are no symptoms specific to menopause (onset hot flashes), a more comprehensive examination should be performed to rule out the possibility of organic diseases. The typical angina pectoris is sudden or suffocating pain in the lower sternum or pre-cardiac region, and radiates to the left shoulder arm. The duration is rarely more than 10–15 min. The pain is about 1–2 min after the nitroglycerin tablets are included. That is to ease or disappear. The pain in the precordial area of patients with menopausal syndrome is mostly persistent and dull pain. Patients with essential hypertension have a significant history of primary disease, elevated blood pressure is persistent, and systolic and diastolic pressures often exceed normal values. In patients with menopausal syndrome, systolic blood pressure is increased, diastolic blood pressure is normal, and the fluctuation range is large during the day, and often falls to the normal range after sleep. Hyperthyroidism during sweating and mental symptoms are mostly persistent, and are mainly caused by daytime attacks, and the paroxysmalness of menopausal syndrome is mainly caused by nocturnal attacks.

17.2.6 Treatment of Peri-menopausal Hypertension

First, due to dysfunction of vasomotor, the incidence of hypertension in menopause is significantly increased, which may be due to the development of hypertension on the basis of essential hypertension, but also for menopausal hypertension. Effective adjustment of the body's hormone levels to the latter is the key to treatment.

17.2.6.1 Estrogen Replacement Therapy (HRT) [44, 45]

Signs of estrogen therapy: menopausal symptoms, including hot flashes and vaginal atrophy, prevent osteoporosis and hardening of the arteries.

Contraindications: (1) Known or suspected pregnancy, unexplained vaginal bleeding, known or suspected breast cancer, known or suspected hormone-dependent malignancy, active venous or arterial thromboembolic disease within the last 6 months, severe liver and kidney dysfunction, porphyria, osclerosis, and now meningioma. (2) Patients with existing uterine fibroids, endometriosis, endometrial hyperplasia, thrombosis, systemic lupus erythematosus, benign breast disease and

family history of breast cancer, epilepsy, migraine, asthma, gallbladder disease should be careful.

Medication method: Oral administration is generally recommended. Local administration is limited to senile vaginitis and should not be used for a long time. To control hot flashes, a large dose is required at first, and gradually the dose is reduced after controlling the symptoms. The duration of short-term estrogen therapy is usually 1–2 years.

1. Single progesterone supplement: It is suitable for early menopause transition to adjust the menstrual problems in the process of ovarian function decline. (1) oral administration: ditriprogesterone 10–20 mg/day or particulate progesterone 200–300 mg/day or medroxyprogesterone acetate 4–6 mg/day, 10–14 day from the 14th day of menstruation or withdrawal bleeding. (2) intrauterine placement: ING-IUS is especially suitable for patients with endometrial hyperplasia.
2. Monoestrogen supplement: For women with hysterectomy, usually continuous. (1) oral administration: estradiol valerate 0.5–2 mg/day, or 17 beta-estradiol 1–2 mg/day, or the combined estrogen 0.3–0.625 mg/day. (2) transdermal: apply semi-hydrated estradiol paste (1/2–1)/7d, or estradiol gel 0.5–1 measuring stick per day on the skin of arms, thighs, buttocks (avoid the breast and perineum).
3. Sequential estrogen and progesterone regimens: For women with a complete uterus, perimenopausal or postmenopausal women who still want to have menorrhagia. (1) Continuous sequence: in the process of treatment every day with drugs, can use continuous sequence compound preparation: estradiol/estradiol distradione tablets (1/10 or 2/10)1 tablet/day, a total of 28d; continuous use of oral or transdermal estrogen for 28 days, followed by progesterone for 10–14 days. (2) cycle sequence: in each cycle of the treatment process, there is no need for any drug for 3–7 days, the use of cycle sequence compound preparation: estradiol valerate tablets/estradiol cyprogesterone tablets, 1 tablet/day, a total of 21d; continuous administration of oral or transdermal estrogen for 21–25d, followed by progesterone for 10–14d, followed by withdrawal of 3–7d is also recommended. And then the next period.
4. Continuous combination of estrogen and progesterone: It is suitable for women who have complete uterus and do not want to have menorrhagia after menopause. Continuous administration of daily estrogen (oral or transdermal) plus progesterone; Compound preparations such as estradiol/dilazone tablet 1 tablet/day can also be used for continuous administration.
5. Tibolone: 1.25–2.5 mg/day continuous application.
6. Application of vaginal local estrogen: Estriol cream, proestrene vaginal capsule or cream, combined with estrogen ointment, 1 time/day, continuous use for 2 weeks, symptoms relieved after 2 times/week.

Short-term (3–6 months) topical application of estrogen vaginal preparation, no need to add progesterone, but lack of safety data over 1 year of use, long-term users should monitor the endometrium.

17.2.6.2 The Blood Pressure Management of Peri-menopausal Hypertension

1. General principles

   In 2017, the consensus on blood pressure management among Chinese women experts on cardiovascular disease prevention was put forward [46]: (1) The ideal blood pressure level for women should be no more than 120/80 mmHg and can be achieved through lifestyle improvements, including: weight control, strengthening physical activity, moderate alcohol, smoking ban, salt restriction, increasing intake of vegetables, fruits and low-fat dairy products, and maintaining mental health. (2) The ideal blood pressure level for women should be no more than 120/80 mmHg, and it can be achieved through lifestyle improvement, including: weight control, strengthening physical activity, moderate alcohol, smoking ban, salt restriction, increasing intake of vegetables, fruits and low-fat dairy products, and maintaining mental health.(3) Currently, there is still no evidence-based medical evidence for hypertension in women, and the overall strategy of blood pressure reduction is consistent with that of common hypertension. Drug selection should be individualized according to the specific situation of patients [47]. In view of the fact that peri-menopausal women often have obesity, hyperinsulinemia, insulin resistance, and RAS and sympathetic nervous system, they are treated with angiotensin-converting enzyme inhibitor (ACEI) and angiotensin receptor blocker (ARB). Mainly, taking body blockers or verapamil sustained-release tablets can improve the effects of sympathetic excitability on hypertension. The combination of two drugs combined with calcium antagonists may be the mainstream treatment for postmenopausal hypertension [49].

2. Antihypertensive drug treatment

   Peri-menopausal and postmenopausal women have large changes in neuroendocrine hormones, such as renin-angiotensin-aldosterone system activation, sympathetic over-excitation, endothelial dysfunction, oxidative stress, increased salt sensitivity, etc. Mechanisms, and each mechanism has mutual influence and mutual causality, resulting in increased blood pressure and high risk of cardiovascular disease [48]. (1) Diuretics: Thiazide diuretics are still the main therapeutic drug for most patients. For high-risk women, diuretics can be combined with ACEI/ARB to better control blood pressure. Long-term high-dose diuretics may cause electrolyte and glycolipid metabolism disorders, so low-dose diuretics are often used clinically or in combination with other antihypertensive drugs. For postmenopausal women, thiazide diuretics can reduce the risk of bone loss and hip fracture [49]. (2) β-blockers: β-blockers block the effects of catecholamines on β-adrenergic receptors, reduce vascular tone and cardiac output, control heart rate, achieve antihypertensive effect, and β-receptors Blockers have mild antianxiety effects and are more suitable for the treatment of hypertension in perimenopausal women. (3) RAS blockers: In view of peri-menopausal hypertension often combined with obesity, hyperinsulinemia, insulin resistance and RAS and sympathetic nervous system, the treatment of ACEI/ARB-based, combined with calcium antagonist treatment

May be the mainstream treatment for peri-menopausal and postmenopausal hypertension. (4) Calcium antagonists: Dihydropyridine calcium antagonists and non-dihydropyridine calcium antagonists can be combined with other four drugs, and are suitable for most patients. Because common adverse reactions include reflex sympathetic activation leading to rapid heartbeat, facial flushing, edema of the ankle, etc., often aggravate the corresponding symptoms of peri-menopausal syndrome, so try to use long-acting, stable drug dosage forms. Clinically, non-dihydropyridine calcium antagonist verapamil sustained-release tablets are used in the antihypertensive treatment of perimenopausal hypertension, which can reduce plasma norepinephrine while acting on calcium channels. Therefore, it is suitable for peri-menopause. Volatile hypertension caused by stress anxiety and stress.

Third, the occurrence of menopausal hypertension is closely related to psychological stress, emotional disorders, and over-stress, and improper diet and exercise reduction are important causes of this disease. Therefore, women must be good at adjusting their work status during menopause. Elevate emotions, alleviate psychological pressure, strengthen the improvement of life patterns, and achieve "no disease prevention, disease prevention and change."

Fourth, in recent years, China's traditional medicine using the combination of Chinese and Western medicine syndrome differentiation and treatment, has achieved good results in the treatment of menopausal hypertension, it is worth learning [50].

17.2.7 Prognosis

The diagnosis of peri-menopausal hypertension must be established on the basis of the exclusion of essential hypertension. Generally, after peri-menopause, blood pressure can return to normal. If blood pressure continues to increase after peri-menopause, consideration should be given to the presence of essential hypertension or other secondary hypertension.

17.3 The Third Section of Hypertensive Disorder Complicating Pregnancy

Yuanyuan Li

Hypertensive disorders in pregnancy is one of the common complications of pregnancy and is the leading cause of morbidity and mortality in pregnant women and perinatal children. Pregnant women often have serious complications of hypertension, including cerebrovascular accident, heart failure, HELLP syndrome (hemolysis, elevated liver enzymes, thrombocytopenia syndrome), acute renal failure, etc., and newborns have premature birth, low body weight. The risk of child, suffocation, and death has also increased significantly. Hypertensive disorder of

pregnancy has become a hot spot for maternal and child health because of its high incidence and great harm. To this end, it is necessary for us to correctly understand the occurrence of serious complications of hypertensive disorder complicating pregnancy, in order to carry out active prevention and treatment measures to reduce the adverse effects of hypertensive disorder complicating pregnancy on pregnancy outcomes, thereby effectively improving maternal and child prognosis and increasing fertility quality.

17.3.1 Name and Classification

The prevalence of pregnancy with hypertension accounts for 5–10% of pregnant women, 70% of which are pregnancy-related hypertension, and the remaining 30% have hypertension before pregnancy [51, 52]. With the deep understanding of hypertensive disorders in pregnancy, domestic and foreign scholars have made great changes to the naming of hypertensive disorders in pregnancy in recent years. It is generally believed that the naming and classification criteria of pregnancy-induced hypertension syndrome should be in line with international standards, and should be unified with the 21st edition of Williams Obstetrics, so the original "pregnancy-induced hypertension syndrome" was changed to "pregnancy-induced hypertension disease." The classification is divided into five categories according to the National High Blood Pressure Education Program (NHBPEP) Working Group Report on High Blood Pressure in Pregnancy [53].

1. Hypertension during pregnancy: the first time after pregnancy in 20 weeks, blood pressure ≥140/90 mmHg (1 mmHg = 0.133 Kpa, interval 6 h, at least twice), return to normal after 12 weeks postpartum, with or without proteinuria. The disease is named to emphasize the causal relationship between hypertension, proteinuria symptoms, and pregnancy in women of childbearing age. In most cases, transient hypertension and proteinuria occur during pregnancy and disappear after delivery.
2. Preeclampsia: the first increase in blood pressure after 20 weeks of gestation, accompanied by other manifestations, such as headache, blurred vision, upper abdominal discomfort, or thrombocytopenia should be highly suspected of preeclampsia.
3. Eclampsia: pregnant women with convulsions cannot be explained by other reasons.
4. Pregnancy with chronic hypertension: blood pressure ≥140/90 mmHg, first appeared before pregnancy or 20 weeks before pregnancy or after 20 weeks of pregnancy and continued for 12 weeks after delivery.
5. Chronic hypertension complicated with preeclampsia: pregnant women with hypertension have no proteinuria 20 weeks ago. If there is proteinuria 300 mg/24 h or sudden emergence of urine protein 20 weeks ago, blood pressure is further increased, platelets $<100 \times 10^9$/L.

According to the International Classification of Hypertension Research Society classification, diagnosis and management guidelines (2018) HDP is divided into two categories, six subtypes. New classification of hypertensive disorders in pregnancy:

(a) Prepregnancy diagnosis or newly discovered hypertension 20 weeks before pregnancy (<20 weeks): (1) chronic hypertension (including primary and secondary); (2) white coat hypertension; (3) occult hypertension.
(b) Hypertension occurred after 20 weeks of gestation (≥20 weeks): (1) transient gestational hypertension; (2) gestational hypertension; (3) preeclampsia: including new or chronic hypertension with preeclampsia.

In particular, the term "pregnancy-induced hypertension" cannot be replaced by the term "pregnancy-induced hypertension." "Pregnant hypertension disease" is not exactly the same as "pregnancy-induced hypertension syndrome." The former contains chronic hypertension. Specifically, "hypertension disorder in pregnancy" is a group of diseases, not a specific one during pregnancy disease. The term "pregnancy-induced hypertension" is replaced by "pregnancy hypertension," preeclampsia, and "eclampsia," which is not only in the same category, but also in line with international standards. In addition, in order to prevent ambiguity, the term "preeclampsia" no longer appears. However, it is emphasized that the preeclampsia with symptoms such as headache, dizziness, vertigo, nausea, etc. should prevent the occurrence of eclampsia. The following are the pathophysiology, clinical manifestations, new progress of diagnosis, and treatment of five types of hypertensive disorders of pregnancy. These are discussed separately.

17.3.2 Hypertension in Pregnancy, Preeclampsia, Eclampsia

Pregnancy-induced hypertension, preeclampsia, and eclampsia, formerly known as pregnancy-induced hypertension (PIH), also known as edema-hypertension-proteinuria syndrome, once referred to as pregnancy-induced hypertension, is a pregnancy period-specific disease. Due to systemic small arterial spasm, leading to insufficient blood supply to important organs, resulting in ischemia and hypoxia of tissue cells, and a group of syndromes with corresponding organ dysfunction, the clinical manifestations of hypertension, edema and proteinuria in pregnant women are serious during pregnancy. It is one of the important complications that threaten the safety of mother and child.

17.3.2.1 Cardiovascular changes during pregnancy

An understanding of cardiovascular changes during pregnancy helps to understand the occurrence of PIH. It is well known that pregnancy is the process by which embryos and fetuses grow and develop in the mother. Egg fertilization is the beginning of pregnancy, and the discharge of the fetus and its appendages from the mother

is the termination of pregnancy. The entire process of pregnancy is about 38 weeks, which is a very complex but extremely coordinated physiological process. Due to the needs of embryos and fetal growth and development, a series of adaptive anatomical and physiological changes occur in various systems in pregnant women under the action of hormones produced by the placenta and maternal neuroendocrine. Cardiovascular system changes are the basis for the development of pregnancy-induced hypertension.

1. Cardiac output: Increase from about 10 weeks of gestation to maintain fetal growth and development. By the peak of 32 weeks of gestation, the cardiac output in the left lateral position was increased by about 30% compared with the nonpregnancy, and the average cardiac output was about 80 mL each time. Thereafter, this level was continued until delivery. The response of pregnant women to cardiac output is more obvious than that of pregnant women. After labor, especially during the second stage of labor, the cardiac output increased significantly.
2. Circulating blood volume: Starting from 6–8 weeks of gestation, reaching a peak at 32–34 weeks of gestation. About 30–45% increase, an average increase of about 1500 mL, maintaining this level until delivery. Increased blood volume includes an increase in plasma and red blood cells, an increase in plasma over red blood cells, an increase in plasma of approximately 1000 mL, and an increase in red blood cells by approximately 500 mL. Hemodilution occurs.
3. Blood pressure: The most significant change in pregnancy is the decrease in blood pressure and peripheral vascular resistance in pregnant women after pregnancy, and peripheral vasodilation (which can be expressed as palm flushing and telangiectasia, similar to spider mites). Most scholars believe that peripheral vasodilation and decreased resistance are caused by increased vasodilator substances such as prostaglandin synthesizers; in particular, prostacyclin (PGI_2), which antagonizes circulating vasoconstrictors such as angiotensin II and norepinephrine. Therefore, although the cardiac output is increased, the peripheral blood vessel resistance is lowered, and finally the blood pressure is low in the early and middle stages of pregnancy. In the third trimester of pregnancy, blood pressure gradually increased to the original level, showing no change in systolic blood pressure. Diastolic blood pressure was slightly reduced due to peripheral vasodilation, hemodilution, and placental formation of arteriovenous short circuit, resulting in a slight increase in pulse pressure difference. Twenty-four hour ambulatory blood pressure monitoring showed that the blood pressure of normal pregnant women also had circadian rhythm, which was the lowest at night.

17.3.2.2 Epidemiology

Due to the different naming and classification standards, the incidence of hypertensive disorders in pregnancy reported at home and abroad is different. In recent years, foreign literatures have reported that the incidence rate in healthy first mothers is 6–17% and 2–4% [54–56]. According to a large-scale epidemiological survey of pregnancy-induced hypertension syndrome in 25 provinces and cities in China in

1988, about 9.4% of pregnant women developed different degrees of gestational hypertension, including mild pregnancy-induced hypertension syndrome 4.7%, and moderate pregnancy-induced hypertension. The syndrome was 2.6%, preeclampsia was 1.7%, and eclampsia was 0.2%. The ratio of prenatal, postpartum, and postpartum eclampsia was 49:31:20; slightly higher than the 7% reported in the United States. Current clinical research shows that the incidence of PIH in China is gradually rising, and it has been reported that it can reach 10.4% [43].

17.3.2.3 Etiology and Pathogenesis

Hypertension, preeclampsia, and eclampsia in pregnancy are diseases unique to pregnancy. The etiology and pathogenesis of this disease have not yet been fully elucidated. At present, there are mainly several hypotheses about its mechanism, namely [57]:

1. Immunology: Pregnancy is considered a successful natural allogeneic transplant. The maintenance of normal pregnancy depends on the establishment and stability of the maternal immune balance. Once this immune balance is dysregulated, it can lead to a series of vascular endothelial cell lesions, resulting in PIH. With the rapid development of immunology in recent years, great progress has been made in the relationship between preeclampsia–eclampsia and immune problems. Immunology believes that the cause of preeclampsia is the immune response of certain antigenic substances in the placenta. At present, although the specific mechanism of PIH pathogenesis cannot be clarified from the perspective of immunology, it is generally believed that immunity may be the main factor in the occurrence of the disease and deserves further investigation.
2. Uterus-placental ischemia theory: This theory was first proposed by Young in 1918 and was accepted more generally. The theory suggests that PIH is prone to occur in the first trimester, multiple pregnancy, and polyhydramnios. The increase in uterine tension affects the blood supply to the uterus, resulting in uterus-placental ischemia and hypoxia. Secondly, the study suggests that abnormal trophoblast cells invade the myometrium, and the uterine spiral artery undergoes extensive lesions, causing stenosis and atresia, resulting in reduced perfusion of the placental blood flow. In addition, the systemic blood circulation cannot adapt to the needs of the uterus-placenta, such as pregnant women with severe anemia, chronic hypertension, diabetes, etc., is also easy to accompany this disease. Some scholars believe that utero-placental ischemia is not the cause of disease, but the result of vasospasm.
3. Neuroendocrine theory: The imbalance of the renin-angiotensin-aldosterone system (RAAS) may be related to the occurrence of preeclampsia–eclampsia. Angiotensin-converting enzyme (ACE) may play a leading role. In recent years, plasma levels of renin and AgII in patients with preeclampsia and eclampsia have been lower than those in normal pregnant women, especially in critically ill patients. Therefore, it is believed that the onset of preeclampsia may be related to the increased sensitivity of the body to AgII. In addition, studies have shown that RAS activation in placental tissue may be the primary source of PHI.

4. Plasma endothelin pathogenesis: Endothelin (ET) is a polypeptide hormone secreted by vascular endothelial cells and is a powerful vasoconstrictor. ET maintains homeostasis with thromboxane A2 (TXA2) and vascular endothelial cell relaxing factor (EDRFs) and prostacyclin (PGI2) to regulate blood pressure and local blood flow in the body. In gestational hypertension, ET and TXA2, which regulate vasoconstriction, increase in the body, while EDRFs and PGI2, which regulate vasodilation, decrease, causing imbalance in vasoconstriction and diastolic regulation and hypertension.
5. Nitric oxide theory: Nitric oxide (NO) is a vasodilator released by vascular endothelial cells. In recent years, more and more studies have shown that vascular endothelial injury and a series of vasoactive substances released by them play an important role in the pathogenesis of gestational hypertension. These substances mainly include vasoconstrictor endothelin and thromboxane A2, and vasodilators NO and PGI2, in which NO synthesis or (and) release dysfunction may be a major link in the pathogenesis of gestational hypertension.
6. Coagulation system and fibrinolysis system imbalance theory: During normal pregnancy, especially in the third trimester, there is a physiological hypercoagulability state, and various coagulation factors and fibrinogens are increased compared with nonpregnant women. At the same time, the activity of the fibrinolytic system during pregnancy is also enhanced. Therefore, there is a dynamic balance between coagulation and fibrinolysis during normal pregnancy. In pregnancy-induced hypertension, coagulation system activity includes increased function of platelets and various coagulation factors, while anticoagulant and antithrombin (antiminxnbin, ATM) and tissue plasminogen activator (t-PA), fibrinolysis, the activities of zymogen (PIG), fibrinolysin and the like are decreased, and plasminogen activity inhibitory factor (pAIs) and fibronectin are increased. These changes lead to loss of homeostasis between the coagulation system and the fibrinolytic system, which may be one of the predisposing factors for pregnancy-induced hypertension.
7. Calcium deficiency theory: In recent years, the occurrence of PIH may be related to calcium deficiency. It has been shown that calcium deficiency in humans and animals can cause an increase in blood pressure. Pregnancy is easy to cause maternal calcium deficiency, leading to PIH, and calcium supplementation during pregnancy can reduce the incidence of hypertensive disorders during pregnancy. Therefore, it is believed that calcium deficiency may be an important factor in the occurrence of PIH, and its mechanism is still unclear. In addition, the detection of urinary calcium excretion can be used as a predictive test for PIH.
8. Others: There are genetic factors, prostaglandin system theory, atrial natriuretic theory, oxygen free radical theory, uric acid theory, and social psychology, etc. Some etiology and pathogenesis factors related to the onset of pregnancy-induced hypertension.

The introduction of various doctrines illustrates the complexity of the pathogenesis of PIH. It is generally believed that gestational hypertension is mainly caused

by the low recognition of the maternal trophoblastic antigen by polygenic inheritance, resulting in a weakened protective immune response and enhanced rejection, which reduces the invasive ability of the trophoblastic cells and the shallow implantation of the placenta. It causes placental ischemia and hypoxia and local cellular immune response, resulting in local oxidative stress in the placenta, manifested by lipid peroxidation and release of oxygen free radicals; at the same time, release a large number of inflammatory factors, activate neutrophils, directly or indirectly lead to blood vessels endothelial injury which eventually leads to the development of hypertension during pregnancy.

In addition, according to epidemiological investigations, the incidence of hypertensive disorder complicating pregnancy may be related to the following related risk factors: (1) excessive mental stress or stimulation caused by central nervous system dysfunction; (2) cold season or excessive temperature changes, especially air pressure when raised; (3) young pregnant women (<18 years old) or early pregnant women (>40 years old); (4) pregnant women with chronic hypertension, chronic nephritis, diabetes, etc.; (5) malnutrition, such as anemia, hypoproteinemia; (6) body short stature, that is, body mass index >24; (7) uterine tension is too high (such as polyhydramnios, twin pregnancy, diabetes giants, and hydatidiform moles); (8) families have a history of hypertension, especially pregnant women. The mother has a history of severe pregnancy-induced hypertension.

17.3.2.4 Pathophysiology and Effects on Mothers and Infants

Similar to essential hypertension, the basic pathophysiological changes of this disease are systemic small vasospasm, and the perfusion of organs in various systems of the whole body is reduced, causing harm to mothers and children, and even leading to maternal and child death.

1. Intrauterine placental perfusion: vasospasm causes a decrease in placental perfusion. The abnormal trophoblast cell invasion makes the average diameter of the spiral artery only two-fifth of the diameter of the spiral artery of normal pregnant women, combined with endothelial damage and acute atherosclerosis of the placental vasculature, which causes the placental function to decline, fetal growth restriction, and fetal distress. If the placental bed ruptures, it can cause placental abruption. In severe cases, the mother and child will die.
2. Brain changes: the weight of normal human brain only accounts for 2.2% of body weight, while cerebral blood flow accounts for 15% of cardiac output, and brain oxygen consumption accounts for 23% of total oxygen consumption. When the lesion appears, the cerebral vasospasm, increased permeability, can cause cerebral edema, congestion, ischemia, thrombosis, and bleeding. CT examination showed a low-density area of the cerebral cortex with corresponding ischemic and punctiform hemorrhage. This pathological change was associated with cerebral infarction and was associated with coma and decreased vision and blindness. Central nervous system symptoms caused by a wide range of cerebral edema are mainly characterized by dullness and confusion. Individual patients can develop coma and even cerebral palsy. Cerebral vascular resistance

and cerebral perfusion pressure were increased in preeclampsia. Cerebral blood flow during eclampsia can be normal on one side and increased on the other side. High pressure can cause obvious headache. Studies have shown that eclampsia is associated with loss of cerebral vascular autoregulation.

3. Kidney: renal arteriolar spasm. Under the light microscope, the glomerulus is slightly reduced, the diameter of the capillary lumen of the renal tubule is reduced, the glomerular capillaries are thickened under the electron microscope, the endothelial cells are enlarged, the capillary lumen is small or even occluded, and the blood flow is reduced. There may be a large or pile of grape-like lipids in the glomerular lesion, possibly cholesterol or cholesterol. Renal blood flow decreased in PIH patients, and glomerular filtration rate decreased. The glomerulus can also have infarction, and there are fibroids under the endothelium, which can make the anterior small artery of the glomerulus extremely narrow, causing glomerular damage, increasing its permeability, decreasing selectivity, and macromolecular protein can also pass, resulting in proteinuria. The amount of proteinuria marks the severity of hypertensive disorders during pregnancy. Due to vasospasm, renal blood flow, and glomerular filtration excess, resulting in elevated plasma uric acid concentration and elevated plasma creatinine, severe kidney damage can cause oliguria and renal failure. When the condition is severe, due to renal parenchymal damage, renal function damage will not be reversed.
4. Cardiovascular system: systemic arterial spasm, elevated blood pressure; coronary spasm, causing myocardial insufficiency, interstitial edema, severe myocardial punctiform hemorrhage and necrosis. Patients with PIH water retention, blood concentration, and increased blood viscosity, causing cardiac preload and decreased cardiac output and increased left ventricular afterload, leading to left heart failure and pulmonary edema. Echocardiography showed that the right ventricular diastolic diameter of patients with PIH was significantly enlarged, left ventricular end-diastolic pressure increased, ventricular systolic function decreased, and left ventricular ejection fraction decreased. In addition, critically ill patients may have varying degrees of anemia, hypoproteinemia, and reduced plasma colloid osmotic pressure, resulting in a small or moderate amount of fluid in the pericardium. Endocardial biopsy of severe patients showed cardiac cell hypertrophy, brain-like particle-like changes, localized fibrotic changes in myocardial interstitial, and point-like hemorrhage and localized necrosis.
5. Blood: mainly manifested as abnormal blood volume and coagulation function. Due to small vasospasm, increased permeability of blood vessel walls, and concentrated blood, the blood volume of most patients does not increase as in normal pregnant women in the third trimester of pregnancy, and thus the hematocrit increases. When the hematocrit decreases, more anemia or red blood cell damage or hemolysis occurs, especially in severe cases, microvascular hemolysis can occur, mainly showing thrombocytopenia, platelets $<100 \times 10^9$/L, and liver enzymes are elevated, i.e., HELLP syndrome. Microecological hemolysis occurs in preeclampsia or eclampsia, which may be accompanied by red blood cell destruction, which is characterized by hemolysis, erythrocytes, spherocytocytes, reticulocytes, hemoglobinuria, and the like.

6. Liver: there may be abnormal liver function in preeclampsia, elevated levels of various transaminase, and elevated plasma alkaline phosphatase. The characteristic damage of the liver is bleeding around the portal vein, and severe necrosis around the portal vein. Hepatic subcapsular hematoma formation, liver rupture can also occur to endanger mother and child life.
7. Endocrine and metabolism: due to elevated mineralocorticoid and deoxycorticosterone during pregnancy, sodium water retention can be caused; in addition, leakage of proteinuria leads to hypoproteinemia, which causes plasma colloid osmotic pressure to decrease, patients are prone to edema, However, edema is not related to the severity and preconditioning of hypertensive disorder complicating pregnancy. If there is no diuresis or dehydration, it is generally not accompanied by electrolyte abnormalities. Acidosis can occur after convulsions in eclampsia.

17.3.2.5 Clinical Manifestations

The clinical manifestations of patients with hypertensive disorder complicating pregnancy are mainly related to their type. The main symptoms and signs are concentrated in elevated blood pressure, edema, proteinuria and nervous system discommarizes the characteristics of five different types of hypertensive disorders of pregnancy [53].

1. Hypertension: Before pregnancy or before 20 weeks of gestation, blood pressure (i.e., basal blood pressure) is not high, and after 20 weeks of gestation, blood pressure begins to rise to 140/90 mmHg, or systolic blood pressure exceeds 30 mmHg of original basal blood pressure and diastolic blood pressure. Those who exceeded the original basal blood pressure of 15 mmHg were hypertensive. The patient can have no symptoms or mild dizziness. Note that blood pressure is 30/15 mmHg higher than the baseline blood pressure, but below 140/90 mmHg, it is not a diagnostic basis, but it must be closely observed (Table 17.1) [58].
2. Proteinuria: The appearance of proteinuria is often slightly later than the increase in blood pressure, the amount is small, more than 0.5 g/24 h, and the urine protein (+) in severe cases indicates that the amount of protein in the urine is >0.5 g in 24 h. When the amount of protein in the urine is >0.5 g in 24 h, there may be different degrees of edema and a series of symptoms appear.
3. Edema: Initially manifested as abnormal weight gain (recessive edema), more than 0.5 kg per week. If there is too much fluid in the body, it will lead to clinically visible edema. The edema is mostly caused by the sacral part, and gradually extends to the calf, thigh, genital area, and abdomen, which is a depressed edema. The ankle and calf have obvious depression edema, and those who do not retreat after rest are indicated by "+"; the edema extends to the thigh and is represented by "++"; "+++" means edema extends to the vulva and abdomen; "+ +++" refers to systemic edema or ascites. Usually normal pregnancy, anemia, and hypoproteinemia can cause edema; edema of hypertensive disorder complicating pregnancy is not specific, so it cannot be used as a diagnostic criteria and classification basis.

Table 17.1 Definition and characteristics of five types of hypertensive disorders in pregnancy

Classification	Clinical manifestation
Hypertension during pregnancy	BP ≥ 140/90 mmHg appeared for the first time after 20 weeks of gestation and returned to normal at 12 weeks postpartum; urinary protein (−); a small number of patients may be associated with upper abdominal discomfort or thrombocytopenia. Can be diagnosed after the birth
Preeclampsia	Mild: BP ≥ 140/90 mmHg after 20 weeks of gestation; urine protein ≥0.3 g/24 h or random urine protein (+); may be associated with upper abdominal discomfort, headache, and other symptoms
	Any of the following manifestations can be diagnosed as severe preeclampsia: Continuously elevated blood pressure: systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg; persistent headache, visual impairment or other abnormalities of the central nervous system; persistent upper abdominal pain and subcapsular hematoma or liver rupture; liver enzyme abnormalities: elevated levels of blood alanine aminotransferase (ALT) or aspartate aminotransferase (AST); impaired renal function: urine protein >2.0 g/24 h; oliguria (24 h urine volume <400 mL) Or urine volume <17 mL/h, or serum creatinine >106 μmol/L; hypoproteinemia with ascites, pleural effusion or pericardial effusion; abnormal blood system: platelet count is continuously decreasing and below 100×10^9/L; microvascular hemolysis showed anemia, jaundice, or elevated blood lactate dehydrogenase (LDH); heart failure; pulmonary edema; fetal growth restriction or oligohydramnios, fetal death, placental abruption
Eclampsia	Preeclampsia pregnant women with convulsions cannot be explained by other reasons
Chronic hypertension complicated with preeclampsia	Hypertensive pregnant women have no urine protein before 20 weeks of gestation, if urinary protein ≥0.3 g/24 h; hypertensive pregnant women suddenly increase urine protein or blood pressure after 20 weeks of pregnancy or platelet $<100 \times 10^9$/L
Pregnancy with chronic hypertension	Prepregnancy or 20 weeks before pregnancy, diastolic blood pressure ≥90 mmHg (except for trophoblastic disease), no significant exacerbation during pregnancy; or first diagnosis of hypertension after 20 weeks of gestation and continued until 12 weeks after delivery

Preeclampsia is a further development of the disease, the general blood pressure is as high as 160/110 mmHg or higher; on the basis of hypertension and proteinuria, the patient has symptoms such as headache, vertigo, nausea, stomach pain, and vomiting. These symptoms indicate a further deterioration of the condition, especially the further development of intracranial lesions, indicating that impotence is about to occur, so it is also called preeclampsia. Preeclampsia is divided into light and severe according to the severity of symptoms. The clinical features of severe preeclampsia are progressive or fulminant, and multiple organ systems can be involved. In the nervous system, it is characterized by severe headache, visual disturbance, and progressive hyperreflexia, which is a warning signal for impending convulsions (eclampsia). Severe vasospasm leads to increased peripheral resistance, which increases the burden on the cardiovascular system, and some patients may have pulmonary edema. The blood system is characterized by decreased vascular

volume, increased blood viscosity, and blood concentration, which contribute to the development of coagulopathy, such as hemolysis, elevated liver enzymes, thrombocytopenia, so-called HELLP syndrome, and disseminated intravascular coagulation (DIC). Renal manifestations include a decrease in glomerular filtration rate and even progression to oliguria and acute renal failure. Elevated alanine aminotransferase and aspartate aminotransferase reflect hepatocyte damage. Subcapsular hemorrhage can lead to upper right abdominal pain or, more rarely, severe intra-abdominal hemorrhage due to rupture of the liver membrane. Obstetric complications include fetal growth restriction (FGR), placental abruption, and even fetal or maternal death.

On the basis of preeclampsia, there is a seizure attack, or coma, called eclampsia. In a small number of cases, the disease progressed rapidly, and the signs of preeclampsia were not obvious and sudden convulsions occurred. The typical episode of eclampsia is to show the fixation of the eyeball first, the pupil is dilated, and the head is twisted to one side, the jaw is closed, and then the mouth and facial muscles are vibrated. After a few seconds, the whole body and the limbs are strong, and the hands are tight. The arm flexes and a strong twitch occurs quickly. Breathing pauses when twitching, her face is blue and purple. After about 1 min, the intensity of the twitch is weakened, the muscles of the whole body are relaxed, and then the body is deeply inhaled, and the snoring sounds to resume breathing. The patient lost consciousness before and during the seizure. Those with less twitching and longer interval can wake up in a short time after convulsion; those who have frequent convulsions often have a deep coma. Various traumas often occur during convulsions, such as biting, falling, or even fractures. Vomiting in coma can cause asphyxia or inhalation of pneumonia.

Eclampsia occurs mostly in late pregnancy or before labor (65%), called prenatal eclampsia; a small number occurs during childbirth, called eclampsia (rare); about 25% of eclampsia occurs within 24 h after delivery, called postpartum eclampsia [59–62].

17.3.2.6 Laboratory and Auxiliary Inspection

1. Blood test: including complete blood count, hemoglobin content, hematocrit, blood viscosity, blood coagulation function, according to the severity of the disease can be repeatedly checked. Some scholars analyzed prothrombin time, activated partial thromboplastin time, thrombin time, and plasma fibrinogen in pregnant hypertensive patients, and found that pregnant women with normal late pregnancy and patients with pregnancy-induced hypertension were in a hypercoagulable state. The latter is in a state of severe hypercoagulability, so it is considered that the detection of four indicators of blood coagulation in pregnant women is conducive to the diagnosis of PHI. In the late pregnancy, there is a pathological hypercoagulable state with a tendency to thrombosis.
2. Urine examination: urine specific gravity, urine routine should be measured, urine concentration is $\geq$1.020, urine concentration is indicated, urine protein (+) indicates urine protein content 300 mg/24 h, urine protein (++++) urine. The protein content is 5 g/24 h. Urine protein examination should be performed once a day in patients with severe preeclampsia.

3. Determination of liver and kidney function: impaired hepatocyte function can lead to elevated transaminase and white/globulin ratio inversion; a large amount of urinary protein excretion can lead to hypoproteinemia. When renal function is impaired, serum creatinine, urea nitrogen, and uric acid increase, and creatinine rises in parallel with the severity of the disease. Uric acid is not significantly elevated in patients with chronic hypertension, so it can be used for the differential diagnosis of PIH and chronic hypertension. Severe preeclampsia and eclampsia should be measured for electrolyte and carbon dioxide binding to detect acidosis and correct it early.
4. Fundus examination: the main pathological change of PIH is small vessel disease. The observation of retinal arterioles can reflect the small blood vessel lesions of the whole body, directly reflecting the severity of PIH. Usually fundus examination can be seen in retinal arteriolar spasm, retinal flocculation or bleeding, papilledema, patients with blurred vision or blindness, retinal detachment can occur in severe cases.
5. Others: including D-dimer (DD), electrocardiogram, echocardiography, placental function, fetal maturity check, cerebral blood flow chart examination, etc., depending on the condition. Recent studies have shown that plasma DD detection levels are significantly elevated in patients with pregnancy-induced hypertension, and positively correlated with disease severity; ROC curve is used to evaluate the diagnostic value of plasma D-D for pregnancy-induced hypertension, and D-D is found to exceed 0.514 mg/L. It has an auxiliary diagnostic value for pregnancy-induced hypertension.

17.3.2.7 Diagnosis and Differential Diagnosis

1. Diagnosis [58]

   According to the patient's medical history (have high risk factors of PIH), clinical manifestations (blood pressure, edema and proteinuria, especially whether there is headache, vision change, upper abdominal discomfort, etc.), physical signs and auxiliary examination, and whether there are complications and coagulation mechanism obstacles.

   Note that the diagnosis of hypertension is continuous blood pressure rise to systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Drastic changes in diastolic blood pressure without changes in patient mood are an important indicator for the diagnosis and assessment of prognosis in pregnancy. In special cases, hypertension can be diagnosed if the measured diastolic blood pressure is ≥90 mmHg at intervals of 4 h or more.

   Automated office blood pressure (AOBP) can reduce the white coat effect and deserve further research and promotion. Twenty-four hour ambulatory blood pressure testing or home measurements can detect white coat hypertension. If the patient intends to monitor blood pressure at home, she should be informed of the correct blood pressure measurement method. It is generally accepted that automatic blood pressure recorders may be useful for self-monitoring during pregnancy and for assessing changes in blood pressure.

   Note the need to note when urinary protein is diagnosed: urinary protein is defined as two random urine protein concentrations of 30 mg/L (qualitative +) in a urine protein content of ≥300 mg or 6 h apart within 24 h. Due to fluctuations

in proteinuria, 24-h urine should be taken for quantitative examination. Avoid vaginal discharge or amniotic fluid contaminating urine. Urinary infections, severe anemia, heart failure, and dystocia can cause proteinuria.

2. Differential diagnosis
   (a) Preeclampsia and chronic nephritis combined with pregnancy: pregnant women with preeclampsia manifested as hypertension, edema, and proteinuria, such as no data before 20 weeks of pregnancy, it is not easy to have pregnancy with chronic nephritis, the latter is generally more ill than the former; heavy, symptoms are not easy to correct; postpartum follow-up, 12 weeks postpartum still have hypertension, proteinuria, edema is chronic nephritis with pregnancy
   (b) Patients with eclampsia and epilepsy, encephalitis, brain tumors, etc.: patients with epilepsy often have a history of recurrent episodes; patients with encephalitis have acute infectious symptoms and signs of nervous system; brain tumors are progressively aggravated, and corresponding nervous system localization signs

17.3.2.8 Treatment

The purpose and principle of gestational hypertension and preeclampsia treatment of eclampsia is to strive for the mother to fully recover from health, to survive after the fetus, and to terminate the pregnancy in a way that minimizes the impact on the mother and child.

1. Hypertension during pregnancy: can be hospitalized or treated at home.
   (a) Rest: Ensure adequate sleep, rest for no less than 10 h, but it is not recommended to stay in bed. The sleeping position takes the left lateral position, and the left lateral position can reduce the pressure on the abdominal aorta and inferior vena cava of the uterus, so that the blood volume of the uterus is increased and the blood supply to the placenta is improved. Studies have found that the left lateral position for 24 h can reduce the diastolic blood pressure by 10 mmHg.
   (b) Sedation: A sedative may be given to people who are nervous, anxious, or have poor sleep. Such as diazepam 2.5–5 mg, three times a day, or 5 mg orally before going to bed.
   (c) Close monitoring of mother and child status: The pregnant woman should be asked if there are symptoms such as headache, visual acuity, and upper abdominal discomfort. For hemorrhoids, measure body weight and blood pressure daily. Urine protein was reviewed every 2 days. Regular monitoring of blood, fetal development, and placental function was done. Blood pressure continues to increase and is treated as mild preeclampsia.
   (d) Intermittent oxygen: This can increase blood oxygen content; improve the oxygen supply of the main organs and placenta.
   (e) Diet: It should include sufficient protein and calories, not limited to salt and liquid, but for systemic edema, salt intake should be appropriately restricted. It is recommended to control the salt intake to 6 g/day (sodium urinary excretion 100 mmol/day), but should not excessively limit the salt, so as not to cause low blood volume, affecting placental circulation.

(f) Exercise: Exercise and weight management during pregnancy can reduce the incidence of hypertension during pregnancy.

2. Preeclampsia: should be hospitalized to prevent eclampsia and complications. The principles of treatment are rest, sedation, antispasmodic, antihypertensive, reasonable expansion, and diuresis if necessary, close monitoring of maternal fetal status, and timely termination of pregnancy.
   (a) Rest: High blood pressure during pregnancy.
   (b) Sedation: Proper sedation can eliminate the patient's anxiety and mental stress, and achieve the effect of lowering blood pressure, relieving symptoms, and preventing eclampsia.
      - Diazepam: It has strong sedative, anticonvulsant, and muscle relaxation effects, and has less influence on the fetus and newborn. Usage: 2.5–5 mg orally, three times a day; or 10 mg intramuscular injection or slow intravenous infusion (>2 min). The administration was repeated 15 min after the necessity; it was also administered rectally, and 20 mg of 0.9% sodium chloride solution was added to retain the enema. Respiratory inhibition may occur if more than 30 mg is administered within 1 h, and the total amount does not exceed 100 mg in 24 h.
      - Hibernating drugs: Hibernating drugs can inhibit the nervous system extensively, help relieve blood pressure and reduce convulsions in eclampsia. Usage: (1) pethidine 50 mg, promethazine 25 mg intramuscular injection, can be reused at intervals of 12 h, if it is estimated that within 6 h of delivery should be banned. (2) meperidine 100 mg, chlorpromazine 50 mg, promethazine 50 mg added to 10% glucose 500 mL intravenous infusion; in case of emergency, one-third amount can be added to 25% glucose solution 20 mL slow intravenous bolus (>5 min). The remaining two-third amount was added to an intravenous drip of 10% glucose 250 mL. Because chlorpromazine can cause a sharp drop in blood pressure, resulting in a decrease in blood supply to the kidney and uterus, resulting in fetal hypoxia, and has a certain damage to the mother and child liver, it is only used in patients with poor magnesium sulfate treatment.
      - Other sedative drugs: Sodium phenobarbital, sodium pentobarbital, morphine, etc. have better anticonvulsant and anticonvulsant effects, and can be used for controlling convulsions and postpartum prevention or controlling eclampsia. Because the drug can cause fetal respiratory depression, it should be prudent 6 h before delivery.
   (c) Spasmolysis: Because the basic pathological changes of hypertensive disorder during pregnancy are systemic small arterial spasm, the primary treatment is to relieve spasm. Magnesium sulfate is currently the drug of choice for the treatment of pregnancy-induced hypertension, regardless of mild or severe, and has the effect of preventing and controlling eclampsia.
      - Mechanism of action: (1) magnesium ion inhibits the release of acetylcholine from motor nerve endings, blocks information transmission between neuromuscular junctions, and relaxes skeletal muscle; (2) mag-

nesium ions stimulate vascular endothelial cells to synthesize prostacyclin, inhibit endothelin synthesis, and reduce body pair angiotensin II response, thereby relieving vasospasm; (3) magnesium ions block calcium glucone flow by blocking glutamate channels, relieve vasospasm, and reduce vascular endothelial damage; (4) magnesium ions can increase the affinity of pregnant women and fetal hemoglobin, improve oxygen metabolism.

- Indications for medication: (1) control convulsions of eclampsia and prevent further convulsions; (2) prevent the development of severe preeclampsia into eclampsia; (3) preeclampsia medication before pregnancy to prevent convulsions.
- Medication regimen: intravenous administration combined with intramuscular injection. (1) intravenous administration: the first loading dose of 25% magnesium sulfate 20 mL was added to 20 mL of 10% glucose injection, slowly intravenous injection, 5–10 min pushed; followed by 25% magnesium sulfate 60 mL added 5% glucose injection 500 mL intravenous drip. Note that the drop rate is 1–2 g/h. (2) According to the blood pressure, decide whether to use intramuscular injection, the usage is 25% magnesium sulfate 20 mL plus 2% lidocaine 2 mL, deep gluteal muscle injection, one or two times a day. The daily total amount is 25–30 g, and the serum magnesium ion concentration can be monitored during the medication.
- Toxicity: the concentration of serum magnesium ion in normal pregnant women is 0.75–1 mmol/L, and the effective concentration is 2–3.5 mmol/L. If the serum magnesium ion concentration exceeds 5 mmol/L, magnesium poisoning can occur. The first manifestation is that the knee reflex is weakened or disappeared, followed by generalized muscle tone loss, difficulty breathing, diplopia, and unclear language. In severe cases, respiratory muscle paralysis may occur, and even respiratory arrest, cardiac arrest, and life-threatening.
- Precautions: check whether the knee reflex is weakened or disappeared regularly; breathe not less than 16 times/min; urine volume is not less than 25 mL/h or not less than 600 mL per 24 h; calcium phosphate should be prepared during treatment of magnesium sulfate. Once a poisoning reaction occurs, 10 mL of 10% calcium gluconate is administered intravenously immediately. Generally, 1 g of intravenous calcium gluconate injection can reverse mild to moderate respiratory depression. Magnesium sulfate should be reduced or stopped when renal insufficiency; blood magnesium concentration should be monitored when conditions are met; 24–48 h after delivery.

(d) Antihypertensive drugs: the purpose of blood pressure reduction is to extend the gestational age or change the perinatal outcome. In the past, people thought that the treatment of PIH was mainly antispasmodic. Antihypertensive drug treatment could not be classified as routine, because antihypertensive drugs can reduce blood pressure, but also reduce

the perfusion of important organs, especially the blood flow of the placenta. Lead to iatrogenic fetal distress, or limited intrauterine growth. At present, with the research progress of antihypertensive drugs, people have a new perspective on the use of antihypertensive drugs. In 1995, Beefort and 1996 Kook et al. studied nifedipine (NIF), which proved that NIF can improve the blood flow of uterus placenta and umbilical arteries, and has a positive therapeutic effect on the perinatal outcome of PIH mother and child, avoiding blood pressure. Too high causes vascular endothelial damage and cerebral hemorrhage. It is generally believed that when the diastolic blood pressure is ≥110 mmHg, the self-regulation ability of the blood vessel disappears, and the arterial smooth muscle cannot maintain this protective contraction, causing uncontrolled expansion of the blood vessel, increasing blood flow, and prone to intracranial hemorrhage. Therefore, when the diastolic blood pressure is 100–110 mmHg, the systolic blood pressure is ≥160 mmHg or the average arterial pressure is ≥140 mmHg, antihypertensive drugs are needed. The principle of antihypertensive drug selection: no toxic side effects on the fetus, does not affect cardiac output, renal plasma flow and uterine placental perfusion, does not cause blood pressure to drop sharply or drop too low. Ideally, the blood pressure is reduced to 140–155 mmHg and the diastolic pressure is 90–105 mmHg.

- Hydralazine: a peripheral vasodilator that dilates the surrounding small arteries, reduces peripheral resistance, lowers blood pressure, and increases cardiac output, renal plasma flow, and uterine placental blood flow. The antihypertensive effect is fast and the diastolic blood pressure drops significantly. Usage: 5–10 mg every 15–20 min until satisfactory response (diastolic pressure is controlled at 90–100 mmHg); or 10–20 mg, 2–3 times daily; or 40 mg 5% glucose 500 mL intravenous drip. Note: it is not advisable to use this medicine if you have heart disease due to hypertensive disorder complicating pregnancy. Use with caution in early pregnancy. Side effects are headache, increased heart rate, hot flashes, etc.
- Labetalol (labetalol): alpha, beta-adrenergic receptor blocker, lowering blood pressure but not affecting renal and placental blood flow, and can prevent platelet aggregation and promote fetal lung maturation. The drug is effective and does not cause hypotension or reflex tachycardia. Usage: 100 mg orally, 2 times/day, the maximum amount of 240 mg/day, or baberolol hydrochloride 20 mg intravenously, after 10 min, the dose is doubled, the maximum single dose of 80 mg, until the blood pressure is controlled. The maximum total daily dose is 220 mg. The side effects were scalp tingling and vomiting.
- Nifedipine (nifedipine): calcium channel blocker, can relieve peripheral vasospasm, systemic vasodilation, blood pressure drop, due to its rapid antihypertensive effect, does not currently advocate sublingualization. Usage: 10 mg orally, three times a day, the total amount of 24 h does not

exceed 60 mg. The side effects are palpitations, headaches, and synergy with magnesium sulfate.

- Nimodipine: it is also a calcium channel blocker, which has the advantage of selectively dilating cerebral blood vessels. Usage: 20 mg orally, two to three times a day; or 20–40 mg, add 5% glucose 250 mL intravenously, once a day, the total daily dose does not exceed 360 mg, the side effect of the drug is headache, nausea, palpitations, and facial flushing.
- Methyldopa (methyldopa): an alpha receptor that excites the vasomotor center, inhibits peripheral sympathetic nerves and lowers blood pressure, and has a better effect during pregnancy. Usage: 250 mg orally, three times a day. The side effects are lethargy, constipation, dry mouth, and bradycardia.
- Sodium nitroprusside: a powerful, rapid-acting vasodilator that dilates peripheral blood vessels to lower blood pressure. Because the drug can quickly enter the fetus through the placenta and maintain a high concentration, its metabolite (cyanide) is toxic to the fetus and should not be used during pregnancy. If the blood pressure during childbirth or postpartum is too high, use other antihypertensive drugs if it is not effective. The usage was 50 mg and 1000 mL of 5% glucose injection, and a slow intravenous infusion. Do not take more than 72 h. Blood pressure and heart rate should be closely monitored during medication.
- Renin-angiotensin drugs: can cause fetal growth restriction, fetal malformation, neonatal respiratory distress syndrome, neonatal early-onset hypertension, should be banned during pregnancy.

(e) Expansion: generally does not advocate the application of expansion agents, only for severe hypoproteinemia, anemia, optional human serum albumin, plasma, whole blood, and so on.

(f) Diuretic drugs: generally do not advocate the application, only for systemic edema, acute heart failure, pulmonary edema, excessive blood volume, and associated with pulmonary edema. Common diuretics are furosemide, mannitol, and the like.

(g) Termination of pregnancy at the right time: termination of pregnancy is an effective measure to treat hypertensive disorders during pregnancy. In the following cases, it is not conducive to conservative treatment, need to terminate pregnancy: (1) severe hypertension that cannot be controlled by three antihypertensive drugs; (2) progressive thrombocytopenia; (3) liver and kidney dysfunction is further aggravated; (4) pulmonary edema; (5) neurological symptoms or signs, such as intractable headache, blindness, or convulsions; (6) fetal condition deterioration, fetal heart rate monitoring showed repeated late deceleration, and severe variability deceleration; b-ultrasound assessment of fetal weight less than the fifth percentile or 1–2 weeks without growth, end diastolic umbilical cord. The blood flow is reversed. In strict selection of cases and close monitoring, preeclampsia can continue to increase fetal maturity without increasing maternal complications. At present, with the improvement of clinical medical monitoring methods, the establishment of

neonatal intensive care centers and the continuous improvement of the treatment of extremely low birth weight and ultralow weight infants, many clinical studies have shown that cases with stable disease are strictly selected. Close monitoring of the condition of the child is feasible for the conservative treatment of early onset severe preeclampsia. During conservative treatment, if the condition is stable and no maternal complications occur, most scholars expect to continue to maintain pregnancy to 34 weeks of gestation. If the condition of the pregnant woman deteriorates or obstetric complications, the pregnancy should be terminated in time.

End of pregnancy is a cure for severe preeclampsia. In the late stage of severe preeclampsia, the fetus is basically mature or close to maturity and it is usually not difficult for clinicians to make a decision to terminate the pregnancy. However, in the face of early onset of severe preeclampsia, the situation is not. Because of the high mortality rates of very low-weight and ultralow-weight children in early-onset severe preeclampsia, cesarean section is not the best option in such cases, and in some cases, cesarean section will increase maternal danger. When the fetus is in distress, the indication for cesarean section is quite clear. If there is no indication of obstetrics, the overall condition of the pregnant woman should be evaluated. The maturity of the fetus is not the only factor that affects decision-making. The medical conditions and the level of treatment of critically ill and premature infants are also factors that cannot be ignored.

- Indications for termination of pregnancy: (1) patients with preeclampsia who have not improved significantly after 24–48 h of active treatment; (2) patients with preeclampsia have more than 34 weeks of gestational age; (3) patients with preeclampsia have gestational age less than 34 weeks, decreased placenta function, the fetus is mature; (4) preeclampsia patients, gestational age less than 34 weeks, placental dysfunction, the fetus is not mature, dexamethasone can be used to terminate the pregnancy after maternal lung maturity; 5 h after eclampsia control termination of pregnancy can be considered.
- Ways of terminating pregnancy: (1) induction of labor: suitable for patients with mature cervical conditions after disease control. Artificial rupture of the membrane, amniotic fluid clear, can be given intravenous injection of oxytocin. The first stage of labor should closely observe the progress of the labor process, keep the maternal quiet and fully rest. The second stage of labor should be shortened by postoperative perineal-lateral incision, fetal head suction, or low-position forceps. The third stage of labor should prevent postpartum hemorrhage. During the labor process, the safety status of mother and child and blood pressure monitoring should be strengthened. Once symptoms such as headache, vertigo, nausea, vomiting, etc. occur, the condition is aggravated and the childbirth is terminated immediately after cesarean section. (2) Cesarean section: suitable for those with obstetric indications, cervical conditions are imma-

ture, cannot be delivered vaginally in a short period of time, induction of labor failure, placental function is significantly reduced, or there are signs of fetal distress.

- Indications for prolonged pregnancy: (1) gestational age less than 32 weeks after treatment symptoms improved, no organ dysfunction or fetal deterioration, may consider extending the gestational age. (2) gestational age 32–34 weeks, 24-h urine protein quantitation <5 g; mild fetal growth restriction, fetal monitoring index is good; amniotic fluid is too little, color Doppler ultrasound measurement shows no diastolic umbilical artery blood reflux; blood pressure decreased after severe preeclampsia treatment; asymptomatic, only laboratory tests suggest that the fetal hypoxia is improved after treatment.

3. Treatment of eclampsia: eclampsia is the most serious stage of hypertensive disorder in pregnancy, and is the most important cause of maternal and child death caused by hypertensive disorder complicating pregnancy. It should be actively treated. Immediately the left lateral position reduces aspiration, opens the respiratory tract, and establishes a venous access. Another postpartum eclampsia occurs 24 h after delivery until 10 days, so postpartum prevention should not relax the prevention of eclampsia.
   (a) Principles of treatment of eclampsia: control convulsions, correct hypoxia and acidosis, control blood pressure, and terminate pregnancy after convulsion control.
      - Control twitching: 20 mL of 125% magnesium sulfate is added to 2 mL of 25% glucose solution for intravenous infusion (>5 min), followed by intravenous infusion of 2–3 g/h, maintaining blood concentration, and applying effective sedative drugs to control twitching; 220% mannitol 250 mL rapid intravenous infusion to reduce intracranial pressure.
      - Give antihypertensive drugs when blood pressure is too high.
      - Correct hypoxia and acidosis: mask and air bag oxygen, according to carbon dioxide binding capacity and urea nitrogen value, give appropriate amount of 4% sodium bicarbonate to correct acidosis.
      - Termination of pregnancy: termination of pregnancy can be considered 2 h after convulsion control. For patients with early onset preeclampsia, the gestational age can be extended appropriately, but the pregnant women and the fetus must be closely monitored.
   (b) Nursing: keep the environment quiet, avoid sound and light stimulation; absorb oxygen, prevent tongue bite, suffocation, falling ground injury; closely observe body temperature, pulse, respiration, blood pressure, consciousness, urine volume (should retain catheter monitoring) and wait.
   (c) Close observation of changes in the condition: early detection of heart failure, cerebral hemorrhage, pulmonary edema, HELLP syndrome, renal failure, DIC and other complications, and actively deal with.

17.3.2.9 Postnatal Treatment Recommendations

According to the Canadian Guidelines for the Diagnosis, Assessment and Treatment of Hypertensive Disorders in Pregnancy during the Canadian Society of Obstetrics and Gynecology (SOGC) (all recommended assessments are based on the Canadian Preventive Health Task Force's criteria), summarizing [63]:

1. Treatment for 6 weeks after delivery
   (a) Blood pressure fluctuations must be monitored during peak blood pressure 3–6 days postpartum.
   (b) Patients with non-severe postpartum hypertension should also be treated with antihypertensive therapy, especially those with complications.
   (c) Severe postpartum hypertension should be treated with antihypertensive, maintaining systolic blood pressure <160 mmHg, diastolic blood pressure <110 mmHg.
   (d) The following antihypertensive drugs can be used during lactation: nifedipine, labetalol, methyldopa, captopril, and enalapril.
   (e) Preeclampsia women should prevent thrombosis after childbirth, especially in prenatal bed rest for more than 4 days or after cesarean section.
2. Treatment after 6 weeks postpartum
   (a) Women with a history of severe preeclampsia (especially those who discontinue pregnancy before 34 weeks of gestation) should be screened for chronic hypertension, underlying kidney disease, and a tendency to thrombosis.
   (b) The sick woman should be informed that the preeclampsia will occur again after a second pregnancy interval of <2 years or ≥10 years.
   (c) It is suggested that obese women should actively maintain appropriate body mass index in order to reduce the risk of re pregnancy and long-term health.
   (d) All women with gestational hypertension should maintain a healthy diet and lifestyle.

17.3.2.10 Complications [64]

Hypertensive disorders in pregnancy, especially preeclampsia and eclampsia, combined with multiple complications, are important factors leading to the death of mothers and perinatal children and must be actively addressed. Common complications include HELLP syndrome, cerebrovascular accident, placental abruption, preeclampsia–eclampsia complicated with heart failure and postpartum circulatory failure; other complications include DIC, acute renal failure, gestational nephrotic syndrome, fetal palace internal developmental delay, intrauterine fetal death, pregnancy-induced hypertension, and other visual impairments are rare in clinical practice.

1. HELLP syndrome

   HELLP syndrome, also known as hemolysis(H), elevated liver enzymes(EL), low platelet(LP) syndrome; has an incidence of 4% - 12% in the population with severe PIH, of which 2.7% in China. In addition to the symptoms of PIH, its clinical manifestations include pain in the right upper abdomen (liver area),

nausea, vomiting and other gastrointestinal symptoms. In addition to the symptoms of pregnancy-induced hypertension, the clinical manifestations of the right upper abdomen (liver area) pain, nausea, vomiting, and other gastrointestinal symptoms are its characteristics.

Usually used in the laboratory test diagnostic criteria proposed by Sibai in 1990: (1) hemolysis: peripheral blood smear microscopy, visible heterogeneous red blood cells; LDH ≥ 600 IU/L; serum total bilirubin rose more than 1.2 mg/dL (20.5 mmol/L) (2) liver enzyme elevation: alanine aminotransferase AST ≥ 70 IU/L; (3) thrombocytopenia: less than 100,000/mm^3.

The key to treatment is early diagnosis, early treatment, and timely termination of pregnancy. In addition to general sedation, antispasmodic, antihypertensive treatment, appropriate application of anticoagulant therapy and glucocorticoids can alleviate the symptoms of depression and reduce symptoms. Most patients with HELLP syndrome recover within 96 h of termination of pregnancy. Hormone treatment of HELLP syndrome: dexamethasone 10 mg q12h × 2 times, followed by 5 mg q12h × 2 times or 10 mg q12 h until termination of pregnancy or BPC ≥ 100,000/mm^3.

2. Cerebrovascular accident

It is the first cause of eclampsia and preeclampsia death. Through the observation of cerebral vascular hemodynamics and blood perfusion by Doppler of the brain and eyelids, the disease changed to the loss of autonomic regulation function, causing cerebrovascular disease, including cerebral hemorrhage, cerebral infarction, cerebral edema, and cerebral palsy. Cerebral hemorrhage and cerebral infarction are acute complications of preeclampsia–eclampsia. The clinical features are different, and the treatment options are different. The identification points are shown in Table 17.2. The same points of treatment for both include (1) control of blood pressure, (2) control of convulsions, and (3) termination of pregnancy as soon as possible. Different points for the treatment of cerebral hemorrhage still need anti-hemorrhage, reduce intracranial pressure, eliminate brain edema, disable respiratory inhibitors, such as hematoma more than 30 mL

Table 17.2 Clinical features of cerebrovascular accidents

	Hemorrhage	Cerebral infarction
Proportion	Many	Less
Acute onset	Sharp	Slow
Clinical manifestation	Sudden headache, jet vomiting Convulsions or persistent coma, limb paralysis	Drowsiness, mild headache, dizziness Limitations or major episodes, no dilated pupils, hemiplegia
Blood pressure	Often greater than 200/100 mmHg	Around 140–150/100 mmHg
Urinary protein	A lot more common, often ≥+++	Less to medium, +–++
Edema	Obviously, more ++–+++	++
CT or MRI	High-density lesions in the brain, vascular malformations and hemorrhage	Multiple low density area

should be craniotomy; and cerebral infarction treatment still needs anticoagulation, antispasmodic, dredge brain microcirculation, generally no treatment with dehydrating agents when the intracranial pressure is not high.

3. Placental abruption

   About two-third of the placental abruption is caused by PIH. Placental abruption is the most common complication of PIH, and should be terminated as soon as possible.

4. Preeclampsia: eclampsia complicated by heart failure

   Preeclampsia–eclampsia complicated with heart failure is a unique heart disease in the obstetric field, accounting for 4.0–5.7% of pregnancy and heart disease. Low-level high-resistance heart failure, not only increased peripheral vascular resistance, but also decreased left ventricular contractility. General respiratory infections, inappropriate expansion or excessive infusion and severe anemia are the most common causes, and pulmonary edema is more likely to occur when there is significant hypoalbuminemia. Emphasis on early diagnosis, timely and correct reduction of the heart's preload (diuretic, dilated veins) and afterload (expanded arteries), improve cardiopulmonary function is the key, not just for cardiac therapy. If the condition can be controlled within 4–8 h, it is advisable to terminate the pregnancy as soon as possible.

5. Postpartum blood circulation failure

   Postpartum circulatory dysfunction refers to a state of shock that occurs suddenly within 24 h after delivery of the placenta, most of which occurs within 30 min, but there are no common causes such as bleeding, trauma, infection, embolism, etc., which belongs to vasomotor shock. If not discovered and dealt with in time, the consequences are serious. Preeclampsia–eclampsia is more likely to be known to the general maternal than to the normal maternal blood circulation failure. Treatment with hypovolemic shock should be as early as possible to supplement blood volume and use vasoactive drugs.

17.3.2.11 Pregnant Hypertension Prediction

There is currently no effective, reliable and economical method for predicting hypertensive disorders of pregnancy. The following methods have predictive value and should be performed in the second trimester. Those who are predicted to be positive should be followed closely.

1. Mean arterial pressure (MAP) measurement: This method is simple and easy. The calculation formula is MAP = (systolic blood pressure + 2 × diastolic blood pressure) ÷ 3. When MAP ≥ 85 mmHg, it indicates the tendency of preeclampsia; when MAP ≥ 90 mmHg, the incidence of eclampsia increases; when MAP ≥ 140 mmHg, cerebrovascular accident is prone to occur, leading to coma or death of pregnant women.
2. Roll over test (ROT): In pregnant women with a tendency to develop hypertensive disorder complicating pregnancy, the sensitivity of angiotensin II is increased. When the supine uterus is pressed, the uterus compresses the abdominal aorta and the blood pressure rises. The measurement method is as

follows: the blood pressure is measured in the left lateral position of the pregnant woman until the blood pressure is stable, and the blood pressure is measured after being placed on the supine position for 5 min. If the supine pressure in the supine position is ≥20 mmHg compared with the left lateral position, the tendency of preeclampsia occurs, and the positive predictive value is 33. %.

In addition, the study applied the principle of turning test, and the angiotensin content was measured when lying on the side and turning to the supine position, and it was positive when the supine position was raised.

3. Determination of uric acid: Serum uric acid value >5.9 mg/L at 24 weeks of pregnancy, is the predicted value of 33% of preeclampsia pregnant women.
4. Hemorheology experiments: Low blood volume and high blood viscosity are the basis for the occurrence of hypertensive disorders in pregnancy. When the hematocrit is ≥0.35, the whole blood viscosity is >3.6, and the plasma viscosity is >1.6, there is a tendency for preeclampsia to occur.
5. Determination of urinary calcium: Urinary calcium excretion was significantly reduced in patients with hypertensive disorder complicating pregnancy. The decrease in urinary Ca/Cr ratio is earlier than the occurrence of hypertensive disorder in pregnancy. If ≤0.04, the value of preeclampsia is predicted.
6. Dynamic observation of prostacyclin/thromboxin (PGI2/TXA2): Dynamic observation of the ratio of 6-keto-PGFIa/TXB2, a metabolite of PGI2/TXA2. If the ratio decreases, it indicates that PIH is about to occur. PGI2 is produced by mother and child vascular endothelial cells, which can reduce the sensitivity of blood vessels to angiotensin II and cause blood vessels to dilate.

17.3.2.12 Prevention

Doing a good job in preventive work for pregnant women plays an important role in reducing the occurrence and development of hypertensive disorders during pregnancy.

1. Establish and improve a three-level maternal and child health care network to carry out perinatal and perinatal health care.
2. Strengthen health education so that pregnant women can master the basic knowledge of pregnancy and consciously conduct prenatal examinations.
3. Instruct pregnant women to eat and rest properly. Pregnant women should eat foods rich in protein, vitamins, iron, calcium, magnesium, selenium, zinc, and other trace elements and fresh fruits and vegetables to reduce the intake of animal fats and excess salt, but does not limit salt and liquid intake. Keep enough rest and happy mood, adhere to the left lateral position, increase the blood supply of placental villi.
4. Calcium supplementation to prevent hypertensive disorders in pregnancy. For those with high risk factors of hypertensive disorder complicating pregnancy, calcium supplementation can prevent the occurrence and development of hypertensive disorder during pregnancy. The International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends that people with insufficient

calcium intake (<600 mg/day) should receive 1.2–2.5 g/day of calcium to prevent preeclampsia.
5. Aspirin treatment: (International Society for the Study of Hypertension in Pregnancy, ISSHP) recommended], high-risk preeclampsia population (preeclampsia history, chronic hypertension, prepregnancy diabetes, maternal BMI > 30, antiphospholipid syndrome and pregnant women with assisted reproductive technology) were given low-dose aspirin (75–162 mg/day) 16 weeks before prophylaxis.
6. Chinese medicine treatment: Considering the small arteriolar spasm, blood concentration, blood volume reduction is the main pathophysiological change of PIH, so Chinese scholars on the basis of conventional treatment, assist Chinese medicine (such as puerarin, astragalus, and compound salvia miltiorrhiza) to treat PIH, found that can effectively improve PIH pregnant women with blood rheology and microcirculation abnormalities, to achieve the desired therapeutic effect, but not recognized worldwide.

The incidence of hypertensive disorder complicating pregnancy has increased in recent years. Although a large number of studies have been made on its pathogenesis, no clear cause has been confirmed so far, and thus its incidence cannot be completely prevented. Fortunately, the clinical symptoms of pregnancy-induced hypertension syndrome are mild to severe, with staged development. Taking effective interventions according to possible pathogenic factors is an effective method to prevent the occurrence of pregnancy-induced hypertension syndrome.

17.3.2.13 Prognosis

The prognosis of patients with hypertensive disorder complicating pregnancy, in terms of mortality, ranks second in the cause of maternal mortality in China, with cerebrovascular disease and heart failure. There is no consensus on whether high blood pressure in pregnancy causes persistent blood pressure loss or persistent renal damage. The vast majority of patients return to normal blood pressure shortly after delivery, such as chronic hypertension after more than 12 weeks. Some people think that hypertensive disorders in pregnancy can cause irreversible pathological processes in the body, which can lead to high blood pressure, proteinuria, and so on. Others believe that patients with hypertensive disorder complicating pregnancy have high blood pressure after delivery, which is related to the history of recessive hypertension or familial hypertension; the damage caused by preeclampsia and eclampsia is generally reversible. Data from the American Hypertension Research Working Group show that patients with preeclampsia have a tendency to have elevated blood pressure during re-pregnancy. These patients are prone to chronic hypertension, while some women have normal blood pressure during pregnancy and have hypertension. The chance is reduced. International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends that all HDP patients should undergo blood pressure, urine routine, and other laboratory tests 3 months after delivery, return to prepregnancy weight within 12 months after delivery, and adopt

a healthy lifestyle. Perform weight management. All HDP women should be followed up for life, once a year for a health checkup.

17.3.3 Pregnancy with Chronic Hypertension

About 30% of pregnant women with hypertension have high blood pressure before pregnancy, that is, pregnancy with chronic hypertension, which is one of the common diseases in obstetrics. With the increasing incidence and rejuvenation of hypertension, the incidence of pregnancy with chronic hypertension has also increased year by year. Some women with hypertension have good blood pressure control during pregnancy, but there is also elevated blood pressure during pregnancy or preeclampsia, which will adversely affect mothers and children, and even endanger mother and baby life. This chapter focuses on the treatment of chronic hypertension patients before, during, and after pregnancy.

17.3.3.1 Blood Pressure Level Classification and Definition of Hypertension

According to the progress of cardiovascular epidemiology and evidence-based medicine in China in recent years, the 2018 China's guidelines for the prevention and treatment of hypertension have revised the "Guidelines for the Prevention and Treatment of Hypertension in China" with reference to the latest domestic and foreign research reports and guidelines. Regarding the definition of hypertension, it remains the same: in the absence of antihypertensive drugs, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg [41].

17.3.3.2 Pregnancy with Definition of Chronic Hypertension

Pregnancy with chronic hypertension refers to high blood pressure before pregnancy, or blood pressure before pregnancy is unknown, and hypertension occurs before 20 weeks of gestation. In most pregnant women with chronic hypertension, blood pressure drops during the second trimester but this decline is temporary, and blood pressure rises in the third trimester of pregnancy. If the mother has a clear history of hypertension before pregnancy, the diagnosis is not difficult, such as the third trimester of pregnancy, prenatal blood pressure is unknown, need to be identified with preeclampsia and eclampsia, sometimes identification is quite difficult, and even need to be based on the recovery of blood pressure after childbirth to judge.

The causes of hypertension in patients with chronic hypertension with pregnancy are nothing more than two conditions, namely essential hypertension and secondary hypertension. Most of them are primary hypertension. Generally, pregnant women are older. They usually have a family history of hypertension, overweight, or obesity. Most of them have a history of hypertension before pregnancy. Some patients may take antihypertensive drugs for a long time. Secondary hypertension is not common. The causes of secondary hypertension are mainly renal hypertension and thyroid dysfunction hypertension. The rare cases are pheochromocytoma, primary

aldosteronism, and salt corticosteroids. Body mutations cause high blood pressure such as pregnancy. Pregnancy with chronic secondary disease may have a direct impact on pregnancy outcomes. It is recommended that prepregnancy hypertensive women should be as clear as possible about the cause of secondary hypertension. The International Society for the Study of Hypertension in Pregnancy (ISSHP) does not recommend routine detection of secondary causes of all hypertensive patients in the absence of clinical clues.

17.3.3.3 Effect of Pregnancy on Hypertension

Due to hemodynamic changes during pregnancy, blood volume increased to a peak at 32–34 weeks of gestation, with an average increase of about 35%. Hemodynamic changes during childbirth were greater, and each uterus contracted, cardiac output increased by 20%. The arterial pressure is increased by 10–120 mmHg. In addition to the uterine contraction, the abdominal muscles and bones are involved in the second stage of labor, so that the surrounding resistance is increased, the maternal holding up, the pulmonary circulation pressure and abdominal pressure are increased, the visceral blood is rushing to the heart, and the heart load is increased. Severe hypertension and hypertensive heart disease are prone to heart failure.

The risk of cerebral hemorrhage in hypertensive patients with pregnancy is increased. Chronic hypertension patients are prone to preeclampsia and eclampsia during pregnancy, and blood pressure is increased, which aggravates the condition of patients with hypertension. Under normal conditions of blood pressure changes, the cerebral circulation can automatically regulate cerebral vascular resistance at the level of small arteries to maintain a constant cerebral blood flow. When the blood pressure rises, the cerebral blood vessels contract; when the blood pressure drops, the cerebral blood vessels dilate to ensure cerebral blood flow. When the mean arterial pressure is >130 mmHg, this automatic adjustment is out of control and can lead to cerebral hemorrhage. Therefore, for hypertensive patients with preeclampsia and eclampsia, the risk of stroke is significantly increased.

17.3.3.4 Effect of Chronic Hypertension on Pregnancy

1. The effect on the mother: In general, pregnant women who take only one drug and have good blood pressure control are relatively safe during pregnancy, but placental abruption, preeclampsia and eclampsia are still more than normal pregnant women. Placental abruption is two to three times higher than normal pregnant women. The proportion of preeclampsia and eclampsia was significantly different, ranging from 4 to 40%. The longer the course of hypertension (>4 years), the higher the blood pressure in early pregnancy or the preeclampsia and eclampsia in the previous pregnancy, the higher the probability of preeclampsia and eclampsia. A large-scale epidemiological survey showed a maternal mortality rate of 230/100,000 live births in combination with hypertension, and a maternal mortality rate of 10/10 million live births without hypertension. Current statistics suggest that preeclampsia and eclampsia are one of the leading causes of maternal mortality in China. Essential hypertension combined with

preeclampsia and eclampsia increases maternal risk. The main causes of maternal death are cerebrovascular accidents and heart failure.

2. Effects on the fetus and newborn: Hypertensive patients have significantly increased preterm birth, stillbirth, fetal developmental restriction, and perinatal mortality during pregnancy. It has been reported that the incidence of infants whose gestational age is less than the normal gestational age is increased in the pregnant women with essential hypertension, which is 10.9%, compared with 4.1% in the normal control group. Those with severe hypertension before 20 weeks of gestation had the highest incidence of producing infants of less than normal gestational age, premature delivery and preeclampsia.

17.3.3.5 Diagnosis and Differential Diagnosis

Pregnancy with chronic hypertension as defined by its definition, high blood pressure before pregnancy, or blood pressure before pregnancy can be diagnosed before 20 weeks of pregnancy. For pregnant women with chronic hypertension, attention should be paid to the diagnosis of hypertension, except for secondary hypertension. If the medical history is not clear, follow-up to 12 weeks after delivery should be made to confirm the diagnosis of chronic hypertension. Chronic hypertension is common in pregnant women with secondary hypertension as renal hypertension. The main identification points are shown in Table 17.3.

In addition, pregnant women with chronic hypertension need to pay attention to the presence or absence of salt corticosteroid receptor mutations leading to increased pregnancy-induced hypertension. The disease is autosomal dominant, and it is currently believed that the gene mutation responsible for controlling the body's regulation of salt leads to a young, high-risk condition that is significantly exacerbated during pregnancy. Women with a mineralocorticoid receptor mutated gene overstimulate the receptor due to changes in hormones during pregnancy, causing excessive salt reabsorption and a significant increase in blood pressure. The final identification is based on blood pressure changes and genetic diagnosis after childbirth.

17.3.3.6 Pregnancy Combined with Chronic Hypertension Treatment During Pregnancy

Pregnant women should be managed jointly by obstetricians and cardiologists.

1. General treatment
   (a) Rest and sleep: Hypertensive patients should pay more attention to rest and maintain adequate sleep time during pregnancy. Prevent mental stress and emotional excitement.
   (b) Low-salt, low-fat, high-vitamin, high-calcium diet: High sodium can promote the body's water absorption, which can increase the sympathetic nerve activity, affect the body's small arterial self-regulation, and increase peripheral resistance and blood pressure. Appropriate restriction of salt in pregnant women with chronic hypertension not only has antihypertensive effect, but also reduces the amount of antihypertensive drugs. It is recommended to

Table 17.3 Identification of PIH and pregnancy with essential hypertension and chronic nephritis

Project	PIH	Pregnancy with essential hypertension	Pregnancy with chronic nephritis
Past history	No previous history of hypertension	History of hypertension during nonpregnancy	History of acute nephritis during nonpregnancy
Current history	Usually after 20 weeks of gestation, mostly younger ones	Prepregnancy or early pregnancy, mostly age Larger primipara	Prepregnancy or early pregnancy
Hypertension	More than <200/120 mmHg, often accompanied by symptoms	More>200/120 mmHg, no symptoms	There may or may not be high blood pressure in the early stage of the disease.
Edema	Often varying degrees of edema	Often edema	Obliteration is obvious
Fundus	Arteriolar spasm, retinal edema	Arteriosclerosis and arteriovenous indentation Membrane has cotton-like exudate or bleeding	Arteriosclerosis, arteriovenous indentation, cotton-like exudate or bleeding in the retina
Urinary protein	Uncertainty, generally no tube type	Generally no protein or tube type	Sustained protein in the urine, a large amount, red and white cells may be optional, often have various types of tube
Blood chemistry	Increased uric acid	No change	Low plasma protein, increased urea nitrogen, elevated cholesterol
Postpartum follow-up	Gradually returning to normal	Reduced to prepregnancy	Reduced to prepregnancy

control 1.5–3.0 g/day. At the same time, it is advisable to eat low animal fats and avoid eating cholesterol-rich foods. Obese people should control the amount of food and total calories, and properly reduce weight.

(c) Application of sedatives: Diazepam (diazepam) or phenobarbital (luminal) can be used to relieve mental stress and insomnia, but avoid long-term use, use with caution 3 months before pregnancy.

(d) Strengthen the monitoring of mother and child: Pay attention to blood pressure changes, it is best to monitor blood pressure at home. Pay attention to changes in body weight and measure body weight once a week. The weight gain per week is 0.3–0.5 kg, and the weight gain during the whole pregnancy does not exceed 12–15 kg. Especially obese, should not exceed 12 kg. Regular blood tests, urine routine and heart, liver and kidney function tests, self-fetal fetal movement, B-ultrasound fetal conditions, fetal heart rate monitoring once or twice a week after 32 weeks of pregnancy.

2. Antihypertensive drug treatment principles

The guidelines for hypertension at home and abroad have clear regulations for the use of drugs for women with hypertension during pregnancy. According to

the latest revision of the Chinese Guidelines for the Prevention and Treatment of Hypertension in 2018 [41], the main purpose of antihypertensive therapy is to ensure the safety of maternal and child care and pregnancy, reduce complications and reduce mortality. Recommended blood pressure ≥150/100 mmHg. Start medication, with a treatment target of 150/100 mmHg or less. If there is no proteinuria and other target organ damage, consider ≥160/110 mmHg to start drug therapy. Avoid lowering blood pressure below 130/80 mmHg to avoid affecting placental perfusion.

If the blood pressure of pregnant women is mildly elevated, but the preeclampsia is present, the incidence of eclampsia is only 0.5%. It is not recommended to use antihypertensive drugs and magnesium sulfate regularly, but it is necessary to closely observe blood pressure and urine protein changes and fetal status; for women with severe preeclampsia, it is recommended to use magnesium sulfate intravenously, closely observe blood pressure, key reflexes and adverse reactions, and determine the timing of termination of pregnancy.

Because there is still a small amount of research data on mild chronic hypertension during pregnancy, the experience that can be learned is limited, and there is still controversy about continuous antihypertensive therapy during pregnancy. In theory, antihypertensive drugs can lower the maternal blood pressure, and may reduce the placental perfusion, which may harm the fetus. Most studies have shown that most pregnant women without antihypertensive therapy have a good pregnancy outcome if they do not have preeclampsia. Once the preeclampsia–eclampsia is combined, the prognosis is poor. There is no clear positive evidence for antihypertensive therapy in reducing the incidence of eclampsia and improving the prognosis of perinatal children.

Generally, it is not necessary to stop the treatment before starting the antihypertensive treatment, especially when the diastolic blood pressure exceeds 100–105 mmHg. Pay attention to the following problems when taking antihypertensive drugs:

(a) The speed and degree of blood pressure reduction: In addition to high blood pressure emergency, the blood pressure is gradually reduced as well. Because the circulatory system and baroreceptors of hypertensive patients have adapted to the level of hypertension for many years, the sudden drop in blood pressure is unfavorable for both pregnant women and uterus.

(b) Drug selection: The ideal drug can reverse the characteristic hemodynamic changes of hypertension (i.e., increased total peripheral resistance and decreased cardiac output) without affecting the baroreceptor's reflex mechanism, and no effect on the mother and fetus. Significant adverse reactions. The pros and cons of the drug application are as follows:
   - Adrenergic blockers: Laberol (Liu'an Benzidine) and methyldopa, atenolol, etc. are commonly used abroad. It has been reported that atenolol is associated with low birth weight and has a tendency to cause premature birth, so most scholars believe that prepregnancy should be discontinued. It is generally believed that methyldopa is the drug of choice for the treatment of mild to moderate hypertension during pregnancy.

- Calcium antagonists: commonly used are dihydropyridine calcium antagonists, such as nifedipine, nimodipine. Meta-analysis showed that nifedipine tablets are effective drugs for the treatment of severe hypertension during pregnancy, but there are few clinical data on their sustained release drugs.
- Diuretics: usually not used as first-line treatment drugs during pregnancy, especially after 20 weeks of pregnancy. Hypertensive patients often have preeclampsia during pregnancy. At this time, the blood volume of pregnant women is reduced, and diuretics may increase blood viscosity. Therefore, diuretics are only used for systemic edema, cerebral edema, hypervolemia or left heart failure.
- Angiotensin-converting enzyme inhibitor: teratogenic effects, disabled in pregnant women.
- Vasodilators: commonly used sodium nitroprusside, hydralazine and the like. Sodium nitroprusside dilates peripheral blood vessels, reduces peripheral vascular resistance, and produces a rapid antihypertensive effect. The blood pressure is maintained at a desired level by adjusting the drip rate. Suitable for severe acute hypertension. Sodium nitroprusside can also reduce the load of the heart before and after, and is also suitable for the treatment of hypertension combined with acute heart failure. Because the drug contains cyanide and cyanate, it can poison the fetus through the placenta, so it is better to use it for a short time, generally no more than 24–48 h. Prevent blood pressure from diminishing when applied. There are tablets and injections of hydralazine, and parenteral drugs are mainly used to treat acute severe hypertension and reduce blood pressure immediately after delivery. Because oral antihypertensive effect is alleviated, there are many adverse reactions, and it is not used as a first-line antihypertensive drug.
- Magnesium sulphate: in the case of essential hypertension with preeclampsia, magnesium sulfate should be used to relieve arteriolar spasm on the basis of general treatment to prevent eclampsia. The specific usage is the same as before.

3. Treatment during labour
   (a) Time to terminate pregnancy: According to the condition, the principle is to try to be safe for mothers and children. Mild essential hypertension, good blood pressure during pregnancy, no other maternal and child complications, and pregnancy can reach full term; combined with severe preeclampsia or eclampsia without improvement or placental abruption, regardless of gestational age, termination of pregnancy immediately. Even if the mother is not in danger, there is obvious fetal growth restriction, and the pregnancy may occur in the uterus, and the pregnancy may be terminated in time after birth. Pregnancy should also be terminated promptly after 37 weeks of pregnancy in patients with secondary hypertension or mild preeclampsia.

(b) Ways to terminate pregnancy
- Patients with mild to moderate essential hypertension, no other comorbidities, full-term pregnancy, mature cervix can be delivered through the vagina; those who need to terminate the pregnancy, can artificially rupture the membrane, intravenous infusion of oxytocin, vaginal delivery; during childbirth, should be strengthened, appropriate use of analgesics such as meperidine (degree of cold) or epidural anesthesia. If the blood pressure is significantly elevated, or there is fetal distress, the indication for cesarean section should be relaxed.
- Patients with severe essential hypertension, who have obvious arteriosclerosis or renal dysfunction, should not be vaginally delivered, and it is safer to choose cesarean section. It is safer to choose epidural anesthesia for anesthesia.

(c) Strengthen postpartum monitoring: Pregnancy with chronic hypertension is prone to brain edema, heart failure, pulmonary edema, and renal failure 24–36 h after delivery, and should be strengthened. Pregnant women with chronic hypertension or those with severe preeclampsia and eclampsia have high postpartum hemorrhage rate. Prevention should be taken. Once bleeding occurs after production, blood transfusion should be considered as soon as possible.

In short, use antihypertensive drugs as appropriate in pregnancy-induced hypertension. Commonly used intravenous antihypertensive drugs are methyldopa, labetalol, and magnesium sulfate; oral drugs include beta blockers or calcium channel blockers; magnesium sulfate is the drug of choice for the treatment of severe preeclampsia. ACEI or ARB is disabled during pregnancy.

17.4 Polycystic Ovary Syndrome

Tian Shi

Polycystic ovary syndrome (PCOS) is a heterogeneous clinical syndrome mainly caused by endocrine disorders and multiple metabolic abnormalities, which is characterized by excessive androgen and persistent anovulation. The clinical manifestations of PCOS include irregular menstruation, high androgen, obesity, insulin resistance (IR), and increased levels of serum luteinizing hormone (LH), which are often associated with type2 diabetes mellitus, hypertension, and other cardiovascular diseases. The damage of amenorrhea and infertility to women's physical and mental health and the high risk of endometrial cancer and breast cancer caused by continuous estrogen stimulation have attracted more and more attention.

17.4.1 Epidemiology of PCOS

Due to the different diagnostic criteria, races, regions, and subjects, the polycystic ovary syndrome of estimated prevalence rate varies greatly from 2.2 to 26% [65–72]. PCOS is often found by menstrual disorders in women or adolescent girls. However, when these women use Acyeterion, their clinical symptoms are often concealed and missed diagnosis, when they asked for withdrawal, and showed menstrual disorders and anovulation, thus defining the diagnosis of PCOS.

17.4.2 Etiology of PCOS

The etiology of polycystic ovary syndrome is still unclear. Currently considered that the etiology of PCOS is related to genetic and environmental factors [73].

1. Genetics of PCOS

   Many reports indicated that PCOS patients have a clear family aggregation, suggesting that the disease has a genetic susceptibility basis. Although the existing reference tends to show that PCOS has some characteristics of autosomal dominant inheritance, and influenced by environmental factors, there is still no perfect explanation for the genetic model of PCOS. Early studies on PCOS genetics suggested that the genetic pattern of PCOS was autosomal dominant inheritance. Family investigation suggested that the genetic pattern of PCOS may be X-linked dominant inheritance. However, taking familial polycystic ovary (PCO) as the research object, and using ultrasound diagnosis of PCO as the proband, the family was investigated and the segregation ratio was calculated. The results showed that PCO was different from autosomal dominant inheritance and X-linked dominant inheritance. Others suggested that the genetic model of PCOS was incompletely dominant single autosomal dominant inheritance.
2. Environmental factors of PCOS

   Intrauterine hyperandrogenic environment, endocrine disruptors, persistent organic pollutants, antiepileptic drugs, overnutrition, and poor lifestyle may increase the risk of PCOS [74–76]. Environmental factors may not change the genetic code, but affect the expression of related genes through epigenetic modification, leading to disease.

17.4.3 Pathophysiological Mechanism of PCOS

Although scientific researchers have done a lot of work, the pathophysiological mechanism of PCOS is still unclear. Considered the pathophysiological mechanism is related to hyperandrogenism, abnormal uterus and ovary, insulin resistance, hyperinsulinemia, and so on.

The mechanism of PCOS-induced hypertension: Insulin resistance and hyperinsulinemia are important factors in the pathogenesis of PCOS. They are also important pathophysiological mechanisms leading to hypertension. The effects of PCOS on hypertension can be considered from the following aspects:

1. Promoting Na^+ reabsorption in the distal nephron: Insulin directly or indirectly increases the activity of renin-angiotensin-aldosterone system to promote the reabsorption of Na^+ and water by renal tubules, resulting in increased blood volume and cardiac output. At present, it is considered that the retention of water and sodium and the increase of peripheral circulation volume caused by the increase of insulin are one of the main causes of hypertension.
2. Stimulating the sympathetic nervous system produces more norepinephrine: Insulin stimulates the median sympathetic activity of the ventral hypothalamus, promotes the secretion of epinephrine and norepinephrine by the adrenal gland, enhances the sympathetic nervous activity, and increases the level of catecholamine in the blood. As a result, cardiac output and peripheral vascular resistance increase, and sodium and water retention in the kidney increases blood pressure. Increased activity of the central nervous system may induce or worsen the existing insulin resistance, forming a feedback loop, leading to coexistence of hypertension and insulin resistance. The dysfunction of autonomic nervous system aggravates the disorder of blood pressure regulation.
3. Stimulating the proliferation of small artery smooth muscle: Insulin is also a growth factor, which can enhance the activity of mitotic factors, promote the proliferation of vascular smooth muscle cells, make smooth muscle cells migrate from the middle layer of the blood vessel to the subintima, make the intima of the artery thicker, increase the stiffness of the wall and resistance.
4. Abnormality of intracellular and extracellular ions (Ca^{2+}, Na^+) transport: The increase of intracellular Ca^{2+} concentration is the central link of various ion changes involved in blood pressure regulation. Hyperinsulinemia can decrease the activity of Ca^{2+}-ATPase in cell membrane and increase the concentration of Ca^+. Especially when the concentration of Ca^{2+} in vascular smooth muscle cells increases, excitation-contraction coupling increases, vasoconstriction or spasm increases, peripheral vascular resistance increases, and the sensitivity of resistance vessels to pressure substances increases, and blood pressure increases. The activity of Na^+-K^+-ATPase on erythrocyte membrane in patients with hypertension was decreased, which was related to insulin resistance.
5. Promoting the secretion of endothelin: High concentration of insulin can promote the expression of vascular endothelin mRNA and increase the synthesis and release of endothelin. Hyperglycemia can induce the increase of plasma endothelin-1 in hypertensive patients. Insulin has a sensitizing effect on the vasoconstriction of endothelin-1. Its sensitizing degree is not affected by the integrity of vascular endothelium. Hyperinsulinemia participates in the occurrence and development of hypertension through the sensitizing effect of vasoactive substances.

6. Effects of endothelial cells and endothelial function: High concentration of insulin can inhibit endothelial cells from releasing endothelial-derived relaxing peptide, promote endothelial cells to produce plasminogen activator inhibitors, and increase peripheral resistance, leading to increased blood pressure. A variety of agonists can act on endothelial cells, leading to NO release and biological effects, which are weakened when endothelial cells are damaged.

   Hyperinsulinemia can increase the absorption of water and sodium in kidney, increase the activity of sympathetic nervous system, and decrease the elasticity of arteries, which leads to the increase of blood pressure.

17.4.4 Clinical Manifestations of PCOS

1. Abnormal menstruation and ovulation

   Poor menstruation, prolonged menstruation, irregular bleeding, and chronic amenorrhea are the significant characteristics of PCOS patients. Menstrual abnormalities were primary amenorrhea in only 5% of patients, while 51–77% of patients presented secondary amenorrhea, normal or delayed menarche age, followed by rare menstruation, oligomenorrhea, or amenorrhea. Abnormal ovulation is characterized by sparse ovulation (those who do not ovulate for more than 3 months per year) or anovulation.
2. Clinical manifestations of hyperandrogen
   (a) Hypertrichiasis: Upper lip, mandible, chest, and back (including areola), hypogastrium (including periumbilical cord and midline of umbilical cord), thigh medial can be seen thicker body hair, pubic hair for male distribution, and accompanied by acne, seborrhea, and alopecia.
   (b) Acne: Acne with hyperandrogenic manifestations is more common in post-adolescent acne. Skin lesions are acne, papules, pustules, and nodules, usually occurs in the lower-middle part of the face, often accompanied by obvious seborrhea and premenstrual exacerbation. It is resistant to routine treatment.
   (c) Alopecia: Androgenic alopecia often occurs. Hair begins to become thin and sparse on both sides of the forehead, gradually extends to the top of the head, but the frontal hairline does not move backward.
   (d) Masculine sign: Low voice, prominent laryngeal nodule, female secondary sexual characteristics gradually decline and disappear, such as smaller breasts, increased clitoris.
3. Metabolic Syndrome
   (a) Obesity: The prevalence of obesity in PCOS patients ranged from 14 to 75% [77–82], mainly abdominal obesity. Obesity is associated with insulin resistance, excessive androgens, and increased free testosterone ratio and so on.
   (b) Acanthosis nigricans: It mostly occurs in the neck, axilla, groin, and under the breast. The skin is characterized by villous keratosis and gray-brown pigmentation.
   (c) Impaired glucose regulation (IGR)/type 2 diabetes mellitus: IGR includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).

Postprandial hyperglycemia is the main manifestation of PCOS patients. The incidence of IGT and diabetes are higher in normal women with similar age, weight, and race.

(d) Abnormal lipid metabolism: About 70% of PCOS patients had abnormal lipid metabolism, which was mainly characterized by elevated triglyceride (TG), low density lipoprotein (LDL) and non-high density lipoprotein (nHDL); compared with age and body mass index (BMI) matched controls, nonobese PCOS patients also had characteristics of low HDL, high very low density lipoprotein (VLDL) and high LDL.

(e) Nonalcoholic fatty liver disease (NAFLD): PCOS patients are more likely to suffer from NAFLD than age-and weight-matched normal women, and the pathological score is higher [83]. The patients with hyperandrogenic PCOS are more likely to develop NAFLD [84] than those without hyperandrogenic PCOS.

4. Because women of childbearing age are the main group of these patients, diastolic blood pressure is the main cause of hypertension, and the prevalence of hypertension was 19.2% [85] in this group. In addition, combination of diabetes mellitus, hypertension, and other cardiovascular and cerebrovascular risk factors will further lead to more severe atherosclerosis, and aggravate the occurrence of hypertension.
5. Cardiovascular disease risk: With the increase of age, the risk of cardiovascular disease in PCOS patients increased significantly [73]. The long-term impact guidelines for polycystic ovary syndrome at the Royal College of Obstetricians and Gynecologists (RCOG) in 2014 suggest that all PCOS women should assess individual cardiovascular risk factors (obesity, lack of physical exercise, smoking, family history of type II diabetes, dyslipidemia, impaired glucose tolerance, type 2 diabetes) [86].

17.4.5 Auxiliary Examination of PCOS

1. Biochemical characteristics: Compared with women with normal menstrual cycle, PCOS patients often have elevated levels of serum androgen (testosterone or androstenedione). However, due to the inaccuracy and variability of the experimental methods for determining circulating androgen levels, the biochemical definition of hyperandrogenism still has limitations: (1) there are many forms of androgen in serum, which can not be comprehensively evaluated; (2) the level of androgen in normal population varies greatly and lacks normal reference value; (3) age, body mass index, and other factors should be taken into account when defining the normal level of androgen; (4) the data of adolescent girls and elderly women are scarce; (5) the inhibition of androgen by hormone therapy is more significant than other clinical features. Therefore, androgen can still be at normal level for a certain period of time after discontinuation of treatment, thus affecting the diagnosis.
2. Laboratory measurement of insulin resistance in PCOS: Fasting insulin, insulin resistance index of homeostasis model, Li Guangwei index and Composite and

ederholm index related to OGTT can be used to evaluate the I R of PCOS patients. Fasting insulin is only suitable for patients with compensatory insulin resistance. Internal medicine judges insulin resistance when the level of free insulin is higher than 15 mIU/L. The latter four are also applicable to the evaluation of insulin resistance in decompensated period, and the insulin resistance index of homeostasis model is the simplest index. The insulin resistance index of homeostasis model is the simplest index.

3. Imaging characteristics of polycystic ovary syndrome:

   Transvaginal color Doppler ultrasonography is the golden standard for morphological diagnosis of PCO. Before ultrasound examination, hormone drugs should be discontinued for at least 1 month. Ultrasound examination should be performed on the third to fifth day of menstrual cycle (regular menstruation) or under the condition of nondominant follicle. The ovarian capsule is abnormal in appearance. There are more than 10 cystic follicles with diameter less than 10 mm scattered around, and the ovarian volume is larger than 5.5 cm^3. Recommended intracavitary ultrasound, transrectal ultrasound is required for asexuals, and transvaginal ultrasound is recommended for sexually active persons.

17.4.6 Diagnosis

The current diagnostics for PCOS have established standardized diagnostics with the following diagnostic criteria:

1. 1990 National Institutes of Health (NHN): By evaluating the questionnaire survey on PCOS, American scholars attached importance to the role of endocrine change indicators in the diagnosis, thus forming the diagnostic criteria for PCOS in Maryland (with two criteria at the same time): (1) abnormal menstruation or anovulation; (2) clinical manifestations and (or) biochemical hyperandrogenia, and excluding hyperprolactinemia, thyroid disease, delayed congenital adrenal hyperplasia and Cushing's syndrome.
2. The Rotterdam criteria proposed by the European Society of Reproductive and Embryonic Medicine and the American Society of Reproductive Medicine in 2003 (2 in 3): (1) menstrual disorder with less ovulation or anovulation; (2) clinical or biochemical androgen hyperactivity, (3) ultrasound observation to the polycystic ovary (one or both ovaries have more than 12 follicles with a diameter of 2–9 mm), and (or) ovarian volume greater than 10 mL, and exclude other causes (congenital adrenal hyperplasia, androgen-secreting tumors, Cushing syndrome, hyperprolactinemia, etc.)
3. In 2006, the diagnostic criteria of the American Association of High Androgen Excess Society (AES): (1) menstrual disorders accompanied by oligovulation or anovulation; (2) clinical or biochemical androgen hypertrophy; (3) polycystic ovaries were observed by ultrasound. Among them, (1) item is necessary, (2) and (3) any one of the item.

The most commonly used diagnostic criteria are Rotterdam criteria proposed by the European Society of Reproductive and Embryonic Medicine and the American Society of Reproductive Medicine in 2003.

17.4.7 Differential Diagnosis

1. Hyperthecosis: clinical manifestations and endocrine examination are similar to PCOS but more serious. High blood testosterone level, blood dehydroepiandrosterone sulfate is normal, and LH/FSH ratio is normal. Ovarian biopsy showed that the ovarian cortex had a yellowing follicular membrane cell population, and there were no small follicles similar to PCOS in the subcortex.
2. Adrenocortical hyperplasia or neoplasm: When the serum dehydroepiandrosterone sulfate value exceeds two times the upper limit of normal range, it should be differentiated from adrenocortical hyperplasia or neoplasm. In patients with adrenocortical hyperplasia, serum 17alpha-hydroxyprogesterone was significantly increased, ACTH excitation test was hyperresponsiveness, and the inhibition rate of dexamethasone inhibition test was less than 0.70. Patients with adrenal cortical tumors did not respond to either of these tests.
3. Androgen-secreting ovarian tumors: Ovarian testicular blastoma and ovarian hilar cells can produce large amounts of androgen. Most of them are unilateral and solid tumors. Ultrasound, CT, or MRI can assist in localization.
4. Others: Prolactin level increased significantly, pituitary prolactin adenoma should be excluded.

17.4.8 Treatment of PCOS

1. Nondrug therapy
   (a) Psychotherapy: PCOS patients have experienced physiological changes such as irregular menstruation, obesity, and hairy since adolescence, which have a great impact on their self-image. Some patients spend more money but cannot get reasonable and effective treatment. They will suffer from serious mood disorders and lack of self-confidence. Medical workers should timely understand the psychological impact of PCOS on patients, provide necessary support according to patients' needs, and give patients meticulous psychological counseling, so as to gain patients' trust and make them actively cooperate with treatment.
   (b) Lifestyle intervention: low-calorie diet and exercise are advocated for obese PCOS patients. Adjustment of lifestyle should run through the whole treatment process. Quitting smoking and alcohol, overweight or obese patients should adjust their diet structure and avoid snacks. Three meals should be based on a low-calorie diet. Energy-consuming exercise should be strengthened. Improvement of lifestyle as the most effective first-line treatment for

PCOS patients can significantly improve the responsiveness of treatment, which is worthy of vigorous promotion.

2. Drug therapy
   (a) Antiandrogen therapy: It is suitable for PCOS patients with hyperandrogenism phenotype. It includes the following drugs:
      - Short-acting oral contraceptives (OCP): For adolescent and childbearing PCOS patients, hyperandrogenism and clinical manifestations (hirsutism, acne, etc.) suggest OCP as the First choice treatment. Short-acting oral contraceptives have a strong antiandrogen effect; they can inhibit the secretion of gonadotropin by hypophysis, reduce the concentration of free testosterone, and adjust menstrual cycle, which is used for contraceptive patients of reproductive age. At present, the commonly used drugs are Desogestrel and ethinylestradiol cycloproprogesterone.
      - Spionolactone (SPA): Also known as spironolactone, this drug is a diuretic, used in the treatment of hypertension, is an antagonist of aldosterone and androgen receptor, in addition to diuretic effect, but also has obvious antiandrogen activity. SPA can reduce the production of testosterone and increase the clearance rate, reduce the circulating levels of testosterone and androstenedione, and the combined use of SPA with oral contraceptives or dexamethasone is ideal. The commonly used dose is 25–100 mg, twice a day. The dose is titrated to balance efficacy and avoid side effects [87]. However, long-term treatment with high dose of SPA can cause menorrhea. For PCOS patients who have been diagnosed with hypertension, this drug can not only reduce blood pressure, but also inhibit androgen levels, so as to achieve the therapeutic effect of two birds with one stone.
   (b) Reduce insulin resistance: Insulin sensitizers are commonly used in obese or insulin resistant patients. Metformin can correct hyperandrogenic state, improve ovarian ovulation function and improve ovulation therapeutic effect by inhibiting liver glucose synthesis, increasing peripheral tissue sensitivity to insulin, and inhibiting hyperinsulinemia. It is suggested that small doses should be added gradually, and 1000–1500 mg/day should be recommended for nonobese patients. When lifestyle intervention cannot effectively control body weight and improve fatty liver, early adjuvant medication should be taken for obese patients. Usually patients have only mild gastrointestinal discomfort, less lactic acidosis, renal insufficiency, heart failure, and so on. However, if complications occur, the treatment should be discontinued immediately.
   (c) Drug-regulated ovulation therapy: Clomiphene is the first choice for ovulation induction in PCOS patients. It is a nonsteroidal antiestrogen drug. It acts on hypothalamus-pituitary-ovary level, combines competitively with estrogen receptor, blockades the negative feedback effect of endogenous estrogen, increases the release of gonadotropin, and promotes ovulation and ovarian steroid hormone production. Clomiphene was taken orally on the

fifth to ninth day of menstrual cycle, 50–150 mg/day, 3–6 cycles, ultrasound was used to monitor ovulation. Patients who still cannot ovulate at the maximum dose (150 mg/day) of clomiphene can be considered as clomiphene resistance, and can be combined according to specific conditions. Gonadotropin is a commonly used ovulation-inducing drug for PCOS patients who are resistant to clomiphene.

3. Assisted Reproductive Technology

   For PCOS patients with fertility requirements, who have ovulated but not pregnant after treatment of standard ovulation stimulation cycle for more than 6 months, in vitro fertilization and embryo transfer can be selected. In vitro fertilization and embryo transfer are also effective treatments for refractory PCOS patients.

4. Surgical Treatment
   (a) Ovarian wedge resection (OWR): Ovarian wedge resection is the first ovulation induction therapy established by removing 30–50% of polycystic ovarian tissue, reducing androgen production, relieving the inhibition of hyperandrogen on follicular development and promoting ovulation. The incidence of periovarian adhesions after operation is higher and less used clinically.
   (b) Laparoscopic surgery: Laparoscopic multipoint ovarian biopsy, ovarian electrocautery, laser ovarian multipoint vaporization, laser wedge cutting or ovarian perforation can significantly reduce ovarian androgen and inhibin production, enhance ovarian sensitivity to ovulation-promoting drugs, and reduce pelvic and abdominal adhesions, if necessary, secondary surgery can be performed. Laparoscopic ovarian perforation (LOD) is mainly used for clomiphene resistance, pelvic examination due to other diseases, poor follow-up conditions, and inability to monitor gonadotropin therapy.
   (c) Transvaginal ultrasound-guided interstitial ovarian hydrocoagulation: Under local anesthesia, vaginal ultrasound-guided oocyte-picking needle injected 75 C sterile saline into the interstitial ovary. This method is a safe, economical, and feasible method acceptable to patients.
   (d) Transvaginal ultrasound-guided interstitial laser therapy of ovary: generally on the third day of progesterone-induced artificial menstrual cycle. This method can effectively improve the hormone secretion of clomiphene resistant patients, induce ovulation and make their pregnancy successful, without obvious surgical complications.

17.4.9 Prevention and Treatment of Complications

PCOS can affect multiple organ systems, so in the process of diagnosis and treatment, some patients can be added with antihypertensive, lipid-lowering drugs, and regular detection of endometrial and breast changes. Long-term effective follow-up plays an active role in the prevention and treatment of PCOS complications.

1. Antihypertensive therapy: If PCOS is clinically characterized by hypertension, angiotensin-converting enzyme inhibitor (ACEI) can regulate the function of renin-angiotensin system in ovary and enhance postprandial insulin sensitivity. If there is no contraindication, it can be used first. Angiotensin receptor antagonist (ARB) blockades the effect of AngII at the receptor level, thereby antagonizing the activation of AT1, blocking vasoconstriction, catecholamine and antidiuretic hormone release, antagonizing the proliferation of smooth muscle and cardiomyocyte, blocking the negative effect of AngII on cardiovascular system, reducing sympathetic excitability and improving glucose metabolism, can be used in PCOS patients. Antisterone can reduce testosterone production and clearance, reduce circulating levels of testosterone and androstenedione. It can reduce blood pressure through diuretic action and can be used in PCOS patients.
2. Lipid-lowering therapy: Statins can improve blood glucose metabolism, increase insulin sensitivity, and improvement of insulin resistance. Considering that insulin resistance may exist in PCOS patients, statins can be used as lipid-lowering therapy if accompanied by hypercholesterolemia.

In conclusion, PCOS is a metabolic disease with polygenic inheritance tendency, the etiology and pathogenesis of PCOS are still unclear. At present, the research on PCOS involves many fields, most of them focus on adipocytokines and related genes. With the development of medicine, great progress will be made in the understanding of PCOS, which will provide more scientific basis for the treatment of its etiology. At present, it has been recognized that PCOS patients have higher risk of metabolic syndrome, such as abdominal obesity, abnormal lipidemia induced by atherosclerosis, elevated blood pressure, insulin resistance and (or) IGT, proinflammatory state and thrombosis-promoting state, which are risk factors of coronary heart disease, and are all associated with PCOS. Therefore, the study of PCOS provides a convenient condition for assessing cardiovascular hazards such as lipid abnormalities, hormone disorders and changes in glucose metabolism. Patients with menstrual disorders, amenorrhea, infertility, obesity, hirsutism, and other phenomena should be diagnosed as early as possible according to the methods and standards recommended by experts at home and abroad. The selected treatment methods must be based on their own or local conditions, follow the recommended treatment methods of professional societies, and refer to the specific conditions of patients, using individualized treatment programs.

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Monogenic Hypertension

18

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Monogenic hypertension [1], also known as Mendelian hypertension, is a group of infrequent hypertension diseases caused by a single gene mutation, and the genetic pattern conforms to Mendel's law of inheritance. It is often juvenile onset, mostly manifested as moderate, severe hypertension, and its complications occur early. Conventional antihypertensive therapy is often ineffective.

The pathogenesis of monogenic hypertension can be summarized into three categories such as mineralocorticoid receptor over-binding, altered sodium channel activity, and elevated plasma catecholamine levels. Mineralocorticoid receptor over-binding includes: (1) increased aldosterone (familial hyperaldosteronism); (2) increased other mineralocorticoids (congenital adrenal cortical hyperplasia); (3) increased cortisol in distal nephrons (apparent mineralocorticoid excess); (4) mutations of mineralocorticoid receptor, increased substances that can bind to and interact with them (mineralocorticoid receptor mutations lead to increased pregnancy-induced hypertension). Altered sodium channel activity includes increased ENaC activity (Liddle syndrome) and increased Na-Cl co-transporter activity (Gordon syndrome). Elevated plasma catecholamine levels can lead to elevated blood pressure, such as pheochromocytoma with multiple endocrine tumors, von Hippel–Lindau syndrome, hereditary neurofibromatosis, and carotid body paraganglioma.

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18.1 Familial Hyperaldosteronism

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With the further deepening of familial hyperaldosteronism (FH), current guidelines [2] recognize three well-established types of FH, namely FH-I to FH-III; however, data from genetic analyses reveal a more complex situation, with at least four different inheritable forms of primary aldosteronism and possibly still more yet to be discovered. (The main features of each type are shown in Table 18.1).

18.1.1 Familial Hyperaldosteronism Type I

Familial hyperaldosteronism I (FH-I) [3], also known as glucocorticoid-remediable aldosteronism (GRA), is the first confirmed monogenic hypertension, accounting for less than 1% of primary aldosteronism (PA). The case was first reported in 1966 and is autosomal dominant. It is a special type of PA, and patients often present with moderate to severe hypertension with a history of early-onset cerebrovascular accidents. Hypokalemia, low renin, and high plasma aldosterone are common in laboratory tests, and CT scan of adrenal glands has no clear space-occupying lesions. Glucocorticoid therapy has a specific effect on the disease.

18.1.1.1 Epidemiology

Aglony et al. [4] detected 130 untreated hypertensive children (4–16 years old) and found 4 children and 5 adults who had FH-I among 21 first-degree relatives. The disease is characterized by early severe hypertension, which usually occurs before the age of 13 and often causes early cerebrovascular accidents, mostly with cerebral hemorrhage (mean age: 32 years old). At present, families of Celtic descent in the Americas have reported this case. The United States, China, Japan, Italy, and Germany all have detailed family reports, but not in Africa. As the detection rate of PA increases, it is expected that the occurrence of FH-I will also increase.

Table 18.1 Characteristics of four familial hyperaldosteronism

Type	Plasma aldosterone	Plasma renin	Serum potassium	Pattern of heritability	Chromosome localization	Pathogenic gene
FH-I	↑	↓	↓	AD	8q24	CYP11B1/ CYP11B2 Chimeric
FH-II	↑	↓	↓	AD	3q27	CLCN2
FH-III	↑	↓	↓	AD	11q24	KCNJ5
FH-IV	↑	↓	↓	AD	16p13	CACNA1H

Note: AD Autosomal Dominant, AR Autosomal Recessive

18.1.1.2 Etiology and Pathogenesis

Human normal chromosome eight contains two genes regulating the secretion of adrenal cortical hormone: 11β-hydroxylase gene (CYP11B1) and aldosterone synthase gene (CYP11B2). Under normal physiological conditions, CYP11B1 is composed of ACTH regulatory region and cortisol coding region, which is regulated by ACTH and synthesizes glucocorticoid in adrenal zona fasciculata. CYP11B2 is composed of AngII regulatory region and aldosterone coding region, which is regulated by AngII and synthesizes aldosterone in adrenal zona glomerulosa. Both genes are located at 8q21, about 7 kb in size, and contain 9 exons and 8 introns. The sequence of introns and exons is identical, with a distance of about 30 kb. During meiosis, the inaccurate pairing and unequal crossover of two chromatids on chromosome 8 will result in partial gene duplication, so chromosome 8 not only contains normal 11β-hydroxylase gene and aldosterone synthase gene, but also carries a new "chimeric gene," which is chimerized by the promoter region (regulatory region) of CYP11B1 gene and the coding region of CYP11B2 gene, namely 5′-CYP11B1-CYP11B2-3′ [1] (Table 18.2).

It has been found that the [5, 6] chimeric gene has multiple cross-fusion forms, but the cross-fusion points of it mainly focus on intron 2 and exon 4. Different chimeric sites are not completely consistent in their phenotype. Recent studies have found that there are also chimeric gene carriers who do not exhibit salt-sensitive hypertension, and the reasons for phenotypic difference remain unclear.

FH-I is caused by chimerism between the regulatory region of CYP11B1 and the coding region of CYP11B2. The chimeric gene expression increases the heterotopic secretion of aldosterone in adrenal zona fasciculata, which is not regulated by AngII and potassium, and is only regulated by ACTH. The renin-angiotensin system of FH-I patients is inhibited and not easily stimulated by standing, salt limitation, and AngII. The circadian secretory rhythm of aldosterone is parallel to that of cortisol, and plasma aldosterone decreases with the decrease of plasma cortisol after 4 h of standing. In the ACTH stimulation experiment, the response of plasma aldosterone to ACTH in FH-I patients is stronger than that of normal people.

Hypertension in FH-I patients is caused by the retention of water and sodium due to the large amount of autonomic secretion of aldosterone [1].

Table 18.2 Formation of FH-I chimeric gene

Genotype	Gene composition	Regulation	Function	Secretory site
CYP11B1	ACTH regulatory region + cortisol coding region	ACTH	Synthesize cortisol	Adrenal zona fasciculata
CYP11B2	Ang II regulatory region + aldosterone coding region	Ang II, potassium	Synthesize aldosterone	Adrenal zona glomerulosa
Chimeric gene	ACTH regulatory region + aldosterone coding region	ACTH	Synthesize aldosterone	Adrenal zona fasciculata

18.1.1.3 Clinical Manifestations and Complications

The clinical manifestations of FH-I patients resemble primary aldosteronism with familial aggregation. Most of the patients have moderate to severe hypertension (and a few patients have normal blood pressure), presenting salt-sensitive volumetric hypertension. Patients' serum potassium concentration varies greatly, and maybe hypokalemia or normal (about 50% of patients), often accompanied by metabolic alkalosis. Cerebrovascular accidents are more common. According to statistics, the incidence of cerebrovascular accidents in FH-I family is as high as 48%. Adolescent patients are characterized by a cerebral hemorrhage, and the average age of cerebral hemorrhage is reported to be 32 years old [1].

18.1.1.4 Laboratory and Auxiliary Examination

1. Blood biochemical examination: About half of the patients have hypokalemia, often accompanied by metabolic alkalosis.
2. Hormone determination: High plasma aldosterone level and inhibition of plasma renin activity are detected; urinary 18-hydroxycorticoid (18-hydroxycorticoid in 24-h urine is 2 times higher than the normal upper limit, or more than 10 nmol/L) and 18-ketocorticoid are positive; dexamethasone suppression test is the most typical feature of the disease.
3. Molecular genetic diagnosis: Southern blotting or long-distance polymerase chain reaction (PCR) is used to detect chimeric gene, and the sensitivity and specificity are 100%.
4. Imaging examination: B-ultrasound, CT, MR, and other imaging examinations of adrenal glands in general patients show no specific findings; some patients present bilateral adrenal hyperplasia or nodular changes [1].

18.1.1.5 Diagnosis and Differential Diagnosis

Patients with hypertension and hypokalemia should consider this disease, especially in patients with familial disease. According to low renin and high plasma aldosterone, CT scan showed no clear space-occupying lesions; low dose dexamethasone not only inhibits the excessive secretion of aldosterone, but also restores blood pressure, serum potassium, and plasma renin activity to normal, so the clinical diagnosis is established. The disease can be diagnosed by genetic testing. It is recommended that chimeric gene should be screened in patients with an early onset of PA (< 20 years old) and in those with a familial occurrence of PA or stroke at a young age (< 40 years old) [1].

|Differential diagnosis: (1) Other types of primary aldosteronism: hypertension with hypokalemia is common, but dexamethasone suppression test is negative. (2) Familial hyperaldosteronism type II: it is ineffective for glucocorticoid therapy; there is no chimeric gene formation, and it can be identified by genetic testing. (3) Secondary hyperaldosteronism: see Sect. 19.4 of Chap. 19 "Common Adrenal Hypertension" for details [1].

18.1.1.6 Treatment

The treatment of FH-I is mainly based on drug therapy [1].

1. Glucocorticoid: The use of exogenous low-dose glucocorticoid (such as dexamethasone 0.125–0.25 mg/day) can inhibit the secretion of ACTH, fundamen-

tally solving the prognosis of patients. In general, the dosage can be relatively large at the beginning, 2 mg/day, which will be gradually reduced after the aldosterone and biochemical indicators are normal. If serum potassium rises quickly and hypertension is difficult to correct, other antihypertensive drugs such as calcium antagonists and beta receptor blockers can be added to control blood pressure. For children, the dosage of dexamethasone is about 0.05–0.1 mg/(kg·day), and hydrocortisone is available at 12–15 mg/m^2 (body surface area), divided into three times. The latter has less impact on children's growth and development.

2. Salt corticosteroid receptor blockers: Spironolactone and sodium channel blocker amiloride can also lower blood pressure and achieve the purpose of palliative treatment (see Sect. 19.4 of Chap. 19 "Common Adrenal Hypertension" for details).
3. Thiazide diuretics: Not used as a first-line drug, thiazide in combination with spironolactone can help control blood pressure, but secondary hypokalemia should be avoided.

18.1.1.7 Prognosis

The disease is treated with glucocorticoids and the prognosis is good. However, if the diagnosis is delayed, the target organ damage such as cerebral hemorrhage can occur when the patient is young [1].

18.1.2 Familial Hyperaldosteronism Type II

Familial hyperaldosteronism II (FH-II) [3, 5], also known as ACTH-independent hyperaldosteronism, is a relatively rare familial hyperaldosteronism with single-gene autosomal dominant inheritance. It was initially reported in 13 patients with primary aldosteronism in 5 families in 1991, but only one has been reported in China at present. The disease mainly leads to long-term hypertension, which causes cardiovascular and cerebrovascular events such as coronary heart disease, stroke, and so on. It is currently considered to be more common than FH-I, accounting for at least 7% of primary aldosteronism, but the specific prevalence is still unclear.

Linkage analysis in Australia, America, and India [7] found that the pathogenic gene was located on chromosome 7p22; the pathogenesis was related to bilateral adrenocortical hyperplasia and aldosterone adenoma. However, Chinese scholars [8] found that there was no linkage between the pathogenesis and the locus. According to the literature, the diagnostic age of hypertension in FH-II family members is 14–72 years old. At present, the pathogenesis is still unclear. CYP11B2 and the gene encoding angiotensin II receptor type I (AT1R) have been excluded. Candidate genes including GPR30, PMS2, PRKAR1B, ZNF12, and centaurin-α1 around chromosome 7p22 were sequenced in FH-II patients, and no mutation has been found so far [1]. Recently, Scholl et al. [9] analyzed a FH-II family and 80 patients with early-onset primary aldosteronism, and found FH-II related mutations in the CLCN2 gene located on chromosome 3q27 (p.Arg172Gln, p.Met22Lys, p.Tyr26Asn, p.Lys362Del, and Ser865Arg). Fernandes-Rosa et al. [10] found another mutation in the CLCN2 gene (p. Gly24Asp) in a 9-year-old patient by exon sequencing of patients with early-onset aldosteronism, and two new mutations (p.Arg66Gln, p.Pro48Arg) were also found in a cohort study of 100 patients with

idiopathic bilateral adrenal hyperplasia. CLCN2 encodes a voltage-gated chloride channel expressed in adrenal zona glomerulosa, which opens at hyperpolarized membrane potential, depolarizes glomerular cells and induces the expression of aldosterone synthase (the rate-limiting enzyme of aldosterone biosynthesis). The mutation channel significantly increases Cl-conductance at resting potential, aldosterone synthase expression, and aldosterone production. It is noteworthy that in a European multicenter study, 46 members from 21 suspected FH-II families were sequenced and a mutation in the potassium channel gene KCNJ5 was found in one family (consistent with the diagnosis of FH-III, see below). Therefore, patients with KCNJ5 mutation may be clinically misclassified as FH-II [11].

The clinical manifestations of FH-II are hypertension and hypokalemia, with familial inheritance. Its clinical features, including age of onset, blood pressure, serum potassium level, and incidence of adrenal adenoma, are similar to sporadic aldosteronism. FH-I and FH-II should be distinguished in diagnosis, because their symptoms are similar, but the treatment is different. FH-II is ineffective with glucocorticoid, but it is effective with spironolactone. If it is caused by unilateral adrenocortical adenoma, the adenoma can be removed surgically to treat hypertension. Studies have shown that there is no significant difference in FH-I and FH-II in terms of patient age, gender, plasma renin and aldosterone levels, and genetic testing can effectively distinguish the two [1].

FH-II is a kind of familial hyperaldosteronism which cannot be suppressed by glucocorticoid. FH-II patients have a family history of adrenal adenoma or hyperplasia-induced aldosteronism, which cannot be differentiated from sporadic aldosteronism in clinical, biochemical, and pathological aspects. In most families, the vertical transmission of disease suggests autosomal dominant inheritance. The diagnosis of FH-II is based on the fact that at least two people in the same family were diagnosed as primary aldosteronism. Unfortunately, the genetic background of FH-II is still unclear, so the diagnosis is based mainly on the persistent elevation of aldosterone/renin ratio (ARR), positive diagnostic tests (salt loading or fludrocortisone test), and no chimeric gene that leads to FH-I. By screening the first-degree relatives of FH-I and FH-II patients with above methods, the patients with normal blood pressure can be found, indicating that the difference in penetrance of the disease may even exist in the same family [1].

18.1.3 Familial Hyperaldosteronism Type III

In 2008, Geller et al. [12] reported a new kind of familial aldosteronism, known as familial hyperaldosteronism III (FH-III), which is an autosomal dominant hereditary disease characterized by severe early childhood hypertension, significant elevation of aldosterone, hypokalemia, and important target organs damage, and active antihypertensive therapy (including spironolactone and amiloride) is ineffective and requires bilateral adrenalectomy. In 2011, Choi et al. [13] confirmed for the first time that somatic mutation of KCNJ5 gene was associated with aldosterone adenoma and FH-III. KCNJ5 is located on chromosome 11q24 and encodes

G-protein-activated inwardly rectifying potassium channel Kir3.4, which is expressed in adrenal zona glomerulosa and helps maintain the cell membrane in hyperpolarization. It was found that the same family mutation of FH-III (p.Thr158Ala) was located near or inside the Kir3.4 selectivity filter, which increased the Na^+ permeability of the channel, promoted chronic cell membrane depolarization and voltage-gated Ca^{2+} channel opening, activated intracellular calcium signaling pathway, and led to persistent high aldosterone synthesis and adrenal hyperplasia [14]. An in vitro study [15] has reported that KCNJ5 somatic mutation can increase aldosterone synthesis by promoting the upregulation of CYP11B2 mRNA expression. A meta-analysis of 1636 patients with aldosterone adenoma in 13 studies showed that the mutation rate of KCNJ5 in European population was 43%, while that in Asian population was 63% [16].

At present, it has been found that [17] the clinical manifestations of different KCNJ5 mutations are different, but the relationship between gene and phenotype has not been clarified. There were serious phenotypes associated with mutations of p.Gly151Arg, p.Thr158Ala, p.Ile157Ser, and p.Tyr152Cys. The patients had severe primary aldosteronism symptoms and bilateral giant adrenal adenoma, with early onset of hypertension and difficult to control by drug treatment. There were mild phenotypes associated with p.Gly151Glu mutation. The patients had mild hypertension and hypokalemia, and showed good response to aldosterone receptor antagonists such as spironolactone; adrenal CT scan showed no abnormalities, which was difficult to differentiate from sporadic primary aldosteronism.

The clinical manifestations and biochemical indicators of FH-III are more serious than those of FH-I, and are also significantly different from FH-II, which usually develops in adulthood. Not only are aldosterone levels particularly high in FH-III patients, but some types of antihypertensive drugs (including spironolactone and amiloride) are still ineffective in sufficient doses, which can be used to distinguish FH-III from other familial and sporadic primary aldosteronism, because spironolactone is usually effective in other types. Another distinct feature of FH-III is the high production of 18-hydroxycorticoid (18-OHF) and 18-oxocorticoid (18-OXOF). In FH-I patients, 18-OHF and 18-OXOF are about 10 times as normal, and in sporadic case and FH-II patients, 18-OHF and 18-OXOF are 3–4 times as normal, while in FH-III patients, 18-OHF and 18-OXOF are 10 and 1000 times higher than those in FH-I patients, respectively. Moreover, the response of aldosterone and cortisol to dexamethasone suppression test is significantly different from that of other types of FH and normal controls. In fact, during the dexamethasone suppression test, the aldosterone level of FH-III patients increases abnormally to twice the baseline, and cortisol level is within the normal range but is not suppressed, suggesting that aldosterone has abnormalities in production and regulation. This finding further distinguishes FH-III from other types of FH and sporadic case. In FH-I patients, aldosterone is suppressed to below measurable level during dexamethasone suppression test, while in FH-II or sporadic case, aldosterone is temporarily and partially suppressed, but not below measurable level. However, aldosterone in some sporadic cases can be completely suppressed by DST, and they do not carry chimeric gene [1].

18.1.4 Familial Hyperaldosteronism Type IV

Recently, Scholl et al. [18] discovered a mutation in CACNA1H (p.Met1549Val) in 5 children with primary aldosteronism (10 years old or younger) by whole exon sequencing analysis which was reported as familial hyperaldosteronism IV (FH-IV). The patients presented with hyperaldosteronism and low plasma renin activity, but adrenal imaging showed no lumps or hyperplasia, and no seizures or neuromuscular lesions. CACNA1H gene is located on chromosome 16p13 and encodes the pore-forming α1 subunit of the T-type voltage-dependent calcium channel Cav3.2, which is highly expressed in adrenal zona glomerulosa and activated at mild depolarization potential. It is noteworthy that Cav3.2 channel is involved in the equilibrium of spherical membrane potential and the production of aldosterone. Whole-cell patch clamp experiments in human embryonic kidney-293 cells showed that M1549V CACNA1H channel could activate depolarization potential and slow down its inactivation, which was considered to be responsible for the increase of Ca^{2+} influx in glomerular cells. Under basal conditions, the overexpression of M1549V in the mutant channel of HAC15 adrenocortical cells increased the expression of CYP11B2 gene and the production of aldosterone, while the combination with T-type calcium channel blocker mibefradil could block the production of aldosterone, suggesting that M1549V CACNA1H mutation induced autonomous aldosterone production through T-type calcium channel.

Subsequently, another four CACNA1H mutations (p.Met1549Ile, p.Ser196Leu, p.Pro2083Leu, and p.Val1951Glu) with different clinical features were found in patients with primary aldosteronism. In vitro, electrophysiological experiments showed that these new CACNA1H mutations changed the electrophysiological characteristics of channels similar to M1549V. Although further studies are needed, available data suggest that FH-IV may be a rare type of FH, which follows autosomal dominant inheritance but is less dominant, especially in adults. Some family members with M1549V mutation suffered from refractory hypertension and primary aldosteronism, while others had mild clinical manifestations or even normal blood pressure, suggesting that genetic modification, somatic chimerism, or age can inhibit genetic defects. In addition, the type and site of mutation may also play a role in the pathophysiology of FH-IV [3, 5].

18.2 Congenital Adrenal Cortical Hyperplasia

Shunfan Yang

A genetic defect in the cortisol biosynthase can cause a group of syndromes called congenital adrenocortical hyperplasia. These diseases are inherited with autosomal recessive characteristics. Decreased cortisol production can lead to increased ACTH secretion, thus stimulating the production of substrates including defective enzymes and the upstream adrenal steroids. Clinical manifestations include decreased cortisol synthesis. Due to the increase of ACTH secretion and the massive synthesis of

progenitor steroids, androgen and deoxycorticosterone can be increased. Deoxycorticosterone has the activity of corticosteroids and can lead to hypertension. Congenital adrenal cortical hyperplasia associated with hypertension is characterized by 11β-hydroxylase deficiency and 17α-hydroxylase/17,20 carbon chain lyase deficiency.

18.2.1 11β-Hydroxylase Deficiency

11-Hydroxylase deficiency (11-OHD), caused by a mutation in the CYP11B1 gene, is an autosomal recessive genetic disease. It is first reported in 1955 and the clinical characteristic is low renin hypertension. It can be divided into classic and atypical. This disease accounts for 5–8% of all patients with congenital adrenal hyperplasia [19].

18.2.1.1 Epidemiology

11β-hydroxylase deficiency is a rare disease that affects about 1 in 100,000 newborns, with a high incidence among Jews and Arabs in the Middle East. Among Jews of Moroccan descent, the prevalence of 11-OHD is as high as 1/5000 due to the mutation of the R448H gene [20, 21].

18.2.1.2 Etiology and Pathogenesis

11OHD is an autosomal recessive genetic disease, which is caused by the mutation of CYP11B1 gene located on chromosome 8q21-q22, most of which eliminate the enzyme activity [19, 22]. In the past, mutations were thought to be concentrated in exons 2, 6, 7, and 8. However, recent studies have shown that most pathogenic mutations are in exon 3 and 8 (40%), and patients with exon 8 mutations account for the highest proportion of all patients, and patients with R448H mutations account for the highest proportion [23–28]. The phenotype of 11OHD is a mixture of excess androgen (e.g., 21-hydroxylase deficiency) and excess glucocorticoid (e.g., 17-hydroxylase/17, 20 lyase deficiency). The lack of 11β-hydroxylase activity in the adrenal fasciculus blocks the conversion of 11-deoxycorticosterone and 11-deoxycorticosterone to corticosterone and cortisol, respectively, resulting in an increase in adrenocorticotropin secretion, leading to the accumulation of 11-deoxycorticosteroid precursors and adrenocortical hyperplasia. The accumulation of 11-deoxysteroid precursors can cause sodium and water retention, hypokalemia, and hypertension [29]. Since CYP17A1 activity of 11OHD patients is complete, when stimulated by high concentration of ACTH, some upstream steroids can be metabolized into adrenal-derived androgens, resulting in increased androgen secretion and a series of clinical manifestations.

18.2.1.3 Clinical Manifestation

The clinical manifestations of this disease are excessive secretion of corticosteroids DOC and androgen precursor dehydroepiandrosterone sulfate (DHEAS) in the adrenal gland. It can be divided into classic and non-classic. Hypertension typically

occurs in about two-thirds of patients, usually in infancy, often with complications such as left ventricular hypertrophy and hypertensive retinopathy [23]. Women are born with pseudohermaphroditism, while men develop pseudosexual maturity. Female patients are masculine, presenting with hypertrophy of the clitoris, labial fusion of varying degrees, irregular menstruation, and even primary amenorrhea. Most patients are infertile, and may present with hirsutism, acne, muscular development, prominent Adam's apple, and other masculine manifestations. Male patients present with non-growth hormone-dependent precocious puberty, premature penis development, no enlargement of the testicles, small testicles, and spermatogenic disorders resulting in decreased fertility. Other symptoms include accelerated epiphyseal maturation, premature bone age, and premature closure of epiphyses, resulting in a lower final height than normal. The clinical manifestations of atypical 11β-hydroxylase deficiency are not prominent and blood pressure is usually normal or mildly elevated. There was no obvious abnormality at birth, and the clinical manifestations of excessive androgen secretion did not appear until adolescents and adults, such as acne, hirsutism, menstrual disorders, and other hyperandrogenemia manifestations in young women [30, 31].

18.2.1.4 Laboratory and Auxiliary Inspection

1. Hormone assay: The plasma ACTH, 11-deoxycortisol, DOC, and testosterone levels are increased. PRA and aldosterone levels are decreased. Twenty-four hour urine 17-ks and 17-kg levels are increased.
2. The presence of 11-hydroxylase deficiency in the fetus can be determined by measuring 11-deoxycortisol in the amniotic fluid.
3. Imaging examination: The premature bone age can be founded in juvenile patients by radiographs. Adrenal CT examination indicates bilateral adrenal thickening.

18.2.1.5 Diagnosis and Differential Diagnosis

The possibility of 11β-hydroxylase deficiency should be considered in patients with androgen overproduction, hermaphroditism, precocious puberty with or without hypertension and hypokalemia. Further examination showed decreased cortisol levels, abnormally increased plasma ACTH, 11-deoxycortisol, DOC and testosterone levels, decreased renin activity and aldosterone levels, and increased urinary 17-ks and 17-kg levels at 24 h, which supported the diagnosis of the disease [32, 33]. Testing for mutations in 11β-hydroxylase deficiency is the gold standard for diagnosis.

Diseases differentiating with 11β-hydroxylase include other diseases that cause excess androgens, such as 21-hydroxylase deficiency, androgen-secreting tumors, polycystic ovary syndrome, and diseases that cause hypertension and hypokalemia, such as 17α-hydroxylase/17,20 lyase deficiency, glucocorticosterone-inhibiting aldosteronism, Cushing's syndrome, etc. In general, the sexual differentiation characteristics of 21-hydroxylase deficiency, androgen-secreting tumors, and polycystic ovary syndrome are mostly characterized by female manifestation as masculine and male manifestation as precocious puberty. However, 21-hydroxylase deficiency is

often associated with hyponatremia, hyperkalemia, and metabolic acidosis, and few patients have hypertension. Most patients with bilateral McNodular hyperplasia present with subclinical or dominant Cushing's syndrome, but some produce both cortisol and other steroids (including adrenal androgens). Adrenal imaging examination of patients with polycystic ovary syndrome is mostly negative, and the main manifestation is bilateral ovarian enlargement, which is 2–3 times of normal ovary. Multiple (20–30) small follicles within the ovarian cortex echo. The main differentiating points with 17α-hydroxylase/17,20 lyase deficiency are the latter sex differentiation characteristics: female sex is immature, while male sex is feminine. Glucocorticoid can inhibit the abnormal asexual differentiation of aldosteronism and Cushing's syndrome.

Because the clinical manifestations of atypical 11-OHD are atypical and highly variable, some patients may be misdiagnosed as polycystic ovary syndrome due to a slight increase in androgen level, while some patients only show hypertension with hypokalemia [34, 35]. After the ACTH stimulation test, the elevated level of 17-hydroxyprogesterone can be used to distinguish non-classical 21OHD, but there is still no consensus on the diagnostic criteria for non-classical 11-OHD.

18.2.1.6 Treatment

1. Glucocorticoid replacement therapy: ACTH, androgen, deoxycorticosterone, and deoxycortisol can be rapidly reduced to normal. Glucocorticoid reduces the production of adrenal androgens by inhibiting the excessive secretion of ACTH, inhibits the excessive growth rate of children, corrects hyperandrogenemia, and reduces the secretion of corticosteroids to normal to alleviate hypertension [30].
2. Adjuvant: low doses of potassium—sparing diuretics can correct hypokalemia and mild hypertension. Calcium channel antagonists are also available. Thiazide diuretics have the adverse reaction of aggravating hypokalemia, do not use alone commonly, unless with conserved potassium diuretic is used.
3. Treatment for sexual dysdifferentiation: Women with 11β-hydroxylase deficiency present with pseudohermaphroditism, an enlarged clitoris that retracts after glucocorticoid replacement, and some children do not require surgical correction. However, if the child has significant clitoral enlargement and labial fusion, external genital orthopedics should be performed as soon as possible.

18.2.2 17-Hydroxylation Deficiency

17α-hydroxylase/17, 20 carbon chain lyase deficiency (17-hydroxylation deficiency (17-OHD)) is an autosomal recessive congenital adrenal hyperplasia due to a CYP17A1 gene mutation. It can be divided into perfect type and partial type. The main clinical manifestations are low renin hypertension, low blood potassium, female sexual infantilism, primary amenorrhea and male pseudohermaphroditism, as well as the bone age lag associated with sex hormone deficiency, and the height caused by delayed epiphyseal closure.

18.2.2.1 Epidemiology

17-hydroxylase deficiency (17-OHD) is a rare congenital adrenal hyperplasia (CAH). Neonatal morbidity is estimated at 1 in 50,000, or 1% of all CAH cases. At present, only about 150 cases have been reported, and about 60 cases have been reported in China. Brazil has the highest prevalence [36, 37]. Isolated 17-20 lyase deficiency (ILD) was very rare [38, 39], in only 6 cases.

18.2.2.2 Etiology and Pathogenesis

The coding gene of 17α-hydroxylase/17,20 carbon chain lyase is CYP17A1 gene. The gene is located on chromosome 10q24.3 and contains 8 exons and 7 introns. The total length of mRNA was 2.1 kb, and an enzyme protein with 508 amino acids was generated. The gonad and adrenal glands with a molecular weight of 57-kd were both expressed [40]. Cytochrome P450 17A1 enzyme (CYP17A1) catalyzes 17-hydroxylase reaction (formation of 17-hydroxyl steroid) and 17-20 lyase reaction (cleavage of 21-c-17-hydroxyl steroid into 19-c-17-keto-androgen precursor) [41]. CYP17A1 is expressed in both adrenal and gonadal glands of the body. 17α-hydroxylase/17, 20 carbon chain lyase deficiency causes decreased cortisol synthesis, increased ACTH secretion and excessive secretion of corticosterone, to achieve the role of cortisol replacement. At the same time, lots of intermediate products such as progesterone and 11-deoxycorticosterone (DOC), and others such as 18-hydroxycorticosterone and 19-deoxycorticosterone were also produced. These corticosteroids formed by excessive secretion of ACTH eventually lead to low renin hypertension and low serum potassium metabolic alkalosis, but generally there is no expression of adrenal cortical function decline, because the increased secretion of corticosterone has certain glucocorticoid activity [42]. The expression of 17 alpha hydroxylase /17,20 carbon chain lyase in gonads results in the secretion disorder of gonadal hormones such as estrogen and testosterone. It can lead to sexual infantilism, primary amenorrhea in women, and pseudohermaphroditism in men [40].

18.2.2.3 Clinical Manifestation

It can be divided into complete 17OHD and partial 17OHD. The classic manifestations of severe 17OHD in phenotypic women (46,XX or 46,XY karyotype) are hypertension, nondevelopment of secondary sexual signs in adolescence, primary amenorrhea, and absence of pubic and axillary hair. High blood pressure usually appears as a minor and may occur earlier, with varying degrees of severity. Other manifestations include bone age lag, delayed epiphyseal closure, and osteoporosis. Patients with incomplete type 17OHD have some manifestations of estrogen or androgen function. In the partial form of 17OHD, 46, XY are often found in infancy. Although the patient's testicular support cells normally secrete para-mesenchymal inhibitory hormones in embryo, they cannot synthesize androgens. All patients lacked the characteristics of male external genitalia, had pseudohermaphroditism, had underdeveloped testicles in the abdominal cavity or groin, and had no pubic and axillary hair growth [40, 43].

18.2.2.4 Laboratory and Auxiliary Inspection

1. The ratio of precursor to product was determined in ACTH excitation test. If progesterone, corticosterone, and DOC were increased 5–10 times after ACTH stimulation, the diagnosis of 17α-hydroxylase/17 and 20 carbon chain lyase deficiency was supported.
2. There are many CYP17 mutation sites, making genetic diagnosis time-consuming. ACTH stimulation test can help diagnosis.
3. X-ray showed that the patient's bone age was significantly behind that of his peers. Bone density examination showed that bone mass was significantly lower than that of peers. Adrenal CT examination suggests adrenal thickening.

18.2.2.5 Diagnosis and Differential Diagnosis

The diagnostic points of complete 17-OHD are as follows: (1) Women and patients who appear to be women have secondary sexual signs of dysplasia, primary amenorrhea, hypertension, and hypokalemia; (2) Hormone assays showed DOC (>100 ng/dL [>3 nmol/L]), corticosterone (>4000 ng/dL [>116 nmol/L]), low cortisol (<5 MCG/dL [<138 nmol/L]), low androgen and estrogen levels, inhibited aldosterone and renin, and elevated gonadotropin and ACTH levels even in children [44]. The diagnosis of partial 17OHD is as follows: The patient has hermaphroditism in the external genitalia or spontaneous puberty secondary sexual sign development and menstruation, or normal blood pressure and blood potassium, and secretes a certain amount of 17α-hydroxylated hormone (17-hydroxyprogesterone, E2, T) in the body, and responds to the ACTH excitation test.

Patients with 21- hydroxylase deficiency have low adrenocortical function after birth and they can be diagnosed shortly after birth. In contrast, 17 alpha-hydroxylase /17,20 carbon chain lyase deficiency does not typically show hypofunction of the adrenal cortex, so patients are usually diagnosed when they develop high blood pressure, hypokalemia, or puberty (puberty or early adulthood). Patients with 11 beta-hydroxylase deficiency also had elevated levels of 18-hydroxycorticosterone and 18-hydroxydoc. The ratio of corticosterone to DOC (or their 18-hydroxyl product) identifies 17 alpha hydroxylase /17,20 carbon chain lyase deficiency and 11 beta hydroxylase deficiency [45–47].

18.2.2.6 Treatment

The general principle is to inhibit the hormone that are overmuch secreted, and replenish the other hormone that are lacking. For patients of different ages, the treatment objectives are different, and the choice of drugs is distinguishing. For partial type 46XY patients, the underdeveloped testicle should be removed to preventing malignant transformation. Estrogen replacement therapy is needed after puberty. It can promote the development of female secondary sexual characteristics and prevent osteoporosis.

18.3 Apparent Mineralocorticoid Excess

Jina Yili

Apparent mineralocorticoid excess (AME) is a rare autosomal recessive genetic disease, often occurring in children. The clinical manifestations are hypertension, hypokalemia, low renin, and other symptoms of excessive mineralocorticoid, similar to the symptoms of excessive aldosterone. But actually the level of aldosterone is low, so it is named as the apparent mineralocorticoid excess [48].

18.3.1 Epidemiology

In 1977, Ulick et al. first reported a case of a 3-year-old girl suffering from severe hypertension syndrome. Up to now, AME is a rare hereditary form of hypertension, and has been reported in less than 100 cases worldwide [49].

18.3.2 Pathogenesis

AME is an autosomal recessive genetic disease in which 11beta-hydroxysteroid dehydrogenase type 2 (11-β-HSD-2) activity is defective due to a mutation of the 11-hydroxylated steroid dehydrogenase 2 gene HSD11B2 encoded on chromosome 16 [48, 50].

11-β-HSD-2 is a high affinity NAD^+-dependent enzyme, widely distributed in target tissues of corticosteroids such as the renal cortex, especially distal convoluted tubules and collecting ducts, rectum, and sigmoid salivary glands and sweat glands; large amounts of 11-β-HSD-2 are also present in the placenta and adrenal glands.

Normally, 11-β-HSD-2 converts cortisol into corticosterone, which does not bind to glucocorticoid receptors [51]. This transition is of physiological importance because cortisol and aldosterone have the same affinity for the glucocorticoid receptor, and plasma cortisol concentrations are approximately 100 times higher than plasma aldosterone concentrations.

Cortisol becomes the dominant corticoid without the conversion of cortisol to inactive corticosterone at the aldosterone-sensitive site of 11-β-HSD-2. Large amounts of cortisol occupy the distal renal tubules of the corticosteroid receptors, activating transcription factors and serum glucocorticoid kinases. Then Serum glucocorticoid kinase phosphorylates Nedd4 and fail to combine with ENaC, so that ENaC cannot be inactivated and relatively activities of ENaC increased, sodium reabsorption increased. Finally, similar to manifestations of excessive aldosterone are appeared, which is called representational hypercorticosteroid.

The reported 11-β-HSD-2 gene mutation types are mainly missense mutation and deletion mutation [48, 51]. Recent epidemiological data indicate that salt sensitivity is determined by genetic polymorphisms of 11-hsd-2 in most populations and is a major risk factor for hypertension in some adults. Mice with the 11-β-HSD-2

enzyme gene knockout showed significant AME symptoms. Studies have confirmed that the reduced stability of 11-β-HSD-2 protein causes low renin and low aldosterone hypertension, and provides a mechanism for the degradation of 11-β-HSD-2 protein by protease, suggesting that 11-β-HSD-2 protein stability defects, including post-translational modification and proteasome activity defects, are the pathogenesis of AME, rather than genetic defects.

18.3.3 Clinical Manifestations

Because of the symptoms of the binding of cortisol to the renal cortical hormone receptor (MR), the secretion of aldosterone is inhibited in response, so the first manifestation is hyaldosteremia, which can be divided into AME-I type (for children) and AME-II type (for adults).

Type 1 patients, 11-β-HSD-2 is inactive, leads to fatal, volumetric salt sensitive hypertension in children, often accompanied by birth weight is lighter, hypokalemia secondary renal urinary collapse, bone disease, short stature, polyuria, polydipsia, renal calcinosis, left ventricular hypertrophy, and severe patients in childhood or adolescence is dead, the cause of death for intracranial hemorrhage, arrhythmia [48].

AME-II patients, 11-β HSD-2 low activity, some cases difficult to differentiate with primary hypertension, also have high blood pressure patients is characterized by low renin sex, can lead to high blood pressure stroke [52].

18.3.4 Laboratory and Auxiliary Examination

1. Detection of the ratio of free cortisol to free cortisol in 24-h urine is a sensitive diagnostic test [53, 54]. When the function of 11-β-HSD-2 is normal, the level of urinary free cortisol is higher than that of urinary free cortisol, and the ratio of urinary free cortisol to urinary free cortisol is about 0.3–0.5 [55].
2. In most patients with enzyme deficiency, the level of urinary free cortisol is very low or even undetectable, so the ratio of urinary free cortisol to urinary free cortisol is very high [48]. In typical AME syndrome patients, the ratio is 5 in children a.nd 18 in adults [55].
3. The genetic diagnosis of 11-beta-HSD-2 is the gold standard.

18.3.5 Diagnosis and Differential Diagnosis

The possibility of AME-I type should be considered in children with hypertension and the presence of hypokalemia, low renin, and low aldosterone. The diagnosis was mainly based on plasma and urinary cortisol monitoring, and the diagnosis was mainly based on the gene diagnosis of 11-β-HSD-2.

In addition, long-term and chronic intake of licorice or licorice compounds can inhibit the activity of 11-β-HSD-2 enzyme, leading to the accumulation of cortisol, which is the clinical manifestation of the syndrome of apparent corticosteroid overdose, but there is no cortisol metabolite in the urine, which can be clearly diagnosed by asking about the disease history.

Excessive ACTH secretion leads to excessive cortisol production, which exceeds the ability of 11-β-HSD-2 enzyme to transform, and cortisol levels can be elevated, leading to AME symptoms.

18.3.6 Treatment

AME is most commonly treated with a low-salt diet, potassium supplementation, and spironolactone [56] as follows:

1. Low-salt diet: AME-induced hypertension is salt-sensitive, low-renin-type hypertension. Most case reports indicate that low-salt diet plays an important role in the control of hypertension in patients.
2. Potassium supplementation: Oral potassium supplementation is the main method.
3. Potassium conserving diuretics: Spironolactone, triamcinolone, Amiloride and others can successfully treat AME. Thiazide diuretics, such as furosemide 40 mg/day, should be used in combination with hyperuricemia or nephrocalcinosis.
4. Others: Dexamethasone (DXM 0.15 mg/day, and then 1 mg/day) can inhibit cortisol and reduce urinary free cortisol; Nifedipine (Nifedipine 20 mg/day) can alleviate AME hypertension. Angiotensin converting enzyme inhibitors, such as captopril and benazepril, enhance renal 11-hsd-2 activity and are effective in treating patients with partial enzyme activity. It has been reported that benazepril at 10 mg/day reduced blood pressure and reversed left ventricular hypertrophy at 6 months. In AME patients with chronic renal insufficiency, which presents as refractory hypertension, artificial kidney replacement is beneficial to the decrease of blood pressure, which is related to the decrease of blood sodium level and fluid imbalance. It has been reported that two patients were cured after transplantation of kidneys with normal 11-hsd2 activity [57, 58].

18.4 Mutations in the Glucocorticoid Receptor Cause Gestational Exacerbation of Hypertension

Nuerbuwei Tuersun

Salt corticosteroid receptor mutations are chromosomal dominant inheritance and are not limited to females; 15-year-old males with reported congenital symptoms [59]. Its etiology is salt corticosteroid receptor (MR) activated mutation and increased Na reabsorption. Hypertension caused by MR-activated mutations can be seen in non-pregnant women, but pregnancy can aggravate. Because mutant MR

receptors are sensitive to non-saline corticosteroids, such as progesterone, spironolactone can also activate mutant receptors. This disease accounts for 6% of pregnancy complications in pregnant women. Salt corticosteroid receptor (MR, MLR, MCR), also known as aldosterone receptor or NR3C2 (nuclear receptor subfamily 3, group C, member 2), is a member of the nuclear receptor family. Salt corticosteroid has the same affinity with glucocorticoid, but has no affinity with corticosterone. Coding gene: NR3C2, located in 4q31.1–31.2 [60]. Many tissues express MR: kidney, colon, heart, central nervous system (hippocampus), brown adipose tissue, sweat gland. Its function is to activate MR expression in epithelium, induce and regulate the protein expression of water and sodium (mainly ENaC, Na^+/K^+ pump, serum and glucocorticoid-induced kinase SGK1), leading to sodium reabsorption, increased extracellular capacity, elevated blood pressure, and potassium loss (maintaining salt balance in vivo).

Aldosterone activation (MR) causes it to dissociate with chaperones and transfer to the nucleus, which binds to hormone response components (HRC) of target genes and activates target gene expression. Na reabsorption increased: (1) Na^+/K^+-ATPase, (2) SGK1 (kinase-1 that induces serum/glycosterol regulation in the early stage) relieves inhibition (inhibition of sodium channel expression and activity in epithelium), (3) aldosterone stimulates inflammatory response and promotes the expression of fibrous molecules through EGFR. Geller et al. reported for the first time in 2000 that the ligand binding domain of the salt corticosteroid receptor mutated. The 810 serine was replaced by leucine (S810L) [61], which resulted in the molecular interaction between the fifth and third helix of the receptor. The conformation of the mutant receptor changed, resulting in the semi-activated state of the mutant receptor without ligand binding (the activity increased by about 25%).

Progesterone is also an antagonist of the salt corticosteroid receptor under normal circumstances. When the ligand binding domain of the receptor mutates, progesterone becomes an agonist of the receptor. Progesterone in the body increases 100 times after pregnancy, so carriers of salt corticosteroid receptor mutations after pregnancy develop severe hypertension. At the same time, plasma renin activity was inhibited and plasma aldosterone level was decreased. In these cases, hyperfunction of epithelial sodium channel (ENaC), increased Na+ reabsorption, and significant expansion of blood volume lead to hypertension [62].

Salt corticosteroid receptor mutations lead to increased pregnancy in hypertensive patients, pregnancy hypertension [63] and preeclampsia are difficult to differentiate, especially in patients without a history of hypertension before pregnancy, both can appear proteinuria, edema, and neuropsychiatric symptoms, and ultimately differentiate according to postpartum blood pressure changes and genetic diagnosis. Like preeclampsia, the treatment for such patients is termination of pregnancy. For male patients with salt corticosteroid receptor mutation and non-pregnant women, spironolactone and hydrocortisone metabolites in the kidney not only cannot reduce blood pressure, but also can bind to the mutant receptor, leading to further elevation of blood pressure. There is no effective treatment for such patients.

18.5 Gene Mutation of Sodium Channel Leads to Monogenic Hypertension

Zhongrong Wang

The mutation of sodium channel gene leads to monogenic hypertension mainly including pseudo-hereditary aldosteronism (Liddle syndrome) with increased activity of epithelial sodium channel (ENaC) and pseudo-hypoaldosteronism type II (Gordon syndrome) with increased activity of Na-Cl co-transporter.

18.5.1 Liddle Syndrome

Liddle syndrome (known as pseudo-hereditary aldosteronism) is a rare autosomal dominant hereditary disease. Its main clinical features include early salt-sensitive hypertension, early cardiovascular and cerebrovascular events, hypokalemia, metabolic alkalosis, inhibition of renin activity, and lower plasma aldosterone level than normal, sensitive to ENaC inhibitor amiloride or aminophenylpyridine, but not to aldosterone receptor antagonist spironolactone. Its genetic basis is usually due to mutation of the gene βENaC or γENaC encoding epithelial sodium channel subunit, which leads to excessive activation of ENaC and enhanced sodium water reabsorption in renal distal convoluted tubules. However, there have also been reports of mutations in αENaC in recent years. Autosomal dominant inheritance leads to an increase in sodium reabsorption in glomerular collecting ducts and an increase in K^+ excretion and H^+ secretion, leading to systemic hereditary abnormalities in sodium transport. There are no effective measures for the occurrence of this disease at present, but positive symptomatic treatment can prevent the development of the disease and the occurrence of complications.

18.5.1.1 Epidemiology

Liddle discovered the disease in 1963. LS patients are most common between the ages of 10 and 30, or earlier. LS occurs all over the world and has no obvious racial or gender orientation. The incidence of LS is estimated to be less than 1/106 [64] of the global population. The results of the recent two sample sizes of 330 [65] and 766 [66] Chinese patients with hypertension suggest that the prevalence of Liddle syndrome is 1.52% (5/330) and 0.91% (7/766), respectively.

18.5.1.2 Etiology

Gene studies have shown that human ENaC subunits α, β, and γ are encoded by SCNN1A, SCNN1B, and SCNN1G genes, respectively. SCNN1A is located in 12p 13.31, while SCNN1G and SCNN1B are located in the common 400 KB fragment [67–69] of human chromosome 16p 13-p 12. When the gene SCNN1B encoding β subunit and the gene SCNN1G encoding γ subunit mutate, the deletion of PPPXY sequence eventually leads to ENaC dysfunction.

Pagani et al. reported that in Italy near the Messina Strait, three unrelated families with Liddle syndrome were carrying the same mutation βENaC P617L [64]. Furuhashi et al. reported that Liddle syndrome was caused by missense mutations of P616R and W576X in β and γENaC PY motifs. The mutation of βENaC P616R in Xenopus oocyte can increase ENaC activity six times. The 616 codon in the PY motif of exon 13 of SCNN1B gene mutated from CCC to CTC, which changed proline to leucine and led to LS. The substitution of this amino acid increased ENaC activity by 8.8 times. Therefore, the regulation of PY motif on ENaC activity is crucial. Recently, a mutation of P. Cys479Arg, a subunit of α, was found in Caucasian families with Liddle syndrome. The mutation increased the open conformation of the channel and increased Na^+ current, but did not affect the channel density [70] on the plasma membrane. ENaC is present in the parietal membrane of the main cells of aldosterone-sensitive distal nephron (ASDN), which can regulate Na+ reabsorption in ASDN at a limited rate. ENaC activity depends on the open channel probability (Po) and the number of expression on the parietal membrane of the main cells of ASDN. ENaC consists of three subunits: α, β, and γ. At present, α subunit is the basic structural unit, while β and γ are the active regulatory units. Each ENaC subunit consists of two transmembrane domains, one large extracellular domain and two cytoplasmic tails (amino and carboxyl terminus). There is a group of proline-enriched motifs PPPxYxxL (PY motifs) at the C-terminal of the cytoplasmic tail of β and γ subunits, which plays a fundamental role in eliminating internalization and degrading ENaC. PY motif can bind to WW region of ubiquitin protein ligase Nedd4–2, which makes ENaC ubiquitinate and finally ENaC degraded internally. When the PY motif was deleted or mutated, the binding of NED4-2 to ENaC was prevented, and ENaC could not be internalized and degraded, resulting in the increase of ENaC concentration in the parietal membrane of ASDN, which was continuously activated and Na+ reabsorption increased.

So far, different mutations of 24β subunits and 6γ subunits have been identified in 72 families from different countries [71]. Most mutations are concentrated in exon 13 of SCNN1B or SCNN1G gene, including frameshift mutation, nonsense mutation, and missense mutation. They result in deletion or alteration of proline-rich PY motifs. In addition, the mutations of γ-ENaC N530S and αENaC C479R did not change the number of ENaC expression on the cell surface, but increased PO [70, 72].

18.5.1.3 Pathological Mechanism

Aldosterone-sensitive distal nephron (ASDN) consists of proximal distal convoluted tubule (DCT2), connecting tubule (CNT), and collecting duct. The apical membrane of the main cell contains ENaC. Aldosterone stimulates the expression of glucocorticoid-regulated kinase 1 (SGK1), which phosphorylates NEDD4–2 and decreases the endogenous degradation of ENaC. The activity of ENaC in the transition zone between CNT and cortical collecting duct (CCD) depends on aldosterone regulation. In LS patients, the sensitivity of ENaC to aldosterone increases, with the number of ENaC and its activity increasing. ENaC in DCT2/CNT transition region, where overexpression of ENaC is the main site of increased Na^+ reabsorption [73],

is non-aldosterone dependent regulation. Na^+ reabsorption increased, with blood volume dilated and persistent Na+ reabsorption results in increased K^+ and H^+ secretion, leading to hypertension, hypokalemia, alkalosis, and hyporenin hypoaldosteronemia.

18.5.1.4 Pathogenesis

ENaC gene mutation may affect the function of ENaC by increasing the number of its expression and the opening of channel gating. K^+ efflux is indirectly coupled with Na^+ reabsorption. Overactivation of ENaC results in continuous increase of Na^+ reabsorption in distal renal tubules and excessive excretion of K^+ resulting in hypokalemia and hypernatremia. A large number of intracellular K^+ migrates to extracellular space, while H^+ and Na^+ enter intracellular space, resulting in metabolic alkalosis of extracellular fluid. The reabsorption of Na^+ increases, with extracellular fluid volume expanding, and blood potassium decreasing which can decrease nitric oxide synthesis in endothelium, increase tension of vessel smooth muscle, decrease vascular compliance, and finally increase arterial pressure. Expanded blood volume inhibits the synthesis and release of renin in paraglomerular organs and reduces the synthesis of renin-angiotensin-aldosterone. In addition, low potassium, high sodium, and high blood volume can inhibit the secretion of aldosterone in the glomerular zone of adrenal cortex, resulting in hyporenin and hypoaldosteronemia. The tubular epithelial cells can only exchange more H^+ with Na^+, owing to the lack of K^+, resulting in "abnormal" acidic urine.

18.5.1.5 Clinical Manifestations

Typical clinical features are early onset of refractory salt-sensitive hypertension, hypokalemia, metabolic alkalosis, low plasma renin activity, and low serum aldosterone level. It is sensitive to sodium channel inhibitors, but not to aldosterone receptor antagonists. Other complications include stroke, retinopathy, chronic kidney disease, left ventricular hypertrophy, malignant arrhythmia, myasthenia and so on.

18.5.1.6 Laboratory and Auxiliary Examination

1. Blood electrolyte: Hypokalemia, blood potassium is usually as low as 2.4–3.5 mmol/L; blood sodium is mostly above 145 mmol/L.
2. Blood gas: Metabolic alkalosis.
3. Urine routine: Acidic urine, PH is often less than 5.
4. Serum hormone determination: Serum aldosterone is not high or low, urinary 17-hydroxy and 17-ketosterol and ATCH tests are normal.
5. Gene diagnosis: Mutations in SCNN1B and SCNN1G genes mostly occur in exon 13. After excluding common secondary hypertension, sequence screening of SCNN1B and SCNN1G genes can identify the pathogenic mutations of Liddle syndrome. At present, there are many hospitals in China, such as Shanghai Institute of Hypertension and Beijing Fuwai Hospital, which carry out genetic diagnosis of hereditary hypertension. There are many reports on genetic diagnosis of LS.

6. Iconography examination: Routine X-ray and B-ultrasonography can help to exclude other similar diseases.

18.5.1.7 Diagnosis and Antidiastole

Diagnosis

Patients with hypertension and hypokalemia, especially adolescents with family history, the disease should be considered. Further consideration should be take, if the patients carried with hyporenin and hypoaldosteronemia. Further determination of hormone levels, such as patients with hyporenin, hypoaldosteronemia, the possibility of this disease is high. The clinical diagnosis of LS can be established if it can be treated with spironolactone without reaction, and the symptoms of hypokalemia and hypertension can be rectified by low-salt diet and aminophenylpyridine. Sequence screening of SCNN1B and SCNN1G genes is the gold standard for the diagnosis of LS.

Antidiastole

1. Bartter syndrome [74]: A recessive inherited salt-depleting disease associated with secondary aldosteronism and hypotension. The main manifestations are hypotension, hypokalemia, hyponatremia, hyperuricemia, alkalosis, and high aldosterone. Hypercalciuria can also lead to kidney stones or calcinosis.
2. Characteristic salicosteroidosis (SAME): An autosomal recessive inheritance disorder characterized by congenital deficiency of 11-beta hydroxysteroid dehydrogenase (11β-HSD), resulting in elevated plasma cortisol levels and salicosteroid-like effects. It is often accompanied by a lack of secondary sexual characteristics; renin and aldosterone levels are not significantly lower than LS; high blood pressure can be corrected by low salt, potassium supplementation, and spironolactone; gene testing can detect 11β-HSD mutation.
3. Familial aldosteronism type I: A special type of protoaldosteronism. The main manifestations are moderate to severe hypertension, accompanied by hypokalemia, low renin, and high aldosterone. There are no clear space-occupying lesions on CT scan. Increased aldosterone levels of the patients are the differential points.
4. Congenital adrenocortical hyperplasia (CAH): A group of autosomal recessive hereditary diseases. Owing to deficiency of corticosteroid hydroxylase and obstruction of cortisol synthesis, the secretion of ACTH increases, with adrenal cortex proliferating and cortisol precursors rising, such as 11-deoxycortisol and adrenal androsterone. Dexamethasone or hydrocortisone can correct hypertension and hypokalemia. Adrenocortical hyperplasia, the lack of secondary sexual characteristics, 21-hydroxylase deficiency, 17-hydroxylase deficiency, 3-β hydroxydehydrogenase deficiency, and corticosterone methoxygenation deficiency can be detected.

18.5.1.8 Treatment

At present, there is no effective gene therapy for LS. The main treatment is to supplement potassium chloride and use potassium-preserving diuretics, with low-salt diet. Strict or moderate salt restriction with potassium-preserving diuretics triamterene, amiloride) can recover normal blood pressure, plasma renin, and aldosterone levels. Thiazide diuretics can also be effective in the treatment of LS, whose mechanism is to correct hypernatremia by aggravating hypokalemia, but it requires a large amount of potassium chloride supplementation, or restriction of salt, or combination of triamterene or amiloride. The plan should be adjusted according to blood pressure and blood potassium, which should be monitored during the treatment. If blood pressure cannot be controlled, diuretic dosage or further salt restriction should be considered. If blood potassium is still low, potassium chloride, triamterene or amiloride should be added. Alkaline potassium salts are not generally available. Amiloride is safe and effective for gravida with LS [75]. Triamterene interferes with folic acid metabolism and is usually avoided during pregnancy. The safety of amiloride and triamterene during lactation is unknown.

18.5.1.9 Prognosis

The main symptoms of LS are caused by hypertension and chronic hypokalemia. Positive and correct treatment can prevent complications and improve patients' life quality. Generally, the disease has no possibility of self-healing and can die early because of the disease itself or complications. Despite carrying the same mutation, family members differ in age, HT level, hypokalemia, and cardiac complications. Given that LS treatment differs from other forms of hypertension and that untreated individuals are more likely to have severe complications, children with a family history of early hypertension who are resistant to conventional treatment should be screened for genes [75].

18.5.2 Pseudohypoaldosteronemia Type II

Pseudohypoaldosteronemia type II (PHA2, Gordon syndrome) is known as familial hyperkalemia and hypertension (FHH); it has high blood potassium, high blood chlorine, and low renin hypertension, accompanied by short stature, intellectual deficiency, incisor absence, poor muscle strength, and other characteristics of clinical syndromes. The disease is mostly autosomal dominant inheritance and familial, but sporadic cases have also been reported.

18.5.2.1 Epidemiology

A 15-year-old Australian teenager was first reported in 1964. In 1970, Gordon reported a 10-year-old girl with short stature, missing lateral incisors, lower limb weakness, and mental retardation. Blood pressure 160/110 mmHg, blood potassium (8.5 mmol/L), blood chlorine (117 mmol/L), acidosis (blood HCO^{3-} 14 mmol/L, pH 7.30), however with low plasma renin activity and aldosterone excretion. With

normal renal arteriography, renal biopsy, urine concentration function and a good prognosis, it was named Gordon syndrome in 1973. It is reported that most cases are familial, but also some sporadic cases. The incidence is extremely rare. The age of onset ranged from birth to 52 years old, mostly from 10 to 30.

18.5.2.2 Etiology

Recent studies have shown that the disease is caused by mutations in the WNK gene encoding protein kinase, Cullin-3 (CUL3) and Kelch3 (KLHL3) genes [76–78]. WNK genes belong to serine-threonine kinase family proteins, which are expressed in the distal nephron of collecting duct and regulate K-H exchange and chlorine uptake. CUL3 and KLHL3 are components of E3 ubiquitinated ligase complex, which ubiquitinates WNK kinase and degrades it by proteasome. The disease is divided into five types: PHAII-A is associated with chromosomal region 1q31-q42, but no genetic variation has been found. PHAII-B refers to WNK4 gene missense mutation on 17q21.31, PHAII-C refers to deletion of intron 1 in 12p13.33 WNK1 gene, PHAII-D refers to KLHL3 gene mutation on 5q31.2, and PHAII-E refers to CUL3 gene specific mutation [77, 78] on 2q36.2. CUL3-FHHT has the most severe phenotype among the four mutants. Except that some KLHL3 variants are recessive inheritance, others are autosomal dominant inheritance.

18.5.2.3 Pathogenesis

Wild-type WNK4 inhibited the distal nephron Na+-Cl co-transporter (NCC), while mutant WNK4 inhibited NCC [79]. Activation of NCC in the distal convoluted tubule (DCT) is the main driving force of the disease. WNK1, an upstream regulator of WNK4, can inhibit the inhibition of NCC by WNK4 [80]. In WNK1-FHH, WNK1 was increased due to intron 1 deletion [76], which prevented WNK4 from inhibiting NCC and enhanced ROMK (extrarenal medullary K^+ channel) inhibition [80]. WNK4-FHH is a missense mutation in acidic domain exon, which used to bind to KLHL3. After mutation, WNK4 cannot bind to KLHL3 and cannot be degraded by the ubiquitin ligase complex of CUL3-KLHL3 E3, which results in WNK4 accumulation and NCC activity increase. KLHL3-FHH fail to bind to CLL3 or WNK kinase, which results in the increase of WNK kinase. CUL3 can degrade the binding protein KLHL3. CUL3Δ9 (a function gain mutation of CUL3-FHH) can increase degradation of KLHL3, decrease WNK degradation, increase NCC activity, increase Na+, Cl-reabsorption, increase vascular content, decrease K+/H+ secretion, with WNK4 increasing Cl− reabsorption [81], WNK1/4 downregulating ROMK activity, K+ secretion decreasing, resulting in hypertension, hyperchlorination, hyperkalemia, and metabolic acidosis, but normal renal function. In addition, with NCC activity increasing, intracellular Na+ increased, Na+/Ca2+ exchange being inhibited, Ca2+ uptake being reduced, resulting in hypercalciuria [82]. The secretion of renin and aldosterone is inhibited by increased blood volume, while the plasma renin and aldosterone decreased. Volumetric hypertension, inhibition of plasma renin activity, and hyperkalemia were the main manifestations.

18.5.2.4 Clinical Manifestations

Gordon syndrome is mostly familial. The main manifestations are low renin hypertension, high blood potassium, low urine potassium, high blood chlorine, acidosis (distal tubular acidosis), normal or decreased aldosterone, normal adrenal and renal function. Some patients may have high urinary calcium, accompanied by low bone mineral density. Some scholars believe that Gordon syndrome is a trilogy of hypertension, hyperkalemia, and normal glomerular filtration rate (GFR). Most patients are accompanied by short stature, intellectual deficiency, incisor absence, poor muscle strength, and other clinical manifestations.

Hypertension is mainly moderately to severely elevated, and the effect of conventional antihypertensive therapy is poor except thiazide diuretics. Some patients suffer from stroke because of hypertension.

18.5.2.5 Laboratory and Auxiliary Examination

1. Blood electrolyte: High blood potassium is the clue to discover the disease and the basic condition for diagnosis. It is advisable to check blood potassium many times. In general, patients are accompanied by hyperchloric acidosis (normal anion gap). Recently, a 4-month-old girl with blood potassium 7.0 mmol/L, bicarbonate 22 mmol/L, blood pressure 105/58 mmHg, and other biochemical abnormalities was reported. A 6-year-old boy with blood pressure of 120/60 mmHg, blood potassium of 8.6 mmol/L, and bicarbonate of 16 mmol/L had normal glomerular filtration rate [83], whose blood pressure and biochemical parameters become normal after using thiazide diuretics.
2. Renal function test: serum creatinine, urea nitrogen, the clearance rate of endogenous creatinine and the urine concentrate function are usually normal.
3. Plasma renin aldosterone: The activity of plasma renin was significantly decreased, and plasma aldosterone was normal or decreased.
4. Imageology examination: Bilateral kidneys, adrenal ultrasonography, and CT scan were normal.

18.5.2.6 Diagnosis and Antidiastole

Gordon syndrome must be diagnosed with high blood potassium, combined with hyperchloride, metabolic acidosis, hypertension, normal renal function, and low plasma renin activity.

The disease should firstly be differentiated from primary aldosteronism. In addition to hypertension, periodic paralysis, metabolic alkalosis, and low renin activity, others can also manifest as hypokalemia and high plasma aldosterone. Adrenal adenoma or hyperplasia can be detected by B-mode ultrasonography and CT scan, and its hypertension and hypokalemia can be corrected by antisterone.

18.5.2.7 Treatment

The treatment of Gordon syndrome is mainly based on drug. The condition of it can be significantly improved by supplementing a salt-limited diet. Thiazide diuretics are the main therapeutic drugs, which act on the proximal end of DCT by inhibiting Na^+-Cl co-transporter, so that Na^+, Cl-reabsorption is reduced, then correcting

hyperkalemia, hyperchloride and metabolic acidosis, reducing blood volume, effectively lowering blood pressure, and correcting hyperkalemia, hyperchloride and acidosis.

It is suggested that low-dose diuretics should be used and adjusted according to the changes of blood pressure, potassium, and chlorine. Standing use of diuretics may lead to hyperuricemia, hyperglycemia, and hypercalcemia, but such side effects are not common in Gordon syndrome.

18.5.2.8 Prognosis

The disease has a good prognosis. People who can be early diagnosed obtain reasonable treatment, and their abnormal metabolism of water and electrolyte can be corrected early. Sometimes, biochemical disorders may occur at birth, while hypertension occurs later. Hypertension is seldom seen in childhood, but mostly in adulthood, which has a significant impact on the prognosis. Patients who are sensitive to thiazide diuretics have fewer complications than those with normal hypertension. Their life expectancy is usually normal.

18.6 Monogenic Hereditary Hypertension with Pheochromocytoma

Xintian Cai

18.6.1 Familial Pheochromocytoma/Paraganglioma Syndrome

18.6.1.1 Epidemiology, Pathogenesis

About 10% of pheochromocytoma/paraganglioma is familial and is called familial pheochromocytoma/paraganglioma. Familial pheochromocytoma/paraganglioma refers to two or more pheochromocytoma/paraganglioma patients in a family. The mutations of SDHB, SDHC, and SDHD coding genes of three subunits of succinate dehydrogenase (SDH) are confirmed to be pheochromocytoma/paraganglioma associated pathogenic genes in recent years [84].

The mutation rate of SDHD gene in patients with familial pheochromocytoma/paraganglioma syndrome type 1 (FPGL-1) ranged from 26.1 to 100.0%. Some gene mutations are more common in specific populations [85–88]. The mutation rate of gene in Dutch patients was as high as 93.8–100.0%, all of which were missense mutations. At present, the main gene mutations found in Dutch patients were D92Y, L95P, and L139P, all of which were located in the highly conserved region of SDHD gene [85, 89]. Taschner et al. [87] found that 93.8% of 32 patients with familial paraganglioma had SDHD gene mutations, all of which were missense mutations, 24/32 was D92Y, 6/32 was L139P. The gene mutations found in American lines were nonsense mutations Q36X, R38X, W43X, H50fsX68, Q109X and L128fsX134, missense mutations P81L and H102L, intron mutations IVS2-1G > T, in which

P81L mutations were the most common, found in 61% of families [88]. American scholar Astrom et al. detected SDHD gene in 58 patients with paraganglioma in 23 families. It was found that all the cases were inherited in a father-boy manner [88].

Familial pheochromocytoma/paraganglioma syndrome type 4 (FPGL-4) is an autosomal dominant syndrome caused by SDHB gene mutation. SDHB gene mutation is strongly associated with malignant, multicentric, intraadrenal/extraadrenal pheochromocytoma, which can be seen in familial and sporadic cases [90]. SDHB gene mutation is also found in pheochromocytoma/paraganglioma cases, but its mutation is less common than SDHD gene mutation in both sporadic and familial cases. The mutations of SDHB gene have been found in exons 2, 3, 4, 6, and 7, and mutations can also be found in introns. The mutation types are base replacement, deletion, insertion, etc. Some mutations lead to early termination of protein translation and amino acid substitution, even mutations at the same site can lead to different results [91].

Familial pheochromocytoma/paraganglioma syndrome type 3 (FPGL-3) is an autosomal dominant disorder caused by SDHC gene mutation, and multicentric lesions are rare. So far, only a few SDHC gene mutations have been detected in familial pheochromocytoma/paraganglioma cases. The incidence of SDHC gene mutation in familial pheochromocytoma/paraganglioma was 0–4%. If all reports of detecting the gene were taken into account, the mutation rate was about 2% [90].

18.6.1.2 Clinical Manifestation

All patients with SDHx gene mutation have the following clinical features: multiple extraadrenal tumors, easy recurrence, large tumor size, malignant and/or younger age of onset. FPGL-1 is caused by a mutation of gene SDHD. FPGL-1 accounted for 50% of FPGL [92]. However, there were differences in the proportion among different populations. Most of them are benign non-secretory PGL when it locates on the head and neck, but it has been reported that malignant FPCL-1 has been found in the chest and pelvis [93]. FPGL-3 is caused by a missense mutation in gene SDHC and is common in benign non-secretory tumors of the head and neck. FPGL-4 is caused by the mutation of gene SDHB, which results in the loss of tumor suppressor function. FPGL-4 accounts for 20% of FPGL. Similar to FPGL-1, the higher proportion of FPGL-4 in different populations can be found in the head and neck, mediastinum, and abdominal cavity, and has a higher risk of malignant change than other types [94].

18.6.1.3 Diagnosis

Hereditary pheochromocytoma reported at domestic is generally not diagnosed on the basis of genetic tests, so people without syndrome or family history are often unable to determine their heredity, leading to the fact that the percentage of invitational pheochromocytoma reported in China is significantly smaller than that in foreign countries. At the same time, the majority of patients have developed elevated blood pressure and related symptoms. In conclusion, plasma or urine 3-methoxy (norepinephrine) determination is the first option for the diagnosis of hereditary pheochromocytoma, and genetic examination is the most important

method for early diagnosis. If a genetic test is found positive and there is no evidence of clinical, biochemical, or pathological examination, a biochemical examination should be performed once a year, while a person with a negative genetic examination should be examined for pheochromocytoma, Follow-up requires only the necessary biochemical tests to prevent recurrence: if a family member of a patient with hereditary pheochromocytoma is negative for genetic examination, no biochemical or imaging tests should require [95].

18.6.1.4 Treatment

Surgical resection of the tumor is the only effective method to cure the disease. Even the malignant progressive pheochromocytoma, resection of the tumor can improve the prognosis and quality of patient life. Minimally invasive surgery, whether traditional laparoscopic surgery or robot-assisted laparoscopic surgery, due to its small trauma, less blood loss, short operation time, less postoperative pain, etc. At present, it has become the gold standard for the treatment of adrenal tumors whose diameter is less than 6 cm, and the adrenal tumors larger than 6 cm. If the tumor has no invasion of peripheral blood vessels and organs, it can also be treated by laparoscopy. The diameter of the tumor is larger than 10 cm. Laparoscopic surgery is not the first choice [96]. Other patients who could not tolerate surgery should receive radionuclide therapy, chemotherapy, targeted therapy, etc. [94].

18.6.2 Familial Retinal and Central Nervous System Angiomatosis

Familial retinal and central nervous system angiomatosis (Von Hippel–Lindau syndrome) was first reported by German ophthalmologist von Hippel in 1904. It has been found that VHL syndrome is an autosomal dominant disease and a major type of macular hamartoma. It was initially considered to be multiple retinal hemangiomas and a small cerebral angioblastoma. It was found latterly that the disease often has a family history, cysts and tumors of abdominal organs. Common tumors include hemangioblastoma and renal cell carcinoma of the central nervous system and retina, pancreatic cyst and cystadenoma, pheochromocytoma, etc. As a result of pheochromocytoma, the patient may exhibit paroxysmal hypertension caused by high catecholamine.

18.6.2.1 Epidemiology

The onset age of VHL was mostly before 26–30 years old. There was no epidemiological data in China. The incidence rate was 1/36,000–1/45,499 reported abroad. The incidence rate of male and female was similar, and the mortality rate of female was higher. The apparent rate of Chinese patients is high, 87% in foreign patients when age of 60, in contrast to 97% in Chinese patients [97]. Most of the patients developed from 18 to 30 years old with an average age of 26.3–30.9 years. And the male occupied higher ratio. If not treated, the natural death age is before the age of 50, and the most common cause of death is the complications of small cerebral vascular blastoma and renal cell carcinoma metastasis.

18.6.2.2 Etiology and Pathological Mechanism

Normally, VHL gene is a tumor suppressor gene. The function of the gene is to regulate cell growth. When it is inactivated, the cell growth is out of control, leading to the occurrence of tumor. Under normal condition, VHL gene is a tumor suppressor gene. When deletion or mutation leads to the inability to synthesize normal VHL protein, the tumor may occur. In 1993, Latif et al. mapped the VHL gene to chromosome 3p25/26 by linkage analysis and successfully cloned the VHL gene for the first time. VHL disease is an autosomal dominant hereditary tumor syndrome caused by mutation or loss of VHL gene. Mutation, loss, or methylation inactivation of VHL gene leads to upregulation of its downstream substrate (HIF-α, etc.), thus promoting the expression of a series of pro-oncogene factors, which is the main pathogenesis of the disease, and the externalization rate is close to 100% [98].

18.6.2.3 Clinical Manifestation

Because patients may develop multisystem tumors or lesions, including hemangioblastomas of the central nervous system, retinal hemangiomas, adrenal pheochromocytoma, renal cysts and/or clear cell carcinoma, and multiple cysts and neuroendocrine tumors of the pancreas, the clinical manifestations are complicated.

About 44–72% of patients with VHL syndrome developed hemangioblastoma of the central nervous system. Retinoblastoma is also one of the common clinicopathological changes of VHL syndrome. Forty-five percent to 59%VHL syndrome have retinoblastoma, among them about half of the patients are bilateral. Renal lesions generally occur later than brain and fundus lesions, the average age of onset is 40 years old. There are mainly renal cysts (59–63%) and renal cell carcinoma (24–45%), the both condition occurrence are common. Renal hemangioma, adenoma, and angiomyolipoma can also occur. Pancreatic lesions, including single or multiple cysts, cystadenomas, and neuroendocrine tumors, occur in patients with 35–70%VHL syndrome. Pancreatic cancer is rare with poor prognosis. The main symptoms are nervous system and other organ involvement, including headache, nystagmus, ataxia, intracranial hypertension, fundus changes, etc.

Pheochromocytoma is seen in 10–20% of patients and can be the only manifestation of VHL syndrome. Clinically, typical patients can have paroxysmal hypertension, palpitation, tachycardia, and sweating with severe headache [99].

18.6.2.4 Laboratory and Ancillary Examinations

The main diagnostic methods of VHL rely on auxiliary examinations, including blood routine, blood and urine catecholamine determination, imaging examination, ophthalmoscop, etc. Since the main manifestations of the patient are hemangioblastoma of the central nervous system, retinal hemangioma, adrenal pheochromocytoma, renal cysts and/or renal cell carcinoma, and multiple neuroendocrine tumors, imaging examination is important for the diagnosis, monitoring and discovery of new lesions and complications of the disease. The commonly used screening techniques are MRI or CT plain scan and enhanced scan, abdominal B-ultrasound, and multifunctional radionuclide scan (PET), especially thin slice CT enhanced scan is

the first choice for the diagnosis and follow-up of visceral lesions in patients with VHL syndrome. MRI is more advantageous in the display and diagnosis of central nervous system diseases.

18.6.2.5 Diagnosis and Differential Diagnosis

The clinical diagnostic criteria of VHL were as follows: (1) patients with a family history of VHL syndrome had central nervous system hemangioblastoma, retinoblastoma, or a visceral lesion, (2) patients without family history of VHL syndrome; there were two or more kinds of hemangioblastoma or one kind of hemangioblastoma with one kind of visceral lesion [3]. According to the presence or absence of pheochromocytoma, VHL's disease is divided into two types: type 1 VHL does not include pheochromocytoma, and type 2 VHL includes pheochromocytoma, which is further divided into 2A, 2B, and 2C subtypes. Type 2A includes pheochromocytoma, pancreatic cyst or tumor, retinoblastoma, and central nervous system hemangioblastoma, but does not include renal cell carcinoma. Type 2B includes pheochromocytoma, retinoblastoma, pancreatic cyst or tumor, renal cell carcinoma, and central nervous system hemangioblastoma. Type 2C only had pheochromocytoma, which was rare.

Gene diagnosis criteria: At present, gene diagnosis is considered to be the gold standard for diagnosis, which can be diagnosed when there is a pathogenic mutation in the VHL gene. If it is a new mutation, the functional changes caused by it should be further detected at the mRNA and protein levels in order to determine its pathogenicity. About 20% of patients with VHL disease in China are large deletion, and there is chimerism, which should be considered in gene detection [100].

Because of the lag of clinical diagnostic criteria, some patients do not meet the clinical standards in the early stage of the disease, which is easy to lead to a missed diagnosis. Therefore, when a patient meets one of the following conditions, a suspected VHL disease should be considered for genetic testing: single retinal or central nervous system hemangioblastoma, familial or bilateral pheochromocytoma, familial or multiple or early-onset renal cell carcinoma, and endolymphatic sac tumors [101].

18.6.2.6 Treatment and Prognosis

VHL disease is a genetic disease, and there is no cure at present. The treatment of tumors in different organs is also different. The incidence of systemic tumors should be considered comprehensively in the treatment of tumors. The treatment of renal cell carcinoma associated with VHL's disease includes active monitoring, nephron sparing therapy, radical treatment, and drug therapy. VHL's disease is a hereditary tumor syndrome with poor prognosis. The median survival time reported abroad is 67 years old for male and 60 years for female. The data of VHL disease patients in China were 62 years old for males and 69 years old for females, but there was no significant difference between the two groups [102]. Attention should be paid to the pedigree investigation of patients with VHL syndrome. Gene detection is an effective method for early diagnosis. Gene detection and screening of fetuses and selective pregnancy are the key to block the occurrence and inheritance of the disease.

18.6.3 Pheochromocytoma with Multiple Endocrine Tumors Type II (MEN-2)

Multiple endocrine tumor (MEN) syndrome is a kind of syndrome caused by two or more endocrine gland tumors or hyperplasia at the same time or successively in patients. It is autosomal dominant inheritance and can be divided into MEN-1 and MEN-2. The hypersecretion of MEN-1 non-catecholamines is not described here. MEN-2 is a clinical syndrome characterized by medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism. According to whether there is cell proliferation in hyperparathyroidism, it can be divided into multiple endocrine adenoma syndrome II A (MEN-2A) with cell proliferation, and multiple endocrine adenoma syndrome II B (MEN-2B) with only hyperparathyroidism and no cell proliferation. MEN-2A, formerly known as MEN-II, also known as Sipple syndromes, includes pheochromocytoma (possibly bilateral and extraadrenal), medullary thyroid carcinoma, and parathyroid hyperplasia. MEN-2B, once called MEN-III, includes medullary thyroid carcinoma, pheochromocytoma, and mucosal neuroma. In recent years, some scholars considered that MEN2 should be divided into three categories: MEN-2A, MEN-2B, familial medullary thyroid carcinoma [103].

18.6.3.1 Epidemiology

The prevalence of MEN-2 is approximately 1/35,000, with a male to female ratio of about 1:1. More than 500 families have been reported abroad, but in China scattered as the main. Among the subtypes of MEN2, MEN-2A was the main form, accounting for 80% of MEN2, followed by familial medullary thyroid carcinoma, accounting for about 10–20%, and MEN-2 were less, accounting for 5–10% [104, 105].

18.6.3.2 Etiology and Pathological Mechanism

Since the cloning of RET gene in 1995, it has been found that almost all MEN-2 families are caused by RET gene mutation, and it is further found that the type of RET gene mutation is well correlated with the clinical manifestation type of MEN2.

RET proto-oncogene is a tyrosine kinase gene, located in the long arm of chromosome 10, 60 kb in length, containing 21 exons, encoding 1114 amino acids of tyrosine kinase receptor superfamily RET protein. Tyrosine kinase receptors are a group of transmembrane receptors, which are divided into the extracellular domain, a transmembrane region, and intracellular region. The extracellular part contains four adhesin-like repeats, a calcium-binding domain, and a cysteamine-rich structural region. The intracellular part is a structural region containing tyrosine kinase, in which tyrosine residues can be automatically phosphorylated after the receptor binds to the ligand, activating the downstream signal pathway. The proto-oncogene of RET was mutated, and the protein function of the corresponding RET was also changed. The production of tyrosinase was not regulated by phosphorylation, resulting in tumorigenesis of the corresponding endocrine glands [106].

RET proto-oncogene mutation is the genetic basis of the disease. RET proto-oncogene mutation can be detected in 87% of MEN-II families. Different mutation sites can induce different mutation subtypes. Most of the RET mutations associated

with MEN2 were heterozygous point mutations, and the mutation hot spots were mainly located in exons 5, 8, 10, 11, and 13–16 of RET gene. Ninety-five percent of MEN-2A were mutations in exons 10 and 11 of RET extracellular region, showing that cysteine residues were replaced to form distorted homodimers, resulting in constitutive activation of intracellular tyrosine kinase [107, 108], manifested as medullary thyroid carcinoma, hyperparathyroidism, pheochromocytoma. Ninety-five percent of MEN-2B patients were caused by M918T mutation in exon 16 of RET gene, 2–3% by A883F fork in exon 15 of RET gene, and MEN-2B could also be caused by rare V804M, Y806C, S904C, E805K mutations [108]. The clinical manifestations are pheochromocytoma, medullary thyroid carcinoma, and multiple mucosal neuromas (lip, tongue, buccal membrane, eyelid, conjunctiva, cornea, gastrointestinal tract, marfanoid habitus), but no lens or aortic lesion.

Therefore, it is possible to screen some patients with MEN-2 by detecting RET proto-oncogene mutation in patients with clinically diagnosed pheochromocytoma. The detection of RET proto-oncogene mutation in the offspring of these patients is helpful for early diagnosis of MEN-2. According to foreign literature, the mutation rate of RET gene is 4.8–7.8% in patients with sporadic pheochromocytoma. At present, the reported mutation sites of RET are 634TGC → TAC (C634Y), TGC → CGC (C634R), GAG → AAG (E632K), etc.

18.6.3.3 Clinical Manifestation

MEN-2 is characterized by medullary thyroid carcinoma (MTC), accompanied by endocrine tumors such as pheochromocytoma (PHEO) and/or parathyroid hyperactivity (HPT). About 90% of patients with MEN-2A syndrome have MTC, 40–50% patients have pheochromocytoma, and 20–30% patients have parathyroid hyperactivity (parathyroid cell hyperplasia or adenoma). Only a small number of MEN-2A patients with symptoms of secondary tumor syndrome, such as changes in skin starch, excessive skin production of adrenal corticosteroids. A small number of MEN-2A patients showed Hirschsprung's disease, due to the lack of autonomic ganglion cells in the distal colon parasympathetic plexus caused by a congenital giant colon. Ninety percent of patients with MEN-2B syndrome were MTC, 40–50% were pheochromocytoma, and there were very few with endocrine tumors such as mucosal ganglion tumor. Parathyroid hyperactivity is rare in MEN-2B [105, 109, 110]. Clinical features of one glandular lesion often cover up other endocrine gland tumors, so when a certain endocrine adenoma is found, it is necessary to consider the possibility of this syndrome.

18.6.3.4 Laboratory and Ancillary Examinations

The main symptoms of MEN-2 syndrome are medullary thyroid carcinoma and pheochromocytoma. Any clinical symptoms should be examined according to the possible existence of MEN.

1. Blood tests: Blood electrolytes, blood glucose, blood levels of T3, T4, aldosterone, cortisol, glucagon, calcitonin, parathyroid hormone, growth hormone, serotonin and other hormones should be checked regularly. It is convenient for

early diagnosis of this disease. Urinary VMA and serum norepinephrine, epinephrine and calcitonin were significantly increased, which had specific significance for diagnosis.
2. Provocation test: Pure pheochromocytoma was positive with glucagon or tyramine. If pheochromocytoma complicated with other endocrine gland tumors, especially thyroid myeloid carcinoma, the tyramine test was negative. Glucagon was positive (see Chap. 19, Sect. 19.4, adrenal hypertension).
3. Imaging examination: Because of the tissue-specific expression of MEN-2 lesions, thyroid hormone-secreting thyroid gland, calcitonin-secreting parathyroid gland, and adrenal medulla chromaffin cells show marked proliferation and tumorigenesis. X-ray, B-ultrasound, and CT scan are helpful to detect thyroid medullary carcinoma, adrenal tumors, and parathyroid tumors.

18.6.3.5 Diagnosis and Differential Diagnosis

For those with two or more endocrine gland lesions, the possibility of MEN should be considered. Although the main feature of MEN-2 is that almost all patients exhibit thyroid myeloid carcinoma, pheochromocytoma is still be the first symptom of MEN-2. Therefore, it is necessary to screen the RET gene in sporadic pheochromocytoma patients with thyroid myeloid carcinoma.

MEN-2 should be identified with MEN-1. MEN-1 is mainly thyroid, pituitary, and pancreatic tumors, and MEN-2A is characterized by thyroid myeloid carcinoma, pheochromocytoma, and hyperparathyroidism. On the other hand, MEN-2B was mainly polyneuromas with thyroid medullary carcinoma and/or adrenal pheochromocyte.

18.6.3.6 Treatment and Prognosis

The treatment principle is to take corresponding measures for the main endocrine hyperthyroidism. Tumors can be resected surgically, or treated with radiotherapy or chemotherapy. The prognosis of the patients with rapid destruction of canceration is poor. The treatment of MEN-2 hypertension is basically the same as that of pheochromocytoma (see Chap. 19, Sect. 19.4, pheochromocytoma). With regard to the treatment of MEN2-PHEO, Castinetti et al. [111] analyzed the clinical data of 563 cases of MEN2-PHEO. The risk of recurrence after adrenalectomy with adrenocortical function preservation (ASS) was 2.6% [average follow-up time was (10 ± 9.5) years]. ASS significantly reduced Addison-like or lifelong hormone dependence in patients after total adrenalectomy (87% vs. 43%, $P = 0.03$), suggesting that laparoscopic ASS is the priority choice of operation for the treatment of MEN2-PHEO. The ATA-2015 guidelines [108] also recommend that treatment of MEN2-PHEO should give preference to laparoscopic ASS. The guidelines emphasize that women with MEN2-PHEO are better placed to dispose of PHEO 3 months prior to the planned pregnancy or early or mid-term of the marriage. The etiology of MEN-2 is unknown and there is obvious familial tendency of dominant hereditary diseases, so we can refer to the preventive measures of hereditary diseases. Preventive measures run from pre-pregnancy to antenatal.

18.6.4 Hereditary Neurofibromatosis Type I

Neurofibromatosis (NF), also known as polyneurofibroma or Von Recklinghausen's disease, is an autosomal dominant genetic disease caused by ectodermal dyshistogenesis. It is characterized by multiple systems and organs involved, especially the central nervous system. The tumor is divided into two types: NFI is characterized by flaky brown pigmented spots (milk coffee spots) and neurofibroma-like skin tumors, often accompanied by a variety of deformities and other diseases, for example scoliosis, meningioma and iris nodule (Lisch nodule) of the eye, and can appear language disorder, mental retardation, malignant transformation, etc. NFII neurofibromatosis is a central neurofibromatosis characterized by bilateral acoustic neurilemmoma, meningioma, and schwannoma of the dorsal root of the spinal nerve; there are few skin changes. Hereditary neurofibromatosis type I, abbreviated as neurofibromatosis type I, accounts for 5% of pheochromocytoma and is a special type of secondary hypertension.

18.6.4.1 Epidemiology and Pathogenesis

The incidence of hereditary neurofibromatosis was about 1/2600–1/3000. About half of the cases are familial, while the rest are the result of sporadic mutations. The NFI gene is located at 17q11.2. Neurofibromin is a protein product encoded by the gene. It is often highly expressed in many tissues, including brain, kidney, spleen, and thymus, and belongs to the guanosine triphosphate hydrolase (GTP enzyme) activating protein (GAPs) family. It stimulates endogenous GTP enzyme activity in Ras p21 family and negatively regulates Ras signaling pathway. At present, the pathogenesis of NFI is considered to be related to gene mutation, hormone, telomerase, angiogenesis factor, tumor microenvironment, electrophysiological changes, and other factors [112–115].

18.6.4.2 Clinical Manifestation

The main clinical manifestations of NFI included brown or coffee spots; blue-red spots and pseudo atrophic spots; multiple neurofibroma; ocular iris nodule (Lisch nodule); visual and hearing effects; seizures and mental retardation; intracranial and spinal cord tumors, including optic neurogliomas, astrocytomas, schwannomas, acoustic neuromas; malignant tumors, mainly neurofibrosarcoma, Other tumors such as leukemia, malignant schwannoma, Wilms tumor, and collateral cell tumor can also be seen; bone defects and congenital dislocation; oral lesions; endocrine abnormalities; gastrointestinal invasion; hypertension, etc.

Hypertension is not uncommon in adult neurofibromatosis type I patients. The cause may be renovascular (multiple neurofibroma in abdominal cavity oppressing renal vessels), or it may be caused by collateral cell tumor or both. Renovascular was more common under 18 years old, which was 7 times higher than that caused by pheochromocytoma; the incidence of pheochromocytoma in NFI patients was 1: 223, while the incidence of NF in patients with pheochromocytoma was between 1:5 and 1:20.

18.6.4.3 Diagnostic

Criteria for the diagnosis of neurofibromatosis type I: This standard was developed by the National Institutes of Health (NIH) in 1987. If there are two or more of the following, it can be diagnosed as NFI: (1) six or more than six coffee spots. Pre-pubertal patients more than 5 mm in diameter and more than 15 mm in diameter after puberty (2) more than two neurofibroma of any type or one fascicular neurofibroma, (3) multiple freckles (Crown sign) in axilla or groin, (4) optic nerve tumor, (5) more than two Lisch nodules (iris dislocation tumor); (6) bone damage different from other diseases, if the long bone is cortical sphenoid-wing dysplasia or thinning with or without pseudarthrosis, (7) one first-degree relatives (parents, siblings, or children) suffer from NFI according to the above criteria.

Although mutated genes can be found by laboratory tests for NF-1, NF-1 is often diagnosed by the clinical manifestations of the patients in view of the typicality of their lesions [115, 116].

18.6.4.4 Treatment

The treatment of NFI should be based on the age of the patient. (1) Coffee spot does not need to be treated in infancy, but the fracture caused by tibial dysplasia should be prevented actively. (2) Preschool children begin to appear freckles between 3 and 5 years old, neurogliomas and optic nerve abnormalities can also occur (should be diagnosed by craniocerebral MR). Learning disabilities are also one of the most comm on manifestations of NFI, accounting for 40–60% of NFI. Generally speaking, the ability of behavior and coordination was lower than that of normal children. Special attention should be paid to regular examination and assessment of children's blood pressure. Some children with NFI may have migraine, nausea, abdominal pain, but need to exclude other causes of headache, abdominal pain, can use drug for prevention and treatment. (3) Cutaneous neurofibroma was typical in late childhood, adolescence, and before puberty. Scoliosis could appear in late childhood or adolescence, and short segment spinal fusion was needed. (4) The number and location of cutaneous neurofibroma in adult were difficult to predict, and the lesions in some special sites could be resected. Some people used carbon dioxide laser to treat skin neurofibroma and coffee milk spot, and achieved a certain effect.

Hypertensive patients with NFI should be treated with antihypertensive therapy. According to the etiology of hypertension, the treatment plan was determined, such as pheochromocytoma, α receptor blocker combined with β receptor blocker; ACEI/ARB in unilateral renovascular hypertension, which could be combined with calcium antagonist. It is necessary to weigh the advantages and disadvantages of bilateral renal vascular diseases and choose multiple drugs combined with hypotension as appropriate.

The risk of malignant tumor in NFI was 5%. Malignant peripheral schwannoma sometimes originates from plexiform neurofibroma, so if plexiform neurofibroma grows rapidly or appears pain, it should be treated surgically as soon as possible and check for metastasis.

18.6.5 TMEM127 Gene, MAX Gene, and Pheochromocytoma

In recent years, researchers have reported other susceptibility genes of pheochromocytoma and paraganglioma, including SDHA (succinate dehydrogenase subunit A), TMEM127, MAX (Myc related factor X), and SDHAF2 (succinate dehydrogenase complex assembly factor 2). Compared with the classical susceptibility genes, these newly reported susceptibility genes have relatively few clinical data, and the pathogenesis of these susceptibility genes with PHEO/PGL has yet to be determined [117].

The total mutation frequency of SDHA, TMEM127, MAX, and SDHAF2 gene combinations was about 6.0%. The highest mutation rate of SDHA was about 3.0%, while the mutation frequencies of other genes were TMEM127 (2.1%), MAX (0.8%), and SDHAF2 (0.1%). Therefore, half of the mutations in this group of genes are located in the SDHA gene [118].

SDHA gene is located on chromosome 5q15 and consists of 16 exons. The SDHA protein encoded by this gene is composed of 664 amino acids and its mass is about 72.7 kDA. SDHA is a tumor suppressor gene, and heterozygous carrier has an increased risk of paraganglioma, pheochromocytoma, and renal cell carcinoma [119]. The mutation of SDHA gene leads to the decrease of SDH activity and the accumulation of succinic acid. The hydroxylation of HIF-1a is accompanied by the conversion of ketoglutaric acid to succinic acid, and the accumulation of succinic acid can inhibit the modification and degradation of HIF-la hydroxylation and increase the level of HIF-1a protein and its target gene expression. Succinate dehydrogenase increases succinic acid in mitochondria to drive the production of more ROS and promote carcinogenesis.

TMEM127 gene is a tumor suppressor gene, located on chromosome 2q11.2, containing four exons, and the encoded transmembrane protein 127 is a transmembrane protein containing 238 amino acids. TMEM127 gene negatively regulates mammalian rapamycin target protein (mTOR) signaling pathway and regulates cell growth and proliferation; TMEM127 gene mutation mainly affects the abnormality of mTOR signal transduction pathway, which leads to tumorigenesis [120, 121]. TMEM127 gene mutation can lead to PHEO or PGL. TMEM127 gene mutation can be insertion, deletion, nonsense, missense or splicing site mutation. Interestingly, the study found a deletion of the wild-type TMEM127 allele in all TMEM127-related PHEO tissues. It was speculated that the "secondary mutation strike" of somatic cells was an important mechanism and pattern of its pathogenesis [122]. The average diagnostic age of PHEO/PGL was 43.5, 92% were located in the adrenal gland, 44% were bilateral, and 4% were malignant [123]. In addition, in a small number of patients with MTC, breast cancer, and spinal cord dysplasia, there are also germline level TMEM127 gene mutations but not accompanied by PHEO/PGL, the mechanism remains to be determined.

MAX gene is a tumor suppressor gene located on chromosome 14q23 and contains five exons. MAX, a transcription factor encoded by 160 amino acids and belonging to the basic helix-loop helix leucine zipper (bHLHZip) family, plays an important role in regulating cell proliferation, differentiation, and apoptosis as a part of MYC/MAX/MXDI network [124]. Comino-Mendez et al. [8] sequenced the

second generation of total exons in PHEO patients in 2011. It was found that MAX gene mutation could be nonsense, missense, and splicing site mutation, and there was a patrilineal genetic tendency, which was similar to the genetic pattern of SDHD gene. Most of them were bilateral PHEO (61.3%, 19/31), the average diagnostic age was 33.2 years old, and 16.1% ($5 \leq 31$) were malignant. In biochemistry, NE, NMN was significantly increased, E and MN were normal or slightly increased [125]. At present, there are few reports about MAX gene mutation in pheochromocytoma patients, and the related research is lack, and the mechanism of pheochromocytoma occurrence and phenotype is not clear.

SDHAF2, formerly known as SDH5 and also known as SDH assembly factor 2, is located on chromosome 11q13 and consists of four exons. The SDHAF2 protein encoded by this gene is composed of 65 amino acids with a mass of about 6.7 kDA [10]. SDHAF2 gene encodes mitochondrial protein and associated succinate dehydrogenase (SDH) complex (mitochondrial complex II) in mitochondrial respiratory chain, which plays an important role in two electron transfer chains and tricarboxylic acid cycle. SDHAF2 is indispensable in the normal biological function of SDH complex, mainly in SDH-dependent respiration, and interacts with the catalytic subunit of the complex [126]. The decrease of SDHAF2 expression leads to the loss of the function of SDH complex, the decrease of the stability of enzyme complex, and the significant decrease of all subunits, thus losing the role of tumor inhibitors [127].

18.7 Brachydactyly-Hypertension Syndrome

Liwei Rong

Brachydactyly with hypertension (HTNB) is a rare autosomal dominant disease and the monogenic hypertension resembles essential hypertension so far. HTNB was first described by Bilginturan and colleagues in 1973 and then the gene responsible for this syndrome was mapped to chromosome 12p12.2-p11.2. A recent study reported that six missense mutations in PDE3A (encoding phosphodiesterase 3A) in HTNB are responsible for hypertension by contributing to a general increase in peripheral vascular resistance [128, 129].

The exact mechanism and pathogenesis of HTNB are still not very clear. HTNB showed increased sensitivity to sympathetic stimuli and severe abnormalities in baroreflex buffering. Furthermore, the ventrolateral medulla may be compromised in these patients, because neurovascular anomalies are a regular finding. Affected persons exhibited neurovascular contact from a looping posterior inferior cerebellar artery that may impinge on the brain stem at the area of the ventrolateral medulla. A China genome-wide parametric linkage analysis identified a new locus for essential hypertension on chromosome12p which overlaps with the assigned locus that causes HTNB [130]. Maass et al. found the mutation of pDE3A gene in 12p12.2 from six families HTNB. These mutations up-regulate the hydrolytic activity of cAMP and produce low levels of cAMP in cells, which may activate arteriogenesis and lead to hypertension. In addition, cartilage formation is regulated by reducing the expression of PTHLH, which ultimately leads to short fingers [128].

The main clinical manifestations: Affected individuals have type E brachydactyly and are ~10 cm shorter than nonaffected persons, featured sharply increasing blood pressure with age and die of stroke (generally before age 50 years). Endocrine function, electrolyte and acid-base status, and calcium and phosphate homeostasis are normal. HTNB resembles essential hypertension, because renin, aldosterone, and norepinephrine responses are normal and no salt sensitivity is present [131, 132].

The treatment of HTB needs further study. At present, treatment recommendations are based on current guidelines for antihypertensive treatment in childhood and adolescence. The main purpose is to control blood pressure and prevent target organ damage of hypertension. Maass et al. reported that PDE3 inhibition could lower blood pressure in patients with hypertensive heart failure and in patients with pulmonary hypertension. cAMP inhibits myosin light chain kinase (MLCK) and causes VSMC relaxation, milrinone is a specific inhibitor of PDE3A, but a high concentration of this drug is necessary to inhibit the activity of certain types of mutant PDE3A as compared with the wild-type protein. VSMC (vascular smooth muscle cells)-expressed PDE3A deserves scrutiny as a therapeutic target for the treatment of hypertension [128].

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Secondary Hypertension of Other Type

19

Run Wang, Zainuremu Tuerdi, Yunwei Bi, Fengyu Pan, Zhihua Zhang, Wenbo Yang, and Gulinuer Duiyimuhan

19.1 Crush Syndrome

Run Wang

Crush syndrome is a type of traumatic syndrome in which muscle-rich limbs are squeezed for a long time, causing rhabdomyolysis, leakage of muscle cell contents, and absorption into the blood, thereby causing systemic damage.

19.1.1 Epidemiology

The history of crush syndrome can be traced back to the 1909 Messina earthquake and the First World War, and in 1941, the concept of "Crush syndrome" was proposed, also known as Bywater syndrome. It often occurs in accidental injuries such as building collapse, engineering landslides, and traffic accidents. In the event of a serious disaster such as a war or a strong earthquake, it can appear in batches. High-energy crushing and impact injuries have become the main cause of non-group disasters. In addition, long-term self-compression of the limbs caused by various reasons can also cause crush syndromes, such as drunkenness, coma, freezing, anesthesia, and drug poisoning [1].

19.1.2 Pathogenesis

The initiating factor of crush syndrome is perfusion disorder and reperfusion injury of the affected muscle group. Direct muscle trauma and prolonged muscle

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compression cause damage to the microvasculature of the affected muscle group, on the one hand, strengthen muscle contraction; on the other hand, activation of a large number of enzymes in the cell (such as phospholipase A2 and various proteases) causes cell lysis and irreversible ischemic necrosis of the affected muscle group. On the one hand, a large amount of intravascular fluid extravasates into the interstitial space due to increased capillary permeability of the injured limb, resulting in hypovolemic shock; on the other hand, after the injured limb releases external pressure, the necrotic muscle tissue releases or stimulates the body to produce myoglobin, creatine, adrenaline, norepinephrine, and other vasoactive substances and cytokines eventually develop into systemic inflammatory response syndrome and multiple organ dysfunction, leading to a series of systemic damage.

The substances harmful to the kidneys cause renal ischemia and tissue destruction, which are the two major causes of renal dysfunction.

When a crush injury occurs, both traumatic blood loss and exudation of intravascular components can result in hypovolemia. Extensive edema and extracellular fluid retention lead to hypovolemic shock.

During reperfusion, intracellular potassium ions enter the systemic circulation from the necrotic muscle cells through the damaged muscle fiber membrane, resulting in cardiac arrest at this stage, usually 2 h after the rescue.

After the injury, plasma fibrinogen and platelets are significantly increased, necrotic tissue releases a large amount of thromboplastin, blood is hypercoagulable, endothelial cell damage and acidosis lead to hemodynamic changes, and microcirculatory disorders appear in the body and even diffuse intravascular coagulation.

Previous studies view that posttraumatic muscle ischemic necrosis and renal ischemia are the two central links in the pathogenesis. Recent studies have shown that limb ischemia-reperfusion injury is the main pathogenesis, and oxygen free radical (OFR) plays an important role in its pathogenesis [2].

19.1.3 The Mechanism of Hypertension Caused by Crush Syndrome

Patients with crush syndrome are more likely to have hypovolemia and shock, but a few patients may have hypertension. The mechanism of hypertension is as follows:

After the initial injury to the external pressure, the necrotic muscle tissue releases or stimulates the body to produce vasoactive substances such as adrenaline, norepinephrine, vasopressin, angiotensin II, thromboxane, endothelin, etc., through the recovered blood circulation. In the body, it can cause short-term hypertension.

Renal ischemia and tissue damage are harmful to the kidneys, and as a result, acute renal dysfunction, renal blood flow, and glomerular filtration rate decrease, the pressure of the intra-renal arterioles decreases, and blood flow decreases. Then the stretch stimulation of the arteriolar wall is weakened, the stretch receptor is

activated, and the release of renin is increased. At the same time, due to the decreased pressure and blood flow in the small arteries and the activation of the dense plaque receptor, the release of renin can also be increased. In addition, granulosa cells are sympathetically innervated, and when circulating blood volume is reduced, renal sympathetic nerve stimulation can be caused, the release of renin can also be increased, and the secretion of renin is increased, resulting in the activation of angiotensin II. Angiotensin II can causes vascular smooth muscle muscle contraction, while acting on the kidneys and adrenal glands, promoting renal reabsorption of sodium and water, leading to hypertension and even heart failure.

Crush syndrome treatment is not a timely or improper treatment, such as improper use of mannitol causes osmotic nephropathy, leading to chronic renal insufficiency or kidney damage, combined with sodium retention, renin-angiotensin increase, and some relaxation. Insufficient vascular factors can also lead to hypertension [2].

19.1.4 Pathology

The main pathological change in the compression site is ischemic necrosis. It can occur on the skin, muscles, and kidneys, and kidney is the main affected organ.

1. Skin damage: Soft tissue swelling in the compressed area, increased skin tension, erythema, ecchymoses, blisters in the affected area, pale body surface, low skin temperature.
2. Muscle damage: The muscles are white-yellow, brittle, and fragile, and the response to external stimuli is weakened or disappeared. Under the microscope, muscle capillary embolism, rupture, swelling of endothelial cells, and interstitial edema are seen.
3. Renal damage: Kidney damage in crush syndrome is acute renal failure characterized by massive myoglobin deposition in the renal tubules. Gross specimen examination showed swelling of the kidney, enlargement of the volume, dark red color, the unclear boundary between the cortex and medulla, and congestion in the medulla. Light microscopy revealed glomerular congestion and swelling.
4. Electron microscope examination: Electron Microscopy

The glomerular capillary epithelial cells are swollen, the diameter of the window is reduced, and the number is reduced. The electron density of the basement membrane decreases, the foot process is swollen, the inner protrusion fissure shrinks, and part of the foot process can be detached from the basement membrane.

The renal tubules changed to the proximal tubule epithelial cells, the villi detached and disappeared, the tubular epithelial cells swelled, the nuclear chromatin clustered and accumulated in the periphery of the nuclear membrane, the rough endoplasmic reticulum expanded, the mitochondria swollen, the sputum disappeared, and the microfilament decreased. In the advanced stage, renal tubular epithelial cells can be replaced for repair and regeneration [3].

19.1.5 Clinical Manifestations

There are no obvious symptoms in the early stage after the injury, and then the limbs are progressively swollen, the skin is tense, shiny, erythema, blisters, ecchymoses, skin necrosis, swollen limbs, thickening, hardening, and tenderness. The affected muscles contracted weakly, the muscle tension decreased, and the passive traction was severe. The blood supply to the distal part of the affected limb is impaired, the skin is white, and the skin temperature is lowered. The performance is characterized by whitening of the hands and feet and weakening of the terminal blood vessels. The skin is ruptured, and a large amount of bloody exudate and necrotic tissue are visible. Joint activity is limited, and the area of nerve distribution is reduced.

When the injured limb releases the external pressure, due to a large amount of water entering the muscle cells, the effective circulation of blood is insufficient, hypotension, and shock. Shock is divided into two stages. After the injured limb begins to swell, the surrounding blood vessels undergo a strong compensatory contraction, blood pressure may not decrease, but the pulse increases, the pulse pressure difference decreases, and the skin is wet and cold. As the swelling of the injured limbs worsens, a large amount of plasma extravasation and toxins are absorbed, and symptoms of hypovolemia and vascular shock appear, which are manifested by decreased blood pressure, rapid pulse rate, reduced pulse pressure difference, decreased central venous pressure, and superficial vein. Atrophy can lead to burnout, ambition, and even disturbance of consciousness.

In acute renal failure, there are no urine, oliguria, traumatic shock, systemic failure, as well as water, electrolytes, acid-base balance disorders, metabolic acidosis, and azotemia caused by oliguria and anuria. If the muscle recovers faster than acute renal failure in the later stage of the disease, a large amount of fluid enters the blood circulation, and renal failure leads to retention of water and sodium, causing high-capacity state, systemic edema, pulmonary edema, hypertension, heart failure, and the like. At the same time, sodium retention can increase the water and sodium content of vascular smooth muscle cells, thicken the blood vessel wall, decrease the elasticity, increase the vascular resistance and the reaction to catecholamines, which can also increase blood pressure.

Characteristics of hypertension: In most patients, the blood pressure is mildly or moderately elevated, and the blood pressure can gradually return to normal as the renal function gradually recovers. However, due to the continuous deterioration of renal function, some patients gradually develop chronic renal dysfunction and form renal parenchymal hypertension, which is characterized by severe hypertension. Conventional antihypertensive drugs are difficult to control blood pressure, and it is easy to combine target organ damage, such as changes in fundus diseases. Heavy, it is prone to cardiovascular disease, more likely to progress to malignant hypertension. In addition, it should be emphasized that persistent hypertension can accelerate the progression of kidney disease, damage kidney function, and form a vicious circle [2, 3].

19.1.6 Laboratory Inspection

1. Blood routine examination: Early knowledge of blood composition, red blood cells and hemoglobin content decreased, used to determine the amount of blood loss.
2. Urine routine: Urine is brown and soy sauce color, containing myoglobin, hemoglobin and pigmented tube type, rare red blood cells, acidic, and increased specific gravity.
3. Blood electrolyte: High potassium, high phosphorus, low calcium, low sodium, hypochloremia can occur.
4. Blood gas analysis: The monitoring of arterial blood gas and pH is very important for judging acid–base imbalance, and it is generally characterized by metabolic acidosis.
5. Determination of renal function: Elevated serum creatinine and urea nitrogen.
6. Blood creatine kinase (CK): CK is the most sensitive indicator of the degree of muscle damage.
7. Determination of coagulation function: To determine whether the coagulation and fibrinolysis system is normal, to prevent the appearance of DIC.

19.1.7 Diagnosis

According to the patient's history of injury caused by heavy objects for a long time, the compression site is progressively swollen after reperfusion, continuous oliguria or no urine for more than 48 h, and urine color appears reddish brown, dark brown within 24 h, hematuria, and limb swelling. Hematuria is proportional to the degree of limb swelling. The infusion test excludes pre-renal oliguria. It is not difficult to diagnose the crush syndrome, but it is necessary to pay attention to the injury. After the rescue is relieved under heavy pressure, it does not necessarily show serious symptoms immediately. At this time, it can be misdiagnosed as a minor injury and relaxed to observe the delay in treatment.

The diagnostic criteria for renal injury in crush syndrome using the Renal Disaster Relief Task Force(RDRTF) is: the patient has a crush injury and is accompanied by any of the following: urine volume <400 mL/day; blood urea nitrogen >40 mg/dL; serum creatinine >2.0 mg/dL; blood uric acid >8 mg/dL; serum potassium >6 mmol/L; blood phosphorus >8 mg/dL; or blood calcium <8 mg/dL. This standard was generally accepted in the diagnosis of ARF caused by the crush syndrome after the Marmara earthquake in Turkey in 1999. Vanholder R recommends the use of acute kidney injury (AKI) instead of ARF to evaluate earthquake-related renal impairment. AKI defines an increase in serum creatinine over 0.3 mg/dL or a 50% increase within 48 h, or a urine volume of fewer than 0.5 mL/kg/day is more than 6 h.

According to the severity of the injury and clinical manifestations, the crush syndrome can be divided into three levels [1]:

- Class I: Crush injury. There is osteofascial stenosis syndrome, urinary myoglobin test positive, creatine kinase greater than 10,000 u/L, no clinical manifestations of acute renal failure, immediate fascial interfacial incision.
- Class II: Shock and early renal impairment. Based on grade I clinical manifestations, creatine kinase is greater than 20,000 u/L. Hypotension, shock, elevated levels of urea nitrogen and creatinine.
- Class III: Creatine kinase rises rapidly, and there are signs of renal failure such as shock, oliguria, anuria, metabolic acidosis, and hyperkalemia.

19.1.8 Treatment

Crush syndrome advocates early diagnosis and treatment. The treatment includes on-site first aid, anti-shock, prevention of infection, protection of kidney function, blood pressure reduction, maintenance of water and electrolyte balance, artificial kidney replacement, and nutritional support treatment.

1. First aid and proper treatment are the keys to alleviating the disease and reducing the occurrence of crush syndrome. First, rush to the scene as soon as possible to relieve the external force, shorten the compression time, and properly fix the injured limb. At the same time, analgesic and sedative treatments are given, and the affected limbs are fixed to prevent further damage.
2. Discretionary fluid to prevent shock: In the early stage of the disease, due to a large amount of water entering the muscle cells, the effective blood volume is insufficient and the microcirculation perfusion disorder often leads to shock. It is necessary to actively replenish the fluid to prevent shock.
3. Hypertension therapy: The key to early treatment is to actively prevent the mechanism of elevated blood pressure and avoid renal insufficiency. Patients with confirmed crush syndrome should actively resist shock, alkalinize urine, diuretic to promote the excretion of harmful substances, prevent renal damage; for patients with acute renal insufficiency, once diagnosed, blood purification treatment should be done as soon as possible to solve the capacity load. Excessive weight, retention of harmful substances, reduce the burden on the kidneys, prevent the hypertension, and develop chronic renal insufficiency. For patients with chronic renal insufficiency and hypertension, it is necessary to timely and effectively control blood pressure, delay the progression of renal dysfunction, and the principle is the same as general chronic renal insufficiency treatment.
4. Alkaline urine to prevent renal failure: Alkalinity should be started after the rescue, alkaline drugs can not only organize myoglobin deposition in the renal tubules but also alleviate hyperkalemia.
5. Diuretic promotes the excretion of harmful substances: Diuretics should be used when the urine output is greater than 100 ml in 24 hours. For patients with no reduction in urine volume, mannitol can be used, and for patients with no urine, dialysis should be actively prepared.

6. Renal replacement therapy: Hemodialysis, peritoneal dialysis, or continuous renal replacement therapy can be selected according to individual conditions and medical conditions.
7. Effective prevention and treatment of infection: Severe crush injury, the exogenous infection can occur, endogenous infection can occur, especially intestinal infection, secondary infection is the leading cause of death after acute renal failure. During the on-site rescue process, attention should be paid to protecting the wounds and reducing pollution; using sufficient effective antibiotics as soon as possible; completely removing necrotic tissue; preventing the occurrence of tetanus and gangrene.
8. Treatment of hyperkalemia: Inject calcium ions to counteract the cardiotoxicity of potassium ions, or use insulin plus glucose to calm the spots, so that potassium ions in the blood can enter the cells to reduce blood potassium and actively treat the cause.
9. Treatment of osteofacial compartment syndrome: At present, most scholars agree that if the pressure of the compartment is blocked and the blood supply to the distal limb is blocked, the decompression needs to be performed. For the absence of hypotension, the facial pressure exceeds 50 mmHg, or pressure at 30–50 mmHg for 6 h without a drop is recommended for an incision.
10. Amputation: The area of compression is more than 40% of the injured limb, and the time is more than 4 h; the affected limb has no blood supply or severe blood supply disorder, and it is estimated that there is no function after retention or cannot undergo revascularization; symptoms of systemic poisoning. Severe, after treatment such as incision and reduction, no symptoms are relieved, and the patient's life is endangered; specific injuries of the injured limb, such as gas gangrene; composite injury combined with crush syndrome, need to actively rescue, sacrifice the affected limb, preserved healthy limb; combined with other chronic diseases such as heart disease, chronic nephritis, or advanced age have constituted a crush syndrome. Amputation should be considered in the above cases of crush syndrome.
11. Strengthen nutrition support treatment: Severely traumatic tissue catabolism is strong, the body is often malnourished, affecting tissue and organ repair after injury, reducing the body's immune response. Posttraumatic nutrition supports treatment; first, the energy demand after trauma can be increased by 1–2 times, and then consider the ratio of protein, sugar, and fat and the number of electrolytes, trace elements, and vitamins.
12. Hyperbaric oxygen therapy: It helps to improve the hypoxic state of the injured limb and the whole body, promote the recovery of the injured limb, and prevent and alleviate the damage of other organs.
13. Glucocorticoids: High-dose glucocorticoids have strong anti-inflammatory effects. However, high-dose dexamethasone exacerbates the adverse reactions such as existing infections and internal environmental disorders, and the disaster site environment is difficult to predict, and its risk and limitations need to be weighed, and long-term survival rates are yet to be studied [4–6].

19.1.9 Prognosis

In addition to the direct death caused by trauma, the main causes of the early death of the survivors were hypovolemic shock, hyperkalemia, hypocalcemia, metabolic acidosis, etc. The main causes of late death were acute renal failure, coagulopathy, and hemorrhage and sepsis. The mortality rate of crush syndrome complicated with renal failure has been reported to be over 60%. Most patients surviving with acute renal failure can fully recover from renal function. With the recovery of acute renal failure, blood pressure can be restored to normal by hypertension caused by acute renal insufficiency. However, about 5% of acute renal failure cannot be recovered, and maintenance renal replacement therapy is needed. The proportion of elderly patients can reach 16%. This proportion of patients has persistent hypertension, which needs to be based on artificial kidney replacement therapy. Antihypertensive drugs combined with antihypertensive therapy. About 5% of the patients recover renal function, but will gradually develop chronic renal impairment. Showing that serum creatinine decreased to normal levels, but persistent hypertension, with or without proteinuria. This may be related to compensatory glomerular hypertrophy and secondary focal segmental glomerulosclerosis, as well as long-term use of antihypertensive drugs to slow the heart, brain, kidney and vascular damage of hypertension.

19.2 Burn Injury and Hypertension

Zainuremu Tuerdi

Burn injury is tissue damage caused by heat, electricity, chemicals, lasers, radiation, etc. Thermal burn injury is injury to human tissues or organs caused by boiling liquid (water, oil, soup), hot metal (liquid and solid), flame, steam, and high-temperature gas. Burns or narrow burns usually refer to burns caused by heat. Burn injury was mainly skin injuries. In severe cases, they may affect subcutaneous tissues, muscles, bones, and even internal organs, as well as the parts covered by mucosa, such as eyes, mouth, esophagus, stomach, and respiratory tract [7–9]. Burn injury is a common type of traumatic injury, causing considerable morbidity and mortality [10]. Severe burns can cause a series of systemic pathological and pathophysiological changes in the body. High blood pressure after burn is not uncommon; severe burn patients present with hypertension, some can also cause hypertension crisis, which is life-threatening. At the same time, due to the increase of blood pressure, there is a lot of bleeding during the operation, which affects the operation effect. Therefore, attention should be paid to the necessary treatment in the early stage [11].

19.2.1 Epidemiology

Burn injury is one of the common diseases in peacetime and wartime, with a peacetime incidence of 5–10% of the total population, 10% of which require hospitalization [9]. The incidence of hypertension after burn is about 25% [12]. Lei Shaorong

et al. reported that the incidence of hypertension in patients with >50% burn area was 30.14% [13]. The incidence of hypertension in children after injury was more than that in adults, and it has been reported that the incidence of hypertension in children after burn was 34.8% [14]. Lowery Douglas et al. reported that the incidence of burn hypertensive crisis in children was 30–50% [15]. Falkner et al. reported that temporary hypertension in burns in children was 57.4%, while persistent hypertension accounted for 31.5% [16].

19.2.2 Possible Mechanism of Hypertension After Burn

Severe burns complicated with hypertension are not uncommon, and the exact etiology and pathogenesis are still unclear. In addition, there may be the following mechanisms:

1. Hemodynamic changes: Hypertension is the result of hemodynamic abnormalities such as cardiac output, peripheral vascular resistance, and blood volume. Hemodynamic changes are significant after severe burns. In the early stage of burns, increased vascular permeability leads to fluid leakage and decreased blood volume, In order to maintain blood volume and ensure the perfusion pressure of vital organs, the body can regulate the peripheral blood vessels by neurohumoral regulation, thus ensuring that the blood pressure is not low or even slightly higher, but the pulse pressure difference is small. If the blood volume is not timely supplemented, it can cause severe shock and blood pressure drop. Therefore, the occurrence of hypertension in this period is dominated by low drainage and high resistance. After the shock period, the body's capillary permeability is restored. If the fluid is excessive, especially the sodium ion supplementation, combined with early edema recovery, it is easy to appear volume-dependent hypertension. In the rescue of the above two periods, if blood volume is not replenished in time or (and) fluid volume is not enough, although shock or death will not occur, the patient's blood pressure may rise again due to renal pathological changes, renal dysfunction, and even acute renal failure caused by long-term renal ischemia [11, 17].
2. High metabolic and endocrine disorders: High metabolic state can maintain a few weeks after burn, which is closely related to all kinds of hormone disorder, catecholamine, including epinephrine, norepinephrine, dopamine as high metabolism of neurotransmitters such as increased obviously, role in cardiovascular, can cause the heart rate increase fast, enhance myocardial contraction force, cause small artery contraction, increase peripheral resistance, increase blood pressure. After severe burns, the neurohypophysis secretes adrenocorticotropic hormone, which acts on the adrenocortex and increases the adrenocortical hormone. In addition, during the course of burns, glucocorticoid was continuously increased due to the influence of surgery, infection, and various organ complications. It can stimulate the synthesis of renin substrates, increase the activity of renin, and at the same time cause water and sodium retention, hypokalemia, and hypertension through saline corticosteroids [11, 17].

3. Effects of renin-angiotensin system: After severe burns, blood volume decreases, blood pressure decreases, renal arteriolar perfusion pressure decreases, renin secretion increases, and sympathetic stimulation also increases the secretion of renin by the cells of the glomerular paracycles. When blood volume and blood pressure were restored, sympathetic stimulation was gradually relieved. At this time, however, the burn patient still presents with oliguria and high plasma renin levels. Some studies suggest that burn, shock, stress, and other factors cause renal tubules ischemia, resulting in renal tubules to reduce the reabsorption of sodium chloride function. The ascending branch of the renal tubular loop reduces the reabsorption of NaCl, and the NaCl content of the liquid entering the distal convoluted tubule increases, stimulating the dense plaque and passing the information to the glomerular paracycles, and the cells continue to increase the secretion of renin. The increased secretion of renin can decompose the angiotensinogen in the renal vessels and generate angiotensin I. Under the action of angiotensin-converting enzyme, angiotensin I is converted into angiotensin II. Increased angiotensin in the kidney can constrict the renal tubules, especially the renal cortical small vessels, aggravate renal ischemia, and form a vicious cycle, which is independent of blood volume and blood pressure and the process of self-maintenance in the kidney [11, 17].
4. Brain edema and brain injury: After severe burns, tissue edema can be seen in all organs, especially after a large amount of water and sodium in a short period of time, the incidence of brain edema is high, more common in children. Studies have shown that high voltage burns are often accompanied by increased blood pressure, convulsion, anteroposterior paraplegia, and spasm, which were often accompanied by increased blood pressure [11, 17].
5. Infection: Systemic infection has an important relationship with post-burn hypertension. There were several theories about the mechanism by which infection causes hypertension. (a) Adrenalin, angiotensin, and other endocrine changes after burns undoubtedly have a direct relationship with hypertension. During burn infection, bacterial endotoxin acts on tissue a receptors, etc., stimulating the sympathetic nervous system to secrete large amounts of catecholamines from the adrenal medulla [18]. Below infection condition, the aforementioned hormone is secreted and causes blood pressure to increase. (b) Severe infection can induce respiratory failure, produce hypoxemia, can stimulate the secretion of endothelin-1, increase sympathetic excitability, increase vascular resistance, increase systemic blood pressure, and aggravate the damage of target organs [19]. (c) High Na^+, high blood glucose, and other hypertonic states are directly related to the patient's hypertension. High osmotic pressure will aggravate the degree of hypertension, while high Na^+, high blood glucose, and other conditions are often the result of severe systemic infection [13]. (d) Burns will lead to the change of metabolism and inflammation [20] and may be associated with high blood pressure in patients with inflammatory cytokines, such as a TNF-a, IL-6, IL-8, and IL-17 [21], although the causal relationship has not yet clear, but studies have speculated that chronic inflammation may lead to burn area and the link between the hypertension [22]. In clinical practice, hypertension is often relieved to some extent after infection control [13].

6. Other mechanisms: (a) Cell membrane hypothesis: In recent years, studies on the pathogenesis of hypertension have gradually reached the cellular and molecular level, and it is believed that the abnormal permeability of cell membrane to Na^+ and Ca^{2+} and the cationic transport mechanism may be an important link in the pathogenesis of hypertension. When membrane ion transport dysfunction occurs, extracellular Na^+ enters the cell and Ca^{2+} flows into the cell, resulting in increased intracellular Na^+, Ca^{2+}, and water and elevated blood pressure. Some studies have found that the concentration of Ca^{2+} in the red blood cells of burn patients is significantly increased, the content of ATP in the red blood cells ire reduced, the membrane permeability to ions is increased, and Na^+ and water also enter the cells in large quantities. The increase of intracellular concentration can increase blood pressure through the increase of internal and external resistance of blood vessels, the "reset" of baroreceptors, the influence of sympathetic nerve activity and the transmission of nerve mediators and other factors [11, 17]. (b) Burn patients due to acute pain [23], the presence of cutting scab surgery, inflammatory reaction and hypermetabolism, and other factors strongly stimulate the body to produce a stress response, sympathetic—adrenal medulla system excited, catecholamines released in large quantities, blood adrenaline, norepinephrine concentration increased blood pressure [24]. The stress response caused by burns is usually accompanied by an increase in the level of ACTH, which increases the secretion of aldosterone. However, increased aldosterone secretion is usually not as persistent as ACTH secretion [25]. (c) Post-traumatic stress disorder (PTSD) may play a role in the formation of post-burn hypertension. PTSD is common after burns [26]. PTSD is associated with a variety of chronic conditions, including hypertension [27] and cardiovascular disease [28]. (d) Limited physical activity, fatigue, joint pain, limited range of motion and decreased muscle strength in the years after burn [29]. Physical exercise can lower blood pressure [30], so burn patients with limited physical activity may develop hypertension [22].

19.2.3 Clinical Characteristics of Hypertension After Burn

Studies have shown that post-burn hypertension is related to the degree of burn and the degree of acute kidney injury. For every 5% increase in body surface area burned, the risk of postburn hypertension increases by 12%. Due to the complicated course of acute kidney injury in hospitalized patients, the risk of hypertension after burn has increased by 68% [22]. At the same time, some studies suggest that the area of burn in children with hypertension is not proportional to the burn body surface area.

(1) Increased blood pressure after burns in adults is mainly caused by increased diastolic blood pressure, which is often up to 14.7–16 kPa (110–120 mmHg), and systolic blood pressure is mostly in the range of 20–22 kPa (150–170 mmHg), or as high as 26.7 kPa (200 mmHg) or above [31]. The incidence of childhood hypertension is higher than that of adults, and children's hypertension is more common in the increase of systolic blood pressure [11, 17]. (2) The blood pressure of burn patients

generally increases in 2–3 days [12], decreases with the improvement of the disease, and generally returns to normal in 3–4 weeks [11, 17]. About 1/4 to 1/2 of the patients showed increased blood pressure within 2–3 weeks after burn, some of which lasted for 2–3 months, and even recovered after wound healing, but no patients did not recover [32]. (3) Large-area high-voltage burns combined with hypertension can occur in the early stage, and after treatment and recovery, there is a possibility of recurrence in the late stage. (4) Hypertension is accompanied by tachycardia, anemia, etc., and the heart rate is recovered with the improvement of the condition. (5) Hypertensive crisis occurs easily. (6) Most patients have no obvious symptoms, if the blood pressure was too high can appear dizziness, headache, drowsiness and other symptoms, fundus retinal hemorrhage, optic disc water and venous congestion [11, 17]. If it is caused by brain edema, restlessness or convulsion may occur, especially in children, but the clinical manifestations are not completely proportional to hypertension [31]. (7) Autopsy features: obvious hypertrophy of the heart, left and right ventricle hypertrophy, kidney and adrenal weight increases, especially the adrenal gland increases significantly [11, 17].

19.2.4 Diagnosis

A large area of severe burns, most of the limbs have burn wounds. Because tissue edema often leads to measurement of blood pressure is often not accurate enough, there is no routine daily measurement of blood pressure in clinical work, so missed diagnosis, the incidence of statistics is not reliable. Some patients find elevated blood pressure due to surgery and anesthesia. Because there is no preoperative treatment, intraoperative bleeding, hemostasis is difficult. So in terms of diagnosis, the following aspects:

1. Patients with severe burns should be routinely monitored daily for blood pressure, pulse, and respiration for at least 2–3 weeks.
2. If the limb is swollen, it is difficult to measure by airstream sphygmomanometer, and multifunctional monitor can be used, or trauma detection, such as peripheral artery implantation, can be used to measure blood pressure.
3. When the patient complained of headache and restlessness, the blood pressure was measured in time, the fundus was examined, and CT scan of the kidney and adrenal gland is performed when it is necessary to check whether the adrenal gland is enlarged.
4. If there is an increase in blood pressure, laboratory examination is feasible. (a) The normal circadian rhythm of plasma hydrocortisone disappears in hypertension. (b) Blood potassium is sometimes lower than normal. (c) Blood potassium is sometimes lower than normal. (d) Blood sodium reduces [11, 17].

19.2.5 Treatment

Treatment is often divided into the treatment of burns and secondary hypertension treatment. Patients with severe burns are often transferred to qualified hospitals after

a certain period of time due to the limitations of field conditions, who cannot receive systematic and regular treatment. Timing of treatment and prognosis are crucial, especially early and timely and reasonable treatment, which is of great significance for the prevention and control of blood pressure [11, 17].

Sedation may be used in burn patients with mild elevated blood pressure but no other signs. For patients with moderate elevated blood pressure, oral diuresis and ACEI preparation can reduce blood pressure. For patients with severe burns complicated with hypertension, when skin grafting surgery is necessary, antihypertensive drugs should be applied preoperatively or controlled hypotension anesthesia should be applied intraoperatively to prevent massive bleeding on the wound surface and affect the effect of skin grafting surgery. Furosemide should be the first choice for patients with elevated blood pressure combined with cerebral edema and pulmonary edema [12]. If the blood pressure suddenly rises extremely, a hypertensive crisis (diastolic blood pressure>130 mmHg) should rapidly lower blood pressure, and sublingual mouth or ontains or takes 25–50 mg of captopril, which can be reused if necessary [11, 17]. Venous hypotension may also be considered [12].

Sustained release of verapamil is an ideal drug for stress hypertension, which can improve sleep quality, reduce fatigue, improve physical strength, and reduce the impact on patients with cardiovascular disease, and is relatively safe [17].

19.3 Perioperative Hypertension

Yunwei Bi

Perioperative hypertension refers to the period from the determination of surgical treatment to the treatment related to the operation, that is, during the operation, before surgery, and after surgery, the patient's blood pressure is higher than normal blood pressure by 30%, or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. High blood pressure may be a transient increase in blood pressure and may also be an acute exacerbation of chronic hypertension [33, 34]. Clinical perioperative hypertension refers to the period of surgery (including preoperative, intraoperative, and postoperative), and the acute blood pressure is usually increased in 3–4 days (systolic, diastolic, or mean arterial pressure exceeds baseline by more than 20%). Hypertension often begins 10–20 min after surgery and may last for 4 h. Because high blood pressure increases the risk of anesthesia and surgery, especially the perioperative blood pressure fluctuations may cause stroke, acute coronary syndrome, and renal failure, thereby increasing the perioperative death wind, and other complications. Therefore, it is highly valued by the clinic.

19.3.1 The Mechanism of Perioperative Hypertension

Generalized perioperative high blood pressure may be a continuation of the original hypertension, or it may be a temporary symptom caused by surgical stimulation and excessive anesthesia. Most of them still occur in patients with essential

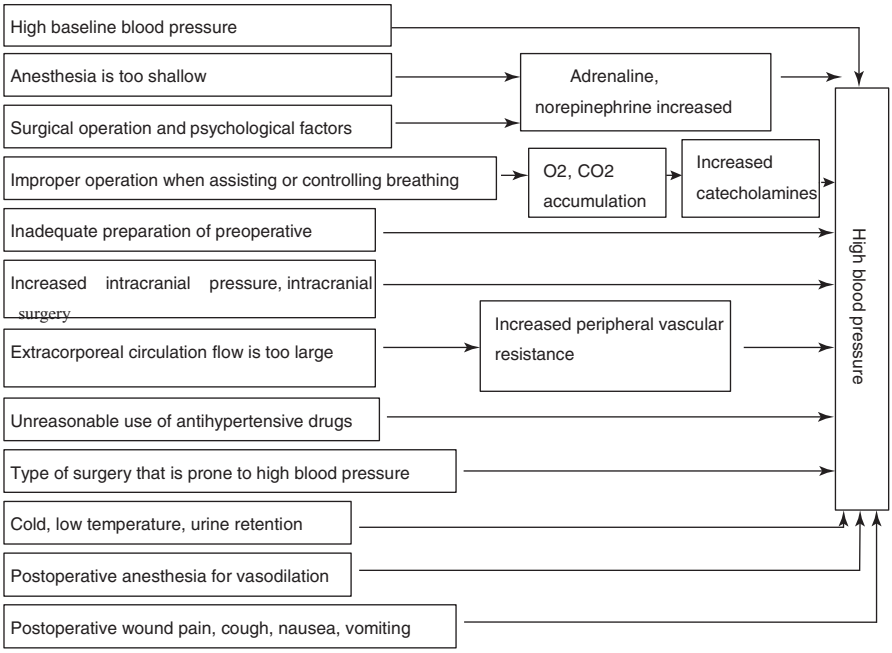

Fig. 19.1 Summary of the mechanisms of perioperative hypertension

hypertension, and some can also occur in patients with secondary hypertension. Only a small number of patients induce acute blood pressure rise due to surgical stimulation, anesthesia, hypoxia, and carbon dioxide retention, and intracranial hypertension [35] (Fig. 19.1).

1. Most of the perioperative hypertension occurs on the basis of the original hypertension. It mainly occurs in essential hypertension (EH) with unknown etiology. EH is currently considered to be a complex disease caused by multiple factors, accounting for about 95% of hypertensive patients. Most of these patients have important heart, brain, and kidney. Organs are damaged by long-term effects of high blood pressure [36].
2. Anesthesia operation leads to high blood pressure, improper anesthesia during anesthesia induction period or incomplete analgesia, sympathetic nerve contraction due to pain during surgery; anesthesia restores early pain, hypothermia, hypoventilation, hypoxia, or carbon dioxide accumulation.
3. Surgical operation: Clamp aorta, stimulation V, X, IV for cranial nerve, tracheal intubation, catheter, drainage tube, and other adverse stimuli; all kinds of sur-

gery can become a factor of mental stress in patients, by activating sympathetic nerves. The system affects the patient's blood pressure.

4. Psychological factors: Stress, anxiety, fear, insomnia, and other psychological stress factors can cause blood pressure, heart rate, arrhythmia.
5. Hypoxia and carbon dioxide (CO_2) accumulation and mild hypoxia can excite chemoreceptors and increase blood pressure, heart rate increases, the circulatory system high dynamic state compensates for the lack of blood oxygen content, but severe hypoxia causes circulation inhibition. Insufficient airway, inhibition of the respiratory center, assisted breathing or improper control of breathing, etc. cause CO_2 accumulation, increased $PaCO_2$, and increased secretion of catecholamines, resulting in elevated blood pressure, tachycardia, and arrhythmia.
6. Unreasonable withdrawal of antihypertensive drugs in essential hypertension: antihypertensive treatment should continue until before operation, including the morning of surgery. It is recommended to use a long-acting antihypertensive drug for a few days before surgery to avoid blood pressure fluctuations during the operation of short-acting drugs.
7. Inadequate preoperative preparation for secondary hypertension: such as pheochromocytoma, adrenal adenoma resection, or renal artery stenosis surgery, such as preoperative adequate drug preparation, very dangerous hemodynamics may occur during surgery fluctuation.
8. Types of surgery that are prone to severe hypertension: cardiac surgery, large vascular surgery (carotid endarterectomy, aortic surgery), nervous system and head and neck surgery, kidney transplantation, and large trauma (burn or head trauma) .
9. Invasive operation in awake state.
10. Excessive infusion causes the volume overload to be too heavy, and the extravascular space is refluxed into the vascular bed 24–48 h after surgery.
11. Others: (a) intracranial surgery to pull or stimulate the cranial nerve; (b) intracranial pressure to increase the self-regulation ability of the cerebral blood vessels, in order to ensure adequate cerebral perfusion, through neuromodulation, systemic vasoconstriction, blood pressure is slightly higher; (c) extracorporeal circulation flow, excessive or increased peripheral resistance; (d) hypertensive patients with impaired vasomotor function, so sensitive to sympathetic excitatory drugs, such as improper use of booster drugs can cause a sharp rise in blood pressure; (e) urinary retention time is longer, will lead to autonomic dysfunction, nervous excitability, etc., will also aggravate or lead to high blood pressure; (f) cold and hypothermia; (g) postoperative wound pain, cough, nausea and vomiting, sympathetic nervous system activity increased after vomiting, heart rate is obviously increased and increased blood pressure, increased cardiovascular complications; (h) postoperative analgesia on vasodilation disappeared, excessive blood volume, resulting in elevated blood pressure.

19.3.2 Pathophysiological Mechanism of Perioperative Hypertension

Perioperative blood pressure elevation usually involves multiple physiological mechanisms [37].

1. Increased sympathetic excitability leads to increased heart rate, increased myocardial contractility, and increased peripheral resistance. A cardiac event may be induced if the patient has a underlying heart disease.
2. Renin angiotensin aldosterone system activation, increases peripheral vascular resistance, while increased aldosterone leads to sodium retention.
3. Endothelial dysfunction, endothelium-dependent vasodilation factor production is reduced, endothelium-dependent vasoconstrictor and vasodilation factor imbalance, leading to increased systemic arterial resistance [38].

19.3.3 Preoperative Evaluation of Perioperative Hypertension [39]

Hypertensive patients have high blood pressure fluctuations, easy to be complicated with atherosclerosis and various metabolic abnormalities. Therefore, there are some potential crises before and after anesthesia, such as hemodynamic instability induced myocardial ischemia, myocardial infarction, and even sudden cardiac death. There may be interactions between drugs and adverse drug reactions in combination. Therefore, for patients with hypertension who are about to undergo surgery, careful evaluation should be carried out to strengthen blood pressure and heart rate control, to provide possible heart protection, to ensure the perfusion of vital organs, and to be accompanied by experienced anesthesiologists.

1. To understand the course of hypertension in patients, long-term hypertension is often accompanied by decreased sensitivity of baroreceptors, resulting in intraoperative hemodynamic instability.
2. According to the blood pressure level, it is necessary to further control blood pressure: mild to moderate hypertension has a relatively small threat to surgery, and severe uncontrolled hypertension is prone to myocardial ischemia and arrhythmia.
3. Understand the antihypertensive drugs used before surgery: central antihypertensive drugs, beta blockers should not be discontinued.
4. Assessment of target organ damage and target organ involvement. Hypertensive patients with significant organ dysfunction have a significantly increased risk of anesthesia. Should pay attention to the presence or absence of angina, heart failure, hypertensive encephalopathy, diabetes, and renal complications, lipid metabolism disorders, and other complications. In the case of the above-mentioned target organ involvement or physiological disorder, the comorbid

disease should be treated while controlling the blood pressure level before surgery.
5. Surgical site and type and evaluation of operation time: (a) high-risk surgery: emergency major surgery (especially the elderly), aortic or other large blood vessel surgery, peripheral vascular surgery, prolonged surgery (>4 h), and/or more blood loss. (b) Middle-risk surgery: carotid endarterectomy, head and neck surgery, intra-abdominal or thoracic surgery, orthopedic surgery, prostate surgery. (c) Low-risk surgery: endoscopy, superficial surgery, cataract surgery, breast surgery.
6. Others: In addition to emergency surgery, elective surgery should generally be performed after blood pressure is controlled and the function of the damaged organ is stabilized.

19.3.4 Characteristics of Perioperative Hypertension

1. High blood pressure fluctuations: preoperative stress, anxiety, postoperative pain, and other factors can cause a wide range of changes in blood pressure. Perioperative blood pressure fluctuations are prone to occur in patients with a history of hypertension, especially those with diastolic blood pressure greater than 110 mmHg.
2. Complications: Perioperative risk of hypertensive patients is mainly related to the degree of target organ damage. Hypertension with left ventricular hypertrophy is easy to induce ventricular arrhythmia, myocardial ischemia, myocardial infarction, and heart failure. Rapid rise in blood pressure exceeds the compensation limit, which can cause hypertensive crisis, hypertensive encephalopathy, acute heart failure, renal failure, cerebral hemorrhage, and cerebral thrombosis; low blood pressure, myocardial ischemia due to insufficient coronary vascular perfusion, even sudden cardiac arrest. Longer periods of hypotension are prone to cerebral thrombosis due to slow blood flow.

19.3.5 Perioperative Blood Pressure Monitoring

Perioperative blood pressure abnormalities are mainly manifested by preoperative high blood pressure, tracheal intubation during anesthesia induction period, intraoperative high blood pressure during the catheterization period, low blood pressure during the induction period, unstable blood pressure during operation, and postoperative hypertension. The degree of preoperative blood pressure rise is related to the level of basal blood pressure and irritation, and the patient's blood pressure should be closely monitored. In principle, patients with no history of hypertension, preoperative mild and moderate blood pressure (SBP 140–179 mmHg, DBP 90–109 mmHg) does not affect the operation, can be closely observed, not rushed to deal with, stabilize patient mood and eliminate tension. After the state, blood pressure can return to normal. Patients with hypertension above the severity of

surgery (>180/110 mmHg) are advised to take a slow-pressure treatment. The recommended blood pressure is still higher than 180/110 mmHg after entering the operating room. However, for life-threatening emergencies, in order to save lives, no matter how high the blood pressure is, emergency surgery; for severe hypertension combined with life-threatening target organ damage and state, measures should be taken to improve life-threatening organs in a short period of time. Features: Intraoperative incision and other stimuli can cause blood pressure to rise, and large blood loss caused by insufficient blood loss and anesthesia can cause hypotension. The average arterial pressure drops by 33% for more than 10 min or 50% for a short time. Causes myocardial ischemia, so the patient's blood pressure should be continuously monitored during surgery. Postoperative blood pressure is generally related to the degree of preoperative hypertension, adequate blood pressure preparation, the size of surgical trauma, the amount of blood loss, the method of anesthesia, and the application of intraoperative vasoactive drugs. Blood pressure will not be too high in a short time after surgery, generally low or normal. However, with the clinical supplement of blood volume and the gradual regression of the effects of anesthetics, sedatives, and hemostatic drugs, blood pressure tends to increase gradually. Therefore, postoperative observation should be closely observed, timely monitoring of blood pressure changes, abnormal findings, and timely treatment [40].

19.3.6 Principles of Blood Pressure Control for Perioperative Hypertension

The purpose of perioperative hypertension blood pressure control is to ensure the perfusion of important organs, reduce the load on the heart, and maintain heart function.

1. Perioperative hypertension blood pressure control goals: (a) age ≥ 60 years, blood pressure <150/90 mmHg; (b) age <60 years, diabetes and chronic kidney disease patients, blood pressure <140/90 mmHg [41, 42]; (c) intraoperative blood pressure: the fluctuation does not exceed 30% of the baseline blood pressure.
2. The control of hypertension should be carried out within a few weeks before surgery. It is not recommended to use emergency antihypertensive therapy within a few hours to avoid adverse reactions of important organ ischemia and antihypertensive drugs [43].
3. Hypertension threshold, there is currently no threshold for hypertensive surgery.
   (a) In principle, mild to moderate hypertension (<180/110 mmHg) does not affect the operation; (b) emergency surgery to save life, no matter how high blood pressure; (c) hypertension combined with life-threatening target organ damage (such as acute left heart failure, unstable angina pectoris, oliguric renal failure, etc.), should take measures to improve organ function in a short period of time; combined with severe hypokalemia (blood potassium

<2.9 mmol/L), should also be corrected as soon as possible; (d) elective surgery patients with blood pressure >180/110 mmHg after entering the operating room are recommended to postpone surgery. If the patient does have an operation (such as a tumor with a small amount of bleeding), surgery with the consent of the family.

4. Preoperative preparation of antihypertensive drugs in hypertensive patients: Hypertensive patients suddenly stop taking long-term antihypertensive drugs is also one of the causes of perioperative hypertension. The withdrawal period should be shortened as much as possible, replaced with a long-acting preparation within a few days before surgery, and still administered on the day before surgery. It should be noted that angiotensin-converting enzyme inhibitor (ACEI) drugs should be discontinued in the early morning before surgery because they are prone to cause intraoperative hypotension. There is evidence that the use of preoperative beta blockers can effectively reduce blood pressure fluctuations, myocardial ischemia, and postoperative atrial fibrillation, as well as reduce mortality from non-cardiac surgery. A single dose of beta blocker before surgery can effectively reduce the occurrence of tachycardia associated with endotracheal intubation.
5. Treatment principle of perioperative hypertensive emergency:
   If hypertensive emergencies occur during the perioperative period, it is usually necessary to give intravenous antihypertensive drugs. The immediate goal is to reduce the diastolic blood pressure to about 110 mmHg, or 10–15%, but not more than 25% within 30–60 min. If the patient can tolerate, the blood pressure should be reduced to 160/100 mmHg for the next 2–6 h. For the aortic dissection, in the case of patients can tolerate, the goal of blood pressure should be as low as systolic blood pressure 100–110 mmHg, generally need to use a combination of antihypertensive drugs, and to give a sufficient amount of beta blockers. Drugs with rapid onset and short duration of action should be selected, such as labetalol, esmolol, nicardipine, nitroglycerin, and sodium nitroprusside. Intraoperative blood pressure surge should actively seek and deal with various possible causes such as pain, hypervolemia, hypoxemia, hypercapnia, and hypothermia.

19.3.7 Treatment of Perioperative Hypertension

1. There are five major categories of antihypertensive drugs recommended by the 2018 Chinese Guidelines for the Prevention and Treatment of Hypertension [44, 45], namely calcium antagonists (CCB), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin II receptor antagonists (ARB), diuretics (thiazines), beta blockers 5, and fixed ratio combinations consisting of the above drugs. In addition, alpha blockers or other types of antihypertensive drugs can sometimes be used in certain high blood pressure populations.

   Antihypertensive drug treatment principles: (a) small dose: the initial treatment should usually use a smaller effective therapeutic dose, and gradually increase the dose as needed; (b) priority application of long-acting preparation:

as much as possible once a day for 24 h, long-acting drugs for antihypertensive effect, effective control of nocturnal blood pressure and morning peak blood pressure, more effective prevention of cardiovascular and cerebrovascular complications; (c) combination medication: can increase antihypertensive effect without increasing adverse reactions, in the treatment of low-dose monotherapy. If you are not satisfied, you can use a combination of two or more antihypertensive drugs. For patients with blood pressure >160/100 mmHg, higher than the target blood pressure of 20/10 mmHg or higher risk, the combination can be started with a small dose of two drugs, or with a fixed ratio combination; (d) individualized: according to the patient's specific situation and tolerance and personal will or long-term tolerance, choose the antihypertensive drug suitable for the patient.

2. Clinical application characteristics of antihypertensive drugs in perioperative period
   (a) CCB: mainly plays a role in dilating blood vessels and lowering blood pressure by blocking calcium channel on vascular smooth muscle cells. Dihydropyridine CCB and non-dihydropyridine CCB are included. Dihydropyridine calcium channel blockers are represented by nifedipine, and non-dihydropyridine calcium channel blockers are represented by verapamil and diltiazem. Dihydropyridine calcium channel blockers have obvious antihypertensive effects and are more commonly used in perioperative antihypertensive therapy. After the drug is administered, the cardiac output is increased while the blood pressure is lowered. In addition to treating hypertension, non-dihydropyridine calcium channel blockers also have the effects of treating arrhythmia and angina pectoris, but non-dihydropyridine calcium channel blockers should be used with caution in patients with hypertension complicated with heart failure. Urgent surgery in patients with hypertension in the perioperative period of sudden increase in blood pressure is an emergency, perioperative intravenous calcium antagonists are mainly nicardipine and diltiazem, diltiazem combined with rapid arrhythmia hypertension, and nicardipine is short. A dihydropyridine-based calcium antagonist that selectively dilates the coronary arteries and internal carotid arteries, improves cardiac and cerebral ischemia, does not cause coronary artery stealing, and does not effectively inhibit the body's stress response by intravenous anesthesia. Therefore, it is necessary to quickly control the blood pressure, and CCB treatment of perioperative hypertension is very effective and well tolerated [46].
   (b) ACEI: The mechanism of action is to inhibit angiotensin-converting enzyme from blocking the renin-angiotensin system to exert a hypotensive effect. ACEI has a clear antihypertensive effect and has no adverse effects on glycolipid metabolism. Limiting salt or adding a diuretic can increase the antihypertensive effect of ACEI. Patients who take this medicine with irritating dry cough before surgery should use other antihypertensive drugs before surgery to prevent postoperative cough and affect wound healing. However, the most common risk of applying such drugs during the perioperative

period is hypotension with tachycardia. Therefore, many anesthesiologists believe that the risk of using a conversion enzyme inhibitor during the perioperative period is more than the benefit [47]. To withdraw the drug, captopril should be used for at least 12 h (at the time of surgery) and enalapril for 24 h.

(c) ARB: The mechanism of action is to block the angiotensin II type 1 receptor from exerting a hypotensive effect. A large number of large-scale clinical trials have been conducted in European and American countries. The results show that ARB can reduce the incidence of cardiovascular complications in patients with cardiovascular history (coronary heart disease, stroke, peripheral arterial disease) and the risk of cardiovascular events in patients with hypertension. Reduce proteinuria and microalbuminuria in patients with diabetes or kidney disease. For patients with left ventricular hypertrophy, heart failure, atrial fibrillation prevention, diabetic nephropathy, coronary heart disease, metabolic syndrome, microalbuminuria or proteinuria, and patients who cannot tolerate ACEI. Perioperative medication is the same as ACEI.

(d) β-Blockers: A first-line recommended drug for controlling perioperative hypertension, which has been shown to benefit from acute myocardial infarction, cardiac insufficiency, elderly patients, and non-cardiac surgery. Patients with chronic obstructive pulmonary disease can also benefit. However, patients with active asthma and tracheal spasm, bradycardia, and uncontrollable cardiac dysfunction should be banned. There are β1 and β2 subtypes, and cardiac selective β-blockers are most suitable. Stress, anxiety, pain, and trauma can cause increased sympathetic excitability. Continuous and excessive norepinephrine can cause various biological changes in cardiomyocytes, which results in the death and apoptosis of cardiomyocytes. It can also stimulate fibroblast proliferation and promote myocardial fibrosis. For patients with coronary heart disease or general surgical patients with risk factors for coronary heart disease, β-blockers are administered during the perioperative period to prevent perioperative arrhythmia and myocardial ischemia and to reduce post-operative cardiovascular disease [48]. For patients with long-term use of β-blockers, the number of β-receptors is upregulated, and it is not appropriate to stop the drug before surgery. If the drug is suddenly discontinued, the patient's sensitivity to endogenous β-receptor stimulation will increase, and the cardiovascular system will be aggravated. Reaction: Patients taking beta-blockers should be monitored during surgery to prevent hypotension and bradycardia. Esmolol, metoprolol, and labetalol are commonly used beta-receptor antagonists during the perioperative period. Esmolol is an ultra-short-acting β-receptor antagonist. The $t_{1/2}$ is only 9 min, which has the advantages of rapid onset of action and rapid disappearance of adverse reactions after stopping the drug. Metoprolol is a selective beta 1 receptor antagonist and is safer for patients with chronic obstructive pulmonary disease, but is contraindicated in asthma patients. Labetalol has both α1 receptor and β-receptor blockade, and the antihyper-

tensive effect is more obvious. Esmolol, metoprolol, and labetalol have intravenous preparations.

(e) Diuretic: By reducing the extracellular fluid, the blood output of the heart is reduced, and the blood pressure is lowered by the action of sodium. Low-dose thiazide diuretics (such as hydrochlorothiazide 6.25–25 mg) have little effect on metabolism, and combined with other antihypertensive drugs (especially ACEI or ARB) can significantly increase the antihypertensive effect of the latter. Preoperative oral thiazide diuretics, such patients with vasodilatation during anesthesia induction, prone to relatively low blood volume hypotension, currently diuretics, have not been used as the main drug in the perioperative period.

(f) α-Blockers: Urapidil has a dual antihypertensive mechanism that blocks α1 receptors in peripheral blood vessels and excites central 5-HT1A receptors, reducing sympathetic feedback regulation of the medullary vascular center. Reducing blood pressure moderately is also one of the drugs currently used for perioperative hypertension treatment.

3. Combination therapy: Clinically, in order to increase the efficacy and reduce adverse reactions, combined drug therapy is usually used to treat hypertension. The recommended combination of the 2018 Chinese Hypertension Guidelines is as follows: (a) dihydropyridine CCB beta receptor blockers; (b) dihydropyridine CCB diuretics; (c) dihydropyridines CCB ACEI or ARB; (d) diuretic ACEI or ARB; (e) dihydropyridine CCB diuretic ACEI or ARB; (f) dihydropyridine CCB ACEI or ARB beta receptor blocker; (g) diuretic ACEI or ARB α-blocker; (h) dihydropyridine CCB ACEI or ARB alpha receptor blocker; may be inappropriately combined as follows: (a) ACEI or ARB; (b) beta blocker central antihypertensive drug; (c) beta blocker ACEI or ARB.
4. The management of preoperative blood pressure
Sufficient sedation is required before surgery and then anesthetized and then depressurized. When high blood pressure occurs during anesthesia, it is first necessary to eliminate various factors that induce an increase in blood pressure, and to ensure an appropriate depth of anesthesia. In addition to emergency surgery, elective surgery should generally be performed after hypertension is controlled. The patient's mood and stable blood pressure are still higher than normal. Patients who meet the WHO/ISH criteria for the diagnosis of essential hypertension and previous history of hypertension have appropriate antihypertensive treatment before surgery to prevent blood pressure fluctuations and heart and brain during surgery. Vascular accidents are important, and their blood pressure reduction target is to drop to normal or ideal levels. That is, for young and middle-aged patients or patients with diabetes, blood pressure drops to 135/85 mmHg or normal range; for elderly patients ≥60 years old, blood pressure is reduced to below 150/90 mmHg [49–51]. Hypertensive patients with long-term oral antihypertensive drugs, cannot immediately stop the drug, avoid withdrawal syndrome, blood pressure below 160/100 mmHg, cannot be specially prepared, blood pressure is too high >180/100 mmHg, Appropriate antihypertensive drugs should be used

before surgery. Drugs: the speed and method of blood pressure reduction should be based on the patient's basic conditions, heart, brain, kidney, and other major organ function, the rational choice of blood pressure reduction measures, but should not cause a sharp drop in blood pressure, generally do not advocate intravenous application. Antihypertensive drugs: unless hypertension hypertensive crisis, hypertensive encephalopathy, rapid hypertension, acute left heart failure, and other high blood pressure emergencies or severe hypertension during surgery [52].

5. The management of intraoperative blood pressure
   During the operation, the appropriate perfusion flow rate was maintained. During the extracorporeal circulation, the arterial pressure was generally maintained between 50 and 80 mmHg. The vascular resistance of the elderly was high, and the perfusion pressure was also high, and those that of children were slightly lower. If the mean arterial pressure is >90 mmHg, anesthesia should be deepened or antihypertensive drugs such as urapidil and nicardipine should be used. If the blood pressure is too high or too low, various factors that induce abnormal blood pressure must be eliminated, and the cause should be treated accordingly. The blood pressure rises sharply, and more than 25–30% of the basal blood pressure should be treated. In the case of general anesthesia, the endotracheal intubation is most likely to cause a sharp rise in blood pressure. There is no safe and effective prevention method. The feasible measures are the throat and trachea. The feasible measures include adequate surface anesthesia in the throat and trachea, a small amount of fentanyl infusion, appropriate anesthesia depth, and induction of medication to deepen the anesthesia until the blood pressure drops to the lower limit of the fluctuation. For irritating operations such as endotracheal intubation, surgical incision, thoracotomy, laparotomy, and visceral exploration, once the blood pressure rises, firstly, the anesthesia should be appropriately deepened. If necessary, it can be supplemented with isopropyl fentanate or fentanyl. If still cannot effectively control blood pressure, you can choose intravenous or intravenous infusion of antihypertensive drugs. For the rise of blood pressure during the recovery period, first of all, it should be ensured that there is no pain, no incitement to struggle, and no nausea and vomiting. When the blood pressure is still high, the appropriate amount of antihypertensive drugs can be adjusted to the allowable range. The immediate goal is to reduce the diastolic blood pressure to around 110 mmHg, or 10–15%, but not more than 25%, within 30–60 min. If the patient can tolerate, the blood pressure should be reduced to 160/100 mmHg for the next 2–6 h. Patients with aortic dissection should have a faster rate of depressurization and gradually reduce blood pressure to baseline levels within 24–48 h [53]. Aortic valve surgery is prone to hypertension during cardiopulmonary bypass and postoperative surgery. It can be treated with urapidil, nicardipine, and sodium nitroprusside. Patients with cardiac hypertrophy should maintain high blood pressure. SBP <120 mmHg should be controlled after mitral valvuloplasty. Coronary artery bypass grafting should maintain a high perfusion pressure during the perioperative period, with an average arterial pressure of >70 mmHg to

avoid an increase in the central rate of the antihypertensive process. It is not recommended to use sodium nitroprusside to control blood pressure to avoid coronary blood stagnation. Arterial catheter ligation reduces the SBP to 70–80 mmHg or 40% of the basal level when the catheter is ligated. Attention should be paid to postoperative hypertension rebound, timely sedation and urapidil, beta blockers or antihypertensive therapy such as calcium channel blockers.

Drugs with rapid onset and short duration of action such as labetalol, esmolol, nicardipine, nitroglycerin, sodium nitroprusside, and fenoldopam should be used. The commonly used intravenous antihypertensive drugs in China are as follows:

Sodium nitroprusside: an arteriovenous balance dilator, inhaled intravenously, immediately effective. Start from 10 μg/min, according to blood pressure every 5–10 min can increase 5 μg/min and stop the infusion for 3–5 min; the effect disappears.

Nitroglycerin: mainly dilated veins, large amounts of arteries are also dilated, and intravenous infusion takes effect within 5 min. Start from 5–10 μg/min, then increase 5–10 μg/min according to blood pressure 5–10 min, to 20–50 μg/min, >40 μg/min, dilate the artery, and disappear after a few minutes of stopping.

Uradil: For patients who need emergency blood pressure control, 10–50 mg (usually 25 mg) intravenous injection, such as no significant decrease in blood pressure, can be repeated. Then 50–100 mg plus 100 mL of liquid was intravenously instilled at 0.4–2 mg/min, and the drip rate was adjusted according to blood pressure. The onset time is 15 min and the duration of action is 2–9 h.

Nicardipine: Intravenous infusion of 80–250 μg/min, onset time 5–10 min, duration of action 1–4 h.

6. The management of postoperative blood pressure

Postoperative blood pressure is affected by the degree of preoperative hypertension, adequate blood pressure preparation, the size of surgical trauma, the amount of blood loss, anesthesia, intraoperative medication, especially vasoactive drugs (including antihypertensive or boosting drugs). Related factors: For larger operations, the patient is affected by blood loss, anesthetic drugs, sedative drugs, analgesics, etc., blood pressure is generally not too high, sometimes even low. However, with the complement of blood volume, the effects of anesthetic drugs, sedative drugs, and analgesic drugs gradually subsided, and blood pressure gradually increased. Patients with blood pressure exceeding 25–30% of basal blood pressure and blood pressure ≥160/100 mmHg may be treated with intravenous drip drop. The drug is controlled to control the blood pressure in an ideal range, and is changed to oral drug maintenance after the disease is stabilized and fasted. For small surgery, local anesthesia, patients with awake state, postoperative blood pressure increased, patients with blood pressure not exceeding basal blood pressure 25–30%, and blood pressure <160/100 mmHg can be sedated according to different conditions of patients. The drug or analgesic drug is combined with oral antihypertensive drugs.

In summary, the prevention and treatment of perioperative hypertension is very important, the original hypertensive patients should continue to antihypertensive treatment before surgery, a few days before surgery should be replaced with long-acting antihypertensive drugs and continue to take the drug on the morning of surgery. Preoperative application of beta blockers can effectively reduce blood pressure fluctuations, myocardial ischemia, and postoperative atrial fibrillation, as well as reduce mortality from non-cardiac surgery. Intraoperative blood pressure surge should actively seek and deal with various possible causes, if necessary, active intravenous antihypertensive treatment. Successful surgical treatment must be complemented by perfect complications and/or associated treatments to maximize patient benefit. Perioperative blood pressure management also determines the surgical success rate and long-term prognosis of surgical patients. Patients should be fully evaluated before surgery, during surgery, and after surgery to give an optimal judgment and choose a good treatment plan. More clinical studies are needed to confirm the significance of perioperative blood pressure management for long-term prognosis.

19.4 Tumor and Hypertension

Fengyu Pan

19.4.1 Carcinoid Syndrome and Hypertension

Carcinoid is a kind of tumor which mainly occurs in the gastrointestinal tract, but also involves most organs of the whole body. It grows slowly and has low malignancy. Although during autopsy incidentally found carcinoid tumors incidence can reach 1%, but in the general population, its annual incidence is about 1/1 million. Carcinoid syndrome is a group of complex symptoms and signs caused by the secretion and release of some bioactive substances by malignant carcinoid cells. When combined with carcinoid crisis, cardiovascular abnormalities such as hypertension and arrhythmia can occur. If not handled in time, it can endanger life.

It is now clear that carcinoid tumors belong to neuroendocrine neoplasms (NENs). NENs are a class of tumors that originate from stem cells and have neuroendocrine markers and can produce bioactive amines and/or polypeptide hormones. If the hormones secreted by tumors can cause the corresponding clinical symptoms, they are classified as functional NENs; if the levels of hormones such as pancreatic polypeptide (PP) can be detected in blood and urine, but there are no related symptoms (even in the presence of tumor compression), they are usually classified as non-functional NENs. NENs still include all highly, moderately, and poorly differentiated neuroendocrine tumors; NETs (neuroendocrine tumors) refer to highly and moderately differentiated neuroendocrine tumors; and NEC (neuroendocrine carcinoma) refers to poorly differentiated neuroendocrine tumors [54].

19.4.1.1 Epidemiology

Carcinoid is a rare tumor. It was first described by Merling in 1808. In 1907, Oberndorfer first proposed carcinoid as a slow-growing intestinal adenocarcinoma. It was formally named carcinoid and has been used until now. Masson proved in 1928 that carcinoid originated from argyrophil cells in intestinal mucosa, so it is also called argyrophilic cell carcinoma. Lembeck first discovered 5-hydroxytryptamine (5-HT) in carcinoid tissues in 1953 and confirmed that 5-HT is a biologically active substance causing carcinoid syndrome. Thorson and Isler independently reported carcinoid syndrome cases in 1954.

Data from the United States Surveillance, Epidemiology and Final Result Database (SEER) show that the incidence of NENs has increased significantly. It is estimated that the incidence of NENs is 5.25/100,000 [55]. Gastrointestinal and pancreatic neuroendocrine neoplasms (GEP-NENs) mainly occur in the digestive tract or pancreas, producing 5-hydroxytryptamine metabolites or polypeptide hormones, such as serotonin. Glucagon, insulin, gastrin or corticotropin, etc. GEP-NENs accounted for 65–75% [56] of NENs. In western countries, although GEP-NENs account for only 2% of gastrointestinal malignant tumors, the prevalence of GEP-NENs is second only to colorectal cancer, ranking second in gastrointestinal cancer. Japanese data show that pancreatic neuroendocrine neoplasms (pNENs), formerly known as islet cell tumors, have an incidence of 2.23/100,000, of which nonfunctional pNENs account for 47% of all NENs. In recent years, reports on GEP-NENs have been increasing in China. However, due to the imperfection of the national registration system, the current epidemic trend, clinical characteristics and prevention, and treatment of GEP-NETs in China are still unclear. Therefore, detailed data and information comparable with other countries/regions are lacking. In 2012, Guo Linjie and others [57] reviewed and analyzed all the relevant literature published in China from 1954 to 2011, and summarized 11,671 cases of GEP-NENs in China, with pNENs being the most common (5807 cases), accounting for 49.8%. Among pNENs, 5205 cases were functional, accounting for 89.6%. Among them, 4962 cases were insulinoma, accounting for 85.4%. At the same time, the clinical misdiagnosis rate of GEP-NENs was 55.1%. In addition, Wang [58] and others reviewed 178 cases of GEP-NEN diagnosed and treated in the First Affiliated Hospital of Guangzhou Sun Yat-sen University from 1995 to 2012, and pNENs was the most common, with a total of 62 cases (34.8%) followed by rectal NEN, with a total of 36 cases (20.2%).

GI-NENs include stomach, duodenum, small intestine, appendix, colon, and rectum, among which ileum, rectum, and appendix NENs are the most common [59]. In recent years, the incidence of NENs in European and American countries has been on the rise before. Japanese scholar [56] reported that the annual incidence of NENs in jejunum and ileum was only 0.20/100,000 in Asian population, while rectal NENs accounted for 60–89% of all gastrointestinal carcinoid tumors, which was quite different from that in European and American countries, while there was no significant difference in other parts of NENs. There is still no comprehensive statistical information in our country.

The exact mechanism of carcinoid syndrome causing hypertension is unclear, and its incidence has not been reported.

19.4.1.2 Etiology

Carcinoid is a neoplasm of neuroendocrine cells, which can synthesize and store both biologically active amines and peptides. The secreted bioactive substances include 5-HT, bradykinin, catecholamine, prostacyclin, vasoactive intestinal peptide, histamine, somatostatin, neurotensin, pancreatic polypeptide, motilin, and gastrin. In addition to 5-HT, the role of bioactive substances secreted by other carcinoid cells in the pathophysiological mechanism of carcinoid syndrome remains unclear.

The most characteristic biochemical abnormality of carcinoid is the excessive production of 5-hydroxytryptamine and its metabolite 5-hydroxyindole acetic acid (5-HIAA). When the diameter of carcinoid is less than 3.5 cm, it usually does not cause symptoms and signs. When carcinoid is large, it produces a large amount of secretion, which converts all tryptophan in food into 5-HT. 5-HT enters the blood and is absorbed and carried by platelets. It distributes in tissues and acts on target cells. Serotonin, as a neurotransmitter, is mainly distributed in the pineal gland and hypothalamus and may be involved in the regulation of physiological functions such as pain, sleep, and body temperature. The 5-HT content and dysfunction of the central nervous system may be related to the onset of psychosis, migraine, and other diseases.

5-HT has to be mediated by the corresponding receptor. It has complex effects on cardiovascular system. Intravenous microgram of 5-HT may induce a three-phase reaction of blood pressure: (1) transient decrease, which is related to 5-HT activating 5-HT3 receptor, causing negative frequency effect of heart; (2) persistent hypertension for several minutes, which is caused by 5-HT activating 5-HT2 receptor, causing vasoconstriction of kidney, lung, and other tissues; (3) prolonged hypotension is caused by skeletal muscle vasodilation, requiring the participation of vascular endothelial cells. In addition, 5-HT activates platelet 5-HT2 receptor, which can induce platelet aggregation.

Carcinoid is not uncommon clinically, but only a few cases have carcinoid syndrome. Carcinoid from different embryonic origins has different biochemical, pathological, and clinical characteristics. Williams classified carcinoid into three types: foregut, midgut, and hindgut. Generally speaking, carcinoids from the foregut are argyrophilic. Because of the lack of aromatic acid decarboxylase, the production of 5-HT is less. Carcinoids from the midgut are argyrophilic and argyrophilic, which can produce more 5-HT. Foregut carcinoid secretes 5-HT and 5-hydroxytryptophan, vasopressin, vasoactive amines, and polypeptide hormones, producing endocrine neoplasm syndrome; midgut carcinoid secretes 5-HT, showing typical carcinoid syndrome. Posterior intestinal carcinoid tumors are mostly nonfunctional and clinically stationary. This chapter focuses on argyrophilic and argyrophilic carcinoids of the intestine.

19.4.1.3 Pathology

The carcinoid tumors were seen as solid yellow or brown masses with naked eyes. Histologically, the carcinoid tumors were columnar cells or adenocytes. All carcinoid cells were similar, with pink cytoplasmic granules, round nuclei, and few mitosis. Because these cells can be stained with potassium chromate, they are called enterophilic cells. At the same time, it is also called argyrophilic cell because of its ability to absorb silver and reduce silver salts.

19.4.1.4 Pathophysiology

The pathophysiology of carcinoid syndrome has not been fully understood until now. A large number of studies have shown that 5-HT and its metabolic abnormalities are the most prominent biochemical manifestations of carcinoid syndrome. About 84% of patients with carcinoid syndrome have increased 5-HT in blood or 5-HIAA in urine. In conclusion, carcinoid syndrome is the result of the synergistic action of various peptide hormones and mediators.

19.4.1.5 Pathogenesis

The clinical manifestation of carcinoid is closely related to its location and origin, and also depends on the peptide and amine mediators it produces. Many carcinoids can secrete two or more hormones; gastrointestinal peptide hormones and chemical mediators secreted by carcinoids can produce corresponding pathophysiological and clinical manifestations. Many carcinoid tumors show typical endocrine neoplasm syndrome, but in many cases, a variety of peptide hormones produced by carcinoid tumors do not produce corresponding clinical symptoms.

The exact mechanism of hypertension caused by carcinoid syndrome is unclear. It may be related to the secretion of 5-HT and activation of 5-HT2 receptor in primary carcinoid and metastatic carcinoid, which can increase the release of vasoconstrictor substances such as histamine, PGF2–α, angiotensin II, and norepinephrine, thus stimulating the proliferation of vascular smooth muscle cells and causing vasoconstriction in kidney, lung, and other tissues.

19.4.1.6 Clinical Manifestations

Carcinoid syndrome [60–62]: In metastatic small intestinal NENs, 20–30% of patients can manifest carcinoid syndrome, of which secretory diarrhea accounts for 60–80%, facial flushing accounts for 60–85%, and 20% manifest carcinoid heart disease (CHD) and right heart fibrosis. In addition, retroperitoneal and ovarian metastases (about 5%) produce excessive tachykinin or 5-HT which can directly cause systemic carcinoid syndrome across the liver. Besides carcinoid syndrome, intestinal ischemia is also a cause of diarrhea and abdominal pain.

1. Intermittent skin flushing: Mainly occurs in the face, neck, and chest and other exposed areas, but also throughout the body. For intermittent, can occur suddenly, bright red or purple, lasting for several minutes to 1–2 days. If the skin flushes for several years, there will be fixed skin changes in the frequently occurring areas, showing most of the vasodilation and slight purple red. Cheek, nose,

upper lip, and mandible are often accompanied by other symptoms, such as tachycardia, hypotension, and gastrointestinal and lung symptoms. Drinking and certain foods, pain, emotional fluctuation, and physical activity are the inducing factors. Epinephrine, norepinephrine, and catecholamine can cause seizures.

2. Pulmonary symptoms: Mainly manifested as asthma and dyspnea, occurring in 20–30% of patients, similar to bronchial asthma, asthma can occur simultaneously with skin flushing.
3. Gastrointestinal symptoms: Abdominal pain, abdominal distension, internal urgency and posterior weight are more common, with varying degrees. Diarrhea is urinary-like, up to 20–30 times a day. Before diarrhea, there may be abdominal pain or colic. Diarrhea and skin flushing do not necessarily occur at the same time, mainly due to excessive secretion of 5-HT. When carcinoid has huge liver metastasis, it may have persistent or paroxysmal right upper abdominal pain, radiation to the right shoulder and back and fever, which is related to the large size of the tumor, the involvement of the liver capsule and relative ischemia, necrosis, or hemorrhage.
4. Cardiac symptoms: 11–60% of patients with carcinoid syndrome complicated with carcinoid heart disease, characterized by deposits in the endocardium and valves, often occurring in the right ventricular cavity (patients with patent foramen ovale may also have left ventricular cavity involvement, resulting in mitral insufficiency), usually leading to severe tricuspid regurgitation. Tricuspid stenosis is rare, and pulmonary stenosis and/or incomplete closure may also occur. The disease is characterized by enlargement of the right heart, audible organic murmurs associated with valve damage, jugular vein enlargement and/or pulsation, hepatomegaly is mostly caused by carcinoid metastasis without the characteristics of liver blood stasis, and hepatic vein and inferior vena cava are often oppressed by carcinoid liver metastasis, so there is less obvious dilatation of the hepatic vein and inferior vena cava when right heart failure occurs. In addition, myocardial fibrosis and constrictive pericarditis may occur. Patients with carcinoid heart disease often show right heart dysfunction characterized by edema due to right heart involvement.
5. Carcinoid crisis: Carcinoid crisis is a serious complication of carcinoid, usually caused by physical activity, anesthesia, surgery or chemotherapy, and other potentially lethal hormone secretion. Clinical manifestations are often sudden severe and common skin flushing, often lasting for hours to days; diarrhea is obvious and accompanied by abdominal pain; severe bronchospasm; central nervous system symptoms are common, from mild dizziness, vertigo to lethargy and deep coma; tachycardia, arrhythmia, hypertension or severe hypotension. Serum 5-hydroxytryptamine and urine 5-hydroxyindole acetic acid increased significantly and provocation test was positive. Imaging and radionuclide imaging are helpful in finding tumors. Rescue measures: Those who find tumors should be operated actively; SSA and 5-HT antagonists can be used in medical treatment.

The manifestation of hypertension is similar to pheochromocytoma crisis. Hypertension is caused by tumors in adrenal gland. It occurs mostly in young

people, with paroxysmal or persistent hypertension, paroxysmal headache, sweating, palpitation, pallor, tremor, dilated pupils, blurred vision, and other symptoms. The reason may be that a large amount of serotonin is released into the systemic circulation. Life is often endangered if not handled promptly.

6. Other manifestations: There may be some manifestations of hormone hyperfunction and corresponding symptoms. The urine 5-HIAA level in patients with carcinoid syndrome was significantly increased, often exceeding 50 mg/24 h (2–9 mg/24 h urine in normal subjects).

19.4.1.7 Auxiliary Examination

1. Urinary 5-hydroxyindole acetic acid (5-HIAA) determination: This examination increased significantly in patients with carcinoid syndrome. Because 99% of 5-HT transformed into 5-HIAA in vivo and was excreted through urine, it is of diagnostic value to detect the increase of 5-HIAA in 24 h urine. Rough screening test drips a drop of patient's urine on the filter paper and sprays azo *P*-dinitrobenzylamine. If it appears red, it is positive, indicating the increase of 5-HIAA in urine. If it is purple, it is pheochromocytoma. This test is helpful to distinguish the two. Most patients with carcinoid syndrome had blood concentration >120 g/L and urine 5-HIAA exceeded 30 mg/24 h. More than 50 mg/24 h urine is of diagnostic value.
2. Urinary determination of 5-HT or 5-HTP.
3. Detection of 5-HT in carcinoid tumors.
4. Detection of 5-HT in blood, plasma or platelets.
5. Pentapeptide gastrin provocation test: Pentapeptide gastrin provocation test is helpful for the diagnosis of carcinoid syndrome. Blood samples were taken at 1, 3, 5, 10, and 15 min after intravenous administration of pentapeptide gastrin at 0.6 g/kg to measure 5-HT. The increase of 5-HT in all cases was >40% or >50 g/L.
6. Determination of plasma chromium granules: Chromium granules are secretory proteins widely distributed in neuroendocrine granules of normal neuroendocrine cells or tumor cells. Three kinds of chrome granulin proteins, chrome granulin A, B, and C, have been identified. Their amino acid structures are different, but they share many common biochemical characteristics. Immunohistochemistry or radioimmunoassay showed that the level of chromium granules in carcinoid tumors increased by 90–100%. Studies have shown that chromium granules A or B are valuable indicators for the diagnosis of pancreatic endocrine tumors.
7. Induction test: In the non-onset stage of flushing, it can be induced by stimulation test. Commonly used methods are: ask patients to drink 10 mL, about one third of patients appear skin flushing after 3–5 min.
8. Imaging examination: Location diagnosis is an indispensable part in the diagnosis of carcinoid syndrome tumors, because the correct treatment plan can only be formulated by determining whether the tumors are single or multiple, the specific location, and whether there is blood or lymph node metastasis.

Routine noninvasive imaging diagnosis is the most common clinical application. At present, there are many means of image diagnosis and advanced equipment. However, in general, although endoscopic ultrasound may be the most sensitive for the diagnosis of gastric carcinoid tumors, endoscopic examination is still generally preferred for the diagnosis of gastrointestinal carcinoid tumors. Thoracic carcinoid tumors with diameter >1–2 cm could be detected by CT and MRI. In the diagnosis of pancreatic endocrine tumors, especially small tumors, the imaging results are still not satisfactory. CT, ultrasound, and MRI can detect 10% tumors with diameter less than 1 cm, 30–40% tumors with diameter of 1–3 cm, and 50% tumors with diameter of 3 cm. Angiography can detect 20–30% tumors with diameter less than 1 cm. In summary, the current imaging diagnosis methods can make a considerable number of small primary endocrine tumors missed diagnosis.

19.4.1.8 Diagnosis [63]

The diagnosis of carcinoid tumors and carcinoid syndrome depends on the vigilance of clinicians. The possibility of carcinoid syndrome should be considered in the following cases:

1. A history of intermittent skin flushing and diarrhea of unknown origin that has persisted for many years.
2. People with abdominal pain, diarrhea, and weight loss.
3. Those with cough, asthma, and dyspnea accompanied by pulmonary and tricuspid murmurs.
4. Late stage liver metastasis, hepatomegaly, pain in liver area and heart failure may occur, such as ascites, lower limb edema, jugular vein enlargement, pulsation, or abdominal mass and lung mass. It is highly suggested that further laboratory and other auxiliary examinations are needed for pancreatic carcinoid, including the determination of 5-HT and its metabolites in blood, urine, and tumors, and imaging diagnosis.

19.4.1.9 Therapy

1. Surgical treatment
   It is suitable for carcinoid tumors without metastasis. Carcinoid tumors occurring in the appendix, bronchus, stomach, small intestine, colon, pancreas, and ovary can be treated surgically. If intestinal obstruction and intussusception have been caused in the intestinal tract, surgical treatment is necessary even if metastasis has occurred. For those with severe symptoms, if the effect of medical treatment is not good, if the tumor is removed, although it cannot be cured, it can also alleviate the symptoms for a long time.
2. Non-surgical treatment
   Its aim is symptomatic treatment, mainly including reducing the production of 5-HT and kallikrein or antagonizing their effects, anti-cancer treatment, controlling the development of tumors, supportive therapy, improving the general situation of patients.

(a) Many drugs can increase the release of 5-HT and should be avoided or used less.
(b) Tryptophan hydroxylase inhibitor: Reducing the production of 5-HTP and 5-HT can effectively alleviate or alleviate nausea, vomiting, and diarrhea, as well as alleviate the degree of flushing attacks on the face and neck skin, but cannot reduce the number of attacks.
(c) 3.5-HT antagonist: Butanolamide methyl ergot can be used. In acute attack, intravenous injection of 1–4 mg or intravenous drip of 10–20 mg in 100–200 mL saline for 1–2 h can control flushing, asthma, and diarrhea.
(d) 4.5-HT release inhibitor: Octreotide is the best drug to control symptoms. The alleviation rate of skin flushing and diarrhea was 70% and 60%, respectively. Octreotide can inhibit the growth of tumors. Octreotide can be used intravenously when used in the treatment and prevention of carcinoid crisis. Studies have shown that octreotide can significantly improve the quality of life of carcinoid patients and reduce the incidence of carcinoid crisis.
(e) Other drugs: Corticosteroids such as prednisone 15–40 mg/day can obtain different degrees of efficacy.
(f) Chemotherapy and radiotherapy: Chemotherapy should be given to patients who have metastasis but have not been removed surgically. It can alleviate symptoms, but the curative effect is poor. The general effective rate is 30–50%. Radiotherapy can relieve pain caused by bone metastasis.
(g) Hepatic artery embolization for hepatic metastases: This method is effective for patients with hepatic metastases of carcinoid tumors. It can relieve skin flushing in 80% of patients and decrease the level of 5-hydroxyindolyl acetic acid. The mortality rate of this treatment is very low (0–2%). Its most serious side effect is carcinoid crisis. However, this side effect can be effectively prevented by intravenous somatostatin analogues.

3. Treatment of hypertension
During the onset of carcinoid crisis, patients presented with obvious abnormal blood pressure (hypertension or hypotension), persistent skin flushing, asthma attack, asphyxia, confusion, and coma in a short period of time. Drugs such as adrenaline, norepinephrine, and catecholamine can cause seizures and can also be induced during anesthesia or invasive treatment. The therapeutic measures were intravenous injection of a large amount of octreotide (50–100 g). It can also be continued as intravenous drip of 50 g (24–48 h). According to the pathogenesis of hypertension, adrenergic receptor antagonists can also be used to reduce blood pressure.

19.4.1.10 Prognosis

Generally, carcinoid is a kind of tumor with slow growth, low malignancy, and relatively good prognosis. Active treatment can improve survival rate, unless carcinoid crisis occurs, it generally does not endanger life. When the blood pressure of carcinoid crisis is too high, it can be treated by intravenous hypotension.

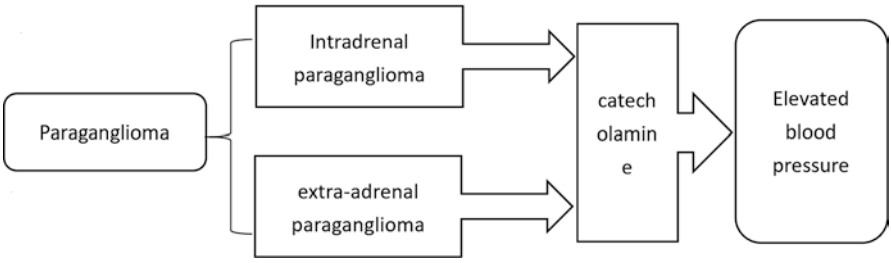

Fig. 19.2 Classification of paraganglioma

19.4.2 Extraadrenal Paraganglioma and Hypertension

Paraganglion is a chromaffin tissue complex of neuroendocrine system, located in paravertebral and paraaortic axis. Paraganglioma (PGLs) is a rare catecholamine-secreting neoplasm originating from adrenal diplomatic sensory nerve tissue. The most common organ is Zuckerkandl organ, which is located below the origin of inferior mesenteric artery. Paraganglion is widely distributed in the body.

Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors. PPGL arises from the crest-derived cells of the sympathetic and parasympathetic nervous systems: pheochromocytoma from the adrenal medulla and paraganglioma from the extramedullary paraganglion [64]. Abnormal blood pressure and metabolic disorders are caused by paroxysmal or persistent overproduction of catecholamines (CA) and other hormones by cancer cells. Patients may suffer from serious heart, brain, and kidney damage caused by long-term hypertension or life-threatening crisis caused by sudden severe hypertension.

Paraganglioma can be derived from paraganglion tissue in human body. Paraganglioma is rare but special. Paraganglion is closely related to chemodectoma and pheochromocytoma (see Fig. 19.2). Because paraganglioma can secrete a variety of hormones to cause hypertension, this chapter mainly discusses the relationship between extraadrenal paraganglioma and hypertension.

19.4.2.1 Pathogenesis and Genetic Characteristics of Paraganglioma

Neural crest cells migrate to all parts of the body during embryonic development and form paraganglia. Most of them disappear in childhood, leaving only the jugular bulb, carotid body, and aorta. Otherwise, they form tumors. In 1912, Pick suggested that pheochromocytoma should be named pheochromocytoma, while extraadrenal pheochromocytoma should be called paraganglioma, non-chromaffin paraganglioma and chemodectoma.

Paragangliomas are rare neuroendocrine tumors of soft tissue. They belong to APUD tumors. They can synthesize, store, and secrete catecholamines and produce a variety of peptide neurohormones and chromaffin granules. According to the site of occurrence, it can be divided into two categories: intra-adrenal and extraadrenal. Intra-adrenal paraganglioma, commonly known as adrenal medullary

pheochromocytoma, occurs outside the adrenal gland, usually named for its anatomical location and functional activity. Most extraadrenal pheochromocytous paragangliomas are located near the abdominal aorta in the posterior abdominal wall from the upper abdomen to the pelvic floor, mainly from the Zuckerkandl corpuscles in this region. According to the literature review, 74% of Zuckerkandl organ PGLs patients are hypertensive patients.

Paragangliomas can be classified into sympathetic paragangliomas and parasympathetic paragangliomas according to their origins. Nearly 25% of parasympathetic paragangliomas, and 50% of sympathetic paragangliomas are familial. Mutations in the susceptibility genes RET and VHL and the gene loci encoding succinate dehydrogenase subunit complex B (SDHB) and succinate dehydrogenase subunit complex D (SDHD) occur. Most of the patients with SDHD and SDHB mutations are extraadrenal paragangliomas. SDHD mutations are more common than SDHB mutations. SDHB tends to develop abdominal extraadrenal tumors and tumors with multiple manifestations, while SDHB tends to develop abdominal extraadrenal tumors and tumors with a risk of malignancy. All patients with pheochromocytoma and paraganglioma should undergo genetic testing.

19.4.2.2 Epidemiology

Paraganglioma is a rare soft tissue neuroendocrine neoplasm without large-scale epidemiological data. Traditionally, paraganglioma accounts for 10–15% of all pheochromocytomas. In recent years, there has been an upward trend in domestic reports, most of which are about 20% [64].

It has been reported that 71% of paragangliomas are located in the para-aortic plexus, 12% in the thoracic cavity, 9.8% in the bladder wall, and other common sites are gallbladder, sigmoid colon, uterus, etc. Paraganglioma originating from the prostate is rare, and there is no epidemiological investigation. Paragangliomas are mostly benign and only about 10% malignant [65]. Paragangliomas are mostly nonfunctional, but occasionally functional. The typical clinical symptoms of pheochromocytoma can occur. Pressing tumors can increase blood pressure.

19.4.2.3 Pathology

1. General anatomy: Generally, the length of visceral paraganglioma is 4 cm. The length of visceral paraganglioma is only 1–5 mm. Some of retroperitoneal paraganglioma are longer than 15 cm. Most of them are oval, slightly lobulated, and elastic. The surface is smooth and the length is close to the vessel wall. The capsule was incomplete. The section is grayish red with rich blood vessels or sinuses. If it is accompanied by old hemorrhage, it is brownish red. Surgical resection specimens are usually 5–6 cm, only about 14% of which are clinically palpable. The size of tumors is not necessarily proportional to the severity of symptoms.
2. Microscopic examination: Image of endocrine tumors. Typically, epithelioid primary cells are nested, separated by rich sinusoidal dilated fibrovascular stroma, which is basically consistent with the normal structure of accessory ganglia. Histological subtypes can be roughly divided into four types: classical, alveolar,

hemangiomatous, and pheochromocytoma-like, i.e., extraadrenal pheochromocytic paraganglion.

3. Electron microscopy: The main cell is oval or polygonal, and there are many neurosecretory granules in the cytoplasm. The length is 60–300 nm. There are many neurosecretory granules in the bright cells. Dark cells are rich in mitochondria and have fewer neurosecretory granules. Sertoli cells and nerve fibers were found in well-differentiated tumors.
4. Immunohistochemistry: CK, EMA, SMA, FN, and lysozyme all showed negative reaction. The positive markers of the main cells were NSE, chromogranin A (CgA), synaphysin, methionine enkephalin (MEK), leucine enkephalin (LEK), etc. At least one of them showed positive reaction. In addition, somatostatin, pancreatic polypeptide, vasoactive intestinal polypeptide, substance P, gastrin, Y neuropeptide, frog skin, alpha-melanocyte stimulating hormone, and other neuropeptides can be used to obtain positive labeling results. The positive labeling of supporting cells includes S-100 protein, GFAP, and so on. Calcitonin and serotonin markers also have reference value. In some cases, antiserum of ectopic hormones such as cortisol, testosterone, and ACTH can be selectively used as markers.
5. Clinicopathology: Paragangliomas are mostly benign, with a malignant incidence of 2.14–14%. It has been found that retroperitoneal paragangliomas with persistent hypertension and weight >80 g are more malignant than retroperitoneal paragangliomas. In addition, paragangliomas with embolus in the tumor body and its related blood vessels are more malignant than those in the bladder and heart. Current studies have found that distant metastasis is the reliable basis for the diagnosis of malignancy. Malignant paraganglioma can recur and metastasize over time.

To sum up, neurosecretory granules can be displayed by electron microscopy and cytochemistry in functional paraganglioma. Biochemical assay can accurately quantify the contents of norepinephrine and epinephrine (up to 24.5 g/g in tumor tissue). Typical pheochromocytoma symptoms can occur when the content reaches 1.5 mg/g.

19.4.2.4 Clinical Manifestations

In 2014, the American Society of Endocrinology published the Guidelines for Clinical Practice in the Diagnosis and Treatment of Pheochromocytoma and Paraganglioma [64]. Pheochromocytoma is a neoplasm originating from pheochromocytoma of adrenal medulla, while paraganglioma is a neoplasm originating from pheochromocytoma outside adrenal gland. Its clinical manifestations are related to excessive catecholamine secretion, mainly the phenomenon of "6H," namely hypertension (hype), retension, headache, heart consciousness, hypermetabolis, hyperglycemia, and hyperhidrosis. Because of atypical clinical symptoms, patients with the following manifestations should be screened: (1) hypertension with headache, palpitation, sweating, etc. [66]; (2) intractable hypertension; (3) unstable blood pressure; (4) anesthesia, surgery, angiography, high or fluctuating blood pressure

Table 19.1 Different sites of extraadrenal paraganglioma have different clinical manifestations

Position	Clinical characteristics
Glomus jugular tumor	Pulse-jumping tinnitus may aggravate or temporarily disappear after exercise. When the tympanic cavity is full of tumors, progressive conductive hearing loss occurs; with the development of the disease, sensorineural deafness occurs when the labyrinth is involved, and labyrinth symptoms occur; after the lesion penetrates the tympanic membrane, ear leaks occur, often purulent or bloody; and jugular vein syndrome often occurs when the tumors involve the skull base
Tympanoma	Ditto
Vagus paraganglioma	Brain nerve damage and hoarseness caused by vagal paralysis are often the earliest complaints of patients. Pharyngeal pain or neck pain may occur when the tumors spread to the pharyngeal plexus; pulsatile tinnitus, hearing loss, and vertigo may occur when the tumors invade the middle ear. Pheochromocytoma of the external auditory canal is rare. Its clinical manifestations are external auditory canal mass, tinnitus, and deafness
Carotid body paraganglioma	Slowly growing cervical mass with abundant blood supply often causes dysphagia and throat obstruction due to vagus nerve compression. Horner's syndrome may occur when the tumor compresses the sympathetic nerve. Pheochromocytoma of the head and neck can secrete norepinephrine, which is the primary catecholamine. Clinical symptoms include headache, hyperhidrosis, palpitation, pallor, nausea, and hypertension
Laryngeal accessory tumor	Near the glottis, mucosal biopsy is usually negative
Pulmonary accessory tumor	Respiratory distress was the first symptom. X-ray showed a space-occupying mass at the level of anterior mediastinal aortic arch
Abdominal aortic body aneurysm	It often presents as a retroperitoneal mass
Paraganglioma of bladder	Patients often have painless hematuria and/or paroxysmal hypertension during micturition
Cardiac paraganglioma and other paraganglioma	The clinical manifestations vary according to the anatomical location. They have been reported in the nasal cavity and paranasal sinuses, trachea, esophagus, stomach, duodenum, jejunum, mesentery, intercostals, paravertebral, femoral artery, cauda equina, thyroid gland, pineal gland, etc. There are also cases with metastasis as the first symptom

during pregnancy, which cannot be explained; (5) genetic background of PHEO/PGL family; (6) kidney, incidental adrenal tumors, idiopathic dilated cardiomyopathy.

Systemic paraganglioma originates from the extraadrenal paraganglion (pheochromoplast). In the head and neck region, paraganglion is named branchial ganglion chromophil body. Different sites of extraadrenal paraganglioma have different clinical manifestations (Table 19.1).

19.4.2.5 Hypertensive Characteristics of Extraadrenal Paraganglioma

1. Hypertension is the main manifestation of extraadrenal paraganglioma: the incidence is 80–100%. The typical manifestation of extraadrenal paraganglioma is

related to the corresponding symptoms of excessive catecholamine secretion. Hypertension has various forms. Paroxysmal hypertension is the characteristic of the disease. Headache, palpitation, and hyperhidrosis are called the triple sign of all chromaffin tumors, which is of great significance for diagnosis. Patients usually have low blood pressure, which can be induced by emotional excitement, body position changes, smoking, trauma, defecation, enema, angiography, anesthesia inducers, etc. When they attack, their blood pressure rises suddenly. The systolic blood pressure often reaches 200–300 mmHg. The diastolic blood pressure rises obviously, up to 130–180 mmHg. They have severe headache, pale face, sweating, tachycardia, chest tightness, angina, arrhythmia, anxiety, and so on. The manifestations of hypertension include persistent hypertension, paroxysmal exacerbation of persistent hypertension, alternation of hypertension and hypotension, hypertensive crisis, malignant hypertension, etc. Persistent hypertension can be evolved from paroxysmal hypertension, but also manifested as persistent hypertension at the beginning of its onset. The fluctuation of blood pressure may be mild and difficult to detect, and it is difficult to distinguish it from essential hypertension.

2. Hypertension alternating with hypotension, hypotension, or even shock: Catecholamine (CA) drops sharply due to "stroke" of tumors. As well as the alternating secretion of CA vasoconstrictor substances and vasodilator substances (vasodilator intestinal peptide, adrenomedullin, etc.) by tumors, which lead to the alternation of hypertension and hypotension. Partly because of the factors of heart and vascular bed, that is, a large number of CA leads to arrhythmia or heart failure, and the cardiac output decreases sharply. With strong vasoconstriction and tissue hypoxia, microvascular permeability increases, blood volume decreases, vascular alpha receptor depletion, blood pressure also decreases, and shock occurs in severe cases.

19.4.2.6 Diagnosis

To make a definite diagnosis of extraadrenal paraganglioma, the following aspects should be taken into consideration: qualitative diagnosis: (1) 24-h urinary catecholamine; (2) plasma free epinephrine and norepinephrine; (3) 24-h urinary epinephrine and norepinephrine; and (4) 24-h urinary VMA. Location diagnosis: (a) Anatomical imaging localization: CT plain scan + enhancement or MRI. It is recommended that the initial range of CT/MRI scan should be abdominal + pelvic, if negative, chest and head and neck; (b) Functional imaging localization.

The main imaging features are as follows:

1. 131I-MIBG imaging, octreotide (OTC) imaging, 18F-deoxyglucose positron emission tomography (PET).
2. CT: It is of great value in the diagnosis of paraganglioma. It can provide clinical information on the presence, location, size, shape, texture, and adjacency of the tumors to various organs, such as compression, displacement, adhesion, and infiltration. Although paragangliomas occur in different locations, they have similar imaging manifestations: (a) Most paragangliomas are more than 3 cm in

diameter, regular in shape, round or quasi-circular in shape and well-defined in boundary. (b) Paraganglioma is prone to degeneration due to uneven blood supply, so necrosis, hemorrhage, calcification and cystic degeneration are more common. On CT images, soft tissue masses with uneven density are presented, and the difference of tissue density within the lesion is more clear after enhancement. (c) Enhancement characteristics: Paraganglioma is a blood-rich neoplasm, so the enhancement of the lesion is remarkable after enhancement. Some scholars believe that sympathetic paraganglioma has thicker blood supply arteries, so in some tumors, we can see the enhancement of tumor blood vessels, paraganglioma showed early, progressive delayed enhancement.

CT images with high-density resolution can fully reflect the histological characteristics of tumors (such as hemorrhage, necrosis, cystic degeneration, and calcification), especially sensitive to calcification in the lesions. CT enhancement can also show the blood supply of tumors. However, the CT manifestations of paraganglioma still lack specificity. It is difficult to diagnose extraadrenal paraganglioma by CT alone. Clinical diagnosis is often made by determining whether the serum and urine catecholamines and their metabolites are elevated or not. The main purpose of CT examination is to locate and diagnose the extraadrenal paraganglioma and to know the location multiple occurrence, recurrence or metastasis of the Multiplanar CT reconstruction can also display the lesions in many directions and angles and provide more comprehensive anatomical location information.

3. MRI: Some scholars believe that the advantages of MRI and CT in the localization and diagnosis of extraadrenal paraganglioma are similar. The sensitivity of thin-slice enhanced CT scanning to the localization of extraadrenal paraganglioma is 98%, and the sensitivity of MRI is 93–100%.
4. PASS score and MIBG radionuclide imaging: There is no single clinical, biochemical, or histological feature to distinguish malignant from benign pheochromocytoma/paraganglioma [64, 66]. The Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) needs to be validated [67]. Preoperative FDG-PET/CT screening for metastatic tumors is recommended in patients with pheochromocytoma with paraganglioma, elevated 3MT in plasma or urine, and gene mutations (SDHB, Fumarate hydratase, FH, and malate dehydrogenase 2, MDH2). FDG-PET/CT scan is more sensitive than 123I-metaiodobenzylguanidine (MIBG) imaging in detecting metastasis, especially in patients with SDHB mutation [68], but it is relatively expensive and less specific than MIBG imaging.

19.4.2.7 Therapy

Surgical resection is the first choice of treatment for paraganglioma. PPGL patients are at risk of recurrence and metastasis after complete resection of primary tumors. For postoperative follow-up, it is recommended that all PPGL patients be tested for gene as far as possible; catecholamines in plasma or urine should be tested annually to screen for local or metastatic recurrence and new tumors; and high-risk patients (young patients and patients with hereditary diseases, massive pheochromocytoma/

paraganglioma) should be followed up every 6 months. All patients receiving PPGL should be followed up for at least 10 years. At present, the genetic changes of familial and malignant pheochromocytoma/paraganglioma have been well understood, which makes it possible to carry out gene diagnosis and targeted drug therapy for malignant tumors besides MIBG radionuclide therapy and chemotherapy.

1. Surgical treatment: Paraganglioma is insensitive to radiotherapy and chemotherapy. Surgical treatment is the first choice.
2. Radiotherapy: Radiotherapy has been used in the treatment of old, weak, and disabled patients, but with the development of medical science, radiotherapy and chemotherapy are gradually applied to the treatment of malignant paraganglioma. Considering that malignant paraganglioma is easy to recur after resection because of the difficulty of complete resection, local radiotherapy after recurrence can achieve the purpose of controlling the growth of the tumor. Whether additional radiotherapy after operation can reduce the recurrence rate of the tumor, the range and dose of radiotherapy need to be further studied.
3. Hypertension treatment of extraadrenal paraganglioma: As mentioned above, hypertension is the main symptom of extraadrenal paraganglioma. Its mechanism and typical manifestation are related to the excessive secretion of catecholamine. Therefore, its treatment is similar to pheochromocytoma. After definite diagnosis, treatment is as follows: control of blood pressure (alpha-receptor blocker or calcium channel blocker); control of arrhythmia, treatment of hypertension crisis, preoperative preparation, and surgical treatment.

19.4.2.8 Prognosis

Generally, paraganglioma has a good prognosis. Most paragangliomas are benign. The size of the tumors is not necessarily proportional to the severity of the symptoms. Sometimes the smaller ones have obvious symptoms, while the larger ones maintain "physiological tranquility," which is only occasionally found in autopsy. Surgical treatment of patients with occasional recurrence, but most patients can be cured. The hypertension of extraadrenal paraganglioma was cured with the disappearance of the primary disease.

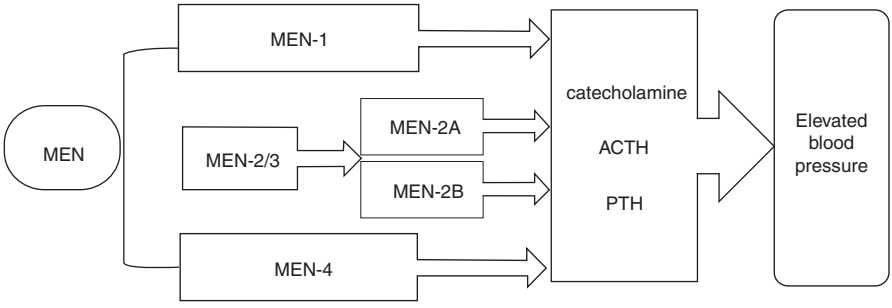

Fig. 19.3 Types of Multiple Endocrine Tumors

19.4.3 Multiple Endocrine Tumors

19.4.3.1 Definition and Classification of Multiple Endocrine Tumors

Multiple endocrine neoplasia (MEN) is a syndrome in which two or more endocrine glands develop tumors and cause excessive hormone secretion. MEN is rare, benign or malignant, nonfunctional or functional, sporadic, and autosomal dominant inheritance. Men can be divided into MEN-1, MEN-2, and MEN-4. MEN-2 can be divided into two subtypes: MEN-2A and MEN-2B (MEN-2 is also called MEN-3) (Fig. 19.3). The incidence of MEN has increased year by year in recent years.

Multiple endocrine tumors are often accompanied by clinical manifestations of hypertension, depending on the hormones secreted, such as ACTH and blood catecholamine.

19.4.3.2 Pathogenesis

1. Multiple endocrine neoplasm type 1 (MEN-1): also known as Wermer syndrome, the incidence of 2–3/100,000 [69] (rare), is a different combination of endocrine gland tumors such as parathyroid, pancreas, adrenal, and pituitary. MEN-1 is an autosomal dominant disease, and the main cause is the mutation of the suppressor gene MEN-1. Studies [70] suggest that the pathogenesis of MEN-1 is the "two-hit theory," that is, the mutation of MEN-1 gene at germ cell level is the first hit, that is, when a patient is born, he has carried an abnormal mutation allele at germ cell level, but he has not developed the disease because another allele is normal. Once another MEN-1 allele mutation at the somatic level is the second hit, it eventually causes disease. Friedman [70] put forward the theory of loss of heterozygosity (LOH) of MEN-1, which is the mutation of MEN-1 gene at the somatic level, confirming the second blow of Knudson's two-hit theory.
2. Multiple endocrine neoplasm type 2 (MEN-2): is a rare autosomal dominant hereditary disease, also known as Sipple syndrome [71]. Subtypes include MEN-2A, MEN-2B, and familial adenomedullary carcinoma (FMTC). RET proto-oncogene mutation is associated with the occurrence and progression of clinical related diseases of MEN-2 and is a key factor in the pathogenesis of MEN-2 [72]. The length of RET proto-oncogene is more than 55 kb, which is located on chromosome 10q11 and consists of 21 exons. The receptor is tyrosine kinase. The proto-oncogene of RET mutated, and the function of protein expressed by RET changed. Tyrosinase production was not regulated by phosphorylation, which resulted in tumorigenesis of endocrine glands [72].
3. Multiple endocrine neoplasm type 4 (MEN-4): CDKN1B gene mutation of protein, which is autosomal dominant inheritance, is rarely reported at home and abroad.

19.4.3.3 Clinical Manifestations, Diagnosis, and Treatment

1. Clinical manifestation, diagnosis, and treatment of multiple endocrine neoplasm syndrome type 1.

Men-1 has a high penetration rate. More than 95% of patients suffer from the disease before the age of 50 years, and the related tumors can be found under the age of 15 years [73]. The clinical manifestations of MEN-1 are related to the affected organs. Parathyroid adenoma is the first symptom in 85% of the patients with MEN-1. Parathyroid adenoma is the first endocrine neoplasm of MEN-1 [69, 74]. Primary hyperparathyroidism (PHPT) caused by parathyroid adenoma is the most common clinical manifestation in MEN-1, and the onset age is the earliest (it can occur before 20 years of age) [75]. PHPT can lead to increased parathyroid hormone (PTH) secretion; bone and kidney are the main target organs, accompanied by high blood calcium, low blood phosphorus, PTH elevation, etc. The main clinical manifestations can be divided into bone type, kidney type, and mixed type. However, the hypercalcemia caused by MEN-1 in PHPT patients is mild, so patients with slightly elevated biochemical indicators should be vigilant in clinic. Hypercalcemia and hypophosphatemia may have no clinical symptoms, but may be accompanied by kidney stones, peptic ulcer, polyuria, thirst, constipation, and fatigue. Therefore, patients with mild or no biochemical changes in clinical parameters should also be examined by imaging to exclude PHPT. The incidence of enteropancreatic neuroendocrine tumors is the second highest in MEN-1, including gastrinoma, insulinoma, pancreatic polypeptide tumors, glucagon tumors, vasoactive intestinal polypeptide tumors, and non-functional tumors. Surgery is the most effective treatment for MEN-1-induced parathyroid adenoma. At present, parathyroidectomy is the most choice for 3.5 parathyroid glands or all four parathyroid glands and autologous transplantation [75].

Gastrinoma is the most common and often malignant neuroendocrine neoplasm of the intestine and pancreas. About 50% of MEN-1 patients develop gastrinoma after 50 years of age [76]. Periodic recurrence of multiple ulcers leading to high perforation rate is the main manifestation of gastrinoma. Gastrinoma is characterized by multiple and atypical sites of refractory peptic ulcer. Gastrinoma is sensitive to proton pump inhibitors. At present, drug therapy is the main treatment for gastrinoma. Insulinoma is the first manifestation in about 10% of MEN-1 patients.

Insulinoma accounts for 10–30% of MEN-1 enteropancreatic neuroendocrine tumors. Most of them are benign and solitary. Most of them occur before the age of 40 years, and 10% of them are accompanied by other endocrine tumors. Insulinoma secretes too much insulin. The main clinical manifestation is Whipple triad. Biochemical examination of blood insulin and C-peptide levels is helpful for diagnosis, and imaging examination is helpful for localization. Once insulinoma is diagnosed, early surgical excision and lymph node dissection are needed. For patients who cannot be operated, refuse operation, have no remission or recurrence after operation, and wait for operation, octreotide and other drugs can be selected [77].

The incidence of MEN-1 glucagonoma is relatively low, with weight loss and skin rash as the main clinical manifestations. Some patients may have no corresponding symptoms, but the clinical examination indicators can indicate posi-

tive. MEN-1 glucagonoma is mainly treated by surgery, and if metastasis has occurred, it will be treated by internal medicine. The incidence of MEN-1 vasoactive intestinal peptide tumors is low. Hypokalemia and diarrhea are the main clinical manifestations of the disease. Surgical resection is the main treatment. MEN-1 nonfunctioning pancreatic tumors have a lower incidence than the above-mentioned ones and often have no corresponding symptoms or slightly elevated levels of pancreatic-related hormones, which makes diagnosis difficult. The guidelines recommend that nonfunctional tumors >1 cm or <1 cm should be resected surgically [77]. The prognosis of MEN-1 nonfunctioning pancreatic tumors is worse than that of functioning pancreatic tumors. MEN-1 pituitary adenomas are mostly about 1 cm in size, and most of them are female.

Prolactin tumors are the most common pituitary adenomas in EN-1, and about 15% of them are the first symptoms. Hyperprolactinemia (60%), high growth hormone (25%), and high adrenocorticotropic hormone (5%) were the main clinical manifestations, such as menopause, lactation, infertility, acromegaly, and Cushing syndrome. MEN-1 pituitary adenomas can be treated with drugs or resected by transsphenoidal approach. MEN-1 pituitary adenoma is aggressive and has poor prognosis. Rare MEN-1 tumors include angiofibroma, collagen tumors, adrenocortical tumors, multiple lipomas, foregut carcinoid tumors, meningiomas, and facial ependymomas. The clinical manifestations are different [78].

Because MEN-1 patients often manifest as hyperparathyroidism and/or Cushing disease, hyperparathyroidism patients have increased circulatory thyroid hormones, hypermetabolism, increased cardiac output, resulting in increased systolic pressure, due to increased fever, peripheral vascular dilatation, increased arteriovenous anastomotic branches, resulting in normal or slightly reduced diastolic pressure. In patients with Cushing disease, cortisol enhances norepinephrine's contractile effect on heart and blood vessels. In addition to cortisol, the secretion of 11-deoxycorticosterone and other saline corticosteroids increases, resulting in water and sodium retention in the body. Because of the long-term elevation of blood pressure, it leads to extensive arteriosclerosis, which aggravates the elevation of blood pressure. These diseases are one of the basic diseases of secondary hypertension, which can cause hypertension manifestations.

2. Clinical manifestations, diagnosis, and treatment of multiple endocrine adenomatosis type 2.

MEN-2 is mainly characterized by MTC and is complicated with endocrine tumors such as pheochromocytoma and/or hyperparathyroidism [79]. MEN-2A is the most common subtype of MEN-2, accounting for about 80% [80]. Ninety percent of the patients with MEN-2A syndrome suffered from medullary thyroid cancer (MTC), 40–50% from pheochromocytoma, and 20–30% from hyperparathyroidism (hyperplasia of parathyroid cells or adenoma) [81]. Few patients with MEN-2A suffer from paraneoplastic syndrome, such as skin amyloid changes and excessive production of adrenocorticotropic hormones. A few patients with MEN-2A presented with Hirschsprung's disease, which resulted from the absence of distal colonic parasympathetic plexus in autonomic ganglion cells.

MEN-2B is relatively small in MEN-2, about 20%. Of the patients with MEN-2B syndrome, 90% were MTC, 40–50% were pheochromocytoma, and few were mucosal ganglioma and other endocrine tumors. MEN-2B rarely causes hyperparathyroidism. The incidence of FMTC was only MTC, accounting for 10–20% [82] of MEN-2. MTC is often the first symptom of MEN-2, and the onset time is early (early onset). The study found that the incidence of MTC was 2–3% in new thyroid cancer cases. The majority of MTC were sporadic (about 70–75%) and unilateral thyroid. The incidence of hereditary MTC is relatively small, mostly bilateral and bilateral thyroid. Clinical manifestations include unilateral or bilateral thyroid masses, convulsions of hands and feet, dyspnea, and other symptoms. Late metastasis is the main cause of death. At present, the main clinical treatment of MTC is surgery (bilateral thyroidectomy + neck lymph node dissection), which is not sensitive to radiotherapy and chemotherapy [83]. Pheochromocytoma is an endocrine neoplasm of adrenal medullary tumors with similar proportion in EN-2A and MEN-2B. It is often accompanied by MTC, and its main manifestation is the secretion of catecholamine. Blood catecholamine, imaging examination, and 131I-m-iodobenzylamine (MIBG) are helpful in the diagnosis of MEN-2 pheochromocytoma. Surgical resection is the main treatment for this disease. MEN-2A hyperparathyroidism mostly has no corresponding clinical symptoms and may occur corresponding hypercalciuria or (and) kidney stones; clinical surgery is the main treatment method [84]. In addition, most of the patients with MEN-2B have Marfan-like body shape. Mucosal neuromas mostly grow on the surface of tongue, lip, subconjunctival area, and gastrointestinal tract.

In a word, 50% of patients with MEN-2A or MEN-2B had pheochromocytoma of adrenal gland, which resulted in the paroxysmal elevation of blood pressure caused by the secretion of large quantities of catecholamine, and hypertension crisis in severe cases.

3. Clinical manifestations, diagnosis, and treatment of multiple endocrine adenomatosis type 4.
   MEN-4 has many clinical manifestations, such as parathyroid adenoma, pituitary adenoma, enteropancreatic neuroendocrinoma, angiofibroma, and so on. Corresponding biochemical examination, imaging examination, and CDKN1B gene detection are helpful for the diagnosis of MEN-4. At present, surgery is the main treatment for MEN4; radiotherapy and chemotherapy are supplementary. The gene research of MEN-4 is still relatively few [85], and the specific mechanism needs to be supplemented.

19.4.3.4 Auxiliary Examination

1. Laboratory inspection.
   (a) Blood examination: To determine the concentration of various hormones in the blood for early diagnosis of the disease. Blood sugar, norepinephrine, adrenaline, and calcitonin can be significantly increased. Blood electrolytes, T3, T4 aldosterone cortisol, and glucagon should be routinely examined.

(b) Stimulation test: Glucagon or tyramine is positive in simple pheochromocytoma. If pheochromocytoma combined with other endocrine gland tumors, especially medullary thyroid cancer, tyramine test is negative and glucagon is positive.
(c) Detection of CDKN1B gene is helpful for the diagnosis of MEN-4.

2. Imaging
Ultrasound can be the preferred method for the detection of parathyroid glands and thyroid glands, which are the most frequently involved glands. Ultrasound and CT are the most common examinations of adrenal gland. Ultrasound can detect adrenal tumors over 1 cm, but the detection rate of left adrenal tumors is low. Pancreatic tumors are sometimes multiple and small in size. Ultrasound and CT plain scans are often false negative. Because the tumors are multivascular, enhanced CT and MR and selective arteriography are helpful for preoperative diagnosis. CT and MR have great significance in the diagnosis of pituitary tumors.

19.4.3.5 Diagnosis

One of the keys to the diagnosis of MEN is that clinicians should be highly alert to the disease. When finding an endocrine gland tumor, the possibility of MEN should be considered and screened.

1. Diagnosis of MEN-1: It is generally believed that MEN-1 can be diagnosed if two of the three most common endocrine organ tumors (parathyroid gland, pancreaticointestinal endocrine gland and pituitary gland) are present. MEN-1 pedigree can be diagnosed if at least one of the first-degree relatives has one of these tumors. Conditional units can choose to detect the mutation of MEN-1 gene.
2. Diagnosis of MEN-2: About 10% of pheochromocytomas (PHEO) are associated with MEN, and 25% of MTCs are associated with MEN and FMTC. The clinical diagnostic criteria for MEN-2 are derived from the International Association for RET Mutation (Table 19.2).

   MTC is the key to clinical features and diagnosis of MEN-2. Family MEN-2A can be diagnosed by any combination of more than two MTC-based lesions with three diseases, MTC, PHEO, and PHPT.

   Because pheochromocytoma can be asymptomatic in patients with MEN-2A, it is difficult to exclude pheochromocytoma with certainty. The most sensitive methods for the diagnosis of MEN-2A are the determination of epinephrine, norepinephrine, and 24-h urinary free catecholamine by special analysis method.

Table 19.2 Diagnostic criteria for each subtype of MEN-2

Subtype	MTC (%)	PHEO (%)	PHPT (%)	Family sickness
MEN–2A[a]	100	50	20	Arbitrarily
MEN–2B[b]	100	50	0	Arbitrarily
FMTC	100	0	0	≥4

[a]The diagnosis of PHEO and/or PHPT is required
[b]The features of tongue, lip, subconjunctival area, or gastrointestinal mucosal neuroma are required

Vanillylmandelic acid excretion is often normal in the early stages of disease. CT or MRI can help to locate pheochromocytoma or establish bilateral lesions. In vitro scintillation scan of metaiodobenzyl guanidine cannot provide more information.

Medullary parathyroid carcinoma can be diagnosed by measuring plasma calcitonin after perfusion with prostaglandin or calcium. Calcitonin is elevated in most patients who can touch the thyroid gland, but in the early stage, basic calcitonin can be normal. Medullary cancer can only be diagnosed if it overreacts to calcium and prostaglandins. Hyperparathyroidism can be diagnosed by hypercalcemia, hypophosphatemia, and elevated parathyroid hormone.

The genetic screening of MEN-2A is now extremely accurate. Identifying gene carriers advocates early preventive thyroidectomy in infants and children, because medullary thyroid cancer can ultimately be fatal if allowed to develop. Early childhood screening for hyperparathyroidism and pheochromocytoma should be carried out annually and indefinitely. For example, pheochromocytoma symptoms (paroxysmal headache, sweating, or palpitation) and history of renal colic should be inquired and blood pressure monitored regularly, and laboratory tests should be improved if conditions permit.

3. Diagnosis of MEN-4: Corresponding biochemical examination, imaging examination, and CDKN1B gene detection are helpful for diagnosis.

19.4.3.6 Therapy

MEN treatment advocates surgical treatment, but gene therapy is more difficult at present. Because the onset of MEN involves multiple organs, the treatment emphasizes the full cooperation of multiple disciplines. Different lesions are mainly treated by various related specialties, but one-sided isolation should be avoided. Urology mainly deals with adrenal-related diseases.

Parathyroid glands are mainly hyperplasia and may be accompanied by ectopic hyperplasia of parathyroid glands, as well as pancreatic islet lesions. Therefore, follow-up after operation is emphasized. Medullary thyroid carcinoma emphasizes cleaning, while pheochromocytoma is mostly bilateral, accounting for 40%. Therefore, unilateral tumors are found preoperatively and intraoperatively. Postoperative tumors on the opposite side are likely to occur. Therefore, close follow-up after operation is necessary. Regular determination of calcitonin, B-ultrasonography, and CT examination of adrenal gland are required. Pituitary tumors can be treated with surgery, gamma knife, or corresponding drugs. Neurofibroma occurs in the intestine and often requires surgery.

Patients with pheochromocytoma and medullary thyroid cancer or hyperparathyroidism should be treated with pheochromocytoma resection, because even asymptomatic, it greatly increases the risk of surgical treatment of medullary thyroid cancer and hyperparathyroid. Treatment of residual thyroid medullary carcinoma and metastatic chemotherapy are ineffective, but radiotherapy can prolong survival time.

MEN patients with hypertension take different conservative medical treatment according to different hormones secreted by MEN. For the secretion of ACTH,

commonly used drugs include mitotane, Aminoglutethimide, methylpyridine, and other cortisol synthase inhibitors, as well as 5-hydroxytryptamine antagonist cyproheptadine, but the efficacy is not satisfactory. If catecholamine is secreted, the treatment is referred to pheochromocytoma.

19.4.3.7 Prognosis

Compared with MEN-2, the prognosis of MEN-1 is better. The prognosis of MEN-2 depends mainly on the progression and stage of MTC. MEN-2 patients who did not undergo surgical treatment before MTC metastasis rarely survived beyond 40 years of age. Early diagnosis and timely radical thyroidectomy can prolong the survival of patients. The 5-year survival rate and 10-year survival rate of MTC were 80–90% and 60–70%, respectively.

19.4.4 Ectopic Endocrine Tumors [86]

19.4.4.1 Definition of Ectopic Endocrine Tumors

Some non-endocrine gland tumors can produce and secrete hormones or hormones, which can cause clinical symptoms of endocrine disorders. These tumors are called ectopic endocrine tumors. The clinical symptoms caused by these tumors are called ectopic endocrine syndrome. Most of these tumors are malignant tumors, most of which are cancers. They can also be seen in sarcomas such as fibrosarcoma and leiomyosarcoma. In addition, tumors of APUD system (diffuse neuroendocrine system) can also produce biogenic amines or polypeptide hormones, such as carcinoid and pheochromocytoma.

19.4.4.2 Common Types of Ectopic Endocrine Tumors

At present, there are 27 and 65 kinds of heterogeneous hormones secreted by endocrine and non-endocrine tumors, respectively. The most common ectopic endocrine tumors found in clinic are ectopic adrenocorticotropic hormone (ACTH) syndrome, ectopic antidiuretic hormone (ADH) syndrome, ectopic hypoglycemia syndrome, ectopic parathyroid hormone, and related peptide (PTH/PTHrP) syndrome.

19.4.4.3 Pathogenesis

The exact mechanism of the production of heterogeneous hormones or hormones in cancer tissues is still unclear. Currently, several theories have been put forward as follows:

1. Gene theory: Also known as the theory of depressant, it is the first convincing theory that deoxyribonucleic acid (DNA) of normal cells is inhibited by regulated genes. Messenger ribonucleic acid (RNA) formed by transcription can only produce normal polypeptide hormones, but when the code of protein genome synthesizing certain peptide hormones in cancer cells is depressed, it can produce them, another protein or peptide hormone.

2. Endocrine cytology: It is believed that tumor cells secreting ectopic hormones originate from cells related to normal endocrine hormone precursors in embryonic stage. They have the ability to secrete other hormones themselves, but they do not secrete hormones under normal conditions. Once tumors occur, these cells degenerate into poorly differentiated or embryonic cells, and they can repossess the ability to secrete hormones. These cells have common histochemical and ultrastructural characteristics, collectively known as the APUD cell system. They originate from the embryonic ectodermal nerve ridge and distribute in endodermal organs such as lung, thymus, thyroid, stomach, small intestine, pancreas, and adrenal gland. These organs can produce ectopic hormones when tumors occur.
3. Abnormal protein synthesis theory: Tumor cells can synthesize some abnormal proteins or peptides with hormone-like effects, such as growth interleukins causing hypoglycemia and substances causing erythrocyte proliferation.
4. Oncogene growth factor theory: It has been confirmed that normal cells also contain oncogenes or proto-oncogenes. The functions of some oncogenes are closely related to endocrine functions. Their products are similar to growth factors, growth factor receptors, or their functional subunits. The relationship between oncogene activation of ectopic hormones is still unclear. It may simply provide stimulation to the proliferation of primitive cells and then induce abnormal differentiation or the expression of endocrine genes activated by chromosome translocation activation or other mechanisms. This theory can explain the ectopic hormones produced by non-ordinary tumors (i.e., non-APUD cell tumors) and the phenomenon that different tumors can produce the same ectopic hormone.

19.4.4.4 Clinical Manifestations

Sometimes, because of the low biological activity of the hormones produced by tumors, it is not enough to cause clinical symptoms. The symptoms they cause can occur before, at the same time, or after the symptoms of the primary tumor.

1. Heterotopic adrenocorticotropic hormone (ACTH) syndrome: Cushing syndrome is a special type. Excessive ACTH secreted by tumors outside the pituitary gland stimulates adrenocortical hyperplasia and produces clinical syndrome caused by excessive corticosteroids, accounting for 5–10% of the total Cushing syndrome. Hypertension caused by ectopic ACTH syndrome is consistent with Cushing syndrome, i.e., water and sodium retention caused by elevated adrenocortical hormone levels in vivo. The most common cause reported in foreign literature is lung or bronchial neoplasms, accounting for about 50%. The most common cause of ectopic ACTH syndrome reported in China is small cell lung cancer and bronchial carcinoid. In clinic, ectopic ACTH syndrome is generally divided into two types, type I is mainly small cell lung cancer patients, mostly in men. Because of its short course, serious condition, and serious consumption, Cushing syndrome symptoms such as centripetal obesity and purple striae do not appear, but mainly manifested as hypertension, edema, severe hypokalemia with

muscle weakness, diabetes with thirst, excessive drinking, polyuria, and weight reduction. Type II ectopic ACTH syndrome is mainly found in lung, pancreas, and intestinal carcinoid. It is characterized by long course, mild condition, and small carcinoid volume. Therefore, the clinical manifestation of Cushing syndrome is typical, which should be differentiated from pituitary Cushing disease. The former has obvious hypokalemic alkalosis, and steroid diabetes is common, pigmentation is more common than pituitary Cushing disease. At present, the location of ectopic ACTH syndrome is very difficult, which makes the clinical diagnosis and treatment not be effectively implemented. The key to the treatment of ectopic ACTH syndrome is to clarify the origin of ectopic tumors, to treat the primary lesions, to remove the tumors and metastases as thoroughly as possible, and to extend the survival time and improve the quality of life as much as possible after radiotherapy and chemotherapy, if necessary.

2. Ectopic hypoglycemia syndrome: It is not a hypoglycemia syndrome caused by abnormal insulin secretion, but also one of the common clinical ectopic endocrine syndrome. Its clinical manifestation is similar to that of hypoglycemia caused by insulinoma, but the level of blood insulin and C-peptide is not high in such patients during fasting or hypoglycemic attacks. Hypoglycemic episodes disappeared after resection of the tumors.
3. Heterotopic antidiuretic hormone syndrome (SIADH), also known as abnormal secretion of antidiuretic hormone syndrome (SIADH). The most common tumors causing ectopic ADH secretion are lung cancer (about 40%) and other malignant tumors including thymus, pancreas, duodenum, esophagus, and breast. The main symptoms are water intoxication, diluted hyponatremia, hypoosmotic pressure, fatigue and weakness, headache, anorexia, nausea, and vomiting. In severe cases, psychiatric symptoms occurred when blood sodium was below 120 mmol/L (120 mEq/L). Laboratory tests showed low serum sodium level, low plasma osmotic pressure, increased urinary sodium excretion, high urine specific gravity, and increased plasma ADH level. However, the diagnosis should be differentiated from SIADH caused by some intracranial diseases and some drugs such as morphine, pethidine, and barbiturates which stimulate the secretion of ADH. In addition to the treatment of primary tumors, those with symptoms of water intoxication should strictly control water inflow, properly supplement with hypertonic saline, and strengthen diuresis to rapidly increase osmotic pressure and prevent brain edema.
4. Ectopic parathyroid hormone syndrome: The main symptoms are hypercalcemia, such as loss of appetite, nausea, thirst, polyuria, severe vomiting, dehydration, sleepiness, and mental disorders. It has been found that malignant tumors such as lung, kidney, bladder, liver, colon, testis, and ovary can cause hypercalcemia, which mainly secretes PTH-like polypeptide and causes ectopic hypercalcemia. The conditions for diagnosis of hypercalcemia caused by ectopic PTH are: (a) high serum calcium and low serum phosphorus in patients with malignant tumors; (b) normal parathyroid function; (c) no bone metastases and other causes of high serum calcium; and (d) decreased serum calcium after resection of tumors. Heterotopic PTH syndrome is different from primary hyperparathy-

roidism. Because of its rapid progress and short course of disease, ectopic PTH syndrome has no urinary calculi and obvious skeletal changes. Therefore, patients with any of the following manifestations of hyperparathyroidism may be suggestive of ectopic PTH syndrome: elevated blood alkaline phosphatase without X-ray changes in subcortical periosteal absorption. Low blood chlorine level and high blood bicarbonate; high blood calcium was positive for adrenocortical hormone; weight loss and anemia.

19.4.4.5 Diagnosis

The key to the diagnosis of ectopic endocrine tumors is to clarify the relationship between ectopic hormones and non-endocrine tumors. The diagnostic requirements are as follows: (1) non-endocrine neoplasms complicated with endocrine syndrome; (2) abnormal increase of some hormone level in blood or urine; (3) the hormone level measured in blood or urine is ineffective in inhibiting physiological feedback; (4) the hormone level decreases after tumor resection or radiotherapy and chemical treatment; (5) the existence of hormones in tumor tissue is confirmed; (6) the culture of tumor tissue in vitro can be followed up. Continuous synthesis of hormones; tumor cells contain the hormone-specific gene, while normal cells of tumors do not have the hormone gene; exclude other possible causes.

19.4.4.6 Treatment and Prognosis

Surgical removal of primary tumors is currently the recommended treatment. The prognosis depends on the primary tumors, which can be recovered after resection. The prognosis of the primary tumors is good for the benign ones, and the prognosis of the primary tumors is bad for the malignant ones.

19.5 Orthostatic Hypertension

Zhihua Zhang

Orthostatic hypertension (OHT) is a kind of orthostatic blood pressure regulation disorder (including orthostatic hypotension and orthostatic hypertension), and it is a special type of hypertension different from primary hypertension. Orthostatic hypertension is currently considered to be associated with the progression of target organ damage and be a new risk factor for cardiovascular disease, but it has been rarely studied and has important clinical significance.

19.5.1 Epidemiology

OHT prevalence varies in different studies because of the different methods used, the different population characteristics and the different criteria for orthostatic hypertension. One study used the position stimulation test from lying to standing, which found that the incidence of OHT was 8.7% in normal subjects. Another study

using similar methods found that the incidence of OHT was 16.2% in young people. In 2011, a survey of 4711 middle-aged and elderly hypertensive patients in China showed that the incidence of OHT was 16.3%. So it can be seen that the incidence of OHT is quite high, but clinical attention has not been paid [87].

19.5.2 Pathogenesis

The mechanism of OHT is still unclear. The earliest researchers believed that the excessive accumulation of blood in the upright position was due to the excessive accumulation of blood in the volume vessels (especially the venous system of the lower extremities), the reduction of venous reflux and ventricular filling, and the stimulation of abnormally active sympathetic nerve discharges through low pressure receptors (cardiopulmonary receptors), which led to an increase in blood pressure. This is also the general view of OHT mechanism.

Researchers assessed the changes of neurohumoral factors between OHT group and normotensive group by vertical tilt test. The results showed that there was no difference in renin levels between the two groups. Norepinephrine and vasopressin levels in OHT group were higher than those in normotensive group after standing. Therefore, it is presumed that vasopressin is compensated for OHT by the change of body fluid distribution in standing position and that sympathetic nervous system activity is closely related to the pathological mechanism of OHT. Relevant pharmacological tests showed that when subjects took doxazosin, an alpha-blocker, their orthostatic and recumbent blood pressures also decreased in hypertensive patients with normal postural blood pressure changes, while those with OHT showed elevated blood pressures returning to normal (although the changes were not statistically significant).

In addition, some researchers have found that OHT is common in patients with renal prolapse, considering that changes in body position activate the renin-angiotensin system. Lee H et al. [88] found that the cardiac output and stroke output of OHT patients had similar changes during tilt compared with the normal control group. This suggests that excessive venous convergence in the legs during erect position leads to a decrease in stroke output and cardiac output, which may not be a trigger for increased total peripheral resistance. Overactive adrenaline may be a more reasonable explanation for the increased total peripheral resistance caused by excessive small artery constriction in OHT patients. In addition, researchers found that patients with OHT had higher autonomic nervous dysfunction than those without OHT. Therefore, the pathogenesis of OHT is quite complex, involving many factors, and there is no unified understanding at present.

19.5.3 Clinical Features

OHT refers to the increase of blood pressure in standing or sitting position, while normal blood pressure in supine position. Most patients have no symptoms. In

physical examination or occasional cases, diastolic blood pressure is mainly elevated, and the fluctuation range is large. Severe cases may be accompanied by palpitation, fatigue, fast sleep, and so on.

Usually the diagnosis of hypertension is based on the blood pressure at rest. At this time, the contraction of resistance vessels is very small. However, even if the blood pressure is normal at rest, functional vasoconstriction will occur in the morning, during tension, sleep apnea and in the upright position, and neurohumoral factors will be activated. Studies have shown that the relationship between vasoconstriction and vascular resistance varies exponentially. Patients with and without small vessel remodeling have greater differences in vascular resistance than those without small vessel remodeling at rest. Therefore, if small vessel remodeling occurs and progress occurs, the increase of blood pressure in patients will be more significant. Studies have shown a positive correlation between elevated morning blood pressure peaks and increased intima-to-lumen ratios and arteriolar thickening assessed by biopsy as a gold standard for small vessel remodeling. Based on these findings, small vessel remodeling can also exist in OHT patients with normal blood pressure at rest. In fact, follow-up studies have shown that OHT is an important risk factor in the development of hypertension.

Use of ambulatory blood pressure monitoring study found in elderly patients with high blood pressure, blood pressure form performance for super scoop type with significant morning peak group have considerable overlap, and OHT patients often show super scoop-type blood pressure form, so that OHT is associated with not only the morning wake up from lying position to standing blood pressure, and also the night blood pressure to drop, cause from night to morning blood pressure (morning peak) significantly.

There is a vicious circle between blood pressure fluctuation and vascular damage, leading to the progression of vascular damage. Studies have shown that the risk of peripheral vascular disease, asymptomatic stroke, chronic kidney disease, and type 2 diabetic neuropathy in OHT patients is significantly higher than that in normal hypertensive patients. In a study of elderly patients with hypertension, OHT is a risk factor for resting cerebral infarction and deep white matter lesions, as well as for future clinical stroke. Comparing OH or OHT with normal blood pressure group, the cognitive function and daily living ability of OH or OHT decreased, and the deep white matter lesion progressed significantly. Moreover, the cardiovascular remodeling of OHT patients progressed faster than those with normal postural blood pressure, and the thickening of ventricular or medial membranes and left ventricular thickening were more severe. Other studies have confirmed that the levels of brain natriuretic peptide and urinary microprotein/creatinine ratio in OHT patients are significantly increased, and the degree of atherosclerosis and target organ damage is significantly increased. The mechanism may be that in the process of body position change, gravity causes venous blood stasis in lower limbs, decreases cardiac output, and widespread contraction of small arteries caused by sympathetic nerve hyperexcitation leads to elevated blood pressure after orthostasis. Frequent body position changes increase blood pressure fluctuation and increase blood pressure variability. Long-term presence will lead to microvascular remodeling, increase

vascular wall damage, and increase target organ damage. These results further suggest that OHT is closely related to the progression of hypertension and the risk of heart, brain, kidney, and other diseases.

19.5.4 Diagnosis Methods

There is no consensus on the standard of OHT. Generally, the systolic blood pressure of postural hypertension is increased by at least 20 mmHg from lying position to standing position (or tilting position) or from lying position to standing position, the systolic blood pressure is increased from less than 140/90 to 140/90 mmHg as the diagnostic criteria. However, the change of postural blood pressure is significantly affected by the amount of circulating blood. It is best to diagnose OHT by multiple postural tests. However, in daily clinical practice, it is difficult to carry out body position test frequently, and the "white coat phenomenon" will interfere with the body position test in the examination of the consulting room. Therefore, some researchers have studied home blood pressure measurement. The results show that home blood pressure measurement not only can detect abnormal pathological conditions but also has high repeatability and can eliminate the phenomenon of "white coat." It is further proved that this method is not only feasible for OHT diagnosis but also simple and feasible. Clinically, patients with postural blood pressure changes should suspect that their blood pressure is elevated latent hypertension at other times even if their blood pressure is normal in the sitting position of the clinic. It is recommended to use home self-measured blood pressure and 24-h ambulatory blood pressure to further clarify.

19.5.5 Treatment and Prognosis

Non-drug therapy: There are few studies on OHT treatment, and most of them are case studies. The antihypertensive drugs selected are also different because of the patient's tolerance. There are great individual differences. At present, there is no clear or consistent recommendation. Therefore, the main treatment measures are to improve lifestyle, exercise properly, increase exercise tolerance, and so on.

Drug therapy: Because the pathogenesis is not clear, the main types of antihypertensive drugs currently used can be selected according to the specific conditions of patients. Studies have shown that alpha-blockers can alleviate OHT, which seems to be the first choice in patients without contraindications.

OHT increases blood pressure variability and is an important clinically pathological state related to target organ damage and future cardiovascular risk. Current studies have far failed to recognize the etiology and pathophysiological characteristics of OHT. More clinical and basic studies are needed to understand the occurrence, development, and prognosis of OHT.

19.5.6 Orthostatic Hypotension

Clinically, orthostatic hypotension (postural hypotension, PH), also known as orthostatic hypotension (orthostatic hypotension, OH), is more common than orthostatic hypertension. It is recognized as a risk factor for falls, fainting, and cardiovascular events. It is closely related to some common chronic diseases, such as essential hypertension, congestive heart failure, diabetes mellitus, and Parkinson's disease. It is difficult to find postural hypotension in hospitalized patients due to medication and bed rest. It can be said that there is a delayed effect in these patients, which increases the risk of cardiovascular events, including acute myocardial infarction, heart failure, stroke and so on. In view of the fact that orthostatic hypotension is a common, easy-to-diagnose and treatable clinical disease, Feldstein and other medical workers are encouraged to actively monitor the blood pressure of inpatients in the standing and lying positions.

19.5.6.1 Epidemiology

It is reported that the prevalence of OH varies, depending in part on age and complications. In unselected communities, the prevalence of OH among residents ranged from 9 to 34% [89, 90]. In geriatric nursing institutions and emergency hospitals, the prevalence of OH is as high as 50% [91] and 41% [92]. Among the complications that have a special impact on the prevalence of OH: neurodegenerative diseases, such as Parkinson's disease (up to 58% [93]), diabetes mellitus (up to 28% [94]), and hypertension (up to 32% [95]).

19.5.6.2 Pathogenesis

The pathogenesis of OH mainly concentrates on the following four aspects:

1. Reduction of effective circulating blood volume: Absolutely insufficient blood volume caused by blood loss and fluid loss after trauma, or relatively insufficient blood volume caused by blood redistribution after the use of vasodilators and other drugs.
2. Decreased cardiovascular responsiveness: Clinical manifestations are mainly in elderly patients, with decreased cardiac compliance and decreased vascular responsiveness to sympathetic nerve excitation.
3. Autonomic nervous system dysfunction: Damage to any part of the baroreceptor reflex arc may cause peripheral vascular tension not to change with body position, resulting in postural hypotension, such as diabetic peripheral neuropathy, peripheral vascular motor lesions, and postural hypotension caused by some central sedatives and antidepressants.
4. Release of vasodilator factors increased: Increased concentration of vasodilator factors such as serotonin, bradykinin, and prostaglandin in blood can cause peripheral vasodilation and postural hypotension.

19.5.6.3 Classification

With the development of research at home and abroad in recent years, the classification criteria of orthostatic hypotension are also varied. Bradbury et al. first reported and used the concept of idiopathic orthostatic hypotension in 1925. The main reason is that autonomic nervous dysfunction, such as sweating, intestinal and bladder dysfunction, and heart rate did not increase during orthostatic hypotension. The occurrence of orthostatic hypotension has not found the cause, and the occurrence of diabetes, hypertension, and other diseases belongs to this type of orthostatic hypotension. This type mainly occurs in the middle-aged and old people aged 50–70 years and is more common in male, mainly occurring in hot weather, during sports, and after meals. Early male sexual dysfunction, impotence, female urinary incontinence, and urinary retention may be related to decreased cardiovascular regulation.

By 1960, Shy et al. reported a case of neurological syndrome with orthostatic hypotension, later known as Shy-Drager syndrome. When the patient was lying, the blood pressure was in the normal range. The blood pressure in the orthostatic position decreased significantly, accompanied by cerebral ischemia and abnormal autonomic nervous function, mostly with extrapyramidal tracts, pyramidal tracts or cerebellar lesions. Multiple systemic atrophy (MSA) is now commonly used to replace the name of the syndrome.

By 2011, Lanier et al. [96] put forward a new viewpoint, that is, according to the severity of the disease can be divided into acute and chronic, equivalent to symptomatic and asymptomatic. The so-called symptoms include dizziness, mild headache, blurred vision, weakness, fatigue, nausea, palpitations, and other uncommon symptoms, such as dyspnea, chest pain, neck, and shoulder pain. With the use of continuous stroke blood pressure monitoring technology in China, there is a new understanding of the types of OH. In addition to the traditional definition of OH, there are two other types of OH: initial OH (IOH) and late OH. IOH refers to a short drop in blood pressure within 15 seconds after orthostasis, with SBP > 40 mmHg and/or DBP > 20 mmHg, accompanied by cerebral hypoperfusion. Late OH refers to the decrease of blood pressure, SBP (>20 mmHg) and/or DBP (>10 mmHg) occurring more than 3 min in the upright position, mostly within 5–45 min. Patients with advanced OH are relatively young and their blood pressure drops to a low level, which is related to mild sympathetic and adrenal dysfunction. In conclusion, no matter which classification method is adopted, more attention should be paid to the blood pressure level and the corresponding symptoms and target organ damage.

19.5.6.4 Clinical Features

OH patients often have symptoms of orthostatic intolerance (dizziness, dizziness, etc.), which are usually aggravated in the morning, standing, activity, and hot weather, while hot showers, meals, and alcohol intake can aggravate the symptoms. But older patients may have atypical symptoms, such as blurred consciousness, fatigue or hanger-like pain.

The occurrence of OH can easily lead to insufficient blood perfusion in important organs such as heart and brain. Besides inducing dizziness, fatigue, and haze,

serious cases may also directly induce cardiovascular and cerebrovascular events. Wu Wenhui et al. studied the changes of blood pressure in 190 elderly people. The results showed that the intima-media thickness of carotid artery, glomerular filtration rate, and pulse wave conduction velocity of brachial and ankle decreased in OH patients, suggesting that OH may cause target organ damage. It is speculated that the frequent changes of body position may increase the fluctuation of blood pressure, increase the variability of blood pressure, increase the damage to vascular wall, and increase the damage to target organ.

Voichanski et al. [97] conducted 24-h blood pressure monitoring and circadian rhythm monitoring in 185 subjects in 2011. The results showed that 95% of OH patients had abnormal circadian blood pressure rhythm, The 58% of former was reverse-dippers, while the 14% of latter was reverse-dippers ($P < 0.001$), suggesting that OH might be a predictor of abnormal circadian blood pressure rhythm (such as non-dipper or reverse-dipper). The so-called non-dipper or anti-dipper blood pressure indicates that the sympathetic nerve is still continuously excited at night, which is harmful to the heart, brain, kidney, and other important organs and vessels.

19.5.6.5 Diagnosis Methods

Postural hypotension is defined as orthostatic hypotension, which changes to 3 min in an upright position. Systolic blood pressure decreases by more than 20 mmHg and diastolic blood pressure decreases by more than 10 mmHg, accompanied by symptoms of hypoperfusion, such as dizziness or syncope. The incidence of OH in the elderly was higher and increased with age, neurological dysfunction, and metabolic disorders. OH may occur in one third of the elderly patients with hypertension. OH usually occurs when the body position changes suddenly and blood pressure drops suddenly. In addition, the elderly have a poor tolerance to insufficient blood volume. Anyone with acute diseases, insufficient oral fluids, and long-term bed-rest can easily cause orthostatic hypotension.

19.5.6.6 Risk Factors

OH has attracted more and more attention, but the risk perception of the disease is still unclear, and there is much controversy. Clark and other scholars [98] believe that the risk assessment of OH mainly includes: (1) age over 65 years; (2) fall events in the previous year; (3) hypertension; (4) stroke; and (5) angina pectoris. The higher the score, the higher the risk of OH and the greater the risk of all-cause death in the next 10 years. However, many experts believe that diabetes mellitus and renal insufficiency are also risk factors for OH, which is not included in this method. Therefore, we need more accurate and objective OH risk assessment and prediction criteria [99]. At the same time, many other factors have been proved to be closely related to OH.

1. Drugs: OH caused by drugs is the most common in clinic, such as antihypertensive drugs, sedatives, anti-adrenaline drugs, and vasodilators. It is commonly seen in elderly patients with combined drugs or large doses of drugs, which should be highly valued.

2. Diabetes mellitus: The relationship between diabetes and hypertension is well known, but recent studies have shown that diabetic patients with poor blood sugar control are prone to OH. The pathogenesis of OH in diabetic patients is mainly due to the damage of sympathetic nerve fibers after standing up quickly, which makes the blood vessels of visceral vascular bed, muscle and skin unable to contract properly and makes blood redistribution, while the effect of cardiac output is only a minor factor. And insulin use is not a risk factor for OH, so it is speculated that whether oral hypoglycemic drugs or insulin, blood sugar control standards may be able to reduce the incidence of OH [100]. Another report [101] found that the levels of high molecular weight adiponectin in type 2 diabetes mellitus patients with OH were significantly higher than those without OH. Adiponectin has the effects of increasing insulin sensitivity, promoting lipid metabolism and anti-inflammation. The specific mechanism is still unclear, but it may be related to renal dysfunction, anemia, atherosclerosis, and hypercoagulability.
3. Stroke: Eigenbrodt et al. [102] included 11,707 middle-aged people without stroke and obvious heart disease at baseline. It was found that OH was still a strong predictor of ischemic stroke even after adjusting for many stroke risk factors. A recent study on the correlation between stroke and OH also found that OH patients accounted for one fourth of outpatient stroke patients, and coronary heart disease was an independent risk factor for OH. Therefore, primary screening should be carried out for stroke patients with OH in order to avoid the impact of OH changes on the treatment of stroke patients.
4. Atrial fibrillation: Recent studies have found that the prevalence of OH in patients with persistent atrial fibrillation is higher than that in patients without atrial fibrillation, and persistent atrial fibrillation, age >60 years, and uncontrolled hypertension are independent risk factors for OH [103]. It is generally believed that the initiation and maintenance of atrial fibrillation are also closely related to sympathetic and parasympathetic dysfunction, and its treatment of renal artery sympathetic ablation and low intensity vagal stimulation can effectively inhibit the occurrence of atrial fibrillation. It can be seen that the function of autonomic nervous system fluctuates greatly in patients with atrial fibrillation, which may be the basis of their predisposition to OH. Especially for patients with persistent atrial fibrillation, the rhythm of atrial fibrillation can lead to the decline of cardiac pumping function, but also lead to its more prone to OH.
5. Arterial stiffness: Meng et al. [104] assessed the arterial stiffness of OH and non-OH patients and found that baPWV and rAI in OH group were significantly higher than those in non-OH group. After adjusting the risk factors, the correlation between baPWV and OH increased, suggesting that arterial stiffness could predict the occurrence of OH, and baPWV could be used as a relatively sensitive and reliable indicator of OH, and its mechanism may be related to impaired baroreceptor sensitivity. Another study also showed that indicators reflecting atherosclerosis (baPWV, carotid-femoral pulse wave velocity and so on) were significantly correlated with OH. Increased arterial stiffness induces OH by regulating heart rate variability, which can assess the ability to regulate autonomic nerve outflow through baroreceptor reflex. Increased

arterial stiffness, due to reduced baroreceptor sensitivity, can have a serious impact on cardiac structure and function and make peripheral blood reflux faster, leading to increased central arterial pressure, which leads to postural changes. Abnormal blood pressure [105]. Current studies have confirmed the correlation between arterial stiffness and OH, and the noninvasiveness of the detection provides more possibilities for further research to confirm whether reducing PWV can improve OH.

6. Autoantibodies: Li et al. [106] found that β_2-adrenergic autoantibodies and/or M_3 muscarinic receptor antibodies could be detected in 75% of OH patients in the study, suggesting that activation of β_2 receptor and/or M_3 receptor antibodies may lead to systemic vasodilation, and these autoantibodies, which act as vasodilators in circulation, may cause or exacerbate OH.
7. Neuroendocrine hormones: Krishnan et al. [107] studied neuropeptides and peptide hormones related to autonomic nervous function. It was found that endothelin-1, an intrinsic vasoconstrictor, increased in OH patients. When vasodilation and hypotension caused by various etiologies lead to OH, elevated endothelin-1 causes strong vasoconstriction and plays an important role in maintaining vascular tension. Elevated vegetable 1 may be one of the markers of OH patients. However, it has been reported that endothelin-1 gene + 138A/− polymorphism is not associated with OH, but the imbalance of endothelin receptor A and B expression is the key to the change of vascular tension [108]. Krishnan [109] also confirmed in prospective studies of OH patients without underlying cardiac disease that significant increases in brain natriuretic peptide or N-terminal pro-brain natriuretic peptide (NT-proBNP) are associated with OH and may cause symptomatic OH. Many unknown causes of OH may be due to unreasonable increases in brain natriuretic peptide or NT-proBNP, leading to OH. The reason for the accumulation of neuropeptides in vivo remains unclear. Therefore, the occurrence and development of OH should be vigilant when abnormal increase of brain natriuretic peptide caused by heart failure, renal failure, inflammation, and other diseases. In conclusion, elevated endothelin-1 is the most valuable predictor of OH. Patients with elevated endothelin-1 should actively screen for OH.
8. Vitamin D: Studies have found that vitamin D deficiency may be a risk factor for OH. A cross-sectional survey of older women showed that vitamin D deficiency was associated with OH in older women. Vitamin D deficiency could cause vascular endothelial cell dysfunction and increase vascular resistance. At the same time, this finding better explained the pathophysiological mechanism of falls in elderly patients with vitamin D deficiency and provided theoretical basis for active prevention and treatment of vitamin D deficiency in the elderly [110].
9. Hereditary factors: Pankow et al. carried out full-gene scan on homologous Caucasians diagnosed as hypertension and found that the gene located on chromosome 18 was related to the decrease of systolic blood pressure, indicating that one or more genes located on chromosome 18 regulated the pathophysiology of systolic blood pressure postural changes. Another study reported that a frameshift mutation of neural precursor cell expressed developmentally downregulated 4-like (NEDD4L) gene on chromosome 18 was associated with the pathogenesis of OH in patients with hypertension. The mechanism may be that

NEDD4L gene participates in controlling blood volume and sodium channel expression in epithelium and is an important factor in regulating sodium uptake by renal tubules. When NEDD4L gene mutated, blood pressure regulation was affected.

Schwartz et al. [111] examined the mitochondrial genome sequence of three families with idiopathic OH. It was found that all OH patients had mitochondrial DNA point mutations, which confirmed that the mitochondrial DNA mutations were related to OH. Tabara et al. [112] detected the genes of sympathetic nervous system and renin angiotensin system and found that there was a correlation between the gene polymorphism of sympathetic nervous system and OH, which may predict the occurrence of OH, while the gene polymorphism of renin angiotensin system was not related to OH. Gao et al. [113] studied the relationship between β-adrenergic receptor (β-AR) gene polymorphism and postural blood pressure disorder in patients with hypertension. It was found that the polymorphism of β_1-adrenergic receptor (β_1-AR) Arg 389/Gly was associated with the increased risk of OH in women with hypertension. Therefore, the occurrence of OH may also have its special genetic background. To clarify the genetic factors related to OH will help to open up more space for the early prevention and diagnosis of OH.

19.5.6.7 Treatment and Prognosis

The aim of OH treatment should be to improve symptoms and quality of life and reduce adverse clinical outcomes, such as falls and syncope, rather than to achieve the target blood pressure.

Non-drug treatment: There is no new effective drug for OH treatment at home and abroad at present. Its treatment is mainly aimed at the causes of OH, avoiding factors that may cause OH, such as getting up quickly, taking a hot bath, lying in bed for a long time, and avoiding actions that increase abdominal or thoracic pressure, such as constipation, excessive exertion in urination or breathing when lifting heavy objects. Full meals (especially high-carbohydrate foods) and heavy drinking easily induce hypotension. It is advocated to eat less, eat more, abstain from alcohol, take proper rest after meals, and exercise properly, such as swimming, aerobics, bicycle riding, and walking, so as to enhance physical fitness, avoid fatigue, and stand for a long time. For patients with long duration and obvious symptoms, the risk of syncope or fracture is higher, so temporary discontinuation of antihypertensive drugs and short-acting drug therapy for OH during the day can be considered.

Drug therapy: Fludrocortisone and alpha-adrenergic receptor agonist midodrine are the main drugs for OH. Fludrocortisone can increase renal sodium reabsorption and blood volume. However, due to side effects and individual differences of drugs, it is suggested that prevention and etiological treatment should be the main treatment for OH patients, and drug treatment should be used when necessary.

Prevention: OH prevention mainly reminds patients who are in bed for a long time to move slowly when standing, doing slight limb movements before standing;

sleepers wake up a few minutes before sitting up, then sit on the bed for a few minutes, gradually transiting to standing, which helps to promote venous blood flow back to the heart, raise blood pressure, and avoid OH.

19.6 Hypertension and Intestinal Microorganism

Wenbo Yang

Human gut contains trillions of microorganisms, which can exert local and systemic effects on host physiology, including sugar fermentation, vitamin biosynthesis, and immune system maturation. Dysregulation of intestinal microbial homeostasis is associated with a variety of diseases, such as inflammatory bowel disease, cancer, autism, diabetes, and cardiovascular disease [114]. Disorders of intestinal microorganisms and intestinal barrier dysfunction exist in the intestinal tract of patients with hypertension [115]. The intestinal microorganisms and its metabolites, such as SCFAs (short-chain fatty acids), trimethylamine N-oxide, and lipopolysaccharides, can affect the regulation of blood pressure by acting on downstream cellular targets through a variety of pathways [116]. The maladjusted intestinal microorganisms have the following characteristics: the diversity and abundance of flora decreased; The Firmicutes/Bacteroidetes ratio increased; bacteria producing short-chain fatty acids such as acetic acid and butyric acid are reduced [117, 118].

19.6.1 Possible Mechanism of Intestinal Microorganisms Acting on Hypertension

19.6.1.1 Possible Signaling Pathways Through Which Intestinal Flora Regulates Blood Pressure

In patients with hypertension, sympathetic nerve activity increases, the release of norepinephrine and angiotensin increases, and mesenteric blood flow and the level of intestinal tight junction protein decrease, resulting in increased intestinal permeability and intestinal barrier destruction [115, 119, 122]. The transport of many substances and metabolites such as short-chain fatty acids, polyamines, and aryl hydrocarbon receptor activators to gastrointestinal tissues, and systemic circulation is significantly increased [116, 121]. Short-chain fatty acids play an important role in regulating blood pressure and intestinal immune, acetic acid, propionic acid, and butyric acid accounted for 80% of the gut microbes producing SCFAs, acetic acid, propionic acid, and small amounts of butyric acid mainly via portal vein to the liver, part of propionic acid were metabolized by hepatocytes, acetic acid, butyric acid, and the remaining propionic acid enter into the systemic circulation [120, 121].

It was found that when the concentration of plasma SCFAs tendency in 0.1–0.9 mmol/L, it mainly activated GPR41 (G-protein-coupled receptor orphan type) located in the vascular endothelium to expand blood vessels to achieve the antihypertensive effect.

However, when the plasma concentration exceeds 0.9 mmol/L, it activates OR51E2, one of the main receptors of propionic acid (a kind of olfactory receptor 51E2), increases the release of renal proximal globular cell renin, antagonizes the antihypertensive effect of GPR41, and maintains the dynamic balance of blood pressure [120, 123]. In addition, short-chain fatty acid binding receptors GPR43 (G protein-coupled receptor 43) and GPR109A (G protein-coupled receptor 109A) also play important regulatory roles in intestinal homeostasis, host metabolism, and immune regulation [121–123].

19.6.1.2 Microorganism: Immune Axis Is Involved in Blood Pressure Regulation

Preclinical models showed that T-lymphocyte subsets such as Th1, Th2, and Th17 were involved in the regulation of blood pressure and organ injury. Inflammatory cells such as T cells and monocytes/macrophages in intestinal wall of hypertension patients are increased. SCFAs can be used as inhibitors of histone deacetylase to modify T cells in intestinal epithelium and other immune responses. Microbial metabolites can also activate toll-like receptors of the immune system and other immune pathways to participate in blood pressure regulation. The metabolites of intestinal microorganisms may be key regulators in the immune response mechanism related to the occurrence and development of hypertension [120, 123–125].

19.6.2 The Role of Dietary Adjustment in Antihypertensive Therapy

Meta-analysis found that increasing dietary fiber intake can increase the fermentation effect of microorganisms in the colon, increase the level of intestinal SCFAs such as acetic acid, propanoic acid, and butyric acid, significantly reduce the systolic blood pressure and diastolic blood pressure in patients with hypertension, and reduce the risk of cardiovascular disease [126, 127]. In animal experiments on OSA rat models, the concentration of acetic acid in the cecum was 48% lower than that in normal rats, and supplementation with probiotics clostridium butyrate and probiotics could significantly increase the number of SCFAs-producing bacteria, reduce the imbalance of microflora, and offset or alleviate OSA. Infusion of acetic acid into the cecum also prevented intestinal inflammation and hypertension in OSA rats [128]. In patients with hypertension, probiotic intake can reduce the blood pressure level, and the blood pressure reduction effect is more obvious when the baseline blood pressure is higher, the intake of multiple probiotics, the intake time is more than 8 weeks, or the daily intake of probiotics dose is greater than 10^{11} cfu [129]. A meta-analysis of 14 randomized, controlled clinical trials showed that 702 subjects who consumed probiotic-fermented milk had a 3 mmHg reduction in systolic blood pressure and a 1 mmHg decrease in diastolic blood pressure [130]. The mechanism of the antihypertensive effect of probiotics and its protective effect on endothelial function have not been fully elucidated, which requires further research. In the future, probiotics may be used as a new way to assist in blood pressure control.

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Drug-Induced and Exogenous Hypertension

20

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20.1 Drugs and Other Substances That May Cause Secondary Hypertension

Nanfang Li

Numerous substances including prescription medications, over-the-counter medications, herbals, and other substances have been reported to be associated with the development of hypertension. The commonly used drugs such as nonsteroidal anti-inflammatory drugs or glucocorticoids may bring about sufficient elevation in blood pressure (BP) to raise the suspicion of secondary hypertension and can interfere with BP-lowering effects of antihypertensive agents in treated hypertensive patients and worsening BP control in known hypertensive patients. In clinical assessment of hypertension, careful collection of drug and food substance history is important when a diagnosis for secondary hypertension is considered, with close attention paid to not only prescription medications but also over-the-counter substances, illicit drugs, herbal products, and food substances, which may also affect BP, changes in BP that occur because of drugs, and other agents resulted from drug–drug or drug–food interactions. When feasible, drugs or food substances associated with increased BP should be reduced or discontinued, and alternative agents should be used [1, 2].

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20.1.1 Frequently Used Medications and Other Substances That May Cause Elevated BP

Salt: Sodium intake is in a positive association with BP in many cross-sectional and prospective cohort studies and explains much of the age-related increase in BP. Except for well-accepted relationship between dietary sodium and BP, excessive sodium consumption is also in independent association with the increased risk of CVD including stroke and other adverse outcomes [2]. Average daily intake of sodium worldwide is 3.5–5.5 g (corresponding to 9–12 g of salt/day). It has been consistently recommended that daily intake of sodium be limited to 2.0 g (about 5.0 g salt/day) to general population and to endeavor to obtain this amount in hypertensive population as well. Salt reduction is not easy to achieve. Strong suggestions must be given to avoid added salt and foods rich in salt. Reducing salt intake at population level is still a priority for public health sections, whereas combined efforts from food industry, government, and the public are highly required, since about 80% of salt consumed by the public involves the salt in processed foods [1].

Alcohol: A positive linear relationship has been well established between alcohol consumption, BP, the prevalence of hypertension, and CVD risk. Binge drinking can have a strong pressor effect [1]. Prevention and Treatment of Hypertension Study investigated the effects of alcohol reduction on BP, and the intervention group showed modest 1.2/0.7 mmHg lower BP than the control group at the sixth month [3]. A Mendelian randomization meta-analysis on epidemiological studies suggested that reducing alcohol consumption is possibly beneficial for CV health, which is even true for light to moderate intakers [4]. Males with hypertension who also drink should be given advice to reduce alcohol intake to 14 units per week and females to 8 units per week (1 unit = 125 mL of wine or 250 mL of beer). Days with no alcohol intake in a week and avoidance of binge drinking are also advised [5], reducing alcohol to ≤1 drink daily for females and ≤2 drinks for males [2].

Caffeine: It has been reported that caffeine intake elevates BP via increasing sympathetic activity and catecholamine release, and caffeine also acts as antagonist of endogenous adenosine, a recognized coronary vasodilator. In the first hour of intake, 200–300 mg of caffeine increases systolic and diastolic BP by 8.1 and 5.7 mmHg, respectively. This kind of acute response of BP to caffeine intake vanishes in 2 weeks, which may suggest that BP elevation is tolerated in regular caffeine intakers [6]. Therefore, caffeine is the component in coffee that is assumed to influence BP in acute conditions, not in chronic ones [7]. Guidelines recommend that one should limit caffeine intake to <300 mg/day and that those with uncontrolled hypertension should avoid using it [2]. Although coffee intake is associated with acute BP increases in hypertensives, long-term use is not associated with increased BP or CVD outcomes [2].

Oral contraceptives: In about 5–10% of women who take first-generation high-dose estrogen contraceptives, oral contraceptives are assumed to bring about hypertension. Recent evidence also indicates that even the lower-dose pills with 20 μg of estrogen would induce significant BP elevation [6]. Positive associations between duration of oral contraceptive use and risk of hypertension have been observed in

the results of a meta-analysis in 270,284 subjects, which reported that the risk of hypertension increases by 13% for every 5-year increment in oral contraceptive intake [8]. Other factors that increase the susceptibility of hypertension encompass family history of hypertension, preexisting pregnancy-induced hypertension, obesity, and age ≥35 years. The phenomenon is reversible. That is, BP usually returns to pretreatment levels within 3 months after discontinuing oral contraceptives [6]. Current guidelines recommend that use low-dose (e.g., 20–30 μg ethinyl estradiol) agents or a progestin-only form of contraception or consider alternative forms of birth control where appropriate (e.g., barrier, abstinence, intrauterine device) and avoid use in women with uncontrolled hypertension [2].

Estrogen: Cross-sectional evidence has shown that menopause doubles the risk of developing hypertension, independent of age and body mass index [9]. Although hormone-replacement therapy contains estrogens, there is no convincing evidence that significant rises in BP will occur in otherwise normotensive menopausal women due to this therapy or that BP will increase further due to hormone-replacement therapy in menopausal hypertensive women [10]. Hormone-replacement therapy and selective estrogen receptor modulators should not be used for primary or secondary prevention of CVD. In summary, current evidence suggests that the use of hormone-replacement therapy is not associated with an increase in BP. Moreover, it is not contraindicated in women with hypertension, and women with hypertension may be prescribed hormone-replacement therapy as long as BP levels can be controlled by antihypertensive medication. Combined estrogen-progesterone oral contraceptive pills can be associated with a small but significant increase in BP and the development of hypertension in about 5% of users [1]. BP usually decreases promptly following cessation of these pills; consequently, BP should be monitored before and during oral contraceptive pill treatment. The rise in BP appears to be related to the estrogen content and may be less likely with the progestogen-only oral contraceptive pill [1].

Stimulant drugs: Amphetamine, cocaine, and ecstasy, usually cause acute rather than chronic hypertension [1].

Amphetamines: Amphetamine, methylphenidate dexmethylphenidate, and dextroamphetamine. It is recommended to discontinue or decrease dose and consider behavioral therapies for attention deficit hyperactivity disorder [2].

Recreational drugs: For example, “bath salts” (methylenedioxypyrovalerone), cocaine, methamphetamine, etc. [2]. Among others, cocaine is one of the most important and used drugs. Cocaine intoxication and abuse are characterized by adrenergic overactivity associated with increased BP. Isradipine significantly reduces cocaine-induced BP elevation, based on one small study [12]. It is recommended to discontinue or avoid use [2].

Liquorice: Chronic excessive consumption of liquorice elevates BP through the main active ingredient, glycyrrhizic acid. Glycyrrhizic acid inhibits 11-beta-hydroxy-steroid dehydrogenase, which converts cortisol to cortisone, producing an excess of mineralocorticoid activity. Based on a recent meta-analysis, chronic consistent use of liquorice or other substances containing glycyrrhizic acid generates a state of pseudohyperaldosteronism, featured as an increase of systolic and diastolic

BP, and as suppression of plasma potassium, renin, and aldosterone [6, 13]. It is recommended to discontinue or decrease dose, depending on indication.

Herbal supplements: Ma Huang (ephedra), St. John's wort (with monoamine-oxidase inhibitors MAOIs, yohimbine) [2]. Some herbs have the potential to increase BP; nonetheless, others may help control. The evidence is anecdotal; hence, it is difficult to estimate the true incidences. Some reports have shown that dietary supplements with ephedra alkaloids raise BP. In addition, some herbs interfere with bioavailability or activity of concurrently administered agents. Raised BP has been observed when ginkgo and a diuretic thiazide are co-administrated [11]; it is recommended to avoid its use [2].

Decongestants: Nasal decongestants including phenylephrine, pseudoephedrine, and naphazoline hydrochloride are usually applied to treat the symptoms of rhinitis and rhinorrhea and activate sympathomimetic nervous system by stimulating alpha-1 adrenergic receptors on vascular smooth muscle causing vasoconstriction [6]. Pseudoephedrine causes small but significant increase in systolic BP and heart rate, not diastolic BP, depending on a meta-analysis from 24 trials in adults [14]. Current guidelines recommend to use short duration if possible, to avoid application in severe or uncontrolled hypertension, and consider alternative treatments (nasal saline, intranasal corticosteroids, antihistamines) when appropriate [2].

Antidepressants: Monoamine-oxidase inhibitors, serotonin norepinephrine reuptake inhibitors, and tricyclic antidepressants [2]. Venlafaxine hydrochloride is a serotonin norepinephrine reuptake inhibitor applied to treat depression and anxiety. It can cause BP elevation possibly through its noradrenergic mechanism [11]. Based on data from meta-analysis, BP elevation with venlafaxine use is more obvious in older subjects and in men and is dose dependent. The incidence of elevated diastolic BP showed statistical and clinical significance only at daily dosages >300 mg [15]. Several other antidepressant agents may also contain the roles to raise BP via similar mechanisms [11]. It is recommended to consider alternative agents such as selective serotonin reuptake inhibitor depending on indication; avoid tyramine-containing foods with monoamine-oxidase inhibitors [2].

Nonsteroidal anti-inflammatory drugs (NSAIDs): Numerous evidence has consistently reported the association between NSAIDs and BP increases. Via blocking cyclooxygenase (COX)-1 and -2 activities, NSAIDs decrease prostaglandin synthesis, particularly PGE2 and PGI2, which contain vasodilation and sodium excretion properties in the kidney. This process reduces peripheral vasodilation and induces water and sodium retention, hence raises BP [6]. Long-term usage of NSAIDs is associated with significant BP increase of about 5 mmHg, based on meta-analysis [16]. In addition, several observational studies reported that clinical efficacy of some anti-hypertensive agents are affected by NSAIDs. Of anti-hypertensive agents, ACEIs or ARBs are easily interfered when exposed to NSAIDs and intensification therapy is required, but not CCBs central acting drugs. Therefore, patients who need NSAID treatment should select agent drugs not interfering with the renin-angiotensin system. Evidence is similarly true for COX-2 selective inhibitors to that observed in non-selective NSAIDs, and COX-2 selective inhibitors seem

to bring about even greater hypertension than non-selective NSAIDs according to meta-analysis.

Nonetheless, this response was not consistent. That is, rofecoxib and etoricoxib are associated with marked increases in BP, but celecoxib is little. Therefore, acetaminophen is considered a safe treatment option [6]. The guidelines recommend to avoid systemic NSAIDs if possible and consider alternatives (acetaminophen, tramadol, topical NSAIDs), based on indication and risk [2].

Immunosuppressive medications: Patients with autoimmune disease and psoriasis treated with cyclosporine often suffer from cyclosporine-associated hypertension, characterized by the absence or reversal of normal nocturnal BP decrease due to disturbed circadian rhythm. Some possible mechanisms may be involved in the development of hypertension in this process. For example, they encompass systemic and renal vasoconstriction, sodium retention, and nephrotoxic effects, depending on animal and human studies. The withdrawal or substitution of cyclosporine immunosuppression leads to decreases in BP whereas may not remit completely. CCBs are well known to raise circulating cyclosporine concentrations, although successfully lower BP. Multi-agent combined treatment should be performed to manage cyclosporine-associated hypertension when cyclosporine is considered necessary to be continued. Tacrolimus, another calcineurin-inhibiting immunosuppressive agent, is related to hypertension as well, whereas it brings about less BP elevations, compared to cyclosporin; hence, tacrolimus can be used when faced with cyclosporine-associated hypertension. Rapamycin and mycophenolate mofetil are immunosuppressive agents, which do not inhibit calcineurin, hence generate little or any nephrotoxicity or hypertension [11].

Systemic corticosteroids: Mineralocorticoids and glucocorticoids may elevate BP level. For instance, mineralocorticoids such as fludrocortisone, used for the treatment of Addison's disease, congenital adrenal hyperplasia syndrome, and orthostatic hypotension in the elderly in clinical setting, exert their roles on the distal tubule of the kidney and promote active re-absorption of sodium, passive reabsorption of water, and concomitant active secretion of potassium. Hence, this process leads to increase in BP and blood volume. Glucocorticoids including hydrocortisone, prednisone, and methylprednisolone exhibit lower, mineralocorticoid activity, whereas such minor activity is sufficient to generate mineralocorticoid receptor activation and increase sodium resorption, particularly while used at high doses [6, 17]. Although the activation of mineralocorticoid receptors by excess glucocorticoid exerts its role in the glucocorticoid-mediated hypertension, accumulating data disagrees this. Experimental and in vitro studies showed the upregulation of angiotensin II type I (AT I) receptors and an increased influx of Na^+ and/or Ca^{2+} into smooth muscle cells of the vascular wall induced by glucocorticoids. Other scholars have considered the endothelium-dependent pathways (reduced NO availability) to the BP response induced by glucocorticoid administration [6]. Avoidence of or limiting of their usage is recommended if possible as well as alternative modes of administration (inhaled, topical) can be also considered if feasible [2].

Antiangiogenic cancer therapies: It has been documented that antiangiogenic drugs including vascular endothelial growth factor inhibitors (bevacizumab),

tyrosine kinase inhibitors (sunitinib), and sorafenib raise BP. In cancer registries, raised BP is the most reported cardiovascular condition, which is generally existent in more than one third of patients [18]. This is mainly due to higher incidence of hypertension in older population of whom cancer is also highly prevalent. In addition, this is also because two groups of the most commonly used anticancer agents, the inhibitors of vascular endothelial growth factor signaling pathway (bevacizumab, sorafenib, sunitinib, and pazopanib) and proteasome inhibitors (carfilzomib), contain the pressor effects. The former agents inhibit the NO synthesis in the arterial wall, the latter ones lower vasodilator response to acetylcholine, resulting in vasoconstriction and vasospasm [19]. The BP elevation generally occurs in the first months of anticancer treatment, suggesting that office BP should be measured weekly during the start of the first cycle of therapy and at least every 2–3 weeks thereafter [20]. BP measurement can be performed at the routine clinical evaluations or at home after the first cycle treatment is completed and until BP become stable. Antihypertensive treatment should be started or optimized for patients who experience hypertension or ≥20 mmHg increases in diastolic BP compared with pretreatment BP. In these specific conditions, the preferred agents are assumed to be RAS blockers and CCBs, and their combination is usually a necessary strategy. The dihydropyridine-type CCBs should be the only option, since the CYP3A4 isoenzyme is blocked by diltiazem and verapamil. The CYP3A4 isoenzyme is involved in metabolic pathway of sorafenib, an obvious priority since it helps increase the drugs' levels, and its short-term discontinuation can be considered if BP is extremely high even on multidrug treatment, severe hypertension-induced symptoms are present, or when a CV event requiring an immediate effective BP control exists [1, 21].

In conclusion, a number of therapeutic and recreational substances lead to short-term or long-term BP elevation or interfere with the effects of antihypertensive treatments, hence become important secondary causes of hypertension, and usually under-recognized. Careful collection of medical history is crucial for the physicians who can be informed on possible drug-induced hypertension. Frequently, the elderly and preexisting hypertensive patients or patients with chronic renal failure suffer more from the deleterious impact of such substances. Possible intake of recreational drugs should be considered, especially when BP is elevated in a sudden and unexplained pattern in young population. Withdrawal of the drug is recommended when drug-induced hypertension is confirmed. When withdrawal is impossible, specific antihypertensive agents at full doses and their combinations may be a choice to achieve satisfactory BP levels [6].

20.2 Environmental Risk Factors for Hypertension

Mulalibieke Heizhati

Background risk factors that bring about raised BP can help explain why certain populations are at an increased risk for hypertension than are others. Risk factors can be of genetically, behaviorally, or environmentally related. A number of

environmental exposures, such as components of diet, physical activity, and alcohol consumption, affect BP. Some dietary components are associated with elevated BP [22]. Of those related to high BP, overweight and obesity, excess intake of sodium, and insufficient intake of potassium, calcium, magnesium, protein (especially from vegetables), fiber, and fish fats are encompassed. A large proportion of hypertension be explained by poor diet, physical inactivity, and excess intake of alcohol, alone or in combination [23, 24].

20.2.1 Sodium Intake

Salt is an essential nutrient to maintain plasma volume, acid–base balance, and normal cell function [25]. Globally, daily sodium intake is between 9 and 12 g of salt, well above the amount needed for physiological function, which is 5 g/day, recommended by the 2007 WHO guideline [26]. Sodium intake is in positive association with BP based on migrant, cross-sectional [27, 28], and prospective cohort studies [29] and accounts for a large fraction of age-related hypertension [30]. In turn, sodium restriction has BP-lowering effects depending on many studies. That is, a reduction of 1.75 g sodium/day (4.4 g salt/day) is associated with a mean 4.2/2.1 mmHg reduction in systolic and diastolic BP, and more strong effects (−5.4/−2.8 mmHg) are observed in hypertensive patients [31]. Certain population from various demographic, physiological, and genetic features are particularly sensitive to effects of dietary sodium on BP, where an increase in sodium load disproportionately elevates BP. Blacks, older population, and those with higher BP values or comorbidities (CKD, diabetes, or the metabolic syndrome) are especially characterized by salt sensitivity [32]. Sodium restriction has profound BP-lowering effects in these specific populations.

20.2.2 Overweight and Obesity

Numerous epidemiological studies, such as Framingham Heart Study and Nurses' Health Study, have consistently observed a continuous and almost linear relationship between BMI and BP values [33]. Risk for hypertension also increases, in line with BMI, continuously with increases in other obesity-related anthropomorphic measurements such as waist circumference, waist-to-hip ratio, and waist-to-height ratio [34]. Increased risk of developing hypertension is 20–30% for each 5% increment of weight gain [35]. About 40% of hypertension can be accounted for by obesity, based on attributable risk estimates in the Nurses' Health Study, and the estimates are 78% for men and 65% for women from Framingham Offspring Study [33]. Obesity at a young age and change in obesity status over time also predict future risk of hypertension. Combined data from four longitudinal studies initiated in adolescence with repeated examination in young adulthood until early middle age showed that being consistent obese status or gaining obesity had a relative risk of 2.7 for developing hypertension [34]. A number of pathophysiological mechanisms are suggested in

contribution of obesity to the hypertension development, such as insulin resistance, chronic low-grade inflammation, oxidative stress, adipokine abnormalities (high leptin, reduced adiponectin), increased sympathetic nervous system and renin–angiotensin–aldosterone system activity, endothelial dysfunction, intestinal microbiota, and increased renal sodium reabsorption with volume expansion [36].

20.2.3 Potassium and Hypertension

Potassium is also essential for maintaining total body fluid volume, acid and electrolyte balance, and normal cell function [37]. The average potassium consumption in many countries where data exists is below 70–80 mmol/day [38], the value recommended by the 2002 Joint WHO/Food and Agriculture Organization Expert Consultation [39]. Migrant, cross-sectional, and prospective cohort studies have consistently documented that potassium intake is in inverse relation with BP [40]. Higher levels of potassium may also blunt the effects of sodium on BP values, and thus a lower sodium–potassium ratio is associated with a lower BP level [41].

20.2.4 Physical Activity and Hypertension

An inverse relationship between physical activity and physical fitness and level of BP and hypertension epidemiological studies has been demonstrated [42]. Even modest levels of physical activity have been associated with a decrease in the risk of incident hypertension [43]. In several observational studies, the relationship between physical activity and BP has been most apparent in white men [42]. Physical fitness, measured objectively by graded exercise testing, attenuates the rise of BP with age and prevents the development of hypertension. In the Coronary Artery Risk Development in Young Adults study [44], physical fitness measured at 18–30 years of age in the upper two deciles of an otherwise healthy population was associated with one third the risk of developing hypertension 15 years later and one half the risk after adjustment for body mass index, as compared with the lowest quintile. In a cohort of men 20–90 years of age who were followed longitudinally for 3–28 years, higher physical fitness decreased the rate of rise in SBP over time and delayed the time to onset of hypertension [45]. A meta-analysis of RCTs has shown that aerobic endurance training, dynamic resistance training, and isometric training reduce resting SBP and DBP by 3.5/2.5, 1.8/3.2, and 10.9/6.2 mmHg, respectively, in general populations [46].

20.2.5 Alcohol Intake

The presence of a direct relationship between alcohol consumption and BP was first reported in 1915 [47] and has been repeatedly identified in contemporary cross-sectional and prospective cohort studies [48]. Estimates of the contribution of alcohol

consumption to population incidence and prevalence of hypertension vary according to the level of intake. In the United States, it seems likely that alcohol may account for close to 10% of the population burden of hypertension (higher in men than in women) [49]. The Prevention and Treatment of Hypertension Study investigated the effects of alcohol reduction on BP; the intervention group had a modest 1.2/0.7 mmHg lower BP than the control group at the end of the 6 months period [50].

20.2.6 Smoking

Smoking is a major risk factor for CVD. Studies using ABPM have shown that both normotensive subjects and untreated hypertensive smokers present higher daily BP values than nonsmokers [51]. No chronic effect of smoking has been reported for office BP [52], which is not lowered by smoking cessation.

20.2.7 Cold Weather and Hypertension

The incidence of hypertension shows obvious seasonality, high in winter. People living in low-temperature areas with high altitude are more prone to hypertension [53]. In addition, systolic BP is increased in both patients with hypertension and individuals with normal BP in cold season. Cold-induced hypertension refers to hypertension caused by exposure to cold stimulation, which is highly seasonal and can only be manifested as hypertension in cold winter. Moreover, target organ damage of such patients may be 1.44 times of that of non-hypertensive patients [54]. A study conducted by Ponjoan et al. in Spain with a sample size of 95,277 showed that the mean systolic BP increased by 3.3 mmHg in cold months compared with warm months, and the prevalence of hypertension increased by 8.2% [54]. Patients with cold-induced hypertension had a 44% higher risk of CV events than those without hypertension [54]. The same results were also observed in a small cohort study of 132 subjects, with four times follow-up in the four seasons, and it was found that average systolic and diastolic BP was 11.07/6.79 mmHg higher in winter than in summer and a 9% increase in the prevalence of hypertension [55], which is higher than the 4.5% of a study conducted in Italy by Corsonello [56]. Potential mechanisms for cold weather to increase BP levels include the constriction of small arteries as a thermoregulatory response and over-activation of hypothalamus pituitary adrenal axis and sympathetic nervous system. Chronic seasonal factors affect BP through additional physiological adaptations such as decreased vitamin D, weight gain, and decreased activity and changes in diet and fluid balance [57–63].

20.2.8 High Temperature and Hypertension

High temperature can cause a series of physiological changes in human body such as weight loss, accelerated respiratory rate, and gastrointestinal function inhibition. Subjects working in high-temperature environment become the main target of

high-temperature-induced hypertension. In recent years, studies have shown that prolonged exposure to high temperature can have adverse effects on central nervous system and CV system, and even organic changes, endangering the health of those working in high-temperature environment. Subjects working in high-temperature environments have become the main targets of hyperthermia-induced hypertension. High temperature leads to excessive sweating, decreased blood volume, and increased cardiac output, which puts the circulatory system in a state of high stress, hence increases BP levels and damages the myocardium. Prevalence of hypertension in workers aged 35 years, 35–45 years, and ≥45 years exposed to high temperature is 29.03%, 21.33%, and 26.08%, respectively, higher than that of corresponding control age group (15.38%, 6.34%, and 22.22%) [64] and the older age, the higher the risk of hypertension. In addition, high temperature can cause obvious depressive symptoms [65], which is one of the psychological factors causing elevated BP. High temperature has negative effects on the kidney of patients with hypertension, especially in the elderly (>75 years old). Each additional 5 °C ambient temperature might result in a 3.4% increase of serum creatinine [66]. The possible mechanism of elevated BP caused by high temperature is as follows: When exposed to high-temperature environment, the heart should deliver enough blood to the working muscle to ensure the activity of the working muscle. On the other hand, it should deliver a large amount of blood to the highly expanded skin vascular network to effectively dissipate heat. Due to the large amount of moisture loss and transfer of body fluids to the muscle through sweating, the effective blood volume is reduced.

The contradiction of supply and demand cause a high-stress state in the circulation system; blood viscosity over time, total peripheral resistance, and time for micro-circulation update and cycle average residence increase, and blood vessel elasticity coefficient decreases; the strongest contraction of blood vessel substances in high temperature environment can make the plasma endothelin secretion increase significantly; and the role of endothelin antagonist sodium hormone becomes relatively insufficient.

20.3 Occupational Harmful Factors and Hypertension

Shan Lu

Occupational hazards are chemical, physical, and biological factors that are present in a production or work environment that adversely affects human health or labor capacity. Studies have shown that a variety of occupational harmful factors are closely related to hypertension.

20.3.1 Occupational Population and Hypertension

A large number of epidemiological studies have shown that there is a large difference in the prevalence of hypertension among different occupational populations. In

2014, onsite survey results of 17,517 in-service personnel in 21 occupational institutions in eight provinces of China showed that the prevalence of hypertension is related to occupational type and education level. The prevalence is the highest in workers, up to 28.4%, and the lowest in those with higher education attainment which is 20.9% [67]. Researchers consider that one of the main reasons for the difference is due to different occupational harmful factors in their work environment. For example, teachers, doctors, and bus and taxi drivers are exposed to tight working environment, miners are often exposed to poor working conditions such as heavy metal and dust pollution, and coke oven operators are often exposed to various organic chemical pollutants and high temperatures. Therefore, actively researching and discovering the harmful factors that cause the elevated BP to rise in the occupational environment and taking reasonable and effective protective measures for different occupational exposure groups will greatly reduce the occurrence of hypertension.

20.3.2 Occupational Harmful Factors and Blood Pressure

20.3.2.1 Chemical Factors

1. Heavy metal element
   (a) Lead: vapor, smoke, and dust of lead and its compounds invade the human body through the respiratory tract or digestive tract, which can cause occupational lead poisoning. This mainly occurs in occupational groups engaged in lead mining, lead smelting, casting, pouring, welding, spraying, battery manufacturing, oil painting, and other industries. The damage of the human nervous system, digestive system, hematopoietic system, and kidneys has been confirmed by acute and chronic lead exposure. In recent years, a large number of epidemiological studies have shown that [68] lead pollution in production or labor environment, especially low-dose lead pollution, has CV toxicity, can cause a significant increase in BP. Blood or bone lead levels in occupational lead exposure are associated with hypertension, which is more pronounced in lead-sensitive population such as men and postmenopausal women. In addition, the effects of lead exposure on BP are persistent. Studies also have found that [69], lead exposure even during childhood can lead to hypertension in adulthood. The boosting effect of lead exposure has also been confirmed in a large number of animal experiments.

      It is speculated that the mechanism of lead exposure leading to hypertension may have the following aspects: (1) interferes with the renin-angiotensin-aldosterone system and kinin system; (2) inhibits Na-K-ATP activity, and changes Ca^{2+}-activated vascular smooth muscle cell contractility and proliferation; (3) changes the responsiveness of the CV system to vasoconstrictors and the expression of vascular smooth muscle cell receptors; (4) induces the production of reactive oxygen species, inactivates nitric oxide, and enhances vasoconstriction; and (5) alters protein kinase C activity and its mediated cellular activities.

Although most animal experiments and population epidemiological studies have confirmed the boosting effect of lead exposure and its close relationship with hypertension, some researchers hold negative attitudes toward the correlation between the two. On the one hand, not all research results have a positive correlation between the two. On the other hand, even if some studies show positive results, the effect of lead exposure on BP is moderate or even weak. Furthermore, it is believed that the rise in BP is not directly caused by lead exposure, but by damage to the human kidney caused by high concentration lead exposure. Therefore, the exact relationship between occupational lead exposure and hypertension remains to be confirmed by more in-depth research in the future.

(b) Cadmium: Inhalation of cadmium soot or cadmium-containing dust can cause cadmium poisoning. Cadmium poisoning mainly occurs in occupational groups engaged in cadmium smelting, spraying, welding, cutting, casting, nuclear reactors, cadmium storage, and cadmium compound manufacturing operations. Cadmium poisoning can not only cause skin, respiratory tract, and digestive tract related symptoms, but epidemiological studies in animal experiments and occupational populations have shown that chronic cadmium exposure is closely related to hypertension and cardiovascular disease.

Possible mechanisms of action of cadmium-induced hypertension include: (1) interference with the renin-angiotensin-aldosterone system; (2) causing endothelial cells to release various inflammatory factors, such as TNF-α; (3) stimulating the release of fibrinogen inhibitor-1 and promoting the adhesion of white blood cells and platelets in endothelial cells; and (4) inducing the production of reactive oxygen species, inactivate nitric oxide, and enhance vasoconstriction.

(c) Other heavy metal elements: There are also reports of chronic sputum, vanadium, and other exposures related to hypertension.

2. Other chemical factors: Epidemiological studies of hypertension in occupational populations show that organotin (triethyltin, tetraethyltin), benzene, toluene, xylene, amines, pentachlorophenol, sodium pentachlorophenol, epoxy exposure of chemicals such as propane, carbon disulfide, and organophosphorus pesticides can cause high blood pressure in humans to varying degrees, leading to high blood pressure.

20.3.2.2 Physical Factors

1. Noise: Noise can not only cause specific damage to the human auditory system, but more and more studies have confirmed that noise has obvious adverse effects on nervous and cardiovascular systems [70]. Animal experiments have confirmed that both acute and chronic noise exposure can cause an increase in blood pressure in animals. According to the surveys of occupational groups in different industries such as construction workers, textile workers, traffic police, drivers, airport workers, sawmills, cement workers, etc., noise exposure is closely related

to high blood pressure in occupational population, noise exposure, and blood pressure. There is a dose–response relationship. Compared with hearing-impaired people, noise exposure has a more pronounced effect on blood pressure in normal hearing populations.

Traffic noise is a recognized environmental risk factor. Cardiovascular diseases, especially high blood pressure, have received the most attention as clinical outcomes that may be associated with multiple sources of traffic noise. A systematic review and meta-analysis of road traffic noise and adult hypertension in residential areas shows that [71] residential road traffic noise is associated with a higher risk of adult hypertension.

The possible mechanisms of noise exposure leading to elevated blood pressure are: (1) noise can weaken the function of the central nervous system to inhibit peripheral sympathetic nerve activity, leading to increased peripheral sympathetic nerve activity and (2) causing vasospasm and increasing the risk of atherosclerosis.

2. Vibration: Vibration is an occupational hazard that is often exposed to occupational workers in mechanical operations. Volunteer trials and epidemiological studies of occupational populations have shown that both whole body vibrations and local vibrations can lead to autonomic dysfunction, increased sympathetic excitability, decreased vagal excitability, and ultimately elevated blood pressure. As the exposure time increases and the exposure dose increases, the blood pressure rises more severely. High-age exposed people are more likely to develop hypertension at lower ages.
3. Ambient temperature: The relationship between the temperature of the working environment and hypertension has been reported. Studies have shown [72] the prevalence of hypertension in high-temperature environment (25.00%), significantly higher than the control group (12.28%).

   The possible mechanisms of high-temperature exposure causing the operator to increase blood pressure are: (1) high-temperature environment makes the operator's body circulation system in a state of high stress, and then the blood viscosity increases, the total peripheral resistance of the blood vessel increases, and the elasticity decreases; (2) other occupational factors, such as high-temperature related noise, can activate the sympathetic nervous system, causing an increase in the secretion of angiotensin II.

   On the other hand, the low-temperature working environment is also considered a harmful occupational factor that causes the blood pressure of the human body to rise. Vogelaere et al. [73] found that low temperature can cause significant changes in human hemodynamics, which may be related to increased cardiac output and increased catecholamines caused by low temperature.
4. Others: Some scholars have regularly checked the staff of the radar tracking system and found that the incidence of cardiovascular disease in the exposed group increased, mainly in hypertension and local myocardial ischemia. Studies have also shown that [74] the prevalence of hypertension in occupational groups exposed

to microwave, medium-, and short-wave radiation is significantly higher than that of the control population, and the relevant mechanisms are to be further studied.

20.3.2.3 Occupational Stress Factors

Occupational stress refers to the physical and psychological stress brought about by the imbalance between objective requirements and personal resilience under certain occupational conditions. Cross-sectional studies and follow-up studies have shown that [75] occupational stress is closely related to hypertension. The prevalence of hypertension in occupational stress workers was 3–4 times higher than that in the control group. For example, the detection rate of hypertension among dispatchers, underground workers, drivers, shift workers, etc. was significantly higher than that of the control group. Some studies have suggested [76] that in high-stress occupational exposure populations, the risk of occupational stress on hypertension can be as high as 60%. Large workload, long time, exposure to harmful substances, high risk, poor self-esteem and job satisfaction, uncoordinated interpersonal relationships, negative emotions, and depression are the main occupational stress factors that cause hypertension and with occupational stress. The increased risk of hypertension is also significantly increased.

Possible mechanisms of occupational stress leading to hypertension are: (1) hypothalamic-pituitary-adrenal axis and sympathetic-adrenal medulla system: Nervous stimulation through the hypothalamic-pituitary-adrenal cortex system increases adrenal glucocorticoids; the secretion of tea phenolic amines is increased and the cardiovascular system is enhanced. (2) Abnormal serotonin secretion: Serotonin is critical in regulating mood and behavior, and long-term stress leads to increased serotonin secretion. (3) Indirect mechanism: Long-term occupational stress can lead to some unhealthy behaviors such as smoking, alcohol abuse, high-fat diet, drug abuse, and lack of physical exercise, all of which can cause blood pressure to rise.

Due to the complexity of the working environment and the limitations of research methods, the exact mechanism for the increase of blood pressure caused by various harmful occupational factors is still not clear, but studies have found that a variety of occupational harmful factors can cause the human body. An increase in blood pressure. Therefore, in the future, we should strengthen the protection awareness of high blood pressure susceptible occupational groups, develop corresponding protective measures for different occupational groups and ultimately reduce the occurrence of high blood pressure.

20.4 Alcohol-Related Hypertension

Niluofeier Aierken

As early as 1915, Lian first found that drinking had an impact on blood pressure in French service workers. Since then, a number of epidemiological studies and clinical observations have shown that long-term heavy drinking is independent of the

type of alcoholic drinks, education level, smoking, and so on. Other traditional risk factors of hypertension can lead to hypertension. Blood pressure can be significantly reduced after the cessation or reduction of alcohol consumption, known as alcohol-related hypertension [77]. Until now, there are few reports about alcohol-related hypertension, the exact epidemiological data is lacking, and the mechanism of production is unclear. However, the cross-sectional survey indicated that the alcohol consumption increased year by year in each country, and the correct diagnosis and treatment of alcohol-related hypertension should be paid more attention.

20.4.1 Epidemiology

The importance of the link between alcohol consumption and high blood pressure has been recognized in national and international guidelines for the prevention and management of hypertension. A systematic review of the relationship between alcohol and stroke [78] (including 41 studies on the relationship between alcohol intake and stroke) showed that there was a J-type relationship between alcohol intake and stroke in ischemic stroke, which was consistent with that reported in coronary heart disease events. Increased alcohol intake, especially recent intake and binge drinking, increased risk of ischemia and hemorrhagic stroke. Alcohol-induced high blood pressure may be the cause of increased stroke risk, although it has been reported that these risks have not been reduced after blood pressure adjustment. A Japanese study has shown that binge drinking and hypertension have synergistic effects that increase the risk of cerebral hemorrhage and cerebral infarction by two and three times, respectively. In contrast, a study of more than 10,000 people attending hypertension clinics in the BMH (the UK Department of Health)'s Hypertension Care Program found that alcohol intake per week reduced the risk of stroke by 40% and that stroke mortality was the lowest. This group did not include heavy drinkers, whose beneficial effects were offset when the weekly intake of alcohol was greater than 160 mL, resulting in an increase in mortality associated with non-circulatory causes. Looking at the "J" curve, it was found that the lowest point was 20 mL alcohol intake per day, which reduced the relative risk by about 20% on average. This protective effect disappears when alcohol intake reaches 72 mL every day and increases the risk of coronary heart disease by an average of 5% when alcohol intake exceeds 89 mL/day.

Multiple cross-sectional studies have shown a correlation between alcohol intake and increased blood pressure, with an average prevalence of hypertension in people with 30 mL or more twice as high as those who do not drink alcohol every day. Those who did not drink had similar blood pressure levels to those who quit drinking [78]. Other studies assessed the relative importance of effects of alcohol on blood pressure in young male workers and the effects of other lifestyle factors on blood pressure. Seven-day retrospective log assessments showed that of 491 20- to 44-year-old male subjects. There is a linear relationship between alcohol consumption and the prevalence of hypertension, which is independent of any other lifestyle factors studied. In a sample survey of urban and rural populations in China, 33% of

the Yi rural population was found to be associated with alcohol consumption [79], compared with 9.5% of the Han urban population. A study of the effects of various factors on blood pressure fluctuations in 1100 Italians using ambulatory blood pressure tests found that alcohol intake was linearly related to daytime blood pressure and that blood pressure in large quantities of drinkers showed greater variability.

20.4.2 Etiology

Long-term heavy drinking is one of the risk factors for hypertension. Most people think that drinking can accelerate the heart rate and increase the BP, but some animal experiments have found that the heart rate increases after drinking, the BP rises first and then drops, with the increase of alcohol consumption, the BP decreases more obviously. In the clinical trial of hypertensive patients, the blood pressure increased slightly and the heart rate increased significantly immediately and within a few hours after drinking a small amount of alcohol. After the load of alcohol, BP significantly decreased, then slowly increased, and the next day it began to rise. One load of alcohol intake can significantly increase the risk of cardiovascular and cerebrovascular events in patients with hypertension [80]. At present, it is believed that hypertension is caused by many factors. Therefore, we speculate that alcoholic hypertension is not only the direct effect of alcohol on BP but also may be caused by the influence on heart and other organs to increase BP.

Alcohol consumption is closely related to cardiac structure. Alcohol drinkers tend to develop left ventricular hypertrophy and left ventricular mass increase (echocardiography). Left ventricular hypertrophy and left ventricular mass increase still exist in alcohol drinkers after BP control, which suggests that the direct effect of alcohol on myocardial hypertrophy may be a more important determinant than alcohol-associated hypertension. This change in cardiac hypertrophy is a feature of long-term severe alcoholism in toxic cardiomyopathy [80].

The direct toxicity of alcohol to myocardial cells is mainly shown in the following aspects: (1) Damage to the integrity of myocardial cell membrane. Mainly through the alcohol lipid-soluble biological characteristics, invasion of the cell membrane caused liquefaction and change in the lipid composition and molecular configuration of the membrane, resulting in ion distribution on the surface of the membrane and membrane potential out of control. It affects inter-cell information transfer and ion exchange. (2) Affect organelle function, including mitochondria, sarcoplasmic reticulum, and other organelles dysfunction, resulting in reduced myocardial energy supply. (3) Affect the permeability of myocardial cell ion, thereby causing potassium. The loss of phosphate or magnesium from the myocardium and the overload of intracellular calcium in cardiomyocytes can lead to a decrease in myocardial contractility, which is an important cause of cardiac dysfunction in alcoholic cardiomyopathy. (4) The change of intermediate metabolism during alcohol metabolism. (5) Drinking for a long time can change the structure of regulatory proteins (protoningin and protomyosin) and affect the function of myocardial relaxation and contraction. Some enzymes in the tricarboxylic acid cycle,

such as aspartate aminotransferase (aspartate aminotransferase), malate dehydrogenase, isocitrate dehydrogenase, lactate dehydrogenase and aldolase, escape from cardiomyocytes and affect the function of cardiomyocytes. It does not effectively utilize fatty acids to produce energy and causes the accumulation of triacylglycerol in the myocardium, abnormal fat transport, and changes in the activity of adenosine triphosphate in myofibrils. Long-term drinking can change the structure of regulatory proteins (procyanine and promyosin) and affect myocardial diastolic and contractile function. (6) Long-term heavy drinking can lead to balanced nutrition disorders in human body. Easy to lead to vitamin deficiency, especially vitamin B deficiency, and can also aggravate cardiac dysfunction. In addition, some alcohol additives contain cobalt, lead, and other toxic substances; long-term drinking can lead to poisoning or myocardial damage. As a result of the interaction and influence of the above reasons, alcohol can affect the myocardial damage [81].

Overall, for different individuals, different amounts of alcohol, the immediate effects are different, and the intensity of the effect is not always the same.

20.4.2.1 Effect of Different Kinds of Alcoholic Drinks on Blood Pressure

Studies have shown that beer, wine, or spirits have similar effects on BP, but wine has less effect on BP. A study of 13,285 drinking population found that drinking a small or moderate amount of wine could significantly reduce the mortality rate of CV and cerebrovascular diseases, while spirits increased the risk. Beer had no significant effect on the mortality rate of CV diseases [81]. The effects of alcoholic beverages on atherosclerosis in rabbits were compared in animal experiments. It was found that red wine could reduce atherosclerosis more effectively than beer, white wine, and whiskey. Red wine also reduces atherosclerosis in apolipoprotein-E (Apo-E)-deficient mice. Moderate amount of wine has more obvious effect on reducing ischemic stroke than the same amount of liquor or beer. However, some epidemiological studies do not show that red wine has a stronger cardiovascular protective effect. Early atherosclerosis studies in hamsters show that ethanol, red wine, dealcoholic red wine, and grape juice all significantly reduce the formation of foam cells in the vascular wall of hamsters fed with high cholesterol and saturated fatty acids. But pure red wine does not show a special advantage. While drinking red wine may have a better protective effect than beer or white wine, it is not necessarily because of red wine itself, some scholars say. In general, people who drink red wine have higher education, less smoking, more exercise, more balanced diet, and less binge drinking. These factors may affect the risk factors of coronary heart disease. Further research is needed on whether red wine is indeed superior to other alcoholic beverages in protecting the cardiovascular system.

20.4.2.2 Effect of Alcohol Consumption on BP

The study showed that there was a “J” curve between the amount of alcohol consumed and BP levels. The BP level of those who drank a little or moderate amount of alcohol (10 g alcohol/day) was lower than that of those who did not drink alcohol or abstinence, and when people drank more than 30 g alcohol/day, with the increase

of alcohol consumption, BP increased significantly, and this relationship remained after the exclusion of age, weight, sodium salt and potassium salt intake, smoking, and educational level. Both domestic and foreign cross-sectional studies and prospective studies showed that there was a positive correlation between long-term heavy drinking and hypertension, and there was a positive linear and causal relationship between alcohol consumption and systolic and diastolic BP. It is believed that the prevalence of hypertension, systolic BP, diastolic BP (3–6 mmHg), systolic BP increased by 5–10 mmHg [82].

In recent years, Benjamin [83] and other studies confirmed that there was a linear relationship between the risk of hypertension and drinking, and the risk in men was higher than that in women. But a new study of women drinking alcohol found that moderate drinking reduced blood pressure and also increased the risk of breast cancer, so the study did not recommend drinking a small amount to reduce BP [84].

It was found that in addition to the influence of heavy drinking on hypertension itself, the antihypertensive effect of patients with hypertension also had a significant impact [85]. The decrease of systolic and diastolic BP in patients with hypertension due to heavy alcohol consumption is not related to a small amount of alcohol consumption. It is not a simple linear relationship between alcohol consumption and BP drop in antihypertensive patients. The curve does not show a trend of BP decline after a period of plateau period, while the dividing point of drinking volume and decreasing BP is 30 g alcohol consumption during the plateau period. That is to say, the amount of alcohol consumed per day is not more than 30 g. It is generally believed that the prevalence of hypertension in heavy drinkers or in daily drinkers is 1.5–2 times higher than that in non drinkers or small drinkers, and the mean systolic blood pressure is increased by 5-10 mmhg, and the diastolic blood pressure by 3–6 mmhg, compared to non drinkers and small drinkers.

The physiological mechanism of the effects of unequal amounts of alcohol intake on the human body is different. Some studies have shown that moderate alcohol increases high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), insulin sensitivity, blood coagulation and platelet aggregation, fibrinolysis, and homocysteine. The decrease of C-reactive protein and interleukin-6, the increase of vascular endothelial growth factor and adiponectin, the decrease of intercellular adhesion molecule, vascular cell adhesion molecule, E-selectin, and the increase of protein kinase C-ε were beneficial to human body as a whole. On the contrary, excessive alcohol increased acetaldehyde, decreased oxidative stress, increased triglyceride, decreased high-density lipoprotein cholesterol, increased reactive nitrogen group, and increased intercellular adhesion molecules, vascular cell adhesion molecules, and E-selectin. The increase of protein kinase C-δ is harmful to human body [86].

The mechanism of the effect of alcohol on BP does not exclude social psychological factors, such as type A personality, anxiety, stress, etc. The study showed that BP increased with the increase of alcohol intake when alcohol intake is ≥30 g/day in all age groups. This indicates that the relationship between alcohol

consumption and BP is independent of other traditional risk factors. Alcohol intake ≥30 g/day is an independent risk factor for hypertension. Other studies have shown that there is no positive correlation between alcohol consumption and BP in young women, but in older women, which may be associated with a lack of sex hormone in older women [87].

Heavy drinking can also affect BP through genes and enzymes [88]: endothelial nitric oxide synthetase (eNOS) gene plays an important role in BP regulation and inhibits nitric oxide synthetase which can increase BP in healthy people, and G894T mutation of eNOS gene is also closely related to hypertension. There was significant positive interaction between drinking and G894T mutation. Other studies showed that Glu298Asp mutation could change the conformation of NOS protein, while alcohol could significantly inhibit the activity of NOS and decrease the production of NOS. In addition, 11 β-hydroxysteroid dehydrogenase type 2 deficiency resulted in elevated BP in animals in two ways. Glycyrrhizin and cholic acid inhibited the expression of 11 β-hydroxysteroid dehydrogenase type 2 mRNA by inhibiting the expression of glycyrrhizin and cholic acid. By inhibiting the expression of aldosterone synthetase mRNA, the secretion of aldosterone in the isolated mesenteric vascular network was decreased, which led to the increase of BP in the isolated mesenteric vascular network of rats, and the expression of aldosterone synthetase in the rat mesenteric vascular network was decreased by inhibiting the expression of aldosterone synthase. Alcohol is also the inhibitor of 11 β-hydroxysteroid dehydrogenase type 2. The arterial BP and cortisol level of drinkers were significantly higher than those of nondrinkers. The longer the drinking time, the greater the amount of alcohol drinking, the higher the BP and plasma cortisol level [89].

20.4.2.3 Effect of Drinking Frequency on BP

Abstinence is often accompanied by elevated BP and increased levels of catecholamine, renin, and antidiuretic hormones in circulation. This observation leads to the view that the effects observed in population studies may be due to the temporary effect of rapid withdrawal from alcohol in this observation environment. The observation of a large number of drinkers in the British Heart study supports this conclusion to some extent. Compared to the weekend, these people had high BP on Monday (assuming that drinkers were on Monday after the weekend after a heavy alcohol withdrawal) [90, 91]. The relationship between different drinking patterns and weekend BP is already in France and Northern Ireland. Observations were made in men. Many people in Ireland would binge on weekends and their BP on Monday was the highest; however, the weekend effect was not seen in the French, considering that it was linked to a week of average drinking. In addition, it has been reported that total alcohol consumption over an average week or longer is more important to BP levels than to ingestion [92].

To resolve the dispute, the team conducted a randomized controlled crossover trial in 55 men, 14 of whom drank more than 60% of the total on weekends, while others drank daily. Weekend drinkers' 24-h baseline blood pressure on Monday was higher than on Thursday, but not that of daily drinkers. This effect disappears when beer is converted to a low alcohol content. Both groups showed a 24-h fall in

ambulatory BP after switching from regular to low-grade beer. The effect was found in weekend drinkers a week later, but not in daily drinkers until the fourth week. The study showed that weekend drinkers had both acute abstinence hypertension and persistent hypertension, while weekly drinkers showed a longer-lasting booster effect. Recent studies have shown that the frequency of alcohol consumption is more important than the effect of alcohol consumption on cardiovascular disease. Under the same amount of alcohol consumption, less heavy drinking is more likely to increase the risk of hypertension and other diseases than a few times of drinking alcohol.

20.4.2.4 Influence of Pressure

Individual mental and mental stress not only increases alcohol intake, but also raises hypertension, the mechanism of which is unclear. It has been reported that alcohol causes only mental symptoms and has no direct effect on hypertension. Emotional stress can increase hypertension by increasing the pharmacological effects of alcohol. Some experiments that stop or reduce BP after alcohol intake suggest that the alcohol-hypertension correlation is not due to individual factors associated with alcohol consumption. However, this is a challenge in the field of research, and the answer to stress is very difficult.

20.4.2.5 Benefits of Moderate Alcohol Consumption

Compared with nondrinkers, men who drank 1–2 standard cups a day and women who drank one standard cup a day had a lower overall mortality rate (about 18%). Increased mortality rates are seen among drinkers and heavy drinkers who exceed moderate drinking limits. Moderate alcohol consumption has a mortality benefit in people without cardiac risk factors, and in patients with risk factors including hypertension, diabetes, and diagnosed coronary heart disease (CHD) [93, 94]. Regular moderate drinking is associated with a reduced incidence of CHD although heavy drinking induces cardiomyopathy, light to moderate drinking reduces the risk of heart failure in men and may reduce mortality associated with ischemic cardiomyopathy.

While heavy drinking increases the risk of all types of stroke, light to moderate drinking may reduce the risk of ischemic stroke, but not the risk of hemorrhagic stroke [95–98]. It has not been determined whether wine has a stronger cardiac protective effect than other types of alcohol, and it is likely that the type of alcoholic drink is not as important as the amount and pattern of drinking. The mechanism by which moderate alcohol consumption reduces the risk of myocardial infarction is most likely through its effects on HDL cholesterol, insulin sensitivity, thrombotic activity, and inflammation. The cardiovascular benefits of moderate drinking must be weighed against the multiple adverse effects of alcohol. The balance of risk–benefit from moderate drinking is likely to vary by age group and by population. The American Heart Association does not recommend that current nondrinkers start drinking small amounts of alcohol. We recommend that abstainers who are cautiously at high risk of CVD be advised of light alcohol consumption (The risk of CVD may be reduced by not exceeding 1–2 standard cups per day for men and for

women). Caution is needed when promoting the benefits of alcohol consumption on the risk of coronary artery disease [99]. It may be difficult to precisely adjust alcohol consumption to safe levels, resulting in a loss of its benefits in terms of mortality, and an increase in the incidence of alcohol-related diseases such as cirrhosis of the liver [100].

20.4.3 Pathogenesis

The mechanism between drinking and rising BP is unclear. The theories about the pathogenesis of alcohol-related hypertension are as follows:

20.4.3.1 Sympathetic-Adrenal System Activation Theory

According to the theory, sympathetic-adrenal system is activated in patients with alcoholism, which resulted in obvious autonomic neuroregulation disorder and increased BP. It has also been shown that drinking for 4 consecutive days can weaken the response of forearm blood vessels to norepinephrine, and alcohol can also lead to high blood pressure in humans through lasting effects on autonomic nerves. Direct recording of muscle sympathetic activity showed an increase in sympathetic activity during drinking compared with nondrinking time.

20.4.3.2 Inhibition of Baroreceptor Reflex Theory

It is suggested that alcohol can inhibit baroreflex and lead to elevated BP. Studies in humans have shown that acute alcohol intake can lead to impaired baroreceptor function, which may contribute to hypertension. It was found that the BP decreased significantly at 0.5 h after one loading (60 g alcohol) intake, increased after 5 h for 6 h, and increased at 8 h for 10 h. Compared with pre-drinking, the 24-h fluctuation curve of BP changed in the form of hump. Drinkers showed increased BP variability.

20.4.3.3 Angiotensin II Elevation Theory

It is suggested that the level of angiotensin II and angiotensin III in the central nervous system increased under the action of alcohol, which resulted in the increase of total peripheral resistance and hypertension. Alcohol can also cause acute vasodilation, but long-term drinking can lead to vasoconstriction effect. The increased circadian rhythm of abnormal BP may be related to the high activity of nocturnal sympathetic nervous system and plasma renin-angiotensin system in patients with alcohol-induced hypertension.

20.4.3.4 Electrolyte Balance Disorder Theory

In recent years, it has been shown that long-term drinking can cause potassium and magnesium deficiency, while potassium has protective effect on the increase of BP caused by drinking, and the decrease of magnesium level in the body can lead to the increase of BP through the action of sodium and potassium pump and the increase of intracellular calcium level. Alcohol can also increase BP by

altering the action of sodium and potassium pumps and by raising intracellular calcium levels.

20.4.3.5 Renal Origin Theory

It is suggested that alcohol can increase the level of serum uric acid and hyperuricemia can cause interstitial glomerulonephritis. The results show that interstitial nephritis in about one fourth of patients is caused by alcohol, and hypertension is one of the manifestations of interstitial nephritis. Therefore, alcohol-related hypertension is caused by kidney damage.

20.4.3.6 Genetic Abnormality

It has been reported that genetic abnormality may play a certain role in the pathogenesis of hypertension. Ethanol can inhibit the expression of 11 β-hydroxysterol dehydrogenase type II and aldosterone synthetase mRNA, increase the synthesis of cortisol, decrease the synthesis of aldosterone, increase the response of blood vessels to noradrenaline and thence increase blood pressure. As the regulation of BP circadian rhythm is influenced by the expression of catecholamine and angiotensin 1 receptor gene in vivo, the mechanism of alcohol-induced BP increase may be related to norepinephrine-mediated vasoconstriction and AT1R-mediated activation of plasma renin angiotensin system.

20.4.3.7 Other Theories

A case–control study of chronic alcohol abuse showed that the brachial artery flow-mediated vasodilation (FMD) decreased in alcoholics after 3 months of abstinence. Instead, a study of 108 Japanese men with coronary heart disease (54 of whom drank alcohol at least once a week) showed that alcohol drinkers had better brachial artery endothelial function despite more severe risk factors for coronary heart disease. In addition, in a randomized controlled crossover trial, 16 healthy male drinkers in Peth reduced their daily alcohol intake from 72.4 to 7.9 mL, showing no change in FMD or biomarkers of endothelial function in the brachial artery. These noninvasive studies do not rule out the effects of alcohol on vasoconstriction or endothelial function in selective vascular beds, but these effects have been suggested in some animal studies.

20.4.4 Clinical Manifestation

The clinical manifestations were related to the alcohol consumption and alcohol concentration of the patients which could be divided into three stages according to different degrees:

- Excitatory period: The blood alcohol concentration is 500–1000 mg/L. Other symptoms: exhalation liquor flavor, namely feeling headache, ecstasy, excited, talkative easy to anger, heart rate, systolic BP and pulse pressure increase, prone to car accidents, and injuries.

- Ataxia period: The blood alcohol concentration is 1500–2000 mg/L. Other symptoms: patients with indistinct speech, incoherent vision, uncoordinated movement, unstable gait, and ataxia.
- Coma: The blood alcohol concentration more than 2500 mg/L. Other symptoms: coma, dilated pupil, low body temperature, fast heart rate, decreased BP, and slow breathing and snoring can cause respiratory and circulatory failure and endanger life.

BP characteristics: Most people drink a lot of alcohol after BP rise; also in some people after drinking BP will begin to drop, and after a few hours or the next day, the BP will rise. In the long-term heavy drinking individuals, the BP will continue to rise, and BP in a few days to weeks after abstinence decreased, but after a few days of drinking, the BP can significantly increase. The systolic and diastolic blood pressure can be decreased by 3.3 mmHg and 2.0 mmHg respectively. The results of hypertension patients were similar to those of non-hypertensive individuals, and there was a dose–effect relationship between the percentage of alcohol consumption reduction and the decrease of BP.

20.4.5 Laboratory and Auxiliary Examination

1. Blood alcohol concentration test: The blood alcohol concentration can judge the condition and prognosis, but the alcohol concentration of alcoholic and nonalcoholic blood is different from the clinical manifestation.
2. Biochemical examination: Common hypoglycemia and abnormal liver function in patients with coma.
3. Serum β-endorphin level: Significantly increased.
4. Arterial blood gas: Usually acute ethanol poisoning can cause mild metabolic acidosis, but does not cause anionic gap increase. Attention should be paid to methanol or ethylene glycol poisoning in severe metabolic acidosis due to the increase of anion gap.
5. Blood pressure and ambulatory blood pressure: blood pressure can increase immediately after drinking alcohol in some patients, whereas most patients experience increase in their blood pressure only several hours after drinking alcohol.
6. ECG: Severe patients can have arrhythmia and myocardial damage ECG changes.
7. Head CT: Alcohol poisoning is prone to trauma. Coma patients should be examined by CT to exclude craniocerebral trauma or lesions.

20.4.6 Diagnosis and Differential Diagnosis

The diagnosis of alcohol-related hypertension is mainly based on the BP measured by medical professionals, and the patients have a definite drinking history. BP measurement requires an approved mercury column or electronic sphygmomanometer to measure BP at the upper brachial artery during rest. If BP is elevated, reference should be

made to the changes in BP and the overall level of BP during a period of follow-up. Whether the increase of BP is related to alcohol consumption should be observed, and the change of BP before and after drinking should be observed. The patients with alcohol-related hypertension usually have a long history of heavy drinking, and after decreasing or stopping drinking, their BP decreases or returns to normal.

Differential diagnosis includes essential hypertension and other secondary hypertension, sedative hypnotic poisoning, cerebrovascular accident, hypoglycemia, asphyxiating gas poisoning, hepatic encephalopathy, diabetic coma, anemia, and so on.

20.4.7 Treatment [101]

Alcohol-related hypertension treatment consists of alcohol abstinence and antihypertensive therapy, with emphasis on alcohol abstinence.

20.4.7.1 Treatment of Alcohol Abstinence

1. Abstinence: Abstinence is a key step in the success of treatment. The first thing to do is to make sure that the source of the wine is cut off. The progress of abstinence is generally controlled according to the degree of alcoholism. The light person may give up alcohol at once; the heavy person may gradually abstain from drinking gradually to avoid life-threatening symptoms of severe withdrawal. In the process of alcohol abstinence, the patients' vital signs, consciousness, and other changes should be closely observed.
2. Alcohol abstinence sulfur therapy: Abstinence sulfur is the alcohol dehydrogenase inhibitor, after taking abstinence sulfur and drinking again, the body produces nausea, vomiting, facial fever and redness, palpitation, headache, dizziness, and so on within a few minutes due to the accumulation of acetaldehyde, which makes the alcohol abhorrence. Do not drink again within 5 days after taking abstinence sulfur, if drink more, it can produce serious acetaldehyde syndrome and can endanger life. It is prohibited to have cardiovascular disease or worse physical conditions. The specific usage is to take alcohol abstinence sulfur 24 h after drinking, once a day, 0.25 and 0.5 g for 1 week and 3 weeks, respectively.
3. Symptomatic treatment: Patients with chronic alcoholism can be intramuscularly injected with vitamin B_1 100 mg; one is to supplement the possible vitamin deficiency, and the other is to prevent the occurrence of Wernicke encephalopathy. If it is possible to develop Wernicke's encephalopathy, intravenous vitamin can be injected immediately, and the safe dose of vitamin can be up to 1 g in the first 12 h. For withdrawal symptoms, convulsive author, intramuscular injection of diazepam 10–20 mg is used. Anxiety, depression, and insomnia can be treated with anti-anxiety antidepressants and other drugs.

20.4.7.2 Hypotensive Treatment

For alcohol-related hypertension, there is no unified treatment scheme at present, and the medication should be selected according to the condition. However, no

matter what medicine or method is used, we must first stop drinking, which is the basic method to prevent alcohol-related hypertension. The following drugs or methods can generally be applied to step down:

1. Clonidine: 0.2–0.3 mg each time, three times a day for 5–7 days. After treatment, not only the blood pressure was normal, but also the abstinence symptoms disappeared.
2. Calcium antagonist: Both experimental and clinical studies have shown that nifedipine, felodipine and nitrendipine calcium antagonists have significant effects on alcohol-related hypertension and alcohol withdrawal syndrome.
3. Angiotensin-converting enzyme inhibitor 1: Renin-angiotensin system plays an important role in the formation of alcohol dependence, so this kind of drug, such as captopril, can be used in the treatment of alcohol-related hypertension; Captopril not only has a good antihypertensive effect but also has a good effect on eliminating the dependence of patients on alcohol.
4. Beta-blocker: It has a good effect on lowering blood pressure in alcohol-related hypertension patients and eliminating abstinence symptoms in alcoholism patients, especially in patients with autonomic nervous dysfunction and heart rate disorder.
5. Magnesium sulfate: The administration of magnesium sulfate to alcohol-related hypertensive patients not only can reduce blood pressure but also can eliminate emotional stress and anxiety and has the effects of tranquilizing and soothing the nerves; especially for patients with ventricular arrhythmia.
6. Correct electrolyte and other metabolic disorders: It is also an important method to treat alcohol-related hypertension. However, the use of diuretics can increase the excretion of potassium and magnesium, aggravate the imbalance of electrolyte, and activate the renin-angiotensin system in the absence of diuretic indication and cardiac insufficiency.

20.4.7.3 Supportive Treatment

Pay attention to the physical and nutritional status of the patients, correct metabolic disorders, maintain the balance of water and electrolyte, promote brain metabolism, and supplement a large number of vitamins, especially B vitamins.

20.4.8 Prognosis

Alcohol-related hypertension can recover after treatment. If there is heart, lung, liver, kidney disease, especially with coma more than 10 h, or blood alcohol concentration more than 4000 mg/L, the prognosis is poor. Alcohol-related hypertension can be improved after alcohol abstinence. Long-term drinking can lead to toxic brain, peripheral nerve, liver, and myocardium disorders, and malnutrition. The prognosis is related to the type and degree of the disease. Early discovery and early treatment can improve.

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