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Series Editor: William B. White

Matthew R. Weir
Edgar V. Lerma *Editors*

Chronic Kidney Disease and Hypertension

Humana Press

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Chronic Kidney Disease and Hypertension

Humana Press

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To all my mentors and friends at the University of Santo Tomas Faculty of Medicine and Surgery in Manila, Philippines, and Northwestern University Feinberg School of Medicine in Chicago, IL, who have in one way or another, influenced and guided me to become the physician that I am.
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To my parents and my brothers, without whose unwavering love and support through the good and bad times, I would not have persevered and reached my goals in life…
Most especially, to my two lovely and precious daughters Anastasia Zofia and Isabella Ann, whose smiles and laughter constantly provide me unparalleled joy and happiness; and my very loving and understanding wife Michelle, who has always been supportive of my endeavors both personally and professionally, and who sacrificed a lot of time and exhibited unwavering patience as I devoted a significant amount of time and effort to this project. Truly, they provide me with motivation and inspiration.

Edgar V. Lerma

To all my patients with chronic kidney disease who I have worked with over my long career, I thank you for they opportunity in providing your care. I have learned so much from you!
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Matthew R. Weir

Preface

More than 430,000 patients currently receive chronic maintenance dialysis in the USA. Opportunities for clinicians to remain up-to-date on optimal clinical practice with both a text reference and online format provides important value. In particular, the online format allows up-to-the-minute information to supplement evidence-based and comprehensive clinical practice options in one unique resource written by authorities on each of the subjects. Sections of the book will provide cross transferable knowledge on a variety of necessary and important topics. We hope this unique approach of a text reference and online format will serve as a "single stop" opportunity for clinicians and other allied health-care providers involved in the care of the ESRD population.

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Chapter 1
Changes in Guideline Trends and Applications in Practice: JNC 2013 and the Future

Hala Yamout and George L. Bakris

The Joint National Committee Report on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) has been in existence for more than three decades with the first report published in 1977. The purpose of this report is to provide an authoritative review and summary of available data from clinical trials that will educate and update healthcare providers on approaches to treatment and cardiovascular risk reduction of appropriate patients. It was initially due to be updated every 4–5 years as data became available that would further solidify or change practice patterns.

The nucleus of the JNC was within the Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health. However, it also had 45 other societies or groups that had input into the JNC report. The last of the true series of these reports was the JNC 7, published in 2003 [1]. Its main goal apart from updating the trial data was to simplify the classification of hypertension as well as the algorithm for initially treating patients with a focus of achieving the blood pressure (BP) goal [1]. As of June 2013, a publication by the NHLBI in circulation clearly states that there will be no further guidelines emanating from NHLBI. They will provide data evaluation but the joint efforts of the American Heart Association (AHA) and American College of Cardiology Foundation are to provide the actual guidelines sometime in 2014.

The JNC reports themselves have transformed over time. There were initially four stages of BP classification in the early JNC reports; these have evolved into two stages in more recent reports (Figs. 1.1 and 1.2). The early JNC reports did not focus on systolic BP (SBP) primarily because it was a younger population of patients and most of the studies were from the late 1960s and early 1970s [2, 3]. However, after the Systolic Hypertension in the Elderly Trial in 1991, there was a major shift in focus to systolic hypertension especially in those over age 50 [4],

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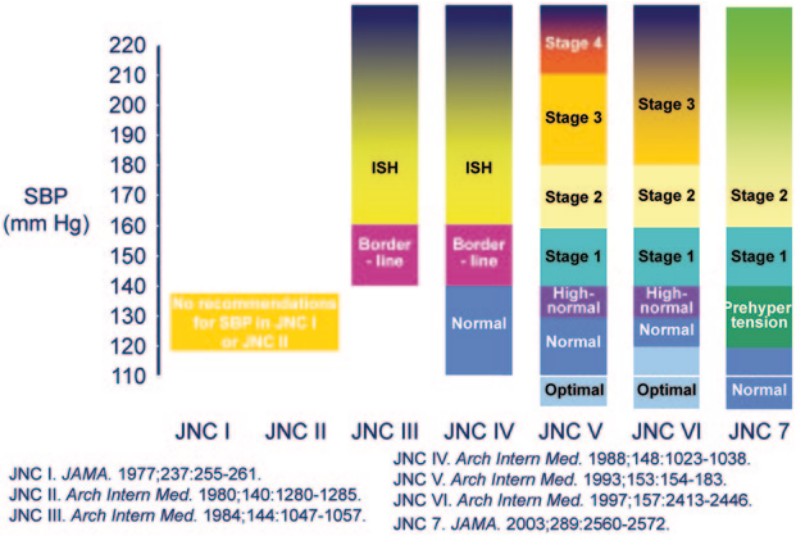

Fig. 1.1 JNC overview of systolic BP. To simplify the classification of hypertension, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has reclassified stages 2 and 3 hypertension as outlined in JNC VI as "stage 2" hypertension. JNC 7 also introduces a new term, "prehypertension" to include individuals with BP measurements between 120 and 139 mmHg systolic BP among those requiring intervention. Background: Simplification of the classification of hypertension was one of the three main goals of the JNC 7 report. The other two goals were to include recently published clinical trials in the recommendations and to urgently provide updated hypertension guidelines. The inclusion of the new class "prehypertension" recognizes that the risk of vascular morbidity and mortality becomes evident at BP levels as low as 115/75 mmHg in adult patients

Fig. 1.1. The JNC 7 changed the BP classification to combine the previous stages yielding only two stages. This was based on the premise that there would be very little difference in treatment options if BP were 200 or 180 mmHg. Additionally, a new term, "prehypertension," was added. This term arose from focus groups of patients who were asked, "What term, if you were told by your doctor would stimulate you to ask him for treatment advice." From among the terms listed, the group, to the exclusion of terms such as borderline, high normal, and others, unanimously chose prehypertension. Prehypertension defined as an SBP reading of 120–139 mmHg now encompassed all the previous terms used for this group. It extended down to a systolic of 120 mmHg based on the most recent data published just before the JNC 7 was released indicating that risk starts at an SBP of 115 mmHg [5]. This extension below 130 mmHg as well as the premise for initial use of combination therapy was derived from Lewington et al. who showed cardiovascular mortality risk doubles with each rise in BP of 20/10 mmHg starting at 115/75 mmHg [5].

Given a history of rigorous review of each of the JNCs by acknowledged experts in the field and further review by more than 45 different groups, all involved in hypertension including the American Society of Hypertension, American Society of

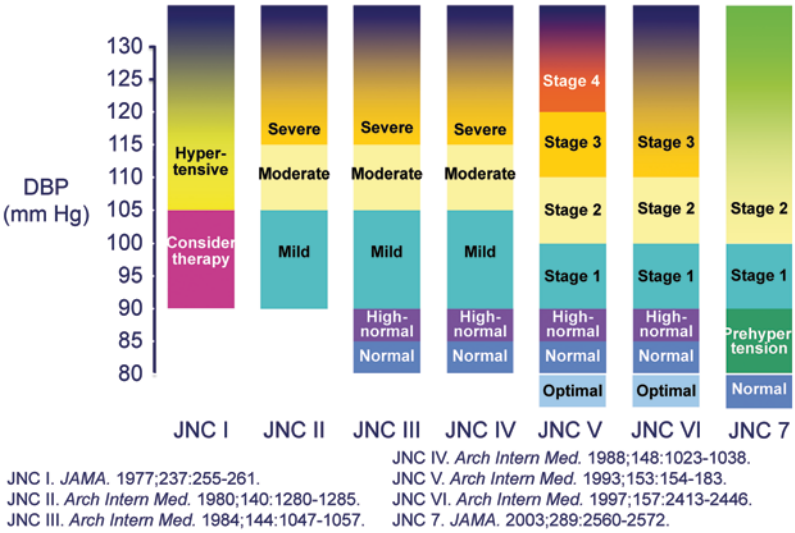

Fig. 1.2 JNC overview of diastolic BP. To simplify the classification of hypertension, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has reclassified stages 2 and 3 hypertension as outlined in JNC VI as "stage 2" hypertension. JNC 7 also introduces a new term "prehypertension" to include individuals with BP measurements between 80 and 90 mmHg diastolic BP among those requiring intervention. Background: Simplification of the classification of hypertension was one of the three main goals of the JNC 7 report. The other two goals were to include recently published clinical trials in the recommendations and to urgently provide updated hypertension guidelines. The inclusion of the new class "prehypertension" recognizes that the risk of vascular morbidity and mortality becomes evident at BP levels as low as 115/75 mmHg in adult patients

Nephrology, and AHA, one has to ask why the process changed in 2007. This was the year, 2007, the next JNC committee was to assemble and develop what would have been JNC 8. The answer is twofold: one is a lack of funds to carry out the process as before and second there was a ground swell of concern initiated by the AHA report that of all their consensus reports only 9% had level 1 quality evidence with the majority of other guidelines being expert opinion [6]. This coupled with a political climate of concern regarding the influence of drug companies on the guidelines, based on little evidence, changed the entire process. The new process mirrors the National Institute for Health and Care Excellence (NICE) guidelines in the UK [7]. The evidence-based grading system used in JNC 8 is shown in Fig. 1.3 [8].

Upon reviewing the JNC guidelines, certain questions arise. First, were the previous JNC reports not evidence-based? Why the format change and what is it changing into? Should evidence-based medicine be the only way to practice or is it just the minimum standard that everyone should achieve? It is clear that not all aspects of hypertension have a good evidence base but clinicians are faced with patients daily that demand answers that are not always evidence-based but also require clinical judgment. This is true regardless of outcomes since the trials are only as

Fig. 1.3 NHLBI evidence quality rating and recommendation strength JNC 2013

good as the inclusion criteria they employ to recruit patients. Hence, there are major limitations as well to evidence-based approaches.

JNC 7 created an algorithm for the treatment of hypertension [1]. This started with lifestyle modifications for all patients. If the BP was not at goal after this (defined as < 140/90 mmHg and < 130/80 mmHg for those with diabetes or kidney disease), then medical therapy would be needed. The choice of medical therapy depends on whether there are compelling indications for a specific drug, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), or beta-blockers. In the absence of compelling indications, the severity of BP guided the decision as to initial mono- or single-pill combination therapy. In stage 1 hypertension, defined as SBP of 140–159 mmHg or diastolic BP (DBP) of 90–99 mmHg, thiazide-like diuretics were suggested as initial agents for most patients. In stage 2 hypertension, defined as SBP > 160/100 mmHg, a two-drug combination was recommended, usually a thiazide-type diuretic in addition to a blocker of the renin–angiotensin system (RAS) [1]. If BP remains uncontrolled despite these treatments, then the doses need to be increased or additional drugs added until the goal BP is achieved. If adding a third or fourth drug fails to achieve the BP goal, a board-certified hypertension specialist should be consulted.

The JNC 7 was helpful in that it gave compelling indications classes of drugs to be used for BP control based on the best available randomized placebo controlled trials [1]. It summarized data for BP management in a variety of concomitant conditions, such as heart failure post myocardial infarction (MI), chronic kidney disease, stroke, and diabetes. It also provided guidance on the delayed development or prevention of hypertension based on evidence from trials.

Given this background in 2008, the NHLBI developed new directions for cardiovascular prevention guideline development that would encompass all future guidelines. In effect, they are starting over with an evidence-based process performed by nonclinician epidemiologists/statisticians who would dispassionately review the data and then provide guidance for grading by the committee. The updated clinical recommendations on BP and cholesterol control and obesity used this process of systematic review of the literature based on selecting studies meeting specific criteria and then grading the evidence and providing recommendations.

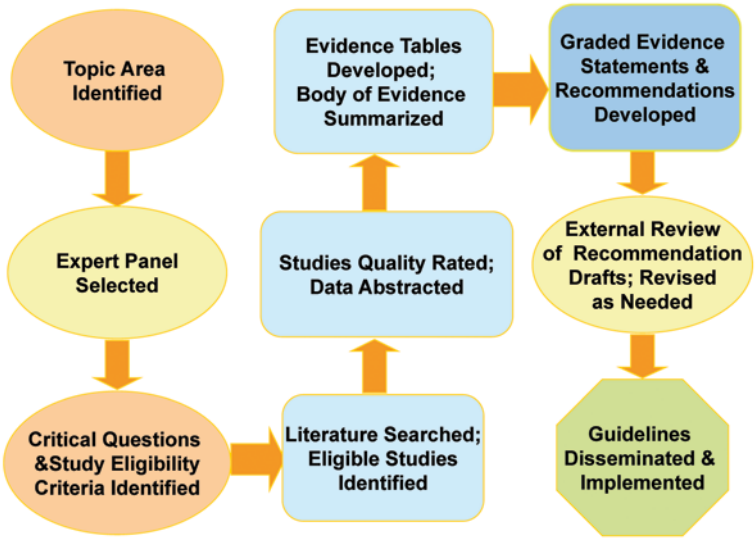

Fig. 1.4 NHLBI systematic review and guideline development process. Here, we see the series of steps for the systematic reviews and guidelines development—from identification of the topic area to dissemination of the final guidelines

They recommend standardizing and coordinating approaches to develop consistent recommendations for lifestyle and risk assessment. After each of these guidelines is completed, which is now the case for all three guidelines as of March 2013, an integrative fourth guideline for clinicians is planned for release within the next 2 years.

The NHLBI recommends a series of steps, from identification of the topic area to the dissemination of the final guidelines, Fig. 1.4. Briefly, after a topic area is identified, an expert panel is selected which asks critical questions and studies eligibility criteria. The literature is then searched with eligible studies identified then selected based on their quality. Evidence tables are developed, the body of evidence summarized, and graded statements and recommendations are developed. These are subject to an external review including by government officials, i.e., Centers for Medicare and Medicaid services (CMS) and revisions are made. The guidelines are then disseminated and implemented.

JNC 8 was initially supposed to address five key questions. Unfortunately, there was only enough time and money to address three questions. The three questions are: (a) Among adults, does treatment with antihypertensive pharmacological therapy to a specific BP goal lead to improvements in health outcomes? (*How low should you go?*) (b) Among adults with hypertension, does initiating antihypertensive pharmacological therapy at specific BP thresholds improve health outcomes? (*When to initiate drug treatment?*) (c) In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes? (*How do we get there?*)

To address these questions, studies from randomized controlled trials done after 1966 with at least a 1-year follow-up and a minimum of 100 patients were included [8]. The review found 56 trials met the criteria for determining specific BP goals, 26 to determine when to initiate treatment, and 66 for determining the choice of treatment.

The question of what is the goal BP needed to improve health outcomes has already been answered by two already published guidelines. The American Diabetes Association notes < 140/80 mmHg for those with diabetes [9] and the Kidney Disease Improving Global Outcomes (KDIGO) and Kidney Dialysis Outcome Quality Improvement (KDOQI) guidelines note < 140/90 mmHg for those with chronic kidney disease [10]. The goal for the elderly of < 150/80 mmHg was proposed by the AHA as well [11]. Although after public review, the goal became < 140/90 mmHg, it remains acceptable if between 140 and 145 mmHg. The JNC 8 does not differ markedly from these results as members of JNC 8 also served on these committees including an author of this chapter.

Multiple post-hoc analyses and one prospective trial support the goal BP put forth for high-risk patients and those with diabetes. A post-hoc analysis of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) noted that the composite outcome of cardiovascular risk, MI, stroke, or hospitalization for congestive heart failure, achieved a nadir at an SBP of 130 mmHg [12]. Post-hoc analyses of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial also demonstrate similar benefits for SBP levels down to 130 mmHg but risk increased as levels went below this nadir [13]. Finally, post-hoc analysis of the diabetes cohort of the International Verapamil SR-Trandolapril Study (INVEST) trial ($N > 7000$) demonstrated that those with an SBP of 130–140 mmHg had fewer cardiovascular events than those > 140 mmHg [14]. However, in those with a BP < 130 mmHg, no additional benefit on mortality was noted. In all these trials, however, stroke risk continued to decline with decreasing SBP without a similar nadir. This suggests that there is an increased risk of cardiovascular events except stroke in patients with extensive vascular disease when the BP is decreased below a critical level [13–15].

The only randomized trial that evaluated BP goal in diabetes was the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. It was found that a BP target of < 120 versus < 140 mmHg did not reduce the rate of a composite cardiovascular outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes (primary outcome annual rate of 1.87 % versus 2.09 %, respectively, $P = 0.20$, confidence interval (CI) 0.73–1.06) [15].

There are three randomized control trials involving 2272 participants with advanced stage chronic kidney disease and proteinuria. All three of these trials randomized BP to either 125/75 mmHg or around 140/90 mmHg. These trials were the Modification of Diet in Renal Disease (MDRD) [16], African American Study of Kidney Disease, Hypertension (AASK) [17], and Ramipril Efficacy in Nephropathy (REIN-2) studies [18]. All of these trials failed to show any clear difference in kidney disease progression in spite of achieving clear separation for at least 3 years.

These trials were all in nondiabetic patients that had a 2–4-year follow-up. Despite its prevalence, however, there have been no randomized controlled trials for BP goals among those with diabetic nephropathy.

In addition to these trials, the Kidney Early Evaluation Program (KEEP) evaluated the association between achieved levels of SBP and DBP and progression to ESRD in more than 16,000 people over an average of 2.8 years [19]. In this study, the risk of ESRD was the same in those with SBP of 130–139 mmHg as compared to those with SBP less than 130 mmHg. However, it is the first study to document that a reduced DBP below 60 mmHg is associated with a higher risk of progression to ESRD [19]. The risk of progression was higher among persons with SBP of 140–149 mmHg, with the rate doubling in those with SBP > 150 mmHg. As for DBP, the study showed that the rates of ESRD were highest among patient with levels of 90 mmHg or higher.

The question of initial therapy for treating hypertension has become clear from a meta-analysis of all antihypertensive agents showing no advantage to any specific class [20]. Thus, from the data available, one could say for patients who are elderly, now referred to by the JNC 8 expert panel as "older adults," either a calcium antagonist or thiazide-like diuretic, i.e., chlorthalidone or indapamide are appropriate first-line agents, a statement that also holds in African-American patients [8]. Diabetes patients can start with a blocker of the RAS or a thiazide-like diuretic, a statement that also holds for people with kidney disease.

Initial combinations for most patients have little data other than the ACCOMPLISH which supports initial use of single-pill combination therapy, and given the JNC 8 is evidence-based, it supports such an approach although there is only one outcome trial and hence, it did not give it a strong recommendation. Preferred combinations with evidence include RAS blockers with thiazide, thiazide-like diuretics, or calcium blockers [8]. This is also consistent with American Society of Hypertension Consensus Report on combination therapy [21]. Beta-blockers are suggested only as an add-on therapy only if there is a compelling indication but not as first-line therapy. The choice of which combination to use should take into account compelling indications in particular patients. All guidelines have relinquished beta-blockers to fourth-line treatment of hypertension without cardiac disease except for the European guidelines [22].

Finally, if one reviews the baseline data of studies and clinical trials used to initiate BP-lowering therapy, it is clear that for most studies the BP is > 150 mmHg in almost all trials. Therefore, one could argue that since the goal for the general population is > 140/90 mmHg, BP-lowering therapy should be initiated until BP with lifestyle modifications should not be started until the level is > 140/90 mmHg on repeated occasions. In older adults, if the goal is < 150/90 mmHg, then, likewise, BP-lowering therapy should not be started until BP is > 150/90 mmHg. It remains to be seen if the JNC 8 will adhere to this goal based on the evidence [8].

The issue of BP goal in older adults has been contested by a subgroup of the JNC 8 expert panel. Although there was almost unanimous agreement on nearly all recommendations, a minority of the panel (the authors of this commentary) disagreed with the recommendation to increase the target SBP from 140 to 150 mmHg in

persons aged 60 years or older without diabetes mellitus or chronic kidney disease [23]. This subgroup argues that the 2014 guideline panel failed to identify evidence of differential benefits or harms of treatment using an SBP goal of 140 mmHg with an age threshold of 60 years. They noted that while there is little randomized controlled trial evidence of risk or benefit in treating persons younger than 60 years to <150 mmHg, there are randomized trials in older adults showing a benefit in post-hoc analyses for those who could achieve an SBP 140–145 mmHg [23]. This is consistent with the guidance offered by the AHA guidelines in 2011 [11].

There are a number of questions not addressed by JNC 8. These questions include: (a) Should ambulatory blood pressure monitoring (ABPM) be used for initial assessment of HTN? (b) What is the role of central arterial pressure in the context of goal BP? (c) Should home BP monitoring be mandated for all patients to optimize control? and (d) Update on resistant hypertension. These questions while important could not be answered due to time constraints and financial concerns. A large evidence base does support the use of these modalities and included in other guidelines [7, 24].

In conclusion, the JNC 8 should state that the BP goal for all patients should be <140/90 mmHg. If a patient's BP is >20/10 mmHg above the goal, control can be achieved with single-pill combinations of RAS blockers with calcium channel blockers or thiazide diuretics as initial medications. Finally, a publication in June 2013 clearly states that NHLBI will no longer be in the "guideline" business. They will serve as the data analysis center and oversee this process but have appealed to the AHA and the American College of Cardiology Foundation to have representatives come together and produce guidelines from the database that currently has been generated [21]. This is a major change and is unclear how future guidelines will be developed, but JNC as we knew it died after JNC 7.

In conclusion, the JNC 8 states that the BP goal for all patients should be <140/90 mmHg, except for older adults where the goal is <150/90 mmHg (JAMES). It appears the panel felt that the strength of the evidence to support a goal of <140/90 mmHg, however, was not strong enough to give it a grade of A or B, and hence, relinquished it to E-expert opinion. In fact, most of the current practice of medicine surrounding BP received a grade of expert opinion. If a patient's BP is >20/10 mmHg above the goal, control can be achieved with single-pill combinations of RAS blockers with calcium channel blockers or thiazide diuretics as initial medications.

The reader should be aware that if they do not like the grades given to some of these guidelines, the problem lies with the amount of evidence and not the panels' interpretation of the evidence. This is evidenced by the disagreement over the goal for older adults where post-hoc analyses were used to support an argument, which violates the premise of evidence based in the true sense. In keeping with the theme of evidence-based medicine, however, if evidence does not exist, common sense is not a substitute. Fortunately, it is a substitute in clinical medicine where good judgment often trumps a lack of evidence.

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Chapter 2
Central BP Monitoring, Home BP Monitoring, Ambulatory BP Monitoring in CKD

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Hypertension is common among patients with chronic kidney disease (CKD) and the prevalence of hypertension increases as overall kidney function deteriorates, ranging from 60 to 100% depending on the population studied [1]. This chapter will specifically discuss the role of central blood pressure (BP) monitoring, home BP monitoring (HBPM), and ambulatory BP monitoring (ABPM) in the CKD population.

Central BP Monitoring in CKD

For over a century, the gold standard for BP measurement has been the peripheral brachial BP by conventional sphygmomanometry. Despite being a traditional predictor of cardiovascular (CV) risk [2], peripheral brachial BP does not accurately represent central aortic pressure which is intuitively more relevant to the true BP burden experienced by the major organs. While the mean and diastolic BP remain mostly unchanged, the systolic BP and pulse pressure (the difference between the systolic and diastolic BP) are amplified from the aortic root to the peripheral brachial artery. Central aortic BP and arterial compliance can now be reliably assessed using noninvasive applanation tonometry [3] and the reproducibility of these measurements has been confirmed in the CKD population [4–6]. Emerging data suggest that measurements of central aortic BP and arterial compliance may be more robust

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predictors of CV outcomes than traditional peripheral brachial BP in various populations including CKD [7–10].

Central BP Measurements and Outcomes in CKD

Central aortic systolic, diastolic, mean, and pulse pressures can be obtained from the central aortic pressure waveforms, which are estimated through a mathematical transformation of the radial or carotid arterial pressure waveforms captured by noninvasive applanation tonometry [3, 11, 12]. Compared to carotid artery applanation tonometry, radial artery applanation tonometry is more comfortable for the patients and easier to use in clinical settings.

The arterial pressure wave forms are the summation of the forward transmissions of the cardiac pressure waves generated by systolic, and the backward wave reflections generated by the peripheral vascular system at the interface between large arteries (conduit) and small (resistant) arteries. The shape of arterial pressure waveforms depends on three key factors, including (1) the amplitude and duration of the ventricular ejection, (2) the amplitude of the reflected wave, and (3) the velocity of the reflected wave returning from the periphery. Under normal physiological conditions, the reflected waves return to the central arteries in very late systole or early diastole during the same cardiac cycle, which augments coronary perfusion. When the reflected waves return earlier in systole due to increased pulse wave velocity (PWV), proximal site of wave reflection, or longer ejection time, the cardiac systolic pressure and workload are increased and the coronary perfusion is decreased.

Central systolic BP increases with age [13]. Before age 50, the increase in central systolic pressure is primarily due to greater amplitude of wave reflection, however, after age 50, the increase in central systolic pressure is mostly due to systolic augmentation, related to wave reflection, returning earlier because of increasing PWV [14]. Slower heart rates lead to longer ejection time and increase the possibility of augmenting systolic pressure as the wave reflection returns earlier during the cardiac cycle. Small statures also lead to earlier return of the wave reflection because sites of wave reflection are closer to the aorta. In a cross-sectional analysis of a large cohort of 2532 CKD patients enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study, central aortic pulse pressure was independently correlated with age, sex, weight, diabetes, and heart rate [15]. In addition, the proportion of high central aortic pulse pressure of ≥ 50 mmHg appears to increase progressively as the stage of CKD advances. In a study of 180 end-stage renal disease (ESRD) patients for more than 4 years, central carotid pulse pressure was shown to be a strong independent predictor of all-cause and CV mortalities while peripheral brachial BP and pulse pressure failed to show any significant predictive value [8].

Pulse wave analysis (PWA) in a group of 375 CKD patients with mean age of 60 years and estimated glomerular filtration rate (eGFR) of 48 mL/min/1.73 m^2 showed that both aortic systolic and pulse pressure derived from PWA were significantly associated with carotid intima-media thickness (IMT) while only aortic pulse pressure was significantly associated with the presence of carotid plaque [16].

Central Arterial Compliance Measurements and Outcomes in CKD

PWV remains the gold standard in measuring arterial stiffness [17]. Increasing PWV due to stiffening of the aorta is mostly seen with aging [18] and observed in isolated systolic hypertension in the elderly, sustained systolic–diastolic hypertension in middle age [19], as well as in populations with metabolic syndrome [20], impaired glucose tolerance or type 2 diabetes [21, 22], proteinuria [23], CKD, or ESRD [24, 25].

Aortic PWV can be determined by capturing arterial waveforms from two sites, typically carotid and femoral, and by measuring the distance between the two sites and the time required for the waves to travel [12]. Compared to ultrasonography or magnetic resonance image-based approach, applanation tonometry is easier to use, less expensive, and less time consuming.

Arterial compliance can be indirectly assessed using the augmentation of the central aortic pressure waveform which is defined as the amount of pressure added to the systolic pressure peak due to the wave reflection. The ratio of the augmentation pressure portion to the total central pulse pressure is termed augmentation index (AIx) and expressed in percentage. The AIx is sometimes "normalized" to a heart rate of 75 bpm.

Central aortic stiffness assessed by PWV is a strong independent predictor of all-cause and CV mortalities in ESRD patients [26, 27]. Central carotid AIx and pulse pressure have also been shown to be predictors of all-cause and CV mortalities while peripheral brachial systolic and pulse pressure showed less predictive value [8, 28]. It is worth noting that a study of young nondiabetic dialysis patients failed to show independent predictive value of AIx in all-cause mortality [29]. More recently in a study of CKD patients and kidney transplant recipients (mean age of 53 years and eGFR of 44 mL/min/1.73 m^2), central pulse pressure derived from peripheral PWA also failed to show significance in determining central aortic PWV and left ventricular mass index [30].

In nondiabetic CKD patients, higher AIx and higher baseline proteinuria were the only independent predictors of decline in GFR at 1 year [31]. In stage 4 or 5 CKD, a higher PWV and AIx as well as baseline eGFR, proteinuria, and smoking were shown to be independent predictors for the progression to ESRD [32]. A cross-sectional examination of a large cohort of 2144 CKD patients in the CRIC study found that brachial systolic blood pressure (SBP) was significantly correlated with proteinuria in both diabetics and nondiabetics [33]. Independent of brachial SBP, central aortic stiffness by PWV was also found to be significantly correlated with proteinuria in diabetics while peripheral brachial pulse pressure, central aortic systolic, and pulse pressure had no significant correlation with proteinuria in both diabetics and nondiabetics.

Furthermore, a study of stage 5 CKD patients showed improvement in arterial compliance by reduction in PWV and AIx, at 3 months after kidney transplant [34], suggesting a possible cause–effect relationship between impaired renal function and arterial stiffness. While the reductions in AIx were comparable, patients older than

Table 2.1 Utility of central BP monitoring in CKD

Central BP assessment obtained by aortic or carotid measurements
Provides more accurate assessment of true BP burden of vital organs
Better assessment of BP-related cardiovascular risk
Arterial compliance by aortic or carotid PWV and AIx
Better assessment of the burden of atherosclerosis and vascular injury

50 years of age appeared to have more pronounced reduction in PWV than the younger patients.

Emerging data suggest that measurements of central BP and arterial compliance are robust predictors of CV outcomes when compared with traditional peripheral brachial BP. Measuring central BP and arterial compliance could become an increasingly important part of routine clinical assessment of BP and related CV risks and treatment effects in high-risk populations such as patients with CKD. The utility of central BP monitoring in CKD patients is shown in Table 2.1.

HBPM in CKD

Office BP measurements significantly overestimate the burden of hypertension in patients with CKD and can lead to an overdiagnosis of hypertension in this population. When compared with ABPM in patients with CKD, HBPM has been shown to be superior to office measurements for the diagnosis of hypertension [35]. One week of home BP readings averaging more than 140/80 mmHg are associated with an awake ambulatory BP of more than 130/80 mmHg, which is considered "hypertensive" in the CKD population. These thresholds of SBP and DBP have been found to have both a sensitivity and specificity of more than 80 %, making HBPM useful upon which to base clinical decisions. HBPM also appears to be more accurate than office BP readings to identify CKD patients with white coat hypertension (WCH) and masked hypertension [35]. HBPM can be very useful in both diagnosis and management of hypertension in hemodialysis patients, where BP management is often difficult due to massive volume shifts [36]. Home BP readings are more reproducible from 1 week to the next when compared to pre or post-dialysis BP readings [37]. Home BP is recommended as a guide to the management of BP in dialysis patients and is useful to track changes in BP induced by reducing estimated dry-weight [37, 38]. Studies have shown that HBPM is superior when compared to pre-dialysis BP readings to manage antihypertensive therapy adjustments [39] and improves BP control [40]. The frequency and timing of HBPM in dialysis patients are important, since home BP increases on average at a rate of 4 mmHg for every 10 h of elapsed time after a recent dialysis treatment [41]. Measurement of BP soon after dialysis or just before dialysis will underestimate, or overestimate the BP, and therefore it is important to measure the BP at various intervals following dialysis [42]. It is recommended that BP be measured twice when waking up in the morning and twice before going to sleep following a midweek dialysis for 4 days [43].

These repeated midweek measurements provide an adequate number of readings to diagnose and manage hypertension. For stable dialysis patients, monthly home measurements of interdialytic BP should be encouraged. Peritoneal dialysis patients differ from hemodialysis patients in that they do not have large fluid shifts and undergo daily dialysis treatments with more stable fluid balance and BP measurements. HBPM has also been shown to be very useful in the diagnosis of hypertension in peritoneal dialysis patients [44].

Home BP Measurement and CKD Outcomes

Home BP readings provide more accurate readings than office or clinic BP readings in CKD and ESRD patients when compared to ABPM. A number of studies have attempted to address whether HBPM correlates with target organ damage, increased CV risk and progression of CKD.

Studies in CKD Population

Out-of-office BP readings in CKD patients are strongly associated with target organ damage [45]. HBPM has been shown to correlate with proteinuria and decline in eGFR [46]. Home BP measured in the morning had the strongest correlation with annual decline in eGFR [47] and as compared to office BP, HBPM is a significant predictor of decline in renal function and development of ESRD [48]. Proteinuria has been shown to be the strongest correlate of SBP by any BP measurement technique and this has been correlated more closely with both home, and ambulatory blood pressure (ABP) measurements when compared to office values [49]. In a prospective study of CKD patients, home BP readings were the most predictive of ESRD and death [50]. HBPM is useful in CKD patients to predict target organ damage, decline in renal function, CV events, and death.

Studies in Dialysis

In patients on hemodialysis, a U-shaped curve has been observed with SBP and mortality. Those with the lowest SBP, typically less than 100 mmHg, have the greatest mortality and there is a slight increase in mortality in patients with very high pre or post-dialysis BP readings [51]. Interdialytic BP readings done at home in dialysis patients outside the dialysis unit have been shown to predict target organ damage, including left ventricular hypertrophy (LVH) and mortality [52–57]. In an observational study using HBPM and pre and post-dialysis BP readings [12], weekly averaged BP readings were shown to have a significant correlation with left ventricular

Table 2.2 Utility of home BP monitoring in CKD patients

More accurate assessment of BP in nondialysis CKD and dialysis patients
Useful to make medication adjustments
Improves BP control
Useful to predict: target organ damage, decline in renal function, CV events, and death in nondialysis CKD patients
Useful to predict: target organ damage, LVH, left ventricular mass index, CV mortality, and all-cause mortality in dialysis patients

mass index and PWV, a marker of aortic stiffness, whereas pre-dialysis BP did not show a positive correlation [53]. Pulse pressures derived from within and outside the dialysis clinic, when averaged over a 1-week period have also been shown to be predictive of CV mortality and all-cause mortality [54]. In chronic hemodialysis patients, HBPM has also been shown to have a superior ability to indicate the presence of LVH when compared with pre-dialysis readings [52], and in longitudinal follow-up, patients with elevated home BP readings have higher mortality, whereas dialysis clinic BP readings do not correlate with mortality. HBPM is better correlated than office or clinic BP with target organ damage in CKD and in dialysis patients, and has greater value in predicting CV mortality and all-cause mortality. HBPM can also be incorporated into some electronic health-care records, which holds great potential to improve BP control for patients. HBPM is also attractive because it provides greater patient empowerment in their care, more insight into the connection of BP (and heart rate) with symptoms, and often better control with less medicine and greater attention to lifestyle measures by the patient. Currently, the most important deficit in the home BP initiatives is the lack of outcome data comparing home BP versus clinic BP management. This is an area of extreme need, particularly in dialysis patients. The utility of HBPM in the CKD population is shown in Table 2.2.

ABPM in CKD

ABPM provides a better measure of BP control when compared to clinic or office BP measurements in the general population and in CKD. An abnormal circadian profile of BP recorded by ABPM measurements is a commonplace in CKD, and the prognostic values of ABPM for predicting renal and CV outcomes are increasingly evident.

Ambulatory BP Interpretation and Utility in CKD

ABPM is undertaken by wearing a device that takes BP measurements over a 24–48-h period, typically every 15–20 min during the daytime and every 30–60 min during sleep [58]. BP follows an expected circadian variation in most normotensive

and most hypertensive patients, with a decline in BP during sleep. The lowest BP is often at about 3 a.m., followed by a rise during the early hours of the morning before arousal, and the highest BP tend to occur midmorning followed by a progressive fall throughout the day [59, 60]. Using 24-h ABPM, a "dipper" is generally classified as someone whose BP declines by at least 10% or more, when comparing the average daytime with the average nighttime BP values. A blunted circadian variation of BP, termed a "non-dipper," is defined as someone who shows less than the expected 10% decline during the night [61]. CKD is associated with altered circadian BP rhythm, typified by a blunted amplitude of circadian variation as well as increased rates of non-dippers and even some whose BP increases during the night ("reverse dippers," or "risers") [62, 63]. Patietns with essential hypertension have a peak BP in the early afternoon and a nocturnal fall in BP of greater than 10%; however, patients with CKD have a peak BP close to midnight and a mean nocturnal increase in BP. Non-dipper status is more prevalent in patients with CKD compared to patients with essential hypertension [64] and the prevalence of non-dipper status increases progressively as the renal function deteriorates reaching more than 75% in patients with advanced (stage 5) CKD, patients on hemodialysis and peritoneal dialysis, and in renal transplant recipients [64, 65]. There is also a greater prevalence of reverse-dipper status (i.e., nighttime BP rise rather than fall) in CKD versus non-CKD patients [65]. The prevalence of reverse dippers also increases progressively from stage 1 to 5 CKD.

The use of ABPM in CKD demonstrates that approximately 50% of patients have morning hypertension (defined as BP exceeded 135/85 mmHg during the first 2 h after awakening). The majority of these patients with morning hypertension have sustained elevation of nighttime BP (defined as BP > 120/70 mmHg all night) resulting in a high nighttime/daytime BP ratio, suggesting that morning hypertension in CKD is of a sustained type, and not the surge type as reported in other populations [17].

The Role of ABPM for Predicting CV Risk and CKD Progression

ABPM is an excellent diagnostic tool to diagnose WCH and masked hypertension in CKD. WCH is present in up to about 18% of patients with CKD leading to possible overdiagnosis and overtreatment of hypertension in CKD [66]. Conversely, masked hypertension has been shown to be present in up to 20% of a broad range of patients with CKD [66, 67]. The African–American Study of Kidney Diseases and Hypertension (AASK), focused on one racial cohort, reported a prevalence of masked hypertension in 43% [68]. The failure to identify masked hypertension in CKD leads to undertreatment of hypertension, and may contribute to CKD progression and CV risk. In CKD, as with general hypertensive patients who have normal kidney function, masked hypertension has been associated with the presence of LVH, the degree of proteinuria, and incident CV events [68–70].

Table 2.3 Utility of ABPM in CKD

White coat hypertension
Masked hypertension
Dipping status (dipping, non-dipping, reverse dipping)
Aid in prediction of CV risk
Aid in prediction of CKD progression
Adjust hypertensive therapy

Despite many years of availability of ABPM, there are only a few prospective studies in nondialysis CKD patients specifically investigating the prognostic significance of ABP readings for renal and CV outcomes. Data have shown that ABPM is a better tool for predicting renal and CV risk than office-based pressures in patients with various underlying causes of CKD. The predictive power for ABPM to predict renal and CV outcomes is independent of diabetes, proteinuria, level of hemoglobin, and preexisting CVD [71]. Nighttime SBP is a stronger predictor for both renal and CV end points than daytime SBP readings. Nighttime DBP is also a better predictor of fatal and nonfatal CV end points. There is also a twofold increased risk of CV end points in non-dippers and reverse dippers.

ABPM has been compared to office BP in predicting ESRD and death in patients with CKD [49]. ABPM has been shown to be a stronger predictor for ESRD and death than office BP readings and non-dipping is also associated with increased risk of total mortality and ESRD.

The longitudinal prognostic value of ABPM has also been shown using baseline ABPM data, and then assessing the rate of CKD progression and subsequent CV outcomes when evaluated over a 5-year period (70). Results showed that higher 24-h SBP, daytime, nighttime, and clinic SBP were each associated with subsequent renal and CV outcomes. However, after controlling for clinic SBP, baseline ABP readings were predictive of renal outcomes in participants with clinic SBP < 130 mmHg and of CV outcomes with no interaction based on clinic BP control.

Combining information using ABPM with eGFR in the prediction of CV outcome has been shown to be superior than using each alone over and adds prognostic value for predicting CKD and CV outcomes [72].

ABPM has also been used to adjust therapy in hypertensive children with CKD [73]. The ESCAPE trial showed that more intense BP control, defined as a mean arterial pressure below the 50th percentile as assessed using ABPM, compared with a target 24-h BP level between the 50th and the 95th percentile resulted in a substantial benefit, i.e., slowing of kidney failure progression among children with CKD. The utility of ABPM in CKD is shown in Table 2.3.

There are several reasons why ABPM provides greater opportunity to profile CV risk and renal disease progression in patients with CKD. It provides many more readings, often more than 50 measurements, compared with a typical office visit of three readings, thereby providing a truer estimate of BP burden on the circulation and the target organs. It captures the pattern of BP over a full

daily cycle and cues the provider into the success, or failure, of BP suppression during the night. In particular, ABPM accurately identifies WCH, which carries less risk than sustained hypertension, and masked hypertension, which carries more risk than normotension. By virtue of the large number of readings, it provides an opportunity to evaluate the variability of BP and heart rate, which have opposing effects on CV outcomes [74]. This information could be used to treat BP in CKD patients more accurately and identify dipping status and aid in stratification of CV risk and risk for CKD progression [75]. The CRIC study will provide more insight into the role of ABPM in CKD patients as it has more than 1500 participants studied with a focus on both CKD progression and CVD outcomes [76]. However, it is important to point out that, as with HBPM, leveraging of the superior capability of ABPM to more accurately profile a patients BP pattern and target organ damage is still largely limited to epidemiologic associations as outcome studies are lacking. This is a challenge and an opportunity for the future.

Summary

Hypertension is highly prevalent in CKD and use of traditional office or clinic BP measurements has not always correlated well with CKD progression and CV outcomes. The use of the different modalities of BP monitoring described in this chapter all have an increasingly useful role in the diagnosis and management of hypertension in CKD and in particular to aid in prediction of CKD progression and CV risk stratification. HBPM is the easiest modality to incorporate into routine management of hypertension in CKD as it is inexpensive and is associated with improved clinical care and outcomes in both nondialysis CKD patients and dialysis patients. It also directly involves patients in their care and puts some of the responsibility and ownership of improving BP control onto the patient. ABPM is the gold standard of BP measurement but, likely, will continue to be used mostly in selected patients in the clinical setting and in research studies due to the impracticalities associate with its use, including patient burden, costs, and poor reimbursement. Central BP monitoring is a promising modality as it allows arterial stiffness to be measured easily and noninvasively and it is well established that arterial stiffness is an independent predictor of CV events. Once CKD is established, the role of arterial stiffness in the progressive loss of kidney function is less clear. There is much ongoing research in this area, and in the long term, this methodology has the potential to be incorporated into routine clinical decision making when assessing CV risk as more accurate assessment of CV risk will lead to earlier interventions and potentially better outcomes in patients with CKD.

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Chapter 3
Resistant Hypertension in Patients with Chronic Kidney Disease

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Introduction

The incidence of chronic kidney disease (CKD) is steadily increasing worldwide due to multiple factors including diabetes, hypertension, and other chronic diseases. The management of CKD to prevent end-stage renal disease (ESRD) requires aggressive control of predisposing risk factors. The main principle in the management of CKD is to stabilize the renal function and avoid ESRD. CKD is an important cause of morbidity, disability, and mortality.

Systemic hypertension is a major global public health problem contributing to premature cardiovascular disease (CVD), cerebrovascular disease (CeVD), and CKD. The prevalence of hypertension is rising globally, in part due to the newer lower thresholds to define "hypertension." A majority of patients with CKD, particularly those with a glomerular filtration rate (GFR) < 60 ml/min (CKD stages 3–5) have significant hypertension. Blood pressure (BP) is poorly controlled in patients with CKD; only 10 % achieve the BP level < 130/85 mmHg [1]. Hypertension in patients with CKD/ESRD greatly increases the risk of CVD which accounts for more than half of mortality in patients with CKD. In fact, patients with CKD are a high-risk group for premature and extensive CVD in the community. A majority of patients succumb to CVD. CKD promotes and *accentuates* the full spectrum

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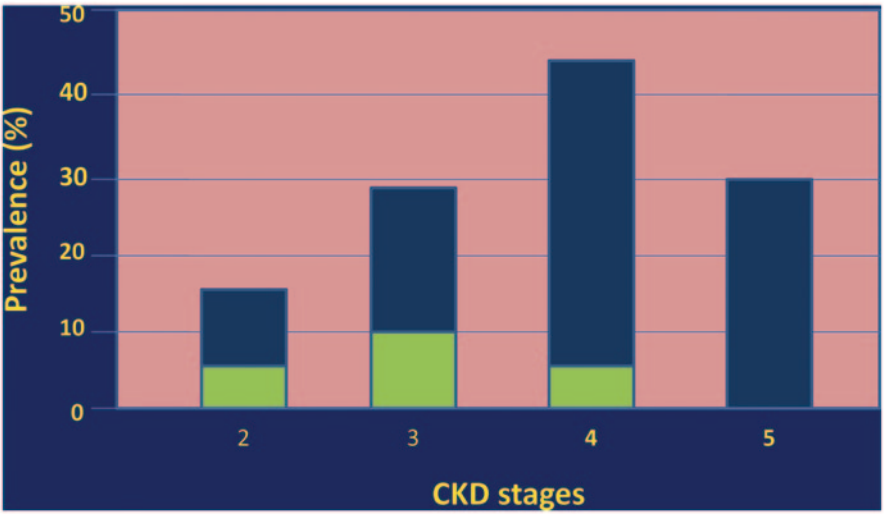

Fig. 3.1 True resistant hypertension (*blue bar*) and pseudoresistant hypertension (*green bar*) in CKD. (Adapted from Nicola et al. [31]. With permission from Elsevier)

of CVD. Hypertension and diabetes are contributing factors for a vast majority of patients with CKD/ESRD.

Hypertension and CKD are linked to each other via common pathophysiological pathways and similar susceptibilities. An overwhelming majority of patients with CKD/ESRD have chronic and often significant hypertension. Both hypertension and CKD contribute to significant CVD. As stated elsewhere, uncontrolled hypertension leads to CKD and vice versa; thus, as comorbidities, they are inseparable.

Resistant hypertension (RH) is very common and problematic in patients with CKD. RH is defined as office BP level >140/90 mmHg for general population and >130/80 mmHg for those patients with CKD [2, 3] despite the use of three antihypertensive drugs including a diuretic or the requirement of four antihypertensive drugs to achieve the target BP level. One has to assess patient adherence and proper optimal dosing of antihypertensive drugs before to make a distinction between true RH and uncontrolled hypertension or pseudo RH (Fig. 3.1). In the context of RH, CKD is an important etiological factor. The prevalence of CKD worldwide is increasing; 10% of the adult global population has CKD [4].

Observational studies have documented a high prevalence of RH in patients with CKD [5–8]. Despite the use of multiple antihypertensive drugs, hypertension remains above goal in patients with diabetic and nondiabetic CKD [9, 10].

Etiological Factors for RH in Patients with CKD

The pathogenetic mechanisms for RH in patients with CKD and ESRD are complex and multifactorial, with an interdigitating basis. The classical explanation

Table 3.1 Resistant hypertension: factors

Noncompliance to therapy
Excessive salt intake
Increasing body weight
White coat hypertension
Drug–drug interactions
Excessive alcohol use
Drugs which cause hypertension—steroids, nasaids, erythropoietin, cyclosporine, certain herbal preparations, etc.

for RH in CKD is an adverse interplay between intravascular volume and the renin–angiotensin–aldosterone system (RAAS). Hence, the traditional therapy for hypertension in CKD patients has been based on reducing the volume and or using RAAS blockade. However, it has become evident that despite volume control and adequate RAAS blockade, BP remains out of control in most patients with CKD. Thus, additional etiopathogenetic factors may be operative in sustaining elevating BP levels in patients with CKD. Among these alternate pathways of persistent RH in CKD are—inappropriate activation of sympathetic nervous system (SNS), enhanced production of endothelin (a potent vasoconstrictor), decreased availability of nitric oxide (NO), blunted endothelial function, obstructive sleep apnea (OSA), and structural changes in the arterial tree. Furthermore, therapies for underlying renal disease—such as steroids, cyclosporine, calcium/vitamin D, erythropoietin, and nonsteroidal anti-inflammatory drugs (NSAIDs) can increase the BP in patients with CKD (Table 3.1).

Obesity and metabolic syndrome may also participate in the pathogenesis of hypertension in CKD.

An important pathophysiological observation in patients with CKD is excess sodium and water retention (due to ↓GFR). The consequent expansion of extracellular volume (ECV) makes the BP control difficult and is the cause of resistance to antihypertensive drugs even at high doses. ECV expansion is inversely related to GFR, thus creating an unfavorable connective loop. Even in the absence of visible edema, ECV expansion is a potent factor in the development of RH. Salt sensitivity and volume retention are twin interactive features of sustained hypertension in patients with CKD [11, 12]. The presence of nocturnal hypertension (nondipping status) is also indicative of ECV expansion in patients with CKD.

It is well known that inappropriate activation of RAAS despite volume excess contributes to sustained hypertension in patients with CKD. From a physiological point, ECV expansion should inhibit the activity of RAAS. However, in patients with CKD such an inverse relationship between volume and RAAS is lost. Any level of RAAS in the face of volume expansion therefore raises the BP level. On this basis, RAAS blockers are widely used as antihypertensive strategy in patients with CKD. BP response to RAAS blockade is indirectly reflective of the role played by RAAS in the pathogenesis of hypertension in patients with CKD.

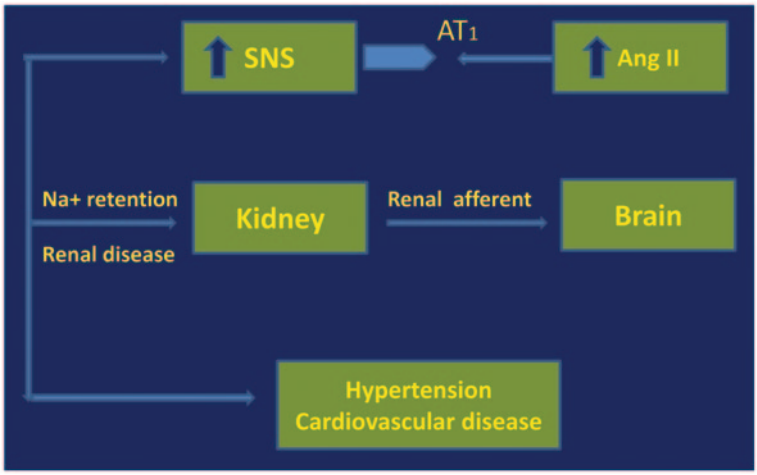

Fig. 3.2 Neurogenic factors in renal hypertension

Increased SNS Activity

Augmented activity of SNS has been demonstrated in CKD. Kidney is a sensor of systemic circulation and is endowed with intrinsic SNS functional activity—both efferent and afferent nerves. The kidney is not only a target of SNS but also a dynamic reservoir of SNS functions. Activation of chemoreceptors in the kidney (by ischemic or uremic toxins) precipitates nerve traffic to and from the central nervous system. Chronic stimulation of the renal (afferent) nerves leads to SNS activation with resultant hypertension (Fig. 3.2). The synthesis and turnover rate of norepinephrine from the hypothalamic region are enhanced in experimentally induced renal dysfunction [13]. Muscle sympathetic nerve activity (MSNA) is excessive in patients with CKD compared to normal. It is possible that excessive SNS activity in CKD may also be mediated to some extent by the RAAS. Reduced baroreceptor function and increased levels of leptin also contribute to SNS activation in CKD.

Endothelin, CKD, and Hypertension

Endothelin-1(ET-1) a peptide derived from endothelial cells is a powerful vasoconstrictor. ET-1 exerts a number of biological effects including vasomotor tone, cell growth, (renal) sodium, and water retention. Thus, excessive activity of ET-1 impacts systemic vascular resistance (SVR) and the BP level. Studies have demonstrated that the ET system is important in the pathophysiology of CKD-associated hypertension [14–16]. A number of intrarenal mechanisms (cytokines, protein load,

nephron loss, decreased GFR) may stimulate ET-1 production which can cause hypertension and further progression of CKD. ET-1 levels correlate with the level of renal function and proteinuria in diabetic nephropathy [17]. It is possible that the deleterious consequences of ET-1 may also be mediated via SNS and RAAS in the pathogenesis of advancing hypertension associated with CKD.

Obstructive Sleep Apnea

OSA is independently linked to hypertension and related CVD [18–21]. A number of pathways in OSA principally mediated by hypoxia cause vasoconstriction and hypertension. It has been reported that OSA is more prevalent in patients with CKD compared to the controls [22–25]. OSA has been correlated with GFR and proteinuria in patients with CKD but whether OSA is an independent risk factor for CKD is not established.

Circadian Variability of BP

It has been suggested that in patients with CKD, normal circadian variability of BP is lost. Normally, BP levels are highest in the early morning gradually decreasing during the course of the day and reach a low level during sleep ("dippers"). The so-called nondippers do not display such BP variability and their nocturnal BP does not drop. In patients with CKD and ESRD, the prevalence of "nondippers" status is high [26–29]. The occurrence of nondipping and therefore nocturnal hypertension in patients with CKD is a factor in the genesis of RH in patients with worsening renal function. Nocturnal hypertension is associated with significant target organ damage (TOD) and excessive cardiovascular events in patients with CKD.

Oxidative Stress

Oxidative stress, a state of imbalance between production and breakdown of reactive oxygen species (ROS), is a marker of vascular function. A high production of ROS causes vascular dysfunction. Excessive production of ROS causes intense vasoconstriction and hypertension. Thus, ROS can cause severe hypertension directly or by depleting nitric oxide (NO). Oxidative stress has been proposed as a possible link between CKD and severe hypertension [30]. Renal damage is associated with oxidative stress even in the early stages of CKD. The oxidative stress not only causes vigorous vasoconstriction but also accelerates kidney injury. Oxidative stress, a potent factor in the development of CVD also plays a role in the occurrence of vascular disease and pathogenesis of hypertension in patients with CKD.

RH in Patients with CKD: Significance and Prognosis

Hypertension in patients with CKD often requires utilization of multiple antihypertensive drugs in maximum doses. A substantial number of patients, however, remain "resistant" to optimal combination of potent antihypertensive drugs. Typically, RH is defined as BP that remains above therapeutic goals despite the concurrent use of three antihypertensive drugs or requirement of four or more classes of drugs to achieve the goal BP level. The so-called treatment RH is common and severe in patients with CKD. Treatment RH in patients with CKD predisposes to adverse cardiovascular outcomes and premature death.

RH in patients with CKD is associated with lower estimated GFR (eGFR) and proteinuria. In addition to aggressive therapy for hypertension, it is important to identify the factors for the decline of renal function in patients with CKD. Close follow-up is recommended based upon the level of BP, GFR, and serum potassium. RH in CKD is often volume-dependent; hence, effective diuretic treatment is of critical value. Selected causes of RH include:

- Excessive sodium intake
- Fluid retention
- Inadequate diuretic dosage
- Erroneous choice of a diuretic
- Inappropriate combination of antihypertensive drugs
- Drug–drug interactions
- Drugs-induced BP elevation
- Obesity
- Sleep apnea
- Insulin resistance

After excluding aggravating/causative factors, intense BP monitoring and aggressive therapy should be implemented. Volume control is of major benefit in patients with CKD who have RH. With the understanding that RH is a risk factor for rapid decline in renal and cardiovascular functions, BP control is of immense importance. Persistent hypertension in patients with CKD is due to an interplay of etiological factors such as volume overload, increased activity of the RAAS and of SNS. ECV expansion in patients with CKD is directly related to the degree of renal failure; thus, tight control of volume is advocated along with blockade of the RAAS and SNS to improve the BP levels in patients with CKD. Renal denervation (RDN) therapy may be indicated for some patients with CKD who have persistent, severe, complicated, or RH.

RH increases the morbidity and mortality in patients with CKD. Uncontrolled hypertension causes further renal damage, which in turn causes rapid deterioration in BP control. It is a vicious cycle. While the office and clinic BP measurements are routinely used to classify and treat hypertension in patients with CKD, ambulatory BP monitoring (ABPM) is the best method to identify true RH in clinical practice. Various cardiorenal events in patients with RH can be correlated to the BP status as

determined by ABPM [31, 32]. Greater application of ABPM in patients with CKD will likely identify those patients who need most rigorous antihypertensive therapy.

It should be clearly understood that RH in patients with CKD predisposes to serious adverse cardiorenal outcomes [33, 34]. RH is a powerful harbinger of adverse prognosis in patients with CKD [35, 36]. RH increases the risk of renal death. RH in contrast to treatable hypertension predicts CVD in patients with CKD; on the other hand, patients with pseudoresistance have favorable prognosis. One can surmise then that persistence of hypertension despite optimal antihypertensive treatment identifies individuals with severe and advancing vascular disease and "fixed" structural vascular abnormalities. Conditions associated with RH in patients with CKD include—left ventricular hypertrophy, diabetes, proteinuria, and high salt intake. Not surprisingly, these concomitant disorders are also accompanied by increased pulse wave velocity, endothelial dysfunction, and arterial stiffness. While a low GFR is a recognized risk factor for premature mortality in patients with CKD, proteinuria is a better marker of CVD.

Principles of Treating RH in Patients with CKD

The complex pathophysiological mechanisms of RH in patients with CKD dictate application of multiple therapeutic strategies to control hypertension in this high-risk population. In addition to hypertension, there are other factors which contribute to the progression of CKD to ESRD; these include (but are not limited to) hyperlipidemia, obesity, diabetes, tobacco use, and OSA. Hence, all of these predisposing factors should also be addressed in the management of patients with CKD. One of the cornerstones of BP reduction in patients with CKD is restriction of sodium intake to prevent ECV expansion. Patients with CKD are particularly prone to the negative consequences of high salt intake. Excessive salt intake may also trigger other markers of CKD such as oxidative stress, endothelial damage, proteinuria, and vascular inflammation. There is evidence to suggest that salt restriction is beneficial to treat RH in patients with CKD. Unless there are contraindications, salt restriction is recommended as an initial measure to manage RH. Most guidelines recommend an upper limit of 100 mmol of sodium per day (=2300 mg or 6 g sodium chloride). Dietary education and counseling are critical measures to ensure that the CKD patients understand and comply with salt restriction.

The definition of RH includes optimal use of a diuretic. However, in patients with CKD, the selection and dosage of a diuretic are important to control the volume status. The choice of a diuretic and its dosage are dictated by the level of kidney function and stage of CKD. Patients with mild renal dysfunction (GFR > 40 ml/min) may respond to thiazide diuretics. With advancing CKD, loop diuretics with proper dosing and titration are recommended [37]. The dosage of loop diuretics has to be adjusted to correct sodium retention and to obtain desired weight reduction. Adequate use of loop diuretics is strongly recommended to treat RH in CKD patients unless there are contraindications. The uncommon phenomenon of "diuretic

resistance" can be overcome by judicious addition of drugs like metolazone, which permit additional inhibition of sodium reabsorption in the distal tubule. Studies have also shown that aldosterone antagonists such as spironolactone may be a useful addition to treat RH in CKD patients [38]. Despite the efficacy of aldosterone antagonists in RH in CKD patients, these drugs should be used with great caution and under close surveillance due to the risk of hyperkalemia.

RAAS Blockers

RAAS blockers like angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are frequently indicated to treat RH in CKD patients. As a rule, RAAS blockers are used in combination with other classes of antihypertensive drugs to treat hypertension in general, and in CKD patients in particular. Despite their pharmacological benefits and protection against TOD, RAAS blockers have not been shown to reduce all-cause mortality in patients with CKD. ACEIs have been shown to exert significant anti-proteinuric and antihypertensive effects in patients with CKD [39]. ACEIs lower the intraglomerular pressure by dilating the efferent arterioles. The reduction in intraglomerular pressure protects the kidney. ARBs like ACEIs exert beneficial antihypertensive, anti-proteinuric, and renal protective properties. ARBs are well tolerated and effective in managing hypertension in patients with CKD. The combination of ACEIs and ARBs has not been shown to offer any advantages in treating hypertension; the combination may show additive effects on proteinuria reduction but no additional outcome benefits. Dual RAAS blockade is not helpful for BP control or target organ protection. Trials with direct renin inhibitors have not yielded any advantages or favorable outcomes and thus are not recommended routinely. The use of RAAS blockers to treat RH in CKD patients while necessary requires close vigilance of renal function and potassium level. Despite the advocacy of RAAS blockade in controlling hypertension, these drugs should be used with considerable caution in patients with worsening renal function (e.g., serum creatinine > 2.5 mg/dl and K+ level > 5.5 meq/l).

Calcium Channel Blockers

Although calcium channel blockers (CCBs) are not preferred for initial therapy in patients with CKD, they are often required to treat RH. Dihydropyridine (DHP) CCBs are effective antihypertensive drugs and should be utilized as a component of combination therapy to control hypertension. All DHP CCBs are equally effective and can be conveniently added to antihypertensive regimen for CKD patients with RH. While there is some concern that DHP CCBs may have an adverse effect on proteinuria in patients with diabetes, such a consideration is irrelevant to reach the target BP goal in patients with RH. Moreover, this potential adverse effect is less likely when DHP CCBs are given on the background of RAAS blockade. Cilinidip-

ine, a new generation DHP CCB with a dual mode of action, may have special renoprotective properties [40]; this novel CCB may have a place in patients with CKD. In patients with CKD, DHP CCBs are generally prescribed as second- or third-line agents in the titration of antihypertensive drugs to achieve desired BP reduction.

α- and β-Blockers and Central Agonists

While of no specific advantage for patients with CKD, α- and β-blockers can be used as add-on drugs for hypertension control based on the clinical circumstances and patient profile. β-blockers in particular may be indicated for cardiovascular protection in CKD patients. Central agonists like clonidine are considered as add-on drugs for BP control in CKD patients with RH. Adrenergic blockers and central agonists are not contraindicated in CKD. Since there is an aggravation of SNS in patients with CKD, β-blockers can be a rational component of antihypertensive drug regimen in this population. In this context, vasodilating β-blockers (like nebivolol and carvedilol) may be most suitable due to their pharmacological advantages.

Direct Vasodilators

Direct vasodilating drugs like hydralazine and minoxidil are potent antihypertensive drugs of importance to control RH in CKD patients. Both hydralazine and minoxidil are effective drugs and should be dosed properly. Due to reflex tachycardia, SNS activation, and fluid retention, direct vasodilators must only be prescribed in conjunction with a β-blocker and a diuretic. In other words, the usage of direct vasodilators is always in conjunction with sufficient dosage of a diuretic and a β-blocker. Both hydralazine and minoxidil are powerful vasodilators which have an important therapeutic role in the treatment of RH. And, one should not hesitate to apply these drugs (along with a diuretic and a β-blocker) to achieve BP targets in patients with CKD.

Summary

RH is common in CKD due to multiple factors—low GFR, sodium retention, inappropriate activity of RAAS and SNS. The cardiovascular and hemodynamic milieu in CKD is complex, governed by multiple hormonal and circulatory aberrations. Thus, RH in CKD is a highly complicated phenomenon with serious prognostic implications. Patients with CKD are at a risk of developing various cardiovascular complications. Hence, RH in CKD qualifies as a high-risk signal. Persistent hypertension in CKD causes inexorable progression of vascular disease leading to excessive mortality, morbidity, and permanent disability.

From a public health perspective, it is imperative to control hypertension aggressively in patients with CKD. Uncontrolled hypertension in CKD is a forerunner of dangerous cardiorenal sequelae. RH in CKD should be managed aggressively. To characterize the level of hypertension and to classify hypertension properly in patients with CKD, ABPM and home BP monitoring should be considered. These diagnostic tools define the hypertension load accurately in patients with CKD. Whenever possible, these modalities should be utilized in the evaluation and management of RH in patients with CKD.

While RH has serious implications, it is not clear to what extent cardiorenal complications can be substantially modified by successful BP control. A concerted effort should be made to advocate salt restriction, nonpharmacological therapy, and careful combination and titration of antihypertensive drugs. There is no evidence to recommend any one particular class of drugs over others to treat RH in patients with CKD. However, implementation of a low-salt diet and adequate use of a diuretic should be the foundation of sequential antihypertensive drugs. A wide variety of antihypertensive drugs are available to treat RH in CKD patients. The precise role of RDN therapy as a modality to control hypertension in CKD patients remains to be determined by ongoing clinical trials and global registries. Due to the high prevalence of RH in patients with CKD and the casual contribution of SNS, RDN therapy is of considerable interest and possible benefit [41].

RH, CKD, and CVD are intrinsically connected through a cascade of a pathophysiological interactions; aggressive control of BP is a rational avenue to interrupt this dangerous link. The principal target of antihypertensive therapy in RH is a BP goal of < 135/85 mmHg. If this target is achieved with a reduction in proteinuria, additional benefits may be conferred. Careful monitoring of BP, renal function, proteinuria, and serum potassium level should all be integrated to provide optimal care to patients with RH and CKD. Recent studies have suggested that excessive reduction of BP (diastolic BP (DBP) < 70 mmHg) in patients with CKD may be harmful [42]. Much research is needed to identify genetic and other markers which predispose to progression of hypertension, nephrosclerosis, and diabetic nephropathy in patients with CKD. Further understanding of mechanisms of RH [43] will likely yield effective strategies to halt the progression of CVD in patients with CKD.

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Chapter 4
Neurogenic Factors in Hypertension Associated With Chronic Kidney Disease

Vito M. Campese

Introduction

Hypertension is very prevalent among patients with chronic kidney disease (CKD) and it becomes more frequent as patients progress towards end-stage renal disease (ESRD). Approximately 85 % of patients with ESRD have hypertension, which is in large part responsible for the high incidence of cardiovascular events and deaths in these patients. Hypertension is also a major contributor to the progression of kidney disease.

The pathogenesis of hypertension in patients with kidney diseases is multifactorial and may vary depending on the underlying renal disease. Several factors have been implicated in the pathogenesis of hypertension in CKD. In this chapter, we focus on the evidence that activation of the sympathetic nervous system (SNS) may play a major role in the pathogenesis of hypertension, as well as cardiovascular disease and progression of kidney disease in this patient population.

Evidence for Neurogenic Factors in Hypertension Associated with Kidney Disease

The kidney is not only an elaborate filtering device but also a sensory organ, richly innervated with sensory and afferent nerves. There are two main functional types of renal sensory receptors and afferent nerves: *renal baroreceptors,* which are activated by changes in renal perfusion and intrarenal pressure; and *renal chemoreceptors,* which are stimulated by ischemic metabolites or toxins [1, 2]. In rats, these "chemoceptive" receptors are further classified into R1 and R2 based on their resting

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level of activity and the types of stimuli that elicit a response. The activation of these chemosensitive receptors may, through the renal afferent nerves, establish connections with integrative nuclei of the SNS in the central nervous system [3, 4]. In experimental animals, stimulation of these afferent nerves by either ischemic metabolites such as adenosine, or by urea, evokes reflex increases in efferent sympathetic nerve activity and increased blood pressure (BP) [5].

Our studies on 5/6 nephrectomized (5/6 Nx) rats have provided the most convincing evidence yet for a role of the SNS in the pathogenesis of hypertension associated with 5/6 Nx. The turnover rate [6] and the secretion of norepinephrine (NE) [7] from the posterior hypothalamic (PH) nuclei were greater in 5/6 Nx than in control rats. Bilateral dorsal rhizotomy at the level T-10 to L-3 prevented the increase in BP and the increase in NE turnover in the PH. Evidence also suggest that increased SNS activity may contribute to the progression of kidney disease in rats [8]. These studies led us to postulate that increased renal sensory impulses generating in the affected kidney and then transmitted to the central nervous system activate regions of the brain involved in the noradrenergic control of BP resulting in hypertension.

The notion that kidney injury may lead to activation of the SNS and to hypertension, independently from changes in glomerular filtration rate (GFR), is supported by our studies in the phenol-kidney injury model. In this model, hypertension is caused by injecting 50 μL of 10% phenol in the lower pole of one kidney. This leads to an immediate elevation of NE secretion from the PH nuclei and a rise in BP that persists at least for 6 weeks after the kidney injury [9]. Renal denervation prevents the rise in NE secretion from the PH nuclei and the rise in BP caused by phenol injection. Serum creatinine did not change after the intrarenal administration of phenol indicating that this model of hypertension does not cause any apparent change in kidney function. These studies have demonstrated that a specific injury to a limited portion of the kidney may cause a permanent elevation of BP in the rat. Hypertension in this model is mediated by neurogenic mechanisms.

The potential importance of this observation is substantial, since clinical experience indicates that not all renal injuries in humans are associated with hypertension. For example, in the absence of renal insufficiency, immunoglobulin A (IgA) nephropathy is more likely to be associated with hypertension than membranous glomerulonephritis or minimal change disease. In addition, it is plausible to expect that not all forms of hypertension associated with kidney disease are due to SNS activation. As a consequence, it is naïve to expect clinical benefits from renal denervation in all forms of hypertension associated with kidney disease.

Both direct and indirect evidence implicates increased SNS activity in the pathogenesis of hypertension in patients with CKD [10–13]. Plasma NE levels are usually increased in hemodialysis patients [14], but these levels, whether measured before or post dialysis, are poorly correlated with levels of BP [15, 16]. Direct recording of neuronal activity from postganglionic sympathetic fibers in the peroneal nerves of ESRD patients have shown a greater rate of sympathetic nerve discharge than in control subjects. Converse et al. [17] observed increased muscle SNS activity (MSNA) and peripheral vascular resistance in hypertensive patients with ESRD. By contrast, patients with bilateral nephrectomy manifested lower MSNA, BP, and

peripheral vascular resistance compared to patients with native kidneys. Ligtenberg et al. observed an increase in muscle SNS discharge in CKD, when compared with age- and weight-matched control [18]. Klein et al. [19] observed increased muscle sympathetic nerve activity in hypertensive patients with polycystic kidney disease regardless of kidney function. Activation of renal afferents appears also to be the primary mechanism for calcineurin inhibitors-induced hypertension in rats [20, 21].

Other mechanisms potentially responsible for the increase in sympathetic nerve activity in CKD patients include reduced central dopaminergic tone [22]. Hypertensive patients with CKD have a heightened DOPA and dopamine sulfoconjugating propensity, and dopamine sulfate attenuates the biologic action of free dopamine. The increase in sympathetic activity in CKD could also be due to reduced baroreceptors sensitivity [23], abnormal vagal function [24], increased intracellular calcium concentration [25], and increased plasma β-endorphin and β-lipotropin [26]. Increased neuropeptide Y in response to fluid overload may also participate to hypertension in ESRD [27].

Effects of Angiotensin II and Oxidative Stress on Central SNS Activation

Substantial evidence indicates that angiotensin II (Ang II) enhances sympathetic nerve (SNS) activity centrally and peripherally [28, 29]. Intracerebroventricular infusion of Ang II raises BP, renal sympathetic nervous system activity (RSNA), and NE secretion from the PH nuclei [30]. As a consequence, the anti-hypertensive effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) could be in part related to inhibition of the SNS. ACE inhibitors reduce peripheral sympathetic nerve activity in patients with chronic renal failure (18). Similarly, AT-1 receptor blockers reduce central SNS activity in a model of neurogenic hypertension caused by renal injury [31].

The effects of Ang II on BP are mediated in part by reactive oxygen species (ROS). Infusion of Ang II into rats is associated with increased vascular superoxide production. Ang II stimulates oxidative stress through nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate (NADH/NADPH)-oxidase activation, and chronic infusion of Ang II raises the concentration of oxidative markers [21]. Antioxidants, such as tempol and vitamin E, prevent Ang II-induced hypertension in rats.

Limited data are available concerning the effects of Ang II on oxidative stress in the brain and the role this might play in SNS-mediated regulation of cardiovascular function. Zimmerman et al. [32] observed that the effects of intracerebroventricular Ang II on BP and heart rate were abolished by pretreatment with adenoviral vector-mediated expression of superoxide dismutase (AdSOD) in mice. Zanzinger et al. [33] showed that removal of extracellular superoxide or reactive nitrogen species within the rostral ventrolateral medulla by microinjection of superoxide dismutase (SOD) reduced SNS activity. We have shown that SOD mimetics

administered intracerebroventricularly abrogate the effects of Ang II on BP and SNS activity, supporting the hypothesis that the effects of Ang II on central SNS activation are mediated by increased oxidative stress in brain regions involved in the noradrenergic control of BP [34].

Effects of Nitric Oxide on SNS Activity

Nitric oxide synthase (NOS) is present in a specific area of the brain involved in the neurogenic control of BP and the cardiovascular system, and it is an important component of transduction pathways that tonically inhibit SNS activity [35, 36].

Vaziri et al. [37] observed downregulation of endothelial and inducible NOS in 5/6 NPX rats, and suggested that this may contribute to BP elevation. Reduced availability of NO in the brain could result in increased SNS activity and in hypertension.

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide (NO) synthases that inhibits NO synthesis and may result in endothelial dysfunction, vasoconstriction, and elevation of BP [38]. ADMA blood levels are significantly elevated in CKD and ESRD patients suggesting that ADMA may contribute to hypertension [39, 40], increased SNS activity, atherosclerosis [41], and mortality [42] in these patients.

The Role of Renalase

Renalase is a flavin adenine dinucleotide-dependent amine oxidase highly expressed in the kidney and heart [43]. It metabolizes catecholamines and catecholamine-like substances via a superoxide ($O_2(-)$)-dependent mechanism using NADH as a cofactor [44]. Renalase infusion in rats caused a decrease in cardiac contractility, heart rate, and BP and prevented a compensatory increase in peripheral vascular tone. In humans, *renalase* gene expression is highest in the kidney but is also detectable in the heart, skeletal muscle, and the small intestine. The plasma concentration of renalase is markedly reduced in patients with ESRD as compared with healthy subjects. This raises the possibility that the reduced secretion of renalase in CKD may contribute to increased SNS activity and hypertension [45]. Schlaich et al. measured serum renalase levels in 22 patients with resistant hypertension and observed an inverse relationship between renalase levels and SBP [46].

Some studies have evaluated the relationship between polymorphisms in the renalase (RNLS) gene and BP levels by examining several single nucleotide polymorphisms (SNPs) of RNLS.[7] In more than 2000 individuals from the International Collaborative Study of Cardiovascular Disease in Asia (InterASIA in China), Zhao et al. [47] observed that two SNPs (rs2576178 A>G and rs2296545 C>G) were associated with essential hypertension.

In one Chinese population-based study, the G allele of the rs2576178 SNP was associated with hypertension among hemodialysis patients (odds ratio (OR), 1.76; P¼0.008) [48]. In a cohort of 590 Caucasian participants with stable coronary artery disease, the CC genotype (for the rs2296545 SNP) was associated with cardiovascular phenotypes such as cardiac hypertrophy, dysfunction, and ischemia but not with BP [49]. By contrast, the same polymorphisms were genotyped in 5696 participants of the population-based Cardiovascular Cohort of the "Malmö Diet and Cancer" (MDC-CC). Before and after adjustment for major cardiovascular risk factors, the hazard ratio for cardiac and cerebrovascular events was not significantly different in carriers of different genotypes [50].

Renal Denervation in CKD

In recent years, renal nerve ablation has been utilized with some success in the management of patients with resistant hypertension [51]. However, the frequency and extent of success is still disputed [52].

Given the strong scientific evidence for increased SNS activity particularly in patients with CKD, renal denervation is expected to be useful in this group of patients. However, the evidence so far is quite limited. In one study, the researchers performed renal denervation using radiofrequency waves on 15 patients with resistant hypertension and stage III or IV CKD [53].

The average BP of the patients at the start of the study was 174 ± 22/91 ± 16 mmHg, despite the use of 5.6 ± 1.3 antihypertensive drugs. After the procedure, the average change in office systolic and diastolic BP at 1, 3, 6, and 12 months was −34/−14, −25/−11, −32/−15, and −33/−19 mmHg, respectively.

The average nighttime systolic BP had decreased, after 3 months, from 154 ± 16 to 140 ± 22 mmHg ($P = 0.03$) and was 144 ± 22 mmHg after 6 months. After the procedure, nighttime diastolic BP declined at 3 months (78 ± 11 vs. 70 ± 8 mmHg) and 6 months (78 ± 11 vs. 75 ± 14 mmHg; $P = 0.02$; Fig. 4.1).

Some concerns of this methodology specifically for CKD patients have to considered. First, in patients with low GFR renal blood flow can be particularly reduced. Since cooling of the catheter tip depends decisively on the blood flow, thermal problems might occur increasing the potential for damage of the renal blood vessels. Second, the procedure requires substantial amounts of contrast media raising the risk of acute kidney injury in these patients. Of interest, Hering et al. observed no deterioration in renal function over the course of the study in CKD patients.

The Simplicity Study III, a randomized controlled study, failed to demonstrate a beneficial effect of renal denervation on BP in a large group of patients with resistant hypertension [54]. Given these unimpressive results, the role of renal denervation in the management of resistant hypertension, particularly in CKD patients, remains to be established. Several issues need to be resolved: first, how to identify patients with increased renal sympathetic nerve activity, who may be more suitable for renal denervation; second, to what extent and with what variability renal

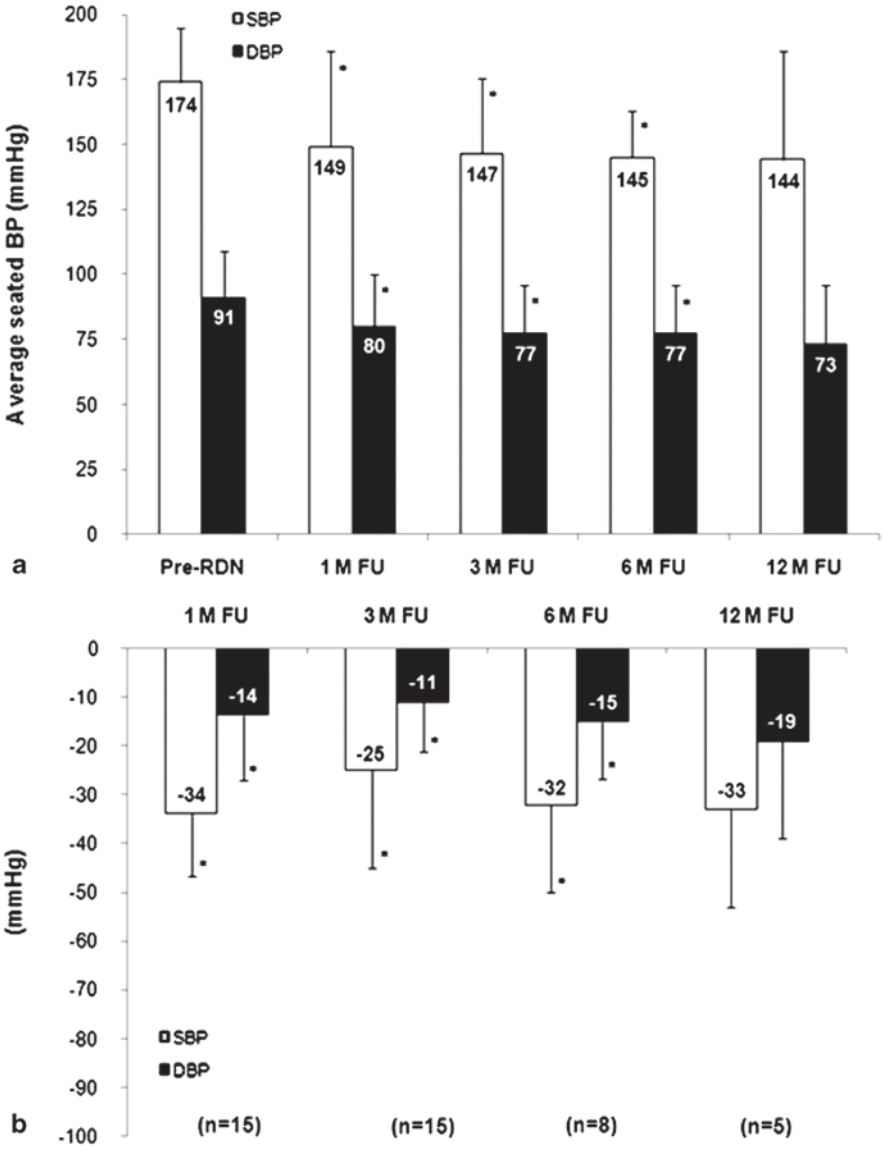

Fig. 4.1 Office BP values at follow-up. Changes in average office BP (**a**) and mean decrease in office BP (**b**) at follow-up. *Error bars* represent SDs. *$P<0.001$ versus baseline (before the procedure). *FU* follow-up, *M* month, *pre-RDN* prerenal denervation. (Reprinted from [53]. With permission from the American Society of Nephrology)

denervation is achieved with the Simplicity catheter by various investigators; third, the issue of regeneration of renal nerves after denervation remains unresolved. Until all these issues are satisfactorily resolved, renal denervation should remain an experimental tool in the management of hypertension associated with kidney disease.

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Chapter 5
Novel Molecules

Valeria Lourdes Vukelic and Marcelo Orias

Abbreviations

C21	Compound 21
cGMP	Cyclic guanosine 3′,5′-monophosphate
COX	Cyclooxygenase
CYP	Cytochrome P-450
ET-1	Endothelin 1
ET-2	Endothelin 2
ET-3	Endothelin 3
ETA	Endothelin receptor type A
ETB	Endothelin receptor type B
ETEs	Epoxyeicosatrienoic acids
ETRA	Endothelin receptor antagonist
FDA	Food and Drug Administration
HETEs	Hydroxyeicosatetraenoic acids
KO	Knockout
LOX	Lipoxygenase
LTs	Leucotrienes
LXs	Lipoxins
MR	Mineralocorticoid receptors
NEP	Neutral endopeptidase
NO	Nitric oxide
sEH	Soluble epoxide hydrolase
sGC	Soluble guanylyl cyclase

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Table 5.1 Novel antihypertensive treatments

Blood pressure mechanism	Antihypertensive agent
Sympathetic system	Human recombinant renalase
Renin–angiotensin–aldosterone system	Renin inhibitors
	Anti-angiotensin vaccine
	Angiotensin II type 2 receptor agonist
	Aldosterone synthase inhibitor
Natriuretic peptide system	Vasopeptidase inhibitors
Other hormones and autacoids	Stimulators and activators of soluble guanylate cyclase
	Soluble epoxide hydrolase inhibitors
	Endothelin antagonists

Novel Drugs for Hypertension

Effective drugs for hypertension treatment have been available for many years and interventions at several levels in the complex mechanisms regulating arterial blood pressure (BP) have been successful with an acceptable adverse event profile. Target values of BP are difficult to achieve and many patients remain uncontrolled [1] and at high risk of end-organ damage. In the chronic kidney disease (CKD) population, this is especially true and remarkable because it is well known that BP reduction not only will reduce cardiovascular risk but also will improve proteinuria, delaying progression to end-stage renal disease. Newer treatments and novel approaches are constantly under investigation with the intention of enhancing BP control and reducing cardiovascular and renal risk. These novel drugs are being considered as monotherapy or combinations to standard treatment. Here, we will outline selected drugs classified by the BP regulation system they interfere (Table 5.1).

Sympathetic System

Renalase

Renalase is a flavin adenine dinucleotide-dependent amino oxidase secreted almost entirely by the kidney. It metabolizes circulating catecholamines [2], and epinephrine is the principal substrate. The hypotensive effect of the protein has been proved in vitro and in vivo [3]. The inactive enzyme appears to circulate in blood and can be activated by circulating catecholamines or increased BP. Renalase knockout (KO) mice display elevated plasma and urinary catecholamines levels, hypertension, tachycardia, ventricular hypertrophy and inadequate cardiac and renal ischemia tolerance [4]. Animal models have shown that renalase levels increase significantly after renal denervation and this higher plasma level may mediate in part the procedure's BP lowering effect [5]. Recombinant human renalase

(hRenalase1) administered subcutaneously had a systolic and diastolic hypotensive effect, and attenuated hypertension-related cardiac damage in 5/6 nephrectomized rat [6, 7]. Administration of hRenalase1 in KO animals also improved ischemic and toxic renal injury [2]. These findings suggest that renalase represents a novel option for hypertension treatment, but human studies are needed.

Renin–Angiotensin–Aldosterone System

Renin Inhibitors

Aliskiren is the first oral direct renin inhibitor available that has been commercialized in the past years. It is an effective antihypertensive drug with an adverse effect profile similar to angiotensin receptor blockers (ARBs). Since effective drug therapy with angiotensin converting enzyme inhibitors and ARBs is standard of care in many hypertensive and cardiovascular diseases, aliskiren was evaluated as add on therapy.

In the ALTITUDE trial, aliskiren and losartan were tested against losartan alone in diabetic type 2 patients with cardiovascular and renal risk. The trial found no benefit and more hiperkalemic and hypotensive events in the aliskiren group. This chapter concluded that the addition of aliskiren to standard therapy with renin–angiotensin system blockade in type 2 diabetes patients who are at high risk for cardiovascular and renal events is not supported by these data and may even be harmful. Since then, the Food and Drug Administration (FDA) has issued a warning that aliskiren should not be used in this clinical situation.

Many physicians use this drug in resistant hypertensive patients.

Anti-angiotensin Vaccines

Renin–angiotensin system vaccines have been investigated in the past and are still under development. Renin was the first target but the product was associated with autoimmune kidney disease development. An anti-angiotensin I vaccine effectively reduced BP in animal models, but failed to prove efficacy in clinical trials. Anti-angiotensin II and anti-ATR1 vaccines are a matter of interest and current studies. Cyt-006-AngQb reduced BP in animal models and hypertensive patients [8]. Ang II-KLH-immunized mice decreased BP values and cardiac hypertrophy [9]. Anti-ATR 1 ATRQβ-001 reduced BP in Ang II-induced hypertensive mice and spontaneously hypertensive rats without evidence of immune-mediated organ damage [10]. Vaccines seem to be a feasible line of treatment for hypertension with longer dosing intervals than traditional therapies, although more clinical trials are needed and safety profile must be verified.

Angiotensin II Type 2 Receptor Agonist

In humans, angiotensin II has two G protein-coupled receptors: type 1 (AT 1R) and type 2 (AT 2R). Through AT 1R, angiotensin II mediates vasoconstriction, tubular Na reabsorption, modulation of glomerular filtration rate, aldosterone release, collagen synthesis and pro-fibrotic and inflammatory effects [1]. AT 2R mediates opposite actions that lead to vasodilation, anti-proliferation and anti-inflammation via the nitric oxide (NO)/cyclic guanosine 3′,5′-monophosphate (cGMP) pathway, and also phosphatase and phospholipase A2 activation [11]. In pathological states, the expression of AT2R is upregulated in certain tissues, especially during tissular hipoxia [12]. Therefore, pharmacological stimulation of AT2R is an encouraging option for hypertension treatment. Compound 21 (C21) is the first selective non-peptide AT 2R agonist. Animal studies have not shown BP reduction, however, it did reduce arterial stiffness, media collagen deposition, oxidative stress, fibrotic processes, hypertrophic effects on the heart and renal cortex inflammatory cell infiltration [13]. In addition, C21 produced vasodilation, and natriuretic effects, improving renal function [14]. When combined with low-dose ARB, C21 enhanced the antihypertensive effect of the former [13], while this did not occur with higher ARB doses. C21 did not show significant BP reduction as monotherapy but its potential multiple beneficial effects may promote new strategies and combinations in hypertension treatment [11].

Aldosterone Synthase Inhibitors

Aldosterone mediates its effects via mineralocorticoid receptors (MR), but also in an MR-independent fashion. Therefore, in order to act on both mechanisms, aldosterone synthase inhibition has emerged as a new therapeutic target. Early in the 1990s, the nonsteroidal aromatase inhibitor fadrozole showed the potential to induce aldosterone secretion impairment without affecting the glucocorticoid response [15]. Fadrozole's enantiomer FAD286A in animal models decreased plasma and urine aldosterone concentrations, preventing cardiac hypertrophy and fibrosis, albuminuria, renal failure and death [16]. Based on FAD286A, the first orally active aldosterone synthase inhibitor was synthesized, LCI699. In a phase II study, LCI699 was compared with eplerenone and placebo for 8 weeks in subjects with stage 1–2 essential hypertension [17]. Primary end point was reduction in diastolic BP, which was significantly lower, compared with placebo, for LCI699 1 mg once daily and eplerenone 50 mg twice daily in similar magnitude. All doses of LCI699 decreased clinic systolic BP and 24-h ambulatory BP significantly. Patients did not develop signs of hypocortisolism although ≈20% of subjects had suppression of adrenocorticotropic hormone (ACTH)-induced cortisol release. Not serious, hyperkalemia or renal function impairment was reported in LCI699 or eplerenone groups [17]. LCI699 was tested in primary aldosteronism in a single-centre, single-blind, placebo-controlled, sequential, force-titration study [18]. A reduction in plasma

and urinary aldosterone concentration was observed as correction of hypokalemia within the first week of treatment, accompanied by limited effects on BP and sodium-positive balance [18]. Despite clinical benefits on BP control, reduction of circulating aldosterone, enhance sodium excretion, glucocorticoid axis inhibition will limit LCI699 use [19]. More selective compounds could provide advantages; however, complete blockage of aldosterone synthesis could entail potential serious adverse consequences [19].

Natriuretic Peptide System

Vasopeptidase Inhibitors

Vasopeptidase inhibitors are soon to be an upcoming approach to hypertension treatment. Neutral endopeptidase (NEP) catalyzes both vasoconstrictor and vasodilator products. The beneficial effect of NEP inhibition is mediated by increased natriuretic peptide concentration [20], but inhibition of this enzyme alone did not improve clinically relevant outcomes [21]. However, benefits of NEP blockage may become evident when vasoconstrictors such as angiotensin II are reduced by concomitant use of angiotensin-converting enzyme (ACE) inhibitors or ARBs [21, 22]. The dual ACE/NEP inhibition has been associated with increased risk of angioedema [23]. LCZ696 is a combination of an angiotensin II receptor blocker (valsartan) and a neprilysin inhibitor (AHU377). Patients treated with LCZ696 had significant dose-dependent reductions in BP compared with valsartan and AHU377 monotherapy. LCZ696 improved pulse pressure and was safe and well tolerated [21].

Hormones and Autacoids

Stimulators and Activators of Soluble Guanylate Cyclase

NO-induced vasorelaxation is mediated by activation of soluble guanylyl cyclase (sGC) that increases cGMP formation and ultimately a decrease in intracellular calcium and vasodilation. In conditions associated with incremented oxidative stress, NO generation, diminished biological availability can lead to NO donor tolerance with prolonged use [24]. Two classes of compounds that activate sGC by NO-independent pathways are under investigation: sGC stimulators and sGC activators. The sGC stimulator BAY 63-2561 (Riociguat) was tested in a population with mild to moderate pulmonary hypertension and improved pulmonary hemodynamics to a greater extent than inhaled NO. Riociguat significantly reduced systolic BP and systemic vascular resistance [25]. Activators of sGC can increase sGC enzyme activity even when it is oxidized and less responsive to NO [24]. BAY 58-2667 (Cinaciguat)

has been administered to patients with acute decompensated heart failure and proved to lower right atrial pressure, pulmonary and systemic vascular resistance reducing preload and afterload [26].

Both sGC stimulators and sGC activators may represent therapeutic options for pulmonary hypertension, states of chronic endothelial dysfunction such as hypertension and atherosclerosis and in patients with acute heart failure [24].

Soluble Epoxide Hydrolase Inhibitors

Arachidonic acid is metabolized by three principal enzymatic pathways: cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P-450 (CYP) (Fig. 5.1). Prostaglandins are produced by COX; hydroxyeicosatetraenoic acids (HETEs), lipoxins and leucotrienes by LOX; HETEs are also generated by CYP hydroxylase and epoxyeicosatrienoic acids (ETEs) are originated from CYP epoxygenase [26]. ETEs mediate vasodilation in many vascular beds including coronary, cerebral, kidney, intestine and skeletal muscle by activating large-conductance calcium-activated potassium channels in vascular smooth muscle cells [26]. They also have anti-inflammatory, anti-aggregation and angiogenic properties.

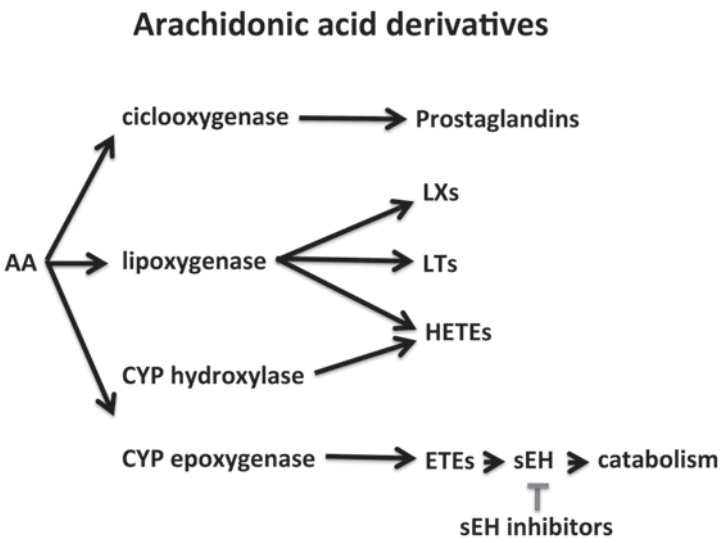

Fig. 5.1 Arachidonic acid derivatives and new potential antihypertensive mechanisms. On the *bottom*, soluble epoxide hydroxylase inhibitors reduce epoxyeicosatrienoic acids degradation and enhance vasodilation in different vascular beds. *AA* arachidonic acid, *COX* cyclooxygenase, *LOX* lipoxygenase, *CYP* cytochrome P-450, *HETEs* hydroxyeicosatetraenoic acids, *LXs* lipoxins, *LTs* leucotrienes, *ETEs* epoxyeicosatrienoic acids

Soluble epoxide hydrolase (sEH) is responsible for ETE catabolism. Inhibition of ETE catabolism increases ETEs levels and enhances their beneficial effects. sEH inhibitors include ureas and amides, among others [27].

In hypertensive animal models, sEH inhibition results in BP reduction, mainly in angiotensin hypertensive mechanisms. Renal vascular and glomerular injury, renal macrophage infiltration and collagen deposition, cerebral ischemia, cardiac hypertrophy, vascular remodelling and atherosclerosis were reduced consistently in these studies [26, 27]. Renal protection seems to be both dependent and independent of the antihypertensive mechanism [28].

In human studies, sEH inhibitor AR9281 did not decrease BP in patients with mild to moderate hypertension [27], but clinical indications of sEH inhibitors may include hypertension-related end-organ damage prevention, metabolic disease treatment, chronic inflammatory therapy and vascular remodelling prevention. Tumour proliferation due to angiogenic properties, pulmonary vasculature vasoconstriction and blood clotting alterations may be unwanted considerable adverse effects [28].

Endothelin Antagonists

Endothelin is a product of endothelial cells with vasoconstrictor effects. Three isoforms are recognized in humans: endothelin 1 (ET-1), endothelin 2 (ET-2) and endothelin 3 (ET-3), but ET-1 is of major interest in the hypertension field. ET-1 secretion is stimulated by angiotensin II and many other agonists and factors including hypoxia [29] and mediates vasoconstriction, inflammation and vascular remodelling. ET-1 has two receptors: type A (ETA) which is prevalent in vascular smooth muscle cells and type B (ETB) mostly in endothelial cells. Darusentan, an endothelin receptor antagonist (ETRA), is approved for pulmonary hypertension treatment [30]. This drug has been utilized to treat resistant hypertension patients in DORADO [31] and DORADO-AC [32] clinical trials. Although BP reductions were achieved darusentan, BP reduction was also observed in the placebo arm in DORADO-AC patients. Sitaxsentan, an ETA antagonist, reduced BP and proteinuria in CKD but glomerular filtration rate diminished by 9 ml/min after 6 weeks of treatment [33]. ETRA's main adverse events include fluid retention and peripheral oedema.

Summary

The next decade or two are filled with exciting therapeutic promises that hopefully will be fulfilled. As we advance knowledge in genetics and pathophysiology of hypertension, novel insights and molecules will be tested in the quest of lowering BP and protecting vital organs. In this diverse array of mechanisms that can influence BP, several appear to be essential and drugs blocking or inhibiting them will be pivotal in the near future.

Stimulators and activators of soluble guanylate cyclase and aldosterone synthase inhibitors have the best potential in the hypertension field. Renin inhibitors, vasopeptidase inhibitors and endothelin antagonists will need newer compounds that surpass and improve results obtained by the original drugs.

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Chapter 6
Dual Inhibitors: RAAS Blockers/Combination Therapies: What Do All These Trials Mean?

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Introduction

Inhibition of the renin-angiotensin system (RAS) by administration of either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) or a direct renin inhibitor (DRI) similarly reduces blood pressure (BP), when each is used as monotherapy in patients with hypertension [1, 2]. Both ACE inhibitors and ARBs also slow down the progressive decline in renal function, which marks renal injury, particularly in patients with diabetic nephropathy [3–5] with the renoprotective effects of these drugs, in part, relating to their capacity to reduce protein excretion [6]. Both ACE inhibitor and ARB therapy also decrease the high cardiovascular (CV) event rate common to high-risk cardiac patients [7–10]. Moreover, ACE inhibitors and ARBs are both of proven benefit in forms of heart failure (HF) characterized by a reduced ejection fraction (EF) [11, 12].

Experimental Basis for Combining an Angiotensin-Converting Enzyme Inhibitor and an Angiotensin-Receptor Blocker or a Direct Renin Inhibitor and/or an Aldosterone Receptor Antagonist

The pharmacologic actions of ACE inhibitors and ARBs and/or a DRI have been well characterized. BP reduction and/or tissue-based protection, achieved through interruption of the RAS, relates specifically to the distinctive pharmacodynamic properties of either an ACE inhibitor, a DRI, or an ARB [13, 14]. Factors that have some bearing on the final response to these drug classes include drug pharmacokinetic

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and pharmacodynamic half-life, the phenomenon of "angiotensin-II", or "aldosterone escape" and/or interruption of the short feedback loop, which increases upstream components of the RAS—so-called reactive hyperreninemia [14, 15].

At the outset of therapy with an ACE inhibitor, both circulating and tissue concentrations of angiotensin-II (ang-II) drop. This fall in ang-II concentrations is to be expected given that ACE inhibition per se dose dependently lessens the enzymatic conversion of angiotensin-I (ang-I) to ang-II. Alternatively, with more long-term ACE inhibitor use, there is a gradual return of circulating and tissue ang-II concentrations to pretreatment levels, a process termed "angiotensin-II escape" [16]. One suggested explanation for ang-II escape focuses on the ability of tissue-based enzymes, such as chymase, cathepsin G, and CAGE (chymostatin-sensitive angiotensin-generating enzyme), to alternatively generate ang-II from a number of peptide substrates [17].

Since an ARB works by blocking the AT_1-receptor, it was initially presumed that this mechanism of action, in addition to possibly AT_2-receptor stimulation, would be additive to an ACE inhibitor effect by lessening the opposing BP effects that could in theory result from "angiotensin II escape." The relevance of ang-II escape however remains unclear. In the treatment of hypertension and HF, there is scant evidence to support a role for ang-II escape in disabling the response to an ACE inhibitor [18]. If ang-II escape with ACE inhibitor use is ever to be clinically relevant, it will be on the basis of "suboptimal tissue protection," a process that is not readily quantified. DRIs were originally held to offer incremental benefit for BP reduction in addition to what might be seen with an ACE inhibitor or an ARB, as they provide a more complete blockade of the RAS. It was posited that a DRI would suppress residual ang-II production and the counter-regulatory increase in plasma renin activity (PRA) observed in patients receiving ACE inhibitor and ARB monotherapy, and/or by blocking "aldosterone escape" that is seen with an ACE inhibitor or an ARB [19].

ARAs can further reduce BP when given together with an ACE inhibitor, ARB, or a DRI. Fundamentally, nullifying the effect of aldosterone effect on BP with an ARA would be expected to further reduce BP beyond what would be seen with any of these classes given alone or together. Such BP reduction relates to an ARA effect on aldosterone/volume, which would not be mechanistically redundant as is the case when an ACE inhibitor is added to an ARB or a DRI [20–22].

Interpretive Considerations in Combining Angiotensin-Converting Enzyme Inhibitors and Angiotensin-Receptor Blockers and/or a Direct Renin Inhibitor or an Aldosterone Receptor Antagonist

The basis for combining an ACE inhibitor with an ARB or a DRI is to achieve a therapeutic outcome better than that seen with either drug given as monotherapy. Giving two RAS inhibitors together is not merely "giving two drugs" in that there

are various pharmacologic considerations that influence the interpretation of the observed response. To accurately interpret the response to the combination of an ACE inhibitor and an ARB and/or a DRI requires that consideration be given to the pharmacologic profile of individual class members, time-of-day of dosing of each compound, the sequence with which the ARB or ACE inhibitor is added, and continuing dual therapy for a long-enough period of time to ensure that a long-term response has been identified [23].

There are more than 20 ACE inhibitors and ARBs, and one DRI marketed worldwide. There was one fixed dose combination of a DRI/ARB (aliskiren/valsartan [Valturna®]); however, it is off the market since 2012. Drugs within each of these classes have divergent durations of action; thus, the combination of the short-acting ACE inhibitor, captopril, with the long-acting ARB, candesartan, can produce a greater end-of-day response than if captopril were to be given with the more short-acting ARB, losartan. This can be mistakenly viewed as an additive response when it may simply reflect a more extended effect from the longer half-life compound. This is particularly the case with the long-acting compound, aliskiren [24]. When an ACE inhibitor and ARB are both long acting, meaningful additivity in BP reduction does not occur [25]. The timing of drug administration should also be accounted for in assessing a response to combination therapy in that, giving an ACE inhibitor and an ARB separated by several hours may conceivably prove more effective than if both medications were given simultaneously. Finally, the sequence in which these medications are given, such as whether an ACE inhibitor or an ARB is first given and when the alternative drug is added, may influence the final BP reduction and/or an end-organ effect such as a drop in urinary protein excretion [26].

Clinical Trial Considerations of Dual Renin-Angiotensin System Blockade

The concept of dual blockade of the RAS being inherently better than a single agent-modifying activity in this class seemed quite logical with the early experimental evidence from Menard et al. and therein rapidly emerged as a therapeutically attractive option [27]. Much of the early enthusiasm for dual blockade of the RAS system, however, derived from beneficial changes in surrogate end points such as BP, proteinuria, and/or endothelial dysfunction; however, a not insignificant amount of this unbridled excitement about combined RAS inhibition proved to be unjustified as the results from various trials became available with studies such as the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET), the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE), and the Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) [28–30].

Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial

ONTARGET was a double-blind, randomized, parallel-group study involving 25,620 patients in 40 countries. Patients were 55 years of age or older with either a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes with end-organ damage. Subjects were randomized to telmisartan 80 mg/day, ramipril 10 mg/day, or telmisartan 80 mg/day plus ramipril 10 mg/day. The primary end points were CV mortality, nonfatal stroke, acute myocardial infarction (MI), and HF hospitalization. The secondary end points were newly diagnosed HF, diabetes mellitus, or atrial fibrillation; revascularization procedures, development of dementia/cognitive decline, and nephropathy. Study results showed that mean BP was lower in the telmisartan (0.9/0.6 mmHg greater reduction) and the combination therapy groups (2.4/1.4 mmHg greater reduction) than in the ramipril group. At study's end, the primary end point had occurred in a similar number of patients in all three patient groups. Patients receiving combination treatment had higher rates of hypotensive symptoms, syncope, renal dysfunction, and hyperkalemia, with a trend toward an increased risk of progressing to a need for dialysis. At its conclusion, ONTARGET provided the largest evidence base available to determine, if the combination of an ACE inhibitor/ARB could reduce CV disease-related events and mortality in high-risk patients, including those with diabetes [28].

Assessment

The ONTARGET results strongly suggested that combination therapy with the ACE inhibitor, ramipril, and the ARB, telmisartan, was not to be recommended in high-risk patients with vascular disease or diabetes in the absence of HF. Shortly after the publication of the ONTARGET trial results, Messerli published in early 2009 a viewpoint advising physicians to avoid using dual RAS blockade because of the greater risk of side-effects [31]. Also, in early 2009 about the same time, the Canadian Hypertension Education Program urged physicians to no longer use these two drug classes together and the Canadian Heart and Stroke Foundation offered a similar guideline for patients with hypertension [32]. The bar for subsequent event trials with dual RAS inhibitor therapy would already appear to have been set high in early 2009 based on the academic perception of the ONTARGET results.

Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints

In the ALTITUDE study, the utility of the renin inhibitor, aliskiren, was tested in 8561 high-risk type 2 diabetic patients, the majority of whom had albuminuria, who were adjunctively given aliskiren 300 mg/day or placebo in addition to treatment

with an ACE inhibitor or an ARB. A composite CV and renal end point was selected. The trial was discontinued prematurely after 18.3% of the aliskiren group had reached the primary end point compared to 17.1% in the placebo group. About 41% of patients had a baseline systolic BP>140 mmHg, and 12% had a diastolic BP>85 mmHg. Oddly, BP actually increased about 3 mmHg in both groups, although this increase was less in the group given aliskiren. Glomerular filtration rate (GFR) decreased 5 ml/min over the 42 months of observation in both groups. Potassium increased in both groups but more so in the aliskiren group. Hyperkalemia (>5.5 mmol/l) was both the most common adverse event reported by investigators and the lead cause of study drug discontinuation. The Data and Safety Monitoring Board terminated this study early citing issues of therapeutic futility as well as an increased incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension over the 18–24 months of follow-up [29].

Assessment

The investigators in ALTITUDE quite appropriately underscored the need to go beyond surrogate biomarkers and obtained risk-benefit data from a clinical end point trial to better inform clinical decisions with aliskiren use in combination. There were several study design issues in ALTITUDE including most importantly the fact that patients in this study did not have any dose reduction or drug withdrawal when aliskiren was added making low BP occurrence more likely (median systolic BP at baseline was 135 mmHg systolic). At the completion of the ALTITUDE, the physician community awaited results from VA NEPHRON-D to make a final decision on the therapeutic positioning of dual RAS inhibitor therapy. Physician opinion was such that the premature termination of the ALTITUDE trial did not bode well for NEPHRON-D [29, 30].

Veterans Affairs Nephropathy in Diabetes

The VA NEPHRON-D trial studied the effect on CKD progression of 100 mg of the ARB losartan with or without the ACE inhibitor lisinopril (10–40 mg/day) in 1448 mainly male veteran patients with type 2 diabetes and overt nephropathy (GFR 54 mL/min). The primary end point was a composite of a 50% decline in eGFR, end-stage renal disease (ESRD) requiring dialysis, or death. Safety end points included mortality, hyperkalemia (serum potassium>6.0 mmol/L or that required an Emergency Department visit, hospitalization, or dialysis), and acute kidney injury adverse events, which were episodes occurring during or requiring hospitalization. BP values were similar in the two groups at enrollment, during adjustment of the losartan dose, and at randomization. The combination group had slightly lower BP readings on treatment by 2 mmHg. A total of 152 primary end point events occurred in the monotherapy group and 132 in the combination therapy group, a nonsignificant difference (hazard ratio (HR) with combination therapy, 0.88; 95% confidence

interval [CI], 0.70–1.12; $P=0.30$). A trend toward a benefit from combination therapy with respect to the secondary end point (HR, 0.78; 95% CI, 0.58–1.05; $P=0.10$) decreased with time ($P=0.02$ for nonproportionality). There was no benefit with respect to mortality (HR for death, 1.04; 95% CI, 0.73–1.49; $P=0.75$) or CVR events. Total mortality or CV end points were not different between treatments. This study was prematurely terminated for safety concerns. Combination therapy increased the risk of hyperkalemia (6.3 events per 100 person-years, vs. 2.6 events per 100 person-years with monotherapy; $P<0.001$) and acute kidney injury (12.2 vs. 6.7 events per 100 person-years, $P<0.001$) [30].

Assessment

Similar to the ALTITUDE study, this was an outcome trial with combination RAS therapy that was prematurely terminated based on safety consideration with modest, if any, outcome benefits. As in ONTARGET and ALTITUDE, combination therapy reduced albuminuria, and despite the favorable change in this surrogate marker of renal function, it did not result in a reduction in risk. This should be the last study undertaken with combination RAS inhibitor therapy.

Additional Considerations in Cardiorenal Disease with Combination RAS Inhibitor Therapy

There have been several areas where dual RAS inhibition has been considered as a suitable treatment option including difficult to manage hypertension, use in patients with high risk of vascular disease, post-MI, reduced EF forms of HF, and proteinuric forms of CKD. The use of dual RAS inhibitor therapy for resistant hypertension has not been studied in any sort of systematic manner and, as such, when used in this manner it has been empiric making it difficult to interpret observed responses [33]. There are currently no guidelines/treatment algorithms that support the use of dual RAS inhibitor therapy in the patient with resistant hypertension. Of note, as an example of the limited amount of information on this topic, patients with BP>160/100 mmHg at entry were excluded from ONTARGET, thus limiting the applicability of these results to the treatment of significant hypertension [28].

Ramipril and telmisartan given together in ONTARGET did not afford a mortality or CVR benefit over and above ramipril therapy and, as such, did not provide any supporting data for the use of dual RAS inhibition in patients at high risk for vascular disease [28]. In addition, in the Valsartan in Acute Myocardial Infarction (VALIANT) trial, the combination of captopril and valsartan, together and individually given, was studied in a cohort within 10 days of acute MI. No additional survival benefits were seen with combination therapy, and the dual therapy group clearly experienced the greatest number of side effects [34].

The benefit of dual RAS inhibition, however, still remains a topic of some considerable interest in two areas, reduced EF forms of HF and proteinuric forms of CKD. In the USA, the ARBs, candesartan and valsartan, have a labeled indication for add-on use to ACE inhibitor therapy in patients with reduced EF forms of HF [35, 36]. Early HF treatment guidelines had recommended "addition of an ARB in patients with HF and a left ventricular ejection fraction ≤ 40 %, who remained symptomatic despite optimal treatment with an ACE and a beta-blocker" [37]. More recently, this recommendation has been revised restricting ARB add-on use to patients who are unable to tolerate an ARA [38]. A meta-analysis addressing this issue of the best next drug to add to standard HF therapy found the risk benefit ratio to favor the addition of an ARA over an ARB or a DRI, albeit with an appreciation for a greater risk of developing hyperkalemia [39].

A number of studies have found that there is an incremental benefit for reduction in proteinuria, regression to normoalbuminuria, reducing BP, and increasing the rate of reaching BP goals with combination RAS inhibition [40]. Not surprisingly, these same studies have shown more short-term declines in BP, a greater frequency of hyperkalemia, and more frequent occurrences of hypotension. The NEPHRON-D study, which evaluated combination ACE inhibitor/ARB therapy in proteinuric patients with diabetic nephropathy, was prematurely terminated based on these same specific safety concerns [30]. The results from NEPHRON-D make combination RAS inhibitor therapy an ill-advised treatment option in the patient with proteinuric diabetic nephropathy. Of note, ARAs reduce proteinuria and BP in adults who have mild-to-moderate CKD treated with an ACE inhibitor or ARB (or both), but increase the risk of developing hyperkalemia [41, 42]. Whether adding an ARA to an ACE inhibitor and/or an ARB reduces the risk of major CV events or ESRD in this population is unknown [41].

Current Status of Combination RAS Inhibitor Therapy in Stroke

Dual RAS blockade, at least on the initial cut of the data from the ALTITUDE trial, was associated with a higher rate of stroke. The rate of stroke, which was mostly ischemic stroke, was numerically higher with aliskiren, although the overall difference did not reach statistical significance (3.4 vs. 2.8 %; HR, 1.25; 95 % CI, 0.98–1.60; $P = 0.07$) [29]. It has been conjectured that this increase in stroke rate might be due to sensitization of the Bezold–Jarisch reflex with ensuing withdrawal of sympathetic tone, prolonged bradycardia and hypotension, and/or merely a chance finding [43]. A recent meta-analysis examining the risk of stroke with dual RAS blockade versus individual renin-angiotensin-aldosterone system (RAAS) monotherapy did not identify a signal for increased risk [44]. These findings together with the failure to prevent strokes despite lower BP with combination RAS blockade argue against any sort of routine use of these combination therapies in the primary or secondary prevention of stroke.

Side Effects with Combined RAAS Inhibitor Therapy

Hypotension is not a specific side effect with dual RAS inhibition; rather, it is a broadening of the physiologic action of these drugs that occurs most commonly when a patient becomes volume contracted. Dual RAS inhibitor therapy-related hypotension can present as a first-dose phenomenon or anytime in the course of chronic therapy, and in the latter instance being prompted by intercurrent illnesses that lead to volume contraction and/or a lessening of sodium intake [45, 46]. If dual RAS inhibition is sufficiently prolonged, a meaningful drop in the GFR will often occur, which reflects a form of functional renal insufficiency. Predisposing conditions to this process include dehydration, HF, nonsteroidal anti-inflammatory drug use, and/or either micro- or microvascular renal disease all of which would not have been thought of as being uncommon occurrences in the target populations enrolled in any of the dual RAS inhibitor trials.

Hyperkalemia is an additional dual RAS inhibitor-associated side effect that has a strong physiologic basis and like all forms of hyperkalemia is highly definitional in nature [45]. Once a specific definitional threshold value has been reached during dual RAS inhibitor therapy, a specific criterion will be satisfied and the patient then counts as an affected case. It is axiomatic in the use of dual RAS inhibitor therapy to always anticipate an increase in serum potassium values, and the frequency with which hyperkalemia is detected will in part be protocol driven according to the frequency of sampling. Study populations consisted of those with diabetes, older age, CKD, and/or HF are inherently at a greater risk for the development of hyperkalemia. As such, subjects in the NEPHRON-D population who were diabetics with nephropathy and a reduced GFR would ostensibly have a greater risk for hyperkalemia development in comparison to a less at risk population studied in ONTARGET [28, 30, 47].

A recent meta-analysis by Makani et al. found that dual RAAS inhibitor therapy compared with RAAS monotherapy was associated with a 55% increase in the risk of hyperkalemia ($P<0.001$), a 66% increase in the risk for hypotension ($P<0.001$), and a 41% increase in the risk for renal failure ($P=0.01$), as well as a 27% increase in the risk of withdrawal due to an adverse event ($P<0.001$) [48]. This constellation of findings would strongly suggest that the risk to benefit ratio for such therapy is too high for any sort of routine use of dual RAAS inhibition therapy.

Regulatory Bodies and Combined RAAS Inhibitor Therapy

The European Medicines Agency (EMA) recently warned that no two drug classes that act separately on the RAAS should be used in combination and this was viewed as particularly the case in patients with diabetic nephropathy. The EMA further advised if such combination therapy use is viewed as a critical treatment option,

including the use of candesartan or valsartan, with ACE inhibitor therapy in patients with HF, then a proper specialist should supervise the use. Comments from EMA further add that "the combination of aliskiren with an ARB or ACE inhibitor is strictly contraindicated in those with kidney impairment or diabetes [49]." The 2014 Evidence-Based Guidelines for the Management of High Blood Pressure in Adults unambiguously state that ACE inhibitors and ARBs should not be used together [50]. The US Food and Drug Administration (FDA), however, has not reviewed the concerns or issued any warnings on the combined use of these drug classes beyond what was has been advised for the use of either an ACE inhibitor or an ARB with aliskiren. Of note, in that regard the fixed dose combination of valsartan/aliskiren (Valturna®) approved for use in the USA in September 2009 was voluntarily removed from marketing by Novartis in July 2012 as per safety concerns originating from the ALTITUDE trial.

Conclusions

There have been multiple commentaries on the topic of combined RAS blockade as relates to renal disease/proteinuria, HF, and use in the instance of CVD, and all have reached a similar conclusion that such a therapeutic approach is no longer advisable [51–53]. Once again, enthusiasm for an attractive pharmacologic concept, such as "blocking" the RAS as much as possible, in the hope that incremental outcome benefits would be garnered, abjectly failed. The alluring nature of a concept, such as combination RAS inhibitor therapy, is just one example of the ways in which the clinician is sidetracked from simpler and more easily accomplished ways to improve BP control and outcomes such as system-based approaches to hypertension management as are employed in the Veterans Administration system and endeavoring to ensure medication compliance.

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Chapter 7
Renal Sympathetic Denervation

Markus P. Schlaich

Introduction

Hypertension affects an estimated 1 billion adults globally representing a major cardiovascular epidemic [1]. Despite the availability of safe and effective antihypertensive pharmacotherapies, hypertension management at the population level continues to remain suboptimal [2, 3] with predictions that approximately 50 % of adults in developed countries will meet the clinical criteria for hypertension by 2025 [4]. Several factors are known to interfere with adequate blood pressure (BP) control including excessive dietary sodium intake, use of medications that can raise BP, non-adherence with prescribed medication, physician inertia and others. The management of hypertension is further complicated by a subset of patients who, despite appropriate lifestyle modification and adherence to combination therapy, remain above target BP values, a phenomenon referred to as treatment resistant hypertension.

Resistant hypertension is commonly defined as office systolic BP ≥ 140 mmHg (≥ 130 mmHg for patients with type 2 diabetes) despite concurrent use of ≥ 3 antihypertensive agents of different classes (one being a diuretic) at maximal tolerated doses [5]. Optimising BP control in patients with resistant hypertension is of major clinical importance as these individuals are at significantly greater risk of target organ damage (including left ventricular hypertrophy (LVH), hypertensive retinopathy and renal disease) and major cardiovascular events compared with patients on combination therapy with controlled BP [6].

Latest findings from the USA indicate that ~ 13 % of adults that are being treated for elevated BP have resistant hypertension [7] with 1 in 50 patients newly diagnosed with hypertension developing resistant hypertension within a median of 1.5 years from initiating pharmacotherapy [6].

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Recommendations for the pharmacologic management of resistant hypertension at present remain largely empiric due to lack of robust data from clinical trials that directly compare the various treatment options available. Current international guidelines advocate the use of the mineralcorticoid receptor antagonist, spironolactone, as part of combination therapy [8, 9]. However, long-term safety data, particularly in patients with impaired renal function, are limited.

In recent years, the novel technique of catheter-based renal sympathetic nerve ablation has emerged as a potential novel therapeutic approach to lower BP, particularly in patients with resistant hypertension. Through targeting the sympathetic nervous system directly, this treatment approach may theoretically prove to be of potential use in a number of other clinical conditions characterized by increased sympathetic drive.

Pathophysiology

Renal sympathetic nerves have been identified as key contributors in the multifactorial etiology of hypertension and specifically resistant hypertension [10]. Indeed, several studies show a direct positive relationship between BP and renal, cardiac and peripheral sympathetic activity in hypertensive patients [11–13].

Postganglionic sympathetic nerve fibres form a dense, neuronal network within the adventitia of the renal artery [14]. Efferent motor fibres innervate all renal structures, including the renal vasculature, tubules and the juxtaglomerular apparatus [15], while afferent sensory nerves connect the kidney with autonomic centres in the central nervous system [16].

Central sympathetic outflow to the kidneys via efferent sympathetic fibres modulates BP by stimulating the release of renin, increasing sodium and water reabsorption, and inducing renal vasoconstriction with effects on renal blood flow and glomerular flow rate.

Activation of renal sensory afferent nerve fibres through renal ischemia, injury or elevated adenosine concentrations [17] alters the activity of central integrative neuronal circuits that are involved in neuronal control of cardiovascular regulation. The resulting increase in efferent sympathetic outflow from the central nervous system to the kidneys and to other highly innervated organs (such as the heart and vasculature) contributes to the development and/or maintenance of hypertension.

The Sympathetic Nervous System as a Therapeutic Target

Targeting the sympathetic nerves directly to achieve improved BP control is by no means a new concept. Prior to the availability of antihypertensive medications, non-selective surgical sympathectomy was used to treat patients with malignant

hypertension in the 1930 and 1940s [18]. Despite impressive reductions in BP and improved long-term cardiovascular outcomes, the highly invasive procedure was abandoned since it was associated with high peri-operative mortality rate and plagued by unwanted and often debilitating side effects such as orthostatic hypotension, syncope, and erectile, bowel and bladder dysfunction [19].

In contrast, the recently introduced transcatheter based approach for renal sympathetic nerve ablation is a rapid, minimally invasive, percutaneous procedure that uses radiofreqency (RF) energy to specifically and selectively target the renal efferent and afferent nerves located in the adventitia of the renal arteries. With a guide catheter positioned in the renal artery via femoral access, the RF ablation catheter is advanced into the renal artery and connected to a RF generator. A series of RF ablations is then being delivered along each renal artery from distally to proximally with longitudinal and rotational separation to achieve circumferential coverage of the renal artery, thereby targeting the renal nerves located in the adventitia of the vessel wall. The procedure is carried out bilaterally in one session.

Since publication of the first in-human study in 2009 [20], over 8000 renal denervation procedures have been performed in patients with resistant hypertension worldwide. Trans-luminal radiofrequency ablation is the most commonly used modality, however, alternative approaches such as ultrasound, cryoablation and perivascular injection of neurotoxins have been used or are currently being investigated. More recently, in addition to the use of single-electrode catheters delivering 4–8 discrete RF ablations along the renal artery lumen, multielectrode and balloon-catheter systems have been introduced and may offer potential advantages including reduction in RF energy delivery time, reduced contrast load, more reproducible ablation patterns and improved catheter positioning.

Indeed, preliminary findings for these second-generation systems are encouraging, with BP reductions comparable to the initial single-electrode systems [21, 22]. However, long-term safety and efficacy data from larger cohorts are required before these novel systems can be recommended for general use.

In the past year, The European Society of Cardiology (ECS) and The European Society of Hypertension (ESH) have released practical recommendations on the use of renal denervation in clinical practice [23, 24] (Fig. 7.1). The expert committees state that only patients with (severe) treatment-resistant hypertension, diagnosed by a hypertension specialist and confirmed with 24-h ambulatory blood pressure monitoring (ABPM), should be considered for the procedure. Secondary causes of resistant hypertension such as primary hyperaldosteronism, renal artery stenosis and obstructive sleep apnoea should also be ruled out or treated accordingly.

To maximise safety, the committees recommend that patients who have previously undergone renal artery intervention, have evidence of renal artery atherosclerosis or impaired kidney function (estimated glomerular filtration rate (eGFR) <45 ml/min per 1.73 m^2) be exempt. Anatomical contraindications including multiple renal arteries, one kidney or a main renal artery of <4 mm diameter or length <20 mm should also exclude a patient from undergoing the procedure.

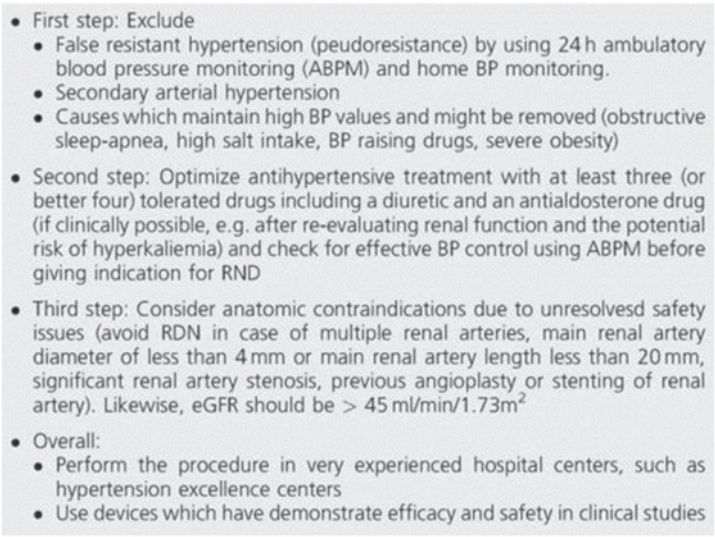

Fig. 7.1 Practical recommendations for the use of renal denervation in clinical practice according to the European Society of Hypertension. (Reprinted from Schmieder et al. [23]. With permission from Wolters Kluwer Health)

Clinical Trial Data on Catheter-Based Renal Sympathetic Denervation

The long-term safety and efficacy of catheter-based renal denervation to control BP has, to date, been evidenced by the Symplicity Clinical Trial Program. In 2009, the first proof-of-principle trial (Symplicity HTN-1) [20] was undertaken in 45 patients with resistant hypertension with an inclusion systolic BP threshold of > 160 mmHg (> 150 mmHg for patients with diabetes). Office BP was significantly reduced by −14/−10 mmHg (SBP/DBP) at 1 month after renal denervation with more pronounced reductions of −22/−11 mmHg and −27/−17 mmHg observed at 6 and 12 months, respectively. Renal sympathetic nerve activity as assessed by renal noradrenaline spillover was reduced on average by 47 %, confirming the impact of the denervation procedure on renal sympathetic nerve activity. Central sympathetic outflow, as assessed by microneurography, was also reduced in treated patients [25]. Importantly, no major procedure-related adverse events were reported.

As observed in a larger, extended Symplicity HTN-1 cohort ($n = 153$), the treatment effect on BP was sustained at 24 months [26] and, most recently, at 36 months [27], suggesting the absence of functionally relevant reinnervation of sympathetic nerves (Fig. 7.2). Four complications in the cohort included one renal artery dissection and three femoral artery pseudo-aneurysms. In 81 patients with magnetic resonance angiography, CT or duplex renal artery assessment post denervation, no stenosis was identified at sites where denervation was performed.

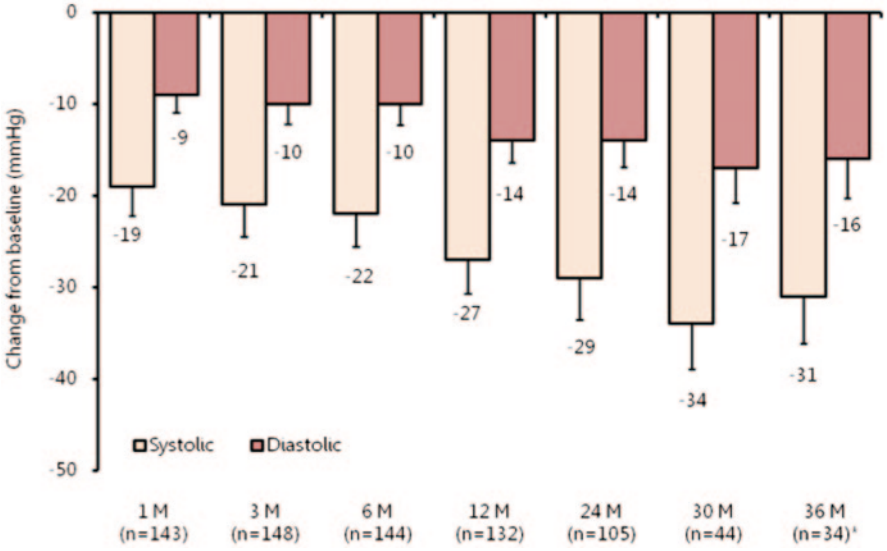

Fig. 7.2 Mean changes in office-based BP after renal denervation with up to 36-month follow-up in the extended Symplicity HTN-1 cohort ($n=153$). Error *bars* represent 95 % confidence intervals (CIs). Compared to baseline, significant differences in office-based BP were observed for patients at all reported time points during the 36-month follow-up period ($P<0.01$). *Asterisk* denotes number of patients with data available at time of data-lock

Encouraging results from the initial Symplicity HTN-1 trial led to the conduct of Symplicity HTN-2, a multicentre, prospective, randomized controlled trial involving 106 resistant hypertensive patients from 24 centres across Europe, Australia and New Zealand [28]. Of the 49 patients who immediately underwent renal denervation, mean office BP at 6 months significantly decreased by −32/−12 mmHg with no change in BP reported in the control group ($n=51$) assigned to standard pharmacological therapy (Fig. 7.3).

A subset of patients in the Symplicity HTN-2 trial (20 in the RDN group and 25 in the control group) underwent ABPM at 6 months, and the mean reduction in BP was 11/7 mmHg in patients with RDN, whereas there was no significant change in controls. Not surprisingly, the reduction in ABPM was less pronounced than the reduction in office BP. Other trials have confirmed that RDN causes greater reductions in office BP than ambulatory BP; however, the magnitude of the difference between office BP and ambulatory BP changes appears to be somewhat more pronounced than that observed in BP-lowering trials using pharmacological approaches.

Renal artery imaging at follow-up ($n=43$) confirmed the safety of the procedure with no reported incidence of renal artery stenosis or aneurismal deformation.

Recently, 12-month follow-up data from 47 patients in the Symplicity HTN-2 trial were published [29]; also included were 6-month post-denervation data for 35 control patients who, per-protocol, elected to undergo to the procedure after randomization. Compared to at baseline, there was no additional reduction in patient's office BP at 12 months compared to at 6 months ($P=0.16$; Fig. 7.3).

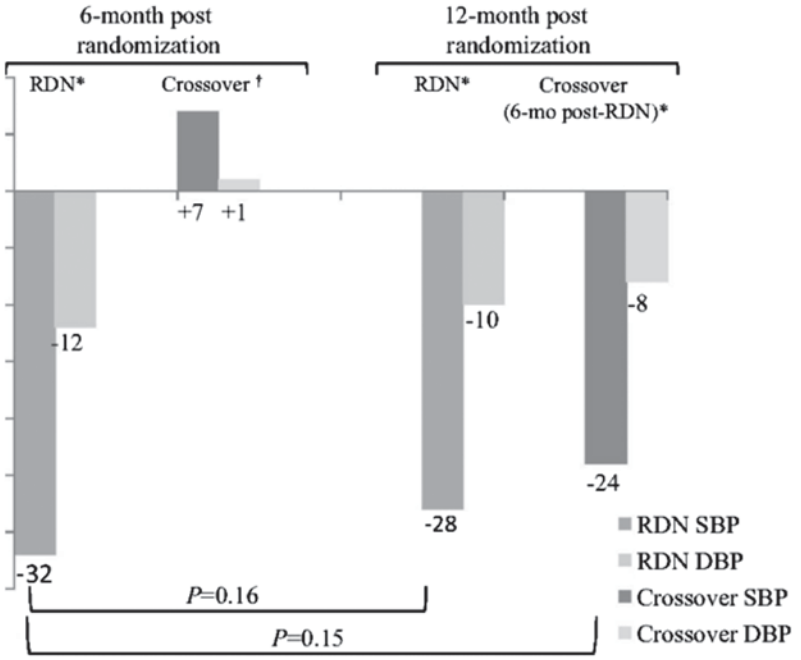

Fig. 7.3 Mean change in office-based BP after renal denervation at 6 and 12 months in the Simplicity HTN-2 trial. Both the initial renal denervation group and the crossover group denervated at 6 months after randomization experienced significant drops in systolic and diastolic BP. *RDN* denotes patient group immediately assigned to renal denervation at baseline, *crossover* denotes patient group who underwent renal denervation after randomization, *DBP* diastolic blood pressure, *SBP* systolic blood pressure. *Asterisks* denote $P<0.001$ for *SBP* and *DBP* change after renal denervation; the *dagger symbol* denotes $P=0.026$ for *SBP* change from baseline and $P=0.066$ for DBP change from baseline for the crossover group before denervation at 6 months (Reprinted from Esler et al. 2012. With permission from Wolters Kluwer Health)

The magnitude of SBP reduction at 12 months was, however, consistent with that observed in the first Symplicity HTN-1 trial (−28 vs. −27 mmHg). Mean change in office BP at 6 months was also shown to be comparable between patients assigned to immediate renal denervation and those who underwent the procedure after randomization ($P=0.15$).

In terms of safety, only two peri-procedural events were reported. One control patient experienced a femoral artery pseudoaneurysm prior to renal denervation that was resolved without further sequelae. A second control patient was hospitalised following renal denervation for a hypotensive episode that was managed with a reduction in their antihypertensive medication.

In both cohorts, renal denervation preserved kidney function as evidenced by nonsignificant changes in eGFR, serum creatinine and Cystatin C at 6 and 12 months. The observation supports a recent study of 88 patients with resistant hypertension who had a preserved eGFR 6 months post renal denervation [30].

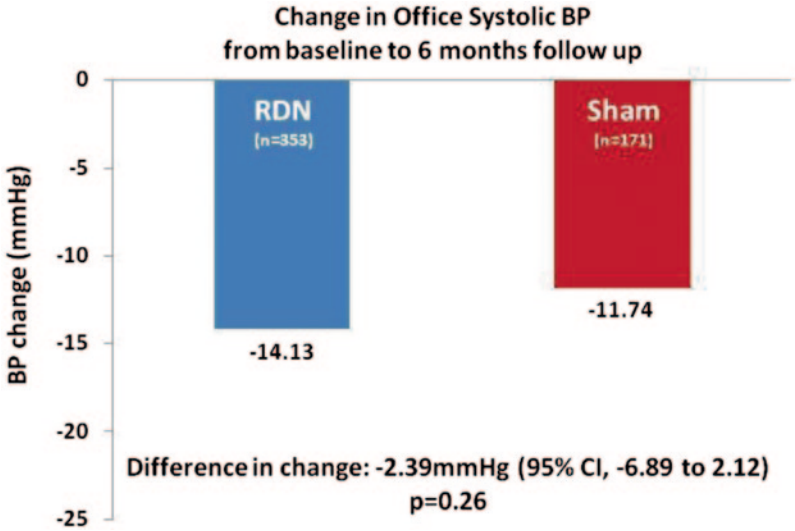

Fig. 7.4 Mean change in office systolic BP from baseline to 6-month follow-up in the Symplicity HTN-3 trial. A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mmHg.

Symplicity HTN-3 [31] is the largest clinical trial on the safety and efficacy of renal denervation thus far, comprising a total of 535 patients with resistant hypertension randomized in a 2:1 ratio to receive renal denervation or a sham procedure. As the US pivotal trial seeking FDA approval, it was rigorously designed taking into account limitations that have been identified with Symplicity HTN-1 and 2. As such, patients had to have a systolic office BP of ≥160 mmHg while being on *full* doses of 3 or more antihypertensive drugs, including a diuretic. Ambulatory BP monitoring was mandatory and the 24-hour average BP had to be ≥135 mmHg to be included. Randomization occurred in the catheter lab after confirmation of suitable anatomy by renal angiogram. Patients were followed up by physicians blinded to the patient's randomization status. The primary safety end point was a composite of major adverse events at 1 month. The primary efficacy end point of the study was the difference in the reduction of systolic office BP between the renal denervation and the sham group with a 5-mmHg superiority margin.

The primary safety end point was met with no difference in the major adverse event rate between the two groups (1.4% in the renal denervation group vs. 0.6% in the sham-procedure group). However, while there was a significant reduction in systolic office BP of −14.1±23.9 mmHg ($P<0.001$) at 6-month follow-up in the renal denervation group, the difference in the change of BP with a superiority margin of 5% (−2.39 mmHg; 95% CI, −6.89–2.12; $P=0.26$) was not statistically significant from that seen in the sham-procedure group (−11.7±25.9 mmHg; $P<$ 0.001; Fig. 7.4), therefore the primary end point was not met. Similarly, the difference in the reduction of ABPM between the two groups, a secondary efficacy end

point was also not met (RDN, −6.75 ± 15.11 mmHg vs. Sham, −4.79 ± 17.25 mmHg; difference in changes, −1.96 (95 % CI, −4.97–1.06); $P = 0.98$).

The results from this trial were in stark contrast to the results of all other studies using different denervation systems, most of which were uncontrolled studies, and were considered by many as a substantial setback for renal denervation as a therapeutic approach to resistant hypertension. Indeed, the trial was excellently designed and the results highlighted the relevance of a sham control in device-based studies. However, several aspects relating primarily to the conduct of the study have been criticized and discussed as potential contributors to the failure of the trial to meet its efficacy end points. These include (i) inexperience of operators (88 centres participated in the trial with 111 operators performing RDN in 364 patients without previous experience in RDN); (ii) a substantial number of patients (~40 % in each group) had medication changes within the first 6 months after the RDN or sham procedure; (iii) no measures of drug adherence were obtained and (iv) no evidence of the degree of renal denervation achieved during the trial could be obtained. Furthermore, in contrast to previous studies, ~25 % of participants in Symplicity HTN-3 were of African American background with subgroup analysis indicating a potential difference in the BP response in this patient group. Future and more detailed analyses of Symplicity HTN-3 will have to determine whether or not these factors may have influenced the results of Symplicity HTN-3. Irrespective of these findings, more research in form of adequately designed studies will be required to ultimately determine the role of RDN in the treatment of resistant hypertension.

Possible Utility of Renal Sympathetic Ablation Beyond Resistant Hypertension

Preliminary studies suggest that catheter-based renal denervation may have therapeutic benefits, beyond BP control, in patients at high risk of cardiovascular events.

Excessive sympathetic activation is a hallmark of both chronic kidney disease (CKD) and end-stage renal disease (ESRD). In the vast majority of patients, chronic elevation in BP from sympathetic overdrive potentiates the progressive deterioration of renal function and leads to increased risk for serious cardiovascular events [32, 33]. Two pilot trials were recently undertaken to assess the feasibility and short-term safety of renal denervation in patients with CKD [34] and ESRD [35]. To date, only patients with normal kidney function (eGFR >45 mL/min per 1.73 m^2) have been assessed in large clinical cohorts [28, 29].

In 15 patients with resistant hypertension and stage 3–4 CKD (mean creatinine-based eGFR 31.2 [SD:8.9] mL/min per 1.73 m^2), renal denervation was shown to safely reduce seated office and night time BP (as measured by 24-h ABPM) by −32/−15 mmHg and −10/−3 mmHg, respectively, at 6 months. Importantly, angiographic evaluation after the procedure revealed no compromise of treated arteries or

disturbances in renal blood flow, electrolytes and eGFR. Improvements in peripheral arterial stiffness were also observed at 3 months.

For nine patients with ESRD and uncontrolled BP, a sustained reduction in office SBP of −18, −16 and −28 mmHg at 3, 6 and 12 months, respectively, was observed following renal denervation. Patients also demonstrated a reduction in both sympathetic outflow, as measured by muscle sympathetic nerve activity, and in renal and whole body noradrenaline release at 3 months ($n=2$). Anatomical limitations prevented three patients from undergoing renal denervation. Two patients also developed peri-operative femoral pseudo-aneurysms that resolved without further sequelae. Larger clinical trials are now warranted to substantiate these initial findings and determine whether renal denervation may represent a useful therapeutic approach in patients with impaired kidney function.

Chronic activation of the central sympathetic nervous system has also been implicated in the initiation and progression of several cardiovascular conditions that increase morbidity and mortality, including LVH, cardiac arrhythmias and chronic heart failure, at times in the absence of elevated BP [36]. Brandt et al. investigated the impact of renal denervation on LVH in 46 patients with resistant hypertension [37] and found the procedure significantly reduced LV mass, increased LV ejection fraction and improved diastolic function at 1 and 6 months.

A recent pilot study [38] evaluated the safety of renal denervation in seven normotensive patients with chronic systolic heart failure. At 6 months, all patients showed an improvement in their functional capacity (as assessed by a 6-min walk test) and overall quality of life. Of note, a recent study confirmed a beneficial effect on health-related quality of life after renal denervation [39]. Importantly, no procedural complications or symptomatic adverse effects were reported. Renal haemodynamics and function were also preserved.

Atrial fibrillation (AF) is associated with a sustained elevation in BP and represents the most common clinically significant cardiac arrhythmia. Usual treatment for AF includes catheter ablation to disconnect the pulmonary veins from the left atrium (known as pulmonary vein isolation; PVI). In patients with resistant hypertension, a combined therapy of PVI and renal denervation ($n=13$) significantly lowered office BP and had a salutary effect on AF patterns compared to PVI alone ($n=14$) [40]. At 12 months, 69 % of patients assigned to PVI with renal denervation were AF-free compared to 29 % assigned to PVI only. Patients on combined therapy also demonstrated a significant and sustained BP reduction of −25/−10 mmHg and reduction in LV mass of approximately 10 % at follow-up.

Renal denervation has recently been shown to improve central haemodynamics in patients with resistant hypertension [41]. In addition to lowering peripheral BP, the procedure significantly improved heart rate, central aortic BP and arterial stiffness (as measured by pulse wave velocity) in 110 patients at 1 month compared to controls ($n=10$) assigned to standard pharmacotherapy.

Current Limitations and Future Perspectives

Renal denervation has emerged as an appealing therapeutic approach for patients who are unable to achieve BP control with standard pharmacotherapy. However, the data from Symplicity HTN-3, which included a sham control, have casted doubt on the efficacy of RDN in this setting. Further well-designed clinical trials including a sham control will be required for regulatory purposes to ultimately proof or disproof its clinical utility. Furthermore, before this procedure can become part of routine clinical care several other areas require further investigation.

There is concern that sympathetic reinnervation may occur in patients who undergo the procedure, as seen in animal studies [42] and after heart transplantation [43]. At present, long-term follow-up data are limited with only one study demonstrating a sustained BP reduction at 36 months [27]. Additional studies are urgently needed to confirm the long-term efficacy of the procedure.

It is apparent that renal denervation does not cause universal BP reduction, and identifying predictors for non-response may help identify patients that will benefit specifically from the procedure.

A recent study compared the cost-effectiveness of renal denervation compared to more established medical treatments to lower BP [44], with impressive reductions in cardiovascular events (21–32%) over 10 years predicted. The long-term impact of renal denervation on CV morbidity and mortality is yet to be elucidated and will not be known for some time.

There is substantial interest in renal denervation as a treatment for less severe forms of hypertension. Initial data from two studies are conflicting, with one small case series of 12 patients not showing a significant BP reduction after renal denervation, [45] while a slightly larger study ($n=20$) demonstrated a BP reduction of −13.1/−5.0 mmHg at 6 months [46]. Most recently, a report on a cohort of 54 patients with moderate resistant hypertension defined as office BP ≥140/90 mmHg and <160/100 mmHg on an average of 5.1 antihypertensive drugs and 24-h ambulatory BP ≥130/80 mmHg demonstrated a reduction of office BP by 13/7 mmHg 6 months after RDN [47]. Office BP was controlled below 140/90 mmHg in 51% of the patients and 37% of patients reduced their antihypertensive medications. In the patients ($n=36$) who had ABPM before and 6 months after the procedure, there was a reduction in average ambulatory BP of 14/7 mmHg.

Clearly, randomized sham-controlled clinical trials in these cohorts will be required to properly define the usefulness of renal sympathetic denervation.

Conclusions

Resistant hypertension is a clinically important condition that is associated with significant cardiovascular risk. The majority of data from the Symplicity Clinical Trials Program and early-phase studies using various RDN modalities in high-risk patient cohorts suggest a therapeutic benefit of this approach in regards to BP reduction;

however, the most rigorous trial conducted thus far clearly failed to demonstrate a BP reduction beyond that of a sham procedure. Whether the criticisms raised in regards to the conduct of the study are valid or not will have to be determined.

The potential clinical utility of RDN may extend to other conditions characterized by chronic sympathetic overactivity, as indicated by several small but mainly uncontrolled studies. At this stage, RDN should be performed primarily within randomized controlled clinical trials to identify those patient cohorts that may derive benefit from RDN.

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Chapter 8
Novel Baroreceptor Activation Therapy

Peter W. de Leeuw and Abraham A. Kroon

Introduction

Hypertension still is a leading cause of cardiovascular complications. Apart from stroke and coronary artery disease, impairment of renal function is a well-known sequel of the hypertensive process. Indeed, hypertension accounts for at least one quarter to one third of all patients coming to dialysis. Over the past 50 years, numerous trials have shown that antihypertensive treatment reduces the risk of complications although the magnitude of the effect differs somewhat for the various forms of organ damage. It seems as if lowering the pressure has a greater impact on the cerebrovascular system than on the kidney. However, it is possible that it takes a longer time to slow down renal deterioration than it takes to protect the brain and that the trials simply have not lasted long enough to show all benefits of treatment.

Whereas it is clear that antihypertensive drug treatment confers substantial benefit in the population at large, there are still many patients in whom blood pressure does not fall or is reduced insufficiently during such treatment. Leaving inadequate blood pressure measurements, white coat hypertension, and problems with adherence as "causes" of ineffective treatment (i.e., pseudo-resistance) aside, true treatment resistance is one of the challenges of contemporary hypertension research. As a matter of fact, true resistance is rare and difficult to define. Admittedly, there is a consensus statement defining the condition [1], but this leaves a lot of room for debate. Indeed, true resistance would imply that a patient does not respond to any antihypertensive drug, whether given alone or in combination with other agents. In reality, however, only a fraction of the available drugs is being tested in a particular patient, and defining resistance as a condition where there is an insufficient response to a combination of three drugs, optimally dosed and containing at least a diuretic, is too simple. Certainly, a better term would be "difficult-to-treat hypertension."

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Pathophysiological Aspects of Difficult-to-Treat Hypertension

Under normal circumstances, the capacity of the body to counteract a rise in pressure is substantial. Accordingly, hypertension must be regarded as a consequence of failing circulatory homeostasis. Two organs have traditionally been linked to the pathogenesis of hypertension: the kidney and the autonomic nervous system. According to Guytonian physiology, hypertension can only persist in the long run when the ability of the kidneys to excrete water and salt is impaired [2]. In other words, if the kidneys for whatever reason fail to appropriately excrete a certain salt load, blood pressure will go up; otherwise, pressure natriuresis in the kidney will get rid of the excess of total body sodium and restore pressure to its initial level. Although the concept has been criticized, a wealth of experimental and clinical data supports this theory.

The autonomic system also has a role in counteracting pressure rises and it does so primarily through the baroreceptor system. An increase in pressure from whatever cause will activate the baroreceptor system, which will then reduce sympathetic outflow and enhance parasympathetic tone. Consequently, blood pressure will return to its original level. For decades, one has believed that this neurogenic mechanism was intended to buffer only acute changes in blood pressure. Nevertheless, several investigators have argued repeatedly that the autonomic system plays an important role in the long-term regulation of blood pressure as well [3].

Clinical trials have shown that treatment with antihypertensive drugs can lower the pressure, although it is often necessary to switch from one drug to another or to combine several agents [4]. This is best explained by the fact that a variety of compensatory mechanisms may counteract or even offset the primary effect of any blood-pressure-lowering drug. As such, virtually all physiological systems with a role in cardiovascular regulation could be involved. Alternatively, structural changes in the cardiovascular system may prevent the drugs to be fully effective. Based on the pressure-natriuresis phenomenon mentioned above, it is also possible that the kidneys respond to a lower pressure by retaining sodium and water in an attempt to bring the pressure back to its level before treatment. This is a form of pseudo-resistance and the reason why one should always administer a diuretic before concluding that a patient is resistant to treatment.

Unless the antihypertensive drugs have a direct effect on the autonomic regulation of blood pressure, the fall in pressure may activate the baroreceptor reflex, which will result in enhanced sympathetic outflow and attenuation of the hypotensive response. Finally, it is conceivable that the set point, i.e., the operating pressure that the kidney and/or the autonomic system try to maintain, is shifted towards a higher value in hypertensive patients (resetting). If that would be the case, the renal and autonomic responses would have to be regarded as appropriate given the higher set point.

In the past, many attempts have been made to modulate these compensatory mechanisms but with only partial success. Recently, however, a new technique has become available, which has made it possible to alter sympathetic outflow by direct

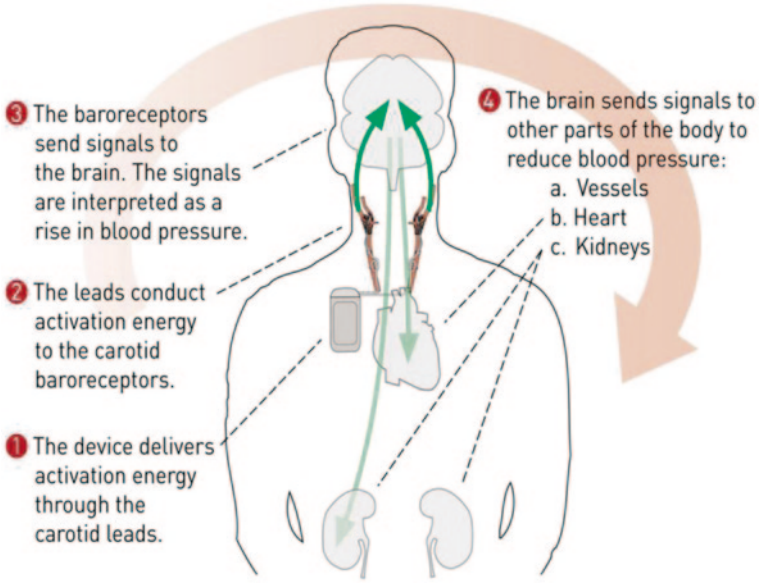

Fig. 8.1 Schematic representation of how baroreceptor activation therapy works. (Courtesy of CVRx Inc.)

stimulation of the baroreceptor area (Fig. 8.1). Currently, this technique is being tested in clinical trials to explore its potential to alleviate the hypertensive burden in patients with treatment resistance.

The Principle of Baroreceptor Activation Therapy

Baroreceptors are located in the aortic arch and at the carotid sinus level. In humans, the carotid and the aortic baroreceptor systems cannot be studied separately unless one of these would be eliminated. Hence, all we know about the functioning of the baroreceptor system in man is based upon the two acting in concert. Nevertheless, it is possible to modulate the input signal at the level of the carotid system only, for instance by applying a positive or negative pressure on the neck by means of a neck chamber. This experimental technique has been very useful to enhance our understanding of the baroreceptor system [5]. Contrary to what is often believed, baroreceptors do not respond to pressure changes but to changes in distension of the vascular wall. In other words, the input signal (a change in transmural pressure) essentially comes from within the vascular lumen. This is also what happens when one applies the neck chamber technique. Baroreceptor activation therapy (BAT), on the other hand, stimulates sensitive elements at the outside of the vascular wall. Indeed, stimulation electrodes are placed at or around the carotid artery at a spot where acute stimulation produces the greatest response. Whether in physiological

terms, the effect of external stimulation is comparable to that of stimulation from within the vessel is presently unknown.

Current devices for BAT stimulate the carotid baroreceptor area only. When one applies BAT, it is necessary to consider several stimulation characteristics during the programming such as start and stop times, ramp function, dose settings, burst settings, pulse amplitude, pulse width, and pulse frequency. In case of bilateral stimulation, this has to be decided on separately for the left and right lead. The most common approach is to set the voltage and the frequency depending on the prevailing level of blood pressure and heart rate and the patient's response to stimulation. Sometimes it is necessary to use different settings during daytime and nighttime. At any rate, it is a matter of trial and error to find the optimal settings in a particular patient.

Another important question is whether one should stimulate the baroreceptor area at both sides or unilaterally. Early data in animals suggested that unilateral stimulation with a bipolar electrode which was attached directly to the carotid sinus nerve was sufficient to reduce blood pressure [6]. In man, studies with BAT initially involved bilateral stimulation but the most recent device has been developed for unilateral stimulation only. Preliminary data indicate that stimulation at one side is indeed as effective as bilateral stimulation [7].

Baroreceptor Activation Therapy in Man

The idea behind BAT in hypertension is not novel as the technique was already applied some 50 years ago. However, at that time, technology was not yet ready for introduction on a wider scale into the clinic. Short-term observations in a limited number of patients confirmed that BAT could reduce blood pressure and heart rate but long-term data yielded equivocal results. No randomized controlled trials with the devices have been done at that time so that the true value of the technique remained enigmatic. Due to the introduction of a variety of antihypertensive drugs that were well tolerated, there was less and less need for invasive procedures and the further development of devices for BAT was considerably delayed for a long period of time.

Since the beginning of the twenty-first century, new devices with improved technology are available. So far, the most important of these and the ones that have been tested clinically are the Rheos™ Baroreflex Hypertension Therapy System and its successor, the Barostim *neo*™ device. These are open-loop systems with electrodes that are attached surgically to the carotid artery at close proximity to the bifurcation. While the Rheos device still worked through bilateral stimulation, the other one has been designed for unilateral implantation and stimulation. The devices further consist of an implantable pulse generator and an external programmer.

The Rheos device was initially tested intra-operatively in patients who needed elective carotid artery surgery [8]. Baseline blood pressure of these patients was 146 ± 30 mmHg systolic and 66 ± 17 mmHg diastolic. When blood pressure and

heart rate had stabilized, the investigators constructed some kind of dose–response curve by applying incrementally increasing electrical currents. Blood pressure and heart rate fell significantly in a voltage-dependent way by, on average, 23 mmHg systolic and 16 mmHg diastolic. These observations paved the way for application of the device in patients with difficult-to-treat hypertension.

The Device-Based Therapy in Hypertension (DEBuT-HT) Trial was the first multicentre, prospective, nonrandomized feasibility study to assess safety and efficacy of the Rheos system over a period of 3 months in treatment-resistant hypertensive patients [9]. Treatment resistance was defined as a blood pressure equal or above 160/90 mmHg despite treatment with at least three antihypertensive agents, including a diuretic. Secondary hypertension and nonadherence to treatment had to be excluded. Patients who qualified for the study had the baropacer implanted (bilaterally) but to allow undisturbed tissue healing, the device was not activated until 1 month after the surgical procedure. To avoid a confounding effect of medication, drug dosages had to remain constant during the 3 months of the study that the device was on. Altogether, 45 patients entered this trial. Their mean age was 54 years and their blood pressure 179 ± 29 mmHg systolic and 105 ± 22 mmHg diastolic. At the end of the 3-month period with the device on, blood pressure had fallen significantly by an average of 21/12 mmHg. Although a few side effects were noted, by and large the safety profile was favorable [9]. Thus, the study showed that it is possible to lower blood pressure in patients with drug-resistant hypertension by modulating baroreceptor function without major adverse events. It is also very likely that the effectiveness of the device relates to its potential to reduce sympathetic traffic in the body. Indeed, when intra-arterial blood pressure and muscle nerve sympathetic activity (MSNA) were recorded simultaneously in 12 patients who had the baropacing system implanted, electrical stimulation caused a sharp fall not only in pressure but also in MSNA [10]. In the responders, the decrement in pressure correlated with the fall in MSNA. Throughout the stimulation period, MSNA remained below baseline levels. Switching the device off was associated with reversal of these effects.

Several patients who had participated in DEBuT-HT could be followed for a longer period of time. Over the years, they maintained their blood pressure reduction and it was even possible to withdraw some of their medication [11]. However, since DEBuT-HT was an uncontrolled feasibility and proof-of-principle trial, it did not have the power to prove unequivocally that BAT is beneficial in resistant hypertension. Therefore, the Rheos Pivotal Trial was designed as a randomized, double-blind, parallel-design clinical trial comparing immediate and delayed BAT. It included 265 patients with resistant hypertension (average baseline blood pressure 178/103 mmHg) over a period of 6 months who were randomized in a 2:1 ratio to either immediate activation of the device (i.e., 1 month after the implant, group A) or delayed activation (7 months after the implant, group B). Thus, the second, smaller group could be considered as a sham-operated or placebo group in this respect. The trial had five primary outcome variables related to efficacy and safety at 6 months of stimulation [12]. After the 6-month assessment, the baropacer was switched on in patients from group B as well and 6 months later all measurements

were repeated. Although the drop in pressure was numerically greater with the device on, the difference in responder rates between both groups at 6 months was smaller than the prespecified primary efficacy end point of 20 %. Thus, in this randomized trial, baropacing was not more effective than sham operation during a period of 6 months. Possibly, the placebo effect and the effect of participating in a trial were greater than anticipated. Nevertheless, the proportion of patients who reached the goal pressure of 140 mmHg systolic or below (a secondary end point) was greater in group A (42 vs. 24 %; $p<0.005$). Moreover, at 12 months when all patients had the device on, the two groups showed a comparable drop in blood pressure as compared to baseline. No major safety concerns were encountered and only short-term procedure-related adverse events were seen, most of which disappeared after some time [12]. After the formal part of the trial, patients were followed for more than 2 years [13]. The vast majority of these patients continued to exhibit lower blood pressures and among the responders to BAT the number of prescribed medications could be reduced by 1–2 classes.

Recently, the very first results obtained with the newer Barostim *neo* device were published [7]. The trial was a single-arm, open-label study in 30 drug-resistant patients. Interestingly, six patients had previously undergone renal nerve ablation without success. In most patients, the implant was done on the right side. After 6 months, blood pressure had fallen by an average of 26/12 mmHg (baseline blood pressure amounted to 172/100 mmHg). Similar results were obtained in patients with or without prior renal nerve ablation. Although this was again an observational study, the data suggest that with the unilateral device comparable results can be obtained as with the bilateral device. It is also reassuring that intact renal nerves are not a requisite for BAT to exert its effect.

Baroreceptor Activation Therapy and Target Organ Damage

A post hoc analysis of a subgroup of patients, who participated in the DEBuT and US Trials of the Rheos System, showed that left ventricular mass index fell significantly from 139 ± 35 to 108 ± 34 g/m^2 ($p<0.01$) after 1 year of BAT as compared to baseline [14]. Midwall fractional shortening was significantly increased ($p<0.01$) as did left ventricular outflow tract diameter and arterial compliance. Unpublished data also suggest that BAT improves myocardial energy kinetics and diastolic flow velocities. Since no significant correlation was observed between the changes in systolic blood pressure and those in left ventricular mass index, it is possible that BAT not only reduces blood pressure but also induces reverse cardiac remodeling due to interruption of sympathetic traffic to the heart.

As far as kidney function is concerned, long-term data are now available from the pivotal trial [15]. During the initial 6 months of BAT serum creatinine increased significantly in both groups by about 6 %. At 12 months, when the two groups had received BAT for 12 and 6 months, respectively, serum creatinine did not change any

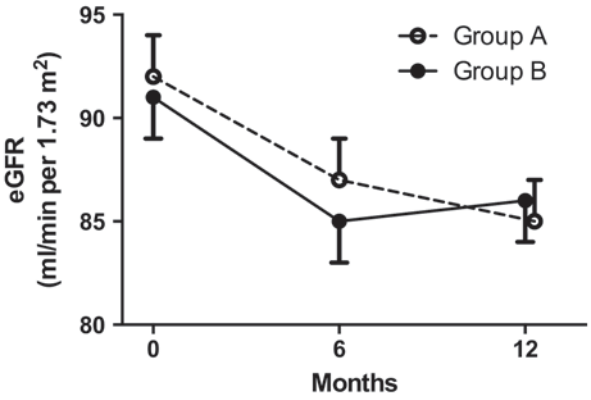

Fig. 8.2 Changes in estimated glomerular filtration rate (*eGFR*) in the pivotal trial. *Group A*, immediate stimulation. *B*, start stimulation 6 months after implant. (Based on data derived from [15])

further but remained significantly increased compared to screening values in both groups. Similar results were found when not serum creatinine but estimated glomerular filtration rate was taken as the dependent variable (Fig. 8.2). The reduction in systolic pressure appeared to be the most significant determinant of the changes in serum creatinine. This suggests a pressure-related hemodynamic phenomenon rather than an intrinsic BAT-related influence on renal function. No significant effects were seen with respect to urinary albumin excretion. Data, which have not yet been published, show that, on average, plasma renin levels do not change during BAT. This may seem odd, as one would expect a decline in renin when sympathetic outflow is reduced. On the other hand, the fall in pressure probably counteracts any fall in renin. Moreover, patients continue to take medication with a possible effect on renin.

At the present time, there is not enough information regarding cerebrovascular changes during BAT.

Conclusions

The available data clearly indicate that BAT is a promising new technique to treat hypertensive patients who are unresponsive to medical treatment. Insofar as the evidence is available, target organ damage is also favorably influenced by BAT. However, in itself, this is insufficient to recommend BAT as a regular form of treatment as it is also necessary that this treatment improves prognosis. Such data do not yet exist.

An area of research that is extremely relevant for the future treatment of drug-resistant hypertension will be a head-to-head comparison of BAT with its competitor: renal denervation [11]. In the few patients in whom renal denervation failed to adequately lower blood pressure, the Barostim *neo*™ still was able to reduce pressure to the same extent as in those without prior renal denervation. Future research must also be directed towards finding the optimal spot to stimulate and to explore whether external stimulation is possible, i.e., without the need to operate.

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Chapter 9
Blood Pressure Vaccines

Sorot Phisitkul and Joel Topf

Background

Current pharmacologic therapy for hypertension is focused on managing it. A better treatment would be to employ the immune system to modulating hypertension mediators and targets in order to control the blood pressure.

Vaccines are therapies that stimulate the immune system to provide protection against disease. Usually, this is via antibodies against infectious diseases; however, vaccines can be used in other chronic disease, e.g., cancer, asthma, smoking cessation, and hypertension [1–3].

Vaccines need a target. In infectious disease, vaccines target bacterial or viral outer surface proteins. What is the appropriate target for hypertension? The causes of hypertension are complex and it is unlikely that there is a single pinpoint cause, however, the renin–angiotensin–aldosterone system (RAAS) is a central actor and makes a logical target for vaccine development. See Chap. 6 for a full discussion of the RAAS. The remainder of this chapter will focus on the research and achievements of vaccines targeting elements of the RAAS.

Renin Vaccine

Renin was discovered in 1898 by Tigerstedt and Bergman. They extracted renin from the kidney of a hypertensive dog and found that it could induce hypertension in another nephrectomized dog [4].

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Johnson and Wakerlin first demonstrated that parenteral administration of renin from one species to another species results in the production of anti-renin antibodies [5]. Goldblatt conducted the first human study of a renin vaccine when he injected human subjects with porcine renin [6]. The subjects, who all had primary hypertension, developed antibodies to the foreign renin, but the antibodies did not lower blood pressure. The investigators theorized that there must have been a lack of cross-reactivity between the antibodies developed against porcine renin and native human renin.

There were several studies on renin vaccine from 1950 to 1980 with both active and passive immunization [7]. Most of the studies were done using cross-species renin infusions to develop the antibodies. The procedure was most successful at reducing renal vascular hypertension (the experimental model for the hypertension usually involved nephrectomy and partial renal artery obstruction). Some studies found blood pressure reductions as high as 20–50 mmHg. The procedure appeared safe with no immune complex depositions discovered in renal biopsies

The early promising results prompt Michael et al. to test a renin vaccine with adjuvant [8]. The use of an adjuvant was in order to generate a more sustained clinical response. He combined purified human renin with Freund's adjuvant, water-in-oil emulsion and dead mycobacterium. When tested in marmosets, this vaccine resulted in high titers of anti-renin antibodies and a significant reduction in blood pressure. However, 1–4 months after immunization, the animals became sick and died. Autopsies showed immunoglobulin deposition in the afferent arterioles. There was also evidence of cellular inflammation around the renal arterioles and interstitial nephritis. This setback closed this avenue of research and no further work being done on renin vaccines.

Angiotensin I Vaccine

Angiotensin I and angiotensin II are small peptides, 10 and 8 amino acids respectively. Because of their small size, investigators theorized that anti-angiotensin antibodies should pose less of an autoimmune threat. Angiotensin I molecules need to be prepared with an adjuvant to make them immunogenic.

Reade et al. immunized spontaneously hypertensive rats (SHR) with angiotensin I coupled to Limulus polyphemus hemocyanin. Despite the successful induction of high titers of angiotensin I antibodies, there was no reduction in blood pressure [9].

Gardiner et al. immunized normotensive rats with angiotensin I coupled to a tetanus toxoid (TT) carrier protein adjuvanted with aluminum hydroxide (ALOH). The vaccine was injected on days 0, 21, and 42. Vaccinated rats had blunted responses to exogenous angiotensin I on day 63 and had no response to angiotensin II administration. The anti-angiotensin antibody titer increased 32, 100 fold [10].

Downham et al. compared angiotensin I vaccines made with two different carriers, TT and keyhole limpet hemocyanin (KLH) vaccine (PMD−3117) in humans and rats [11]. The researchers thought that since tetanus toxoid is a common antigen that most of adults have been exposed to, it may reduce the effectiveness of the

vaccine [12]. In rats, both vaccines induced similar immune responses and similar protection from the presser effects of exogenous angiotensin I. In humans, however, the antibodies were unable to blunt the hypertensive effect of either angiotensin I or angiotensin II challenges.

Brown et al. tested an angiotensin I vaccine on patients with primary hypertension [13]. Patients, who had already been shown to be responsive to an ACEi or ARB, were randomly assigned to receive PMD3117 or placebo over a 6-week period. Patients stopped ACEi/ARB therapy 2 weeks before starting the study drug and resumed it 6 weeks later. The vaccine increased anti-angiotensin antibody titer after the second injection and titers peaked on day 64. Median half-life was 85 (95% CI, 44 and 153) days. The vaccine did not influence blood pressure. Biochemical assessment showed patients randomized to vaccine had higher levels of renin ($P=0.033$) and lower levels of aldosterone (6% of values seen in patients receiving placebo, $P=0.012$). The author concluded that the vaccine had biochemical but not clinical suppression of the RAAS.

Turkie et al. (http://clinicaltrials.gov/show/NCT00702221) created an angiotensin I vaccine using a novel adjuvant, CoVaccine HT. This is an adjuvant made of synthetic sucrose fatty acid sulfate esters immobilized on the droplets on a submicron emulsion of squalane in water. Mild to moderate hypertension patients ($n=124$) were randomly assigned to receive vaccine every 3 weeks for or placebo for a 9-week period. The study had to be terminated due to adverse effects [NCT00702221].

Angiotensin II Vaccine

Johnston et al. theorized that, although immunization against angiotensin II greatly reduced the hypertensive response to exogenous angiotensin II, it played no direct role in the production or maintenance of experimental renal hypertension [14]. He also found that angiotensin II antibodies have a half-life of only 11 h. Similar findings, discrediting angiotensin II as having a key role in hypertension were provided by MacDonald et al. [15].

In 2007, Cytos Biotechnology AG (Switzerland) developed an angiotensin II-specific vaccine called CYT006-AngQb. CYT006-AngQb uses a modified angiotensin II peptide, with a N-terminal CysGlyGly extension. This antigen is covalently bound to virus-like particle (VLP) derived from protein coat of the bacteriophage Qβ (Fig. 9.1).

VLPs have supramolecular structures with rods or icosahedrons with diameters in the range of 25–100 nm. They are composed of multiple copies of one or more recombinant, expressed, viral, structural proteins which spontaneously assemble into particles. In addition to being virus-like in structure, they are often antigenically indistinguishable from the virus from which they were derived [16].

VLPs stimulate a strong B-cell response against self-antigens and this new technology helps overcome the self-tolerance limitations of immunization against angiotensin II [17, 18].

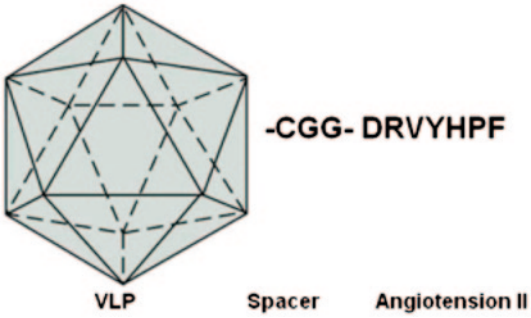

Fig. 9.1 Structure of the CYT006-AngQb vaccine. The modified angiotensin II peptide is composed of the amino acid sequence of Ang Iotensin1–8 octapeptide (*Angiotensin II*) fused at its N-terminus to a spacer sequence containing a cysteine to permit directional conjugation to the Qb virus-like particle (*VLP*)

Tissot et al. did a multi-center, double-blind, randomized, placebo-controlled phase II trial. They randomized 72 patients with mild-to-moderate hypertension to receive subcutaneous injections of either 100 μg CYT006-AngQb, 300 μg CYT006-AngQb, or placebo, at weeks 0, 4, and 12 [19]. Twenty-four-hour ambulatory blood pressures were recorded before treatment and at week 14. After a single injection, all patients receiving the vaccine responded with high anti-angiotensin II IgG titers. The antibody response was boosted after the second injection, and reached peak levels of response about 2 weeks after the third injection. The anti-angiotensin II IgG response was dose dependent, higher titers in patients randomized to 300 mcg than those randomized to 100-mcg dose. The half-life after the third injection was only 17 weeks. In the 300-mcg group, the ambulatory blood pressures fell 9.0/4.0 mmHg from baseline, with very dramatic decreases in early-morning blood pressures (25.0/13.0 mmHg).

The investigators could not document any change in the concentration of C1, C3, or factor C3a, which suggests that there was little to no immune complex deposition. The plasma renin levels increased in the vaccine group, likely due to a reduction in blood pressure. This trial is the first to show that vaccination against a vasoactive endogenous substance can reduce blood pressure in human beings.

Further work by the same team investigated more frequent dosing (at weeks 0, 2, 4, 6, and 10). This modification showed a fivefold increase in antibody titer but only −2.3/−0.4 mmHg improvement in blood pressure. Antibody affinities for angiotensin II were significantly lower in the second study than in the first ($P<0.001$). The authors concluded that both the quantity and the quality of the antibody is important for blood pressure reduction. Future studies on CYT006-AngQb are on hold due to financial reasons.

Angiotensin II Receptor Type 1 Vaccine

The newest vaccine approach does not target renin, angiotensin I or angiotensin II, rather it creates antibodies to block angiotensin II receptor type 1 (ATR; Fig. 9.2).

Zhu et al. immunized spontaneous hypertensive rat with a peptide-based vaccine made of a seven-amino-acid sequence (AFHYESR) from the second extracellular

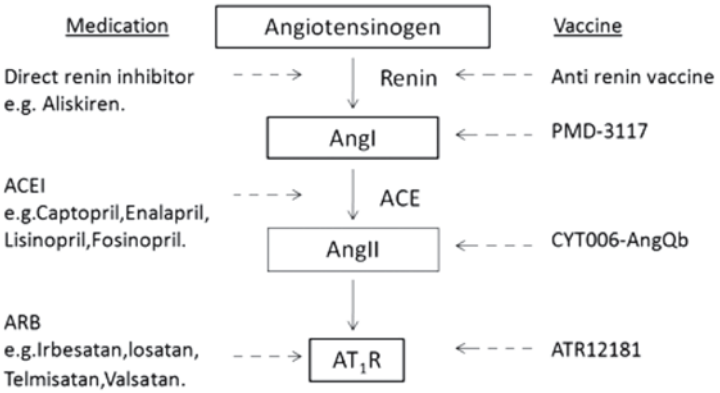

Fig. 9.2 Schematic representation of the classic renin–angiotensin system with oral medication and vaccines blocking at their specific targets. The inhibitory actions are shown in *dashed lines with arrows*. *ACE* angiotensin converting enzyme, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, AT_1R Ang II-type 1 receptors

loop of rat AT−1 A receptor (ATR12181; [20, 21]). The carrier protein is a TT complex in combination with Freund's adjuvant. The vaccine induced anti-ATR12181 antibodies and a 17-mmHg reduction in systolic blood pressure. They also noted decreased cardiac hypertrophy and decreased kidney injuries. No signs of autoimmune disease were found after sacrificing the rats.

The same group changed the adjuvant to VLP, which have a better safety profile than Freund's adjuvant [22]. The vaccine significantly decreased the blood pressure of angiotensin II-induced hypertensive mice up to 35 mmHg and that of spontaneously hypertensive rats up to 19 mmHg and prevented remodeling of hypertensive-vulnerable target organs. The half-life of the antibody was 14.4 days. The antibody specifically bound to angiotensin II receptor type 1 and inhibited angiotensin II-induced calcium-dependent signal transduction events, including protein kinase C-α translocation, extracellular signal-regulated kinase 1/2 phosphorylation (72% decrease; $P=0.013$). They also saw a 68% decrease in intracellular Calcium ($P=0.017$). The antibody did not inhibit angiotensin II binding to the receptor but rather diminished the pressure response and signal transduction initiated by angiotensin II.

Road Block and Future Direction

A vaccine for hypertension has been investigated for over 100 years. Though an effective therapy has not emerged, the journey has resulted in significant scientific breakthroughs. Summary of the clinical trial of hypertension vaccine is given in Table 9.1. The earliest efforts used renin vaccines. This was a proof of concept. By transferring renin across species, renin could be made immunogenic and the anti-renin antibodies effectively lowered blood pressure

Table 9.1 Summary of hypertension vaccines tested in human trials

Title	Vaccine	Target	N	End-point	Effect	Reference
Study 1	Angiotensin I (PMD2580, PMD3117)	Healthy adult	28	Produce antibody against Ang I Blood pressure	Vaccine can induced Ang I antibody but has no effect on blood pressure	Downham et al. [11] compared angiotensin I vaccines made with two different carriers, TT and keyhole limpet hemocyanin (KLH) vaccine (PMD–3117) in humans and rats
Study 2	Angiotensin I (PMD3117)	Hypertensive patients	27	Produce antibody against Ang I Blood pressure	Vaccine can induce Ang I antibody but has no effect on blood pressure	Brown et al. [13] tested angiotensin I vaccine on patients with primary hypertension
Study 3	Angiotensin I (CoVaccine HT)	Hypertensive patients	124	Blood pressure	Study has been terminated due to safety concerns	Wajdi H Turkie et al. studied safety and efficacy of angiotensin I vaccine in subject with mild to moderate hypertension. Clinical trials NCT00702221. No publication
Study 4	Angiotensin II (CYT006-AngQb)	Hypertensive patients	72	Blood pressure	Blood pressure reduced by −9/−4 mmHg	Tissot et al. [19] studied Angotensin II vaccine, CYT006-AngQb phase IIa trial

in animals. Unfortunately, the effectiveness came with devastating autoimmune consequences forcing the abandonment of this target molecule. The autoimmune complications were at least partly due to the large size of the antigen [23]. Renin is a 406-amino acid peptide while angiotensin I, angiotensin II, and the angiotensin receptor target-region are 10, 8, and 7 amino acid peptides respectively. The smaller molecular target decrease the likelihood of simultaneous binding of two antibodies to a single antigen resulting in less cross-linking and decreased immune-complex formation.

Second-generation antihypertensive vaccines targeted angiotensin I were able to successfully generate anti-angiotensin I antibodies but failed to show any blood pressure reduction in both animal and human studies. This not only showed limitations in the therapeutic strategy of an angiotensin I vaccine but also helped researchers better understand the pathophysiology and determinants of primary hypertension.

The adjuvant is critical in boosting the immune response to a vaccine. Freund's adjuvant induces strong immune response in an animal but can be toxic in humans. Aluminum gels and salts are the most commonly used adjuvants in human vaccines. VLP is a newer technology that is more efficient than aluminum [16]. VLP has a good safety profile and is used in commercial vaccines, Gardisil® and Cervavix TM. The hypertension vaccines that use VLP as an adjuvant have not shown any autoimmune side effects.

The third-generation antihypertensive vaccines targeted angiotensin II with a VLP adjuvant. This vaccine was tested in humans and is the only hypertension vaccine ever to be safe and effective in humans. Unfortunately, the efficacy was inconsistent and below the expectations, −9/−4 mmHg and −2.3/−0.4 mmHg from two studies. The vaccines are no longer under active investigation and were never approved for clinical use. The vaccines' effectiveness was limited by an inability to generate sufficient titers with significant longevity. The chief appeal of a vaccine is the ability to treat once and provide a durable therapy.

The fourth-generation hypertension vaccine research changed strategies in order to decrease the need for such high titers. Angiotensin receptor (ATR) vaccines effectively reduce blood pressure and prevent target organ damage in animal models. Uniquely, the ATR vaccine does not sequestrate peptides through antigen–antibody complexes, but desensitizes the angiotensin II receptor. The strategy of changing the receptor will hopefully lower the antibody titers needed to be clinically effective and allow less frequent vaccine injections. This ATR vaccine is the only hypertension vaccine that is currently being investigated.

In summary, the current problem of hypertension vaccine is not a safety issue but one of efficacy. In order to lower blood pressure, individuals must have brisk antibody responses to the vaccine. This can be unpredictable. Additionally, not every antibody is created equal, with some having greater efficacy than others. Continued research and creativity may ultimately produce an effective vaccine for hypertension but for now that seems to be a distant and cloudy future.

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Chapter 10
Masked Hypertension: Does It Lead to CVD or CKD?

F. Wilford Germino

Introduction

"We also propose that the phenomenon might be called 'masked hypertension,' on the grounds that the hypertension is not detectable by the routine methods" [1].

With those words, previously awkward and clumsy terms such as "reverse white-coat hypertension" and "white-coat normotension" became merely historical descriptions of another phenotype of hypertension. This new term, coined barely more than a decade ago, afforded a clarity in its description that earlier terms did not.

The advent of 24-h ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HPM) added additional information and insight to the usual site of blood pressure (BP) measurement—the office blood pressure (OBP). These additional readings allowed the categorization of patients into four phenotypes:

1. *Normotensives*—those with normal OBP and ambulatory blood pressure (ABP)/home blood pressure (HBP)
2. *Sustained hypertensives*—those with elevated OBP and ABP/HBP
3. *White-coat hypertensives*—those with elevated OBP yet normal ABP/HBP
4. *Masked hypertensives*—those with normal OBP yet elevated ABP/HBP

Hypertension is well recognized as a major modifiable factor contributing to key end points—including stroke, cardiovascular disease (CVD), and chronic kidney disease (CKD). The identification and treatment of patients with hypertension clearly benefit patients with this condition. Traditionally, hypertensive patients were identified on the basis of casual blood pressure or OBP. These are the classic sustained hypertensives. Much of the data regarding attributable risk for CVD and CKD in hypertension are derived from this population. This is largely because they were

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diagnosed and classified as hypertensives based on OBP long before the widespread usage of HPM and ABPM in clinical trials. The advent of HPM and ABPM has confirmed that for many patients with elevated OBP, there is a persistency that extends to out-of-office readings now defined as sustained hypertension. But there is little doubt that at least some patients with isolated OBP elevation (white coat) were rendered into this category in the earlier studies. More recently, with greater use of out-of-office measurement, there has been not only greater interest but also greater need to ascertain where on the spectrum from normotensive to sustained hypertensive does the risk lie for these other previously difficult-to-categorize patients—those with elevated HBP in the presence of normal OBP and the reverse and those with normal HBP and elevated OBP. Recent observations revealing that white-coat hypertension is not a totally benign condition, but is associated with some long-term risk, have reinforced the concept that BP needs to be accurately measured in settings other than the clinic or office.

Defining a patient as hypertensive, warranting long-term treatment, needs demonstration that the measured BP is associated with not only long-term risk without treatment but also the reduction of that pressure results in improved outcomes. So where does masked hypertension exist in this continuum of BP? Is this condition associated with target organ damage (TOD), especially as it relates to CVD and CKD end points, and resembles the normotensive or the sustained hypertensive phenotype?

Cardiovascular and Cerebrovascular Risk

A pivotal study, utilizing the measurement of both OBP and ABP, compared normotensives, masked hypertensives (referred to as white-coat normotensives in the manuscript), and sustained hypertensives. They demonstrated a 20% prevalence of masked hypertension. Both masked hypertensives and sustained hypertensives had significantly higher left ventricular (LV) wall thickness and mass compared to normotensives. LV index (LVMI) was similar between masked (86 g/m^2) and sustained hypertensives (90 g/m^2) despite OBP differences of 35/16 mmHg and, as expected, there was a much narrower difference in the awake ABP (14/6 mmHg). Also, masked hypertensives evidenced greater carotid intimal medial wall thickness (cIMT), cross-sectional area, and higher prevalence of atherosclerotic plaque compared to sustained normotensives [2]. Additional studies also support these findings, demonstrating increased incidence in LV hypertrophy (LVH) [3, 4], LV mass index (LVMI) [3–5], LV wall thickness [3, 6], and cIMT [4, 5, 7]. Masked hypertension, compared to normotensive patients, is also associated with an increase in cardiovascular (CV) events [3, 6, 8–10]. The Ohasama study, using HBP measurement, detected greater risk of silent cerebrovascular lesions in both masked and sustained hypertension than in both white-coat and normotensive populations (see Table 10.1) [11]. In these trials, the data suggest that masked hypertension more closely resembles sustained hypertension than normotension.

Table 10.1 Higher risks associated with masked hypertension

LVH	LVMI	LV wall	cIMT	CV events	CVA	ESRD
Sega et al. [3]	Liu et al. [2]	**Sega et al.** [3]	Kotsis et al. [5]	Bobrie et al. [10]	Hara et al. [11]	Agarwal and Andersen [12]
Tomiyama et al. [24]	**Sega et al.** [3]		Hanninen et al. [4]	**Bjorklund et al.** [6]		
Pierdomenico et al. [19]	Kotsis et al. [5]		Hansen et al. [8]	Mancia et al. [9]		
Hanninen et al. [4]	Kuriyama et al. [23]		**Matsui et al.** [7]	Pierdomenico et al. [19]		
Pogue et al. [25]				Hansen et al. [8]		
				Franklin et al. [15]		
				Angeli [20]		

Bold-treatment naïve population
LVH left ventricular hypertrophy, *LVMI* left ventricular mass index, *LV* wall Left ventricular wall thickness, *cIMT* carotid intimal medial thickness, *CV* events cardiovascular events, *CVA* cerebrovascular accidents, *ESRD* end-stage renal disease
[a] Not all results are statistically significant, but may trend towards higher risk than referent normotension

The data for the masked hypertension and CKD are much more sparse. One study, albeit small, did demonstrate that patients with masked hypertension and CKD did exhibit an increased risk to the development of end-stage renal disease (ESRD) compared to normotensive patients [12]. Much of the available data, however, relate to the prevalence of masked hypertension in a CKD population [13, 14].

A large database of over 7000 individuals from four countries that included treated hypertensives examined outcomes based on both ABP and clinic BP. The adjusted hazard ratios for all CV events with normotensive as the referent were 1.22 (95 % CI = 0.96–1.53; $P = 0.09$) for white-coat hypertension (OBP ≥ 140/90 and ABP < 135/85 mmHg); 1.62 (95 % CI = 1.35–1.96; $P < 0.0001$) for masked hypertension (< 140/90 and ≥ 135/85 mmHg); and 1.80 (95 % CI = 1.59–2.03; $P < 0.0001$) for sustained hypertension (≥ 140/90 and ≥ 135/85 mmHg) [8].

More recently, an analysis of an 11-country International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) revealed that untreated diabetics with masked hypertension exhibited higher risk. During the median of 11 years of follow-up, using a composite CV end point (fatal and nonfatal stroke, transient ischemic attack (TIA), death from ischemic heart disease, sudden death, nonfatal MI, angina pectoris, coronary revascularization, fatal and nonfatal heart failure, and fatal and nonfatal peripheral artery disease), the adjusted risk for untreated masked diabetic patients was almost twice as high as normotensives (HR, 1.96; 95 % CI 0.97–3.97; $P = 0.059$) and similar to untreated stage 1 hypertensives (HR, 1.07;CI, 0.58–1.98; $P = 0.82$) and less than untreated stage 2 hypertensives (HR, 0.53; CI, 0.29–0.99; $P = 0.048$). A major limitation of these data is the relatively small numbers of patients and events in each group [15].

Table 10.2 Treatment status of masked hypertensives in outcome studies

Includes treated	Treatment naive
Bobrie et al. [10]	Bjorklund et al. [6]
Pierdomenico et al. [19, 20]	Franklin et al. [15]
Pogue et al. [25]	Selenta et al. [36]
Hara et al. [11]	Sega et al. [3]
Tomiyama et al. [24]	Matsui et al. [7]
Ohkubo et al. [37]	
Ben-Dov et al. [31]	
Uchida et al. [18]	
Kuriyama et al. [23]	
Hanninen et al. [4]	
Mancia et al. [9]	
Kotsis et al. [5]	
Hansen et al. [8]	

Limitations

Among the limitations affecting the calculations of the true prevalence of masked hypertension in CKD are several factors. From study to study, there are key differences in their methodology. These differences range from the timing of BP readings, the number of readings performed, and even the definition of what constitutes the threshold reading to confirm the diagnosis of hypertension in the CKD population. Further complexity is added by including within the analysis two, perhaps very different, populations—the treatment naïve and the currently treated. Only one utilized a treatment-naïve population [7] while others incorporated treated patients [16–20].

Traditionally, masked hypertension refers to treatment-naïve patients, but the definition has been expanded by many to include those patients who are treated with antihypertensive medications and whose patterns resemble those of masked hypertension–normal OBP with elevated HBP or ABP. These partially treated patients have been included, to at least some extent, in many of the studies assessing risk (see Table 10.2). The inclusion of these partially treated patients with the treatment-naïve masked hypertensives makes the assessment of true risk more difficult. The extent to which this influences the assessment of risk for TOD is unknown. Some authors believe that the definition of masked hypertension should be restricted to only those treatment-naïve patients—all others on treatment should be considered as patients with incomplete control of hypertension with partially treated sustained hypertension [21]. Others contend that the pattern of BP may be either sustained, masked, or white coat, all reflective of an underlying pattern of hypertensive phenotype.

The pretreatment patterns are not known for these patients. Were clinic BP readings less proportionally elevated than the HBP and ABP readings prior to treatment? Could these partially treated patients represent part of the spectrum of masked hypertension? Some data may suggest that. In a small prospective trial on nondiabetic

treated hypertensives, those patients who were able to achieve BP control in both OBP and ABP settings demonstrated reduction in LVMI and microalbuminuria, along with other indices. In contrast, those patients whose OBP was controlled, but not the out-of-office readings, demonstrated no such benefit [22]. These data have been confirmed by other authors in different CKD populations. Even in treated hypertensives whose OBP has achieved normalization, if HBP or ABP remain elevated, there exists an increased risk for adverse outcomes including increased LVMI in diabetics with CKD [23], carotid artery disease and LVH [24], LVH and cardiac events [19], and prevalence of LVH [24], and stroke [25]. The extent to which this simply represents the impact of hypertension load upon TOD is not known. Interestingly, in the African-American Study in Kidney Disease (AASK) of 61% of patients with controlled clinic BP, 70% demonstrated elevated BP outside the office setting—a masked pattern [26].

Home Versus Ambulatory Blood Pressure Measurement

Defining a patient as exhibiting masked hypertension requires measurement of blood pressure out of the usual office setting. It may be done with either self-measurement at home or with ABPM. There is no general agreement regarding the use of HPM or ABPM to diagnose masked hypertension. Sega and colleagues found only a 57 and 45% association between ambulatory and home diastolic BP (DBP) and systolic BP (SBP), respectively, suggesting that these measurements are not equivalent [3]. Others have suggested little difference [27]. A recent paper suggested that the method by which BP is measured in the office may also influence the diagnosis of masked hypertension. It appears that an automated measurement of office BP results in a lower prevalence rate of masked hypertension compared to the conventional manual readings. The manual method also results in a greater inconsistency from visit to visit [28]. This concern is addressed to some extent by the work of Ben-Dov and colleagues who found that 72% of patients initially classified as masked hypertension remained so upon repeat ABPM [29]. Work of Pickering et al. gave evidence that a single ABPM may not prove sufficient to phenotype hypertensive patterns [30].

There do seem to exist certain patient types who may have increased likelihood of exhibiting masked hypertension. Generally, these are males—some suggest younger, some older [2, 8]—with a history of cigarette smoking, exercise, job stress, and alcohol consumption [31–34], with a disproportionate number of diabetes. Additionally, the presence of high-normal SBP and DBP in the clinic accompanying some of the aforementioned factors may result in an elevated suspicion for the presence of masked hypertension, necessitating further evaluation [2, 4, 8, 33, 35]. Multivariate correction for these underlying factors does not suggest that they are responsible for the increased TOD demonstrated in these studies.

Prevalence

The determination of the prevalence of masked hypertension in the population is difficult to determine based on the literature. Estimates range from 8 to 20% in the general population up to 61% in treated patients [26, 34, 36–38]. Many of the factors in the discussion of CKD also loom regarding prevalence in the general population. Populations reported often include treatment-naïve as well as treated hypertensives. There is no single consistent method for clinic BP measurement, and often no universal agreement on abnormal BP levels, especially in diabetes mellitus (DM) and CKD. Also, there is some evidence that masked hypertension may be "unmasked" through the use of a low-intensity exercise stress test; a recent well-designed retrospective study suggests otherwise [39, 40]. The authors in the later study utilized both 24-h ABPM and at least two exercise stress tests and found not only no relationship to establish a diagnosis of masked hypertension but also poor reproducibility in the hyperdynamic response to exercise. It is not unrealistic to anticipate that persistent and chronic elevation of BP in an out-of office setting would result in increased risk for TOD—including CVD, CKD, and microalbuminuria. Masked hypertension may impact TOD simply because hypertension load is increased in this population as well as the sustained hypertensive.

Conclusions

The proper management of hypertension increasingly relies upon the measurement of BP beyond the traditional office setting. This becomes imperative not only for determining the proper phenotype of the hypertension but also for modification and adjustment of therapies. If clinicians and patients are unwilling to incorporate this in all patients under consideration for the diagnosis of hypertension or undergoing treatment, then what strategies might one use to find this often-difficult-to-discern phenotype? Certain patient types may have greater likelihood of presenting as masked hypertensives:

1. Patients who present in the office with normal OBP but evidence of TOD.
2. A high-normal or borderline hypertensive patient, especially if male, smoker, with a high-stress job, as well as other additional risk factors should be considered at higher risk for this condition and evaluated further.
3. Consider the out-of-office assessment in all patients with family history of hypertension and high-normal OBP.
4. Consider systematic evaluation for patients who report HBP being elevated despite normal OBP.
5. Consider the diagnosis in those patients who demonstrate a hypertensive response to exercise although this would not be diagnostic.

The measurement of BP outside the office can be expected to increase over the next decade to perhaps being the norm rather than the exception. With widespread use,

one can anticipate the ability to more clearly identify and treat these individuals, regardless of their baseline or posttreatment hypertensive phenotype. However, given the wide variability in BP levels with our current method of BP measurement, it is likely that some patients will remain undiagnosed and therefore untreated, and thus vigilance for evidence of TOD will remain part of the management of patients with both confirmed and suspected hypertension [41].

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Chapter 11
White-Coat Hypertension: Do We Really Understand It Now?

Luis M. Ruilope

Introduction

Office blood pressure (BP) is very frequently higher than that measured out of the office. This difference, recognized for more than 70 years [1], has been ascribed to an alert reaction in response to a situation that results unusual for the patient and has been denominated as white-coat effect. White-coat hypertension (WCH), also described as isolated office or isolated clinic hypertension, is a condition in which BP is maintained elevated in iterative visits to the office and is normal when measured on either ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM). Conversely, BP can be normal in the office and be elevated when measured by ABPM or HBPM, this situation is known as masked (MH) or isolated ambulatory hypertension. The recent Guidelines of the European Society of Hypertension/European Society of Cardiology maintain the recommendation that both terms white-coat and masked hypertension should be reserved to qualify untreated individuals [2]. However, both situations are observed frequently in treated hypertensives requiring our attention to adequate the amount of pharmacological therapy in order to ensure the best cardiovascular (CV) and renal protection in these patients.

This chapter reviews in particular the prevalence of WCH, the risk accompanying it, and the clinical attitude during the follow-up of patients presenting with this form of hypertension. These data are confronted with those of masked hypertension in untreated as well as in treated hypertensives. Data obtained from the Spanish ABPM Registry will be used to describe the prevalence of both forms of hypertension in different clinical situations [3]. Particular attention will be paid to WCH and MH in chronic kidney disease (CKD).

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Prevalence of White-Coat Hypertension

Population-based studies reviewed by Fagard and Cornelissen [4] found an overall prevalence of WCH of 13%. This figure increases to 32% in hypertensive subjects. Table 11.1 contains the data of prevalence of WCH obtained in the Spanish ABPM Registry for the general population of treated and untreated hypertensives [5, 6], including the data of men and women [7]. These data have confirmed that WCH is present in a substantial minority of treated and untreated hypertensive patients and that advanced age, female gender, obesity, and a lower prevalence of smokers are the most relevant factors contributing to WCH, confirming previous results [4]. Interestingly, the sensitivity and specificity of the physician in relation to suspect the existence of WCH in untreated hypertensives have been shown to be 52.9 and 59.7%, respectively [6].

The prevalence of masked hypertension was 5.4% in treated hypertensives [5], with lower incidence in females (5.9%) than in males (7.9%, $p < 0.001$) [6]. Data from the Spanish ABPM Registry describe that 38% of untreated hypertensives presenting BP levels within the high–normal range (130–139/85–89 mmHg) in the office are masked hypertensives [3].

Table 11.2 contains the data of the Spanish ABPM Registry reflecting the prevalence of WCH in situations of elevated global CV risk as diabetes [8], coronary heart disease [9], chronic kidney disease (CKD; [10]), and hypertension with high global CV risk [12]. As can be seen, in all these situations accompanied by particularly elevated CV risk, the prevalence of WCH is elevated particularly when office BP is within the high level of prehypertension or within the stage 1 of arterial hypertension. Table 11.2 also contains the percentage of patients initially classified by office BP as having resistant hypertension who present WCH [12]. Even in this situation, WCH is substantially prevalent.

Overevaluation of BP level can also happen in the form of the term "pseudohypertension", used to describe an elevated brachial pressure assessed with a cuff and sphygmomanometer in the context of normal intra-arterial pressure assessed invasively [13]. Messerli et al. [14] indicated that this form of hypertension could be identified on the basis of palpable thickening of the radial artery (Osler positive sign). Ulterior studies have shown that Osler sign has low sensitivity and selectivity

Table 11.1 Prevalence of white-coat hypertension (WCH) in the general population of hypertensives including differences by gender and in untreated hypertensives [2–4]

	(*n*)	%WCH
Treated hypertensives [5]	*12,897*	*21.4*
Male [6]	15,212	24.2
Female [6]	13,936	32.5*
Untreated hypertensives [7]	*6176*	*29.2*[a]

*$p < 0.001$ vs. males

[a] WCH defined as ABP > 135 and/or 85 mmHg during day time. In the remaining it was defined as 24-h ABP > 130 and/or 80 mmHg

Table 11.2 Prevalence of white-coat hypertension (WCH) in treated hypertensive patients with diabetes, coronary artery disease (CAD), chronic kidney disease (CKD), hypertensive at high CV risk (HCVR) divided according to office BP level, and in resistant hypertension [8–12]

	(*n*)	%WCH
Diabetes	*12,600*	*33.0*
CAD	*2434*	*25.2*
CKD	*5693*	*36.8*
HCVR	*4729*[a]	
Office BP		
130–139 and/or 85–89		60.0
140–159 and/or 85–89		42.4
> or = 160/100		23.3
Resistant hypertension	*8295*	*37.5*

[a] Considering as control values of 24-h ABPM < 130 and/or 80 mmHg

[15]. Actually, available evidence suggests that most individuals labeled with the term of "pseudohypertension" have isolated systolic hypertension [13].

Importance of White-Coat Hypertension in Untreated Hypertensives

WCH in untreated hypertensives is important for several reasons [16]: First, the labeling of the patient as being false hypertensive is in itself of some gravity; second, insurability and cost; and third, the skewing of results of clinical trials that could include a significant number of WCH. This would translate into a lower than expected risk in the population studied. In fact, the most recent guidelines from the UK suggest that all new hypertensive patients undergo either ABPM or HBPM [17]. It has been calculated that identification of WCH in England could represent savings in the order of 10.5 million pounds in 5 years [18] based on the fact that identification of WCH provides the opportunity to avoid unnecessary treatment and medical visits.

Organ damage is less prevalent in WCH than in sustained hypertension and prospective studies have consistently shown this to be the case also for CV events and death [4, 19–21]. However, recent data indicate that the white-coat effect is strongly associated with increased arterial stiffness [22, 23], a strong predictor of CV events [2], is associated with carotid atherosclerosis in the general population [24], includes subjects with a widely different long-term risk of a CV event [25], and is accompanied by increased central aortic pressure levels [26]. These data enhance the possibility that in untreated hypertensives, WCH is accompanied by an increased global CV risk and the fact that patients with WCH frequently receive pharmacological therapy could contribute to explain a lower number of CV events [19]. It is also important to note that patients with this condition are prone to develop sustained hypertension over time; it is therefore advisable to monitor these individuals regularly so that antihypertensive therapy can be initiated when appropriate [27].

In contrast to WCH, in untreated people, MH is particularly prevalent in those presenting high–normal BP values in the office. Data from the Spanish ABPM Registry describe that 38% of untreated hypertensives presenting BP levels within the high–normal range (130–139/85–89 mmHg) in the office are masked hypertensives [3].

Importance of White-Coat Hypertension in Treated Hypertensives

As described previously, the prevalence of WCH in treated hypertensives is elevated. The relevance of this finding consists principally on the fact that patients with normal BP levels in ABPM or HBPM do not require further antihypertensive pharmacological therapy because goal BP is already attained. It has been considered that either ABPM or HBPM are required in treated hypertensives in order to have a better idea of the real BP of the patients so as to avoid an inadequate further drop in BP that could provoke unwanted CV and/or renal damage [28, 29]. Nevertheless, data from theHypertension in the Very Elderly Trial (HYVET) have shown positive data for the outcome of elderly hypertensive patients, albeit an estimate of 50% of them presented WCH in the study [30]. The finding of any form of target organ damage in patients with WCH promotes the need to consider pharmacological therapy [2].

The presence of episodic hypertension in treated hypertensives represents an enhanced risk for them [31]. These episodes could be related to the presence of sporadic episodes of WCH and deserve further investigation.

Prevalence and Relevance of Masked Hypertension

As previously commented, the prevalence of MH is high in untreated and treated hypertensives [3]. Several factors contribute to an increase of out-of-office BP such as younger age, male gender, smoking, alcohol consumption, physical activity, anxiety, obesity, diabetes, CKD, family history of hypertension, and office BP values in the high–normal range [32]. The incidence of CV events in untreated MH is similar to that in sustained hypertension [19, 32].

The Relevance of White-Coat Hypertension and Masked Hypertension in Patients with Chronic Kidney Disease

It is well established that CKD is accompanied by a particularly high prevalence of arterial hypertension and also by a very significant increase of CV risk [33]. The most adequate goal BP in CKD has been considered in previous guidelines to be

below 130/80 mmHg or even lower if proteinuria was present [34]. Actually, the goal considered is less than 140/90 mmHg [2] due to the fact that BP control in CKD must contemplate the very frequent simultaneous presence of CV events for which evidences of lower BP goals are absent [35]. In fact, an estimated glomerular filtration rate (eGFR) value below 60 ml/min/1.73 m^2 has to be considered among the five most relevant precipitators for the development of acute coronary syndrome [36] and the same could be said for stroke [37].

The misclassification of BP control at the office is very frequent in hypertensives with CKD. In a recent publication [10] that included 5693 patients with CKD, we observed that 36.8% exhibited WCH and 32.1% presented with adequate control of BP in the office but elevated values out of office. These data point to the need of a more adequate knowledge of the real values of BP control in CKD. Otherwise, over- or undertreatment could contribute to cause an increase in risk in these patients either as a consequence of unnecessary further treatment in WCH or to the development of CV events due to inadequate therapy allowing the persistence of sustained hypertension out of office.

Can the White-Coat Response Be Reduced in the Measurement of Blood Pressure in the Office?

Clinical practice guidelines have traditionally recommended manual BP measurement setting as the standard method for diagnosing hypertension. At present, BP cannot be estimated using a mercury sphygmomanometer in many countries. Auscultatory or oscillometric semiautomatic sphygmomanometers are used instead. These devices should be adequately validated and checked periodically through calibration [2]. The advent of automated office BP (AOBP) represents a new alternative to obtain a more adequate evaluation of BP levels in the office [38]. AOBP consists of obtaining multiple BP readings using a fully automated sphygmomanometer with the patient resting quietly alone. AOBP provides more accurate BP readings and correlates better with ABPM and HBPM values and with the presence of target organ damage [39].

Conclusion

WCH is quite prevalent in daily clinical practice and only using ABPM or HBPM can be adequately detected, albeit AOBP is presenting data that could facilitate an adequate BP estimation in the office. Detection in untreated hypertensives is cost saving (avoidance of treatment and medical visits), albeit the risk of this situation is above that of true normotensives. Follow-up of these patients is required using adequate ways to measure real BP in order to start pharmacological therapy as soon as

they become true hypertensives which happens frequently with time. If target organ damage is detected, pharmacological therapy can be initiated [2].

In treated hypertensives, WCH is also prevalent and it is important to discover its existence to avoid adding unneeded medication. Follow-up with adequate estimation of BP is also required.

On the other hand, the detection of MH requires the initiation of antihypertensive treatment in those previously untreated [2] and probably the reinforcement of treatment in those already receiving antihypertensive drugs.

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Chapter 12
Uric Acid and Hypertension: Is There Really a Link?

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Introduction

Uric acid is the final end product of purine degradation in humans (Fig. 12.1). This is distinct from most other mammals in which uric acid is further broken down to 5-hydroisourate and eventually allantoin by the enzyme uricase. Humans lost uricase during evolution likely due to a progressive reduction in uricase activity due to mutations in the promoter region, followed by complete silencing during the mid-Miocene. The slow loss of uricase was likely accompanied by adaptations like reduced activity of xanthine oxidase and by alterations in renal urate excretion to prevent the development of severe hyperuricemia. Indeed, this likely explains why the sudden knockout of uricase in mice has been shown to result in a remarkable increase in uric acid, causing urate nephropathy and renal failure [1, 2].

A potential benefit of the uricase mutation in the ancestors of the great apes and humans is likely, as a similar mutation of uricase occurred during the same period in the lesser apes. Different hypotheses have been proposed for what the potential benefit might have been to have a higher serum uric acid level. Earlier hypotheses were that uric acid might function as a circulating antioxidant, or potentially as a neurostimulant, that might increase reaction time or performance. More recently, there has been evidence that uric acid may have a role in maintaining blood pressure (BP) and salt sensitivity for our early hominoid ancestors consuming a very low salt diet [3], and also by acting to improve fat stores that might aid survival during periods of famine [4]. Regardless of the mechanism, serum uric acid is higher in

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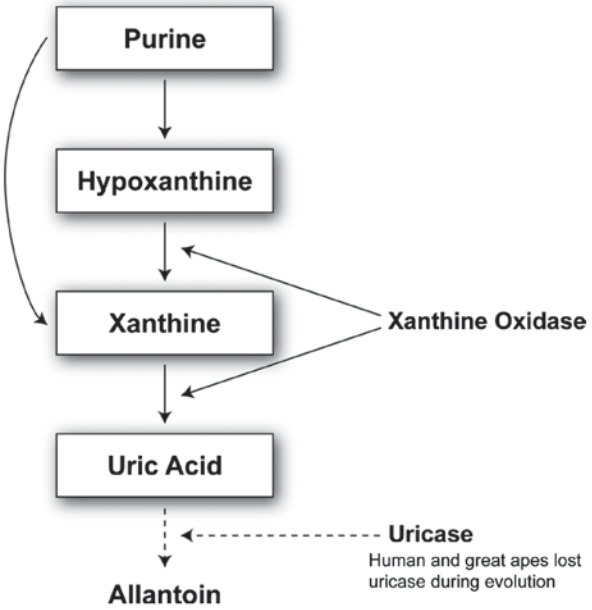

Fig. 12.1 Uric acid metabolism. Purines are degraded to hypoxanthine and xanthine. Xanthine oxidase converts hypoxanthine to xanthine and also xanthine to uric acid. Unlike most other animals, humans and great ape cannot metabolize uric acid due to a mutation of uricase

humans compared to most other mammals and is also less regulatable and more sensitive to change with diet.

Normal serum uric acid levels vary between 3 and 7 mg/dL in humans. Uric acid levels begin to increase during adolescence years in males but not until menopause in females due to increased uric acid excretion in females [5], an effect likely mediated by estrogen compounds. Several factors affect serum uric acid levels in humans. First, diets rich in purines (such as umami-based foods) or fructose (such as table sugar and high-fructose corn syrup) can increase serum uric acid. Uric acid can also be generated endogenously by states associated with increased cell turnover (cancer) or from ischemia (from the breakdown of adenosine triphosphate, ATP). Reduced uric acid excretion may also occur in settings associated with reduced renal function or in conditions such as obesity, hyperinsulinemia, or hypertension (Fig. 12.2).

Uric Acid Is a Causative Factor for Hypertension—Historical Perspective

Earliest evidence linking high BP to uric acid can be traced to the 1800s. The medical resident Mahomed [6], proposed an elevated serum uric acid as one of the important mediators of high BP; this was followed by Haig [7] who also highlighted this

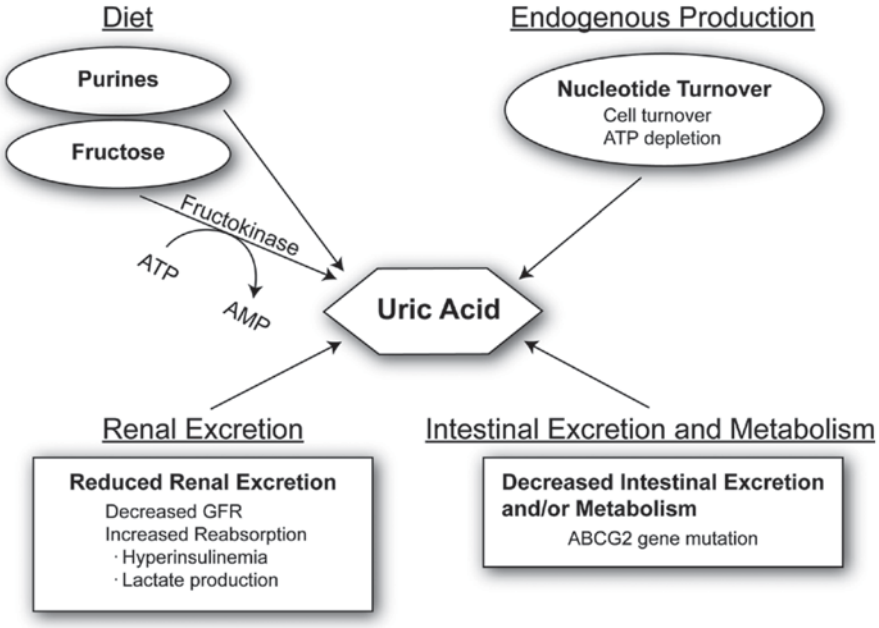

Fig. 12.2 Factors that modulate serum uric acid. Serum uric acid can be modulated by four major mechanisms. Increased production of uric acid can occur from diet or endogenously. Diets rich in purines (umami foods) or fructose can increase serum uric acid. Fructose metabolism by fructokinase leads to degradation of ATP to AMP. AMP accumulation stimulates AMP deaminase, resulting in uric acid production. Increased nucleotide turnover generates nucleotide degradation products metabolized to uric acid. Reduced excretion of uric acid can also alter blood levels. Reduced urinary excretion may occur from reduced glomerular filtration or enhanced tubular absorption. Decreased intestinal excretion and/or metabolism by gut microbiome may alter uric acid levels. ABCG2 stimulates intestinal excretion of uric acid and if mutated can raise uric acid levels. *ATP* adenosine triphosphate, *AMP* adenosine monophosphate, *GFR* glomerular filtration rate, *ABCG2* ATP-binding cassette sub-family G member 2

association in his publications. Subsequently, Davis [8] published a report discussing uric acid as a toxic substance responsible for high arterial tension in gout. The interest in the field was reignited when a report linking uric acid with cardiovascular disease was published by Gertler et al. in 1951 [9]. The strong relationship between uric acid and hypertension was presented in a study by Cannon et al. in 1966, where hyperuricemia was prevalent in 25–50% patients with untreated hypertension and in 75% patients with malignant hypertension or coexistent renal disease [10].

Experimental Studies

Early studies investigating the effects of raising uric acid levels in laboratory animals primarily noted the development of acute kidney injury due to the accumulation of urate crystals in the tubules and interstitium. This was also observed in the

uricase knockout mouse. While these early models were helpful from the standpoint of understanding the pathogenesis of tumor lysis syndrome, they were not relevant to studies of human hypertension.

A breakthrough occurred when Mazzali et al. were able to induce mild hyperuricemia by administering an oral uricase inhibitor (oxonic acid) to laboratory rats [11]. The surprising finding was that the rats developed a progressive rise in BP over several weeks that was not associated with any intrarenal crystal deposition or development of renal failure. Indeed, the primary histologic findings were subtle microvascular disease consisting of thickening of the afferent arteriole, not too dissimilar from the renal lesions observed in human essential hypertension. Over time, the increase in uric acid and BP levels was associated with the development of additional histologic changes, including glomerular hypertrophy, tubulointerstitial injury, and low-grade inflammation, in the absence of urate crystals.

An interesting aspect of the animal model was that the hypertension could be divided into two phases. The initial phase was driven by uric acid-mediated activation of the renin angiotensin system, the induction of oxidative stress, and endothelial dysfunction with reduction in endothelial nitric oxide levels. Lowering uric acid levels with xanthine oxidase inhibitor and uricosuric agents in this early phase could completely prevent or treat the hypertension [12, 13]. However, once animals developed significant microvascular injury and tubulointerstitial inflammation, hypertension persisted independent of serum uric acid level in the setting of a high salt diet [3, 14–16].

Clinical Studies

The observation from the experimental studies suggested two phases of hypertension, with the initial phase being uric acid dependent that would occur independent of salt intake, but then converting to a salt-sensitive hypertension driven by subtle injury to the kidney. Interestingly, there is some evidence that this sequence of events may also be observed in human hypertension [14]. Early hypertension (before the age of 40) is often salt resistant (that is, BP is minimally altered by dietary salt intake), whereas hypertension later in life is more commonly associated with salt sensitivity and renal microvascular disease. An elevated serum uric acid has also been repeatedly shown to independently predict the development of hypertension [17]. The strongest association of hyperuricemia is with early hypertension such as that observed in adolescents [18]. Among 125 children (aged 6–18) referred to a tertiary-care renal program for evaluation of newly diagnosed hypertension, 63 had primary hypertension, 40 had secondary hypertension, and 22 had white-coat hypertension. Serum uric acid concentrations > 5.5 mg/dL were found in almost 90% of subjects with primary hypertension and in 30% with secondary hypertension. The results were striking, and there was nearly a linear relation between serum uric acid and BP (Fig. 12.3).

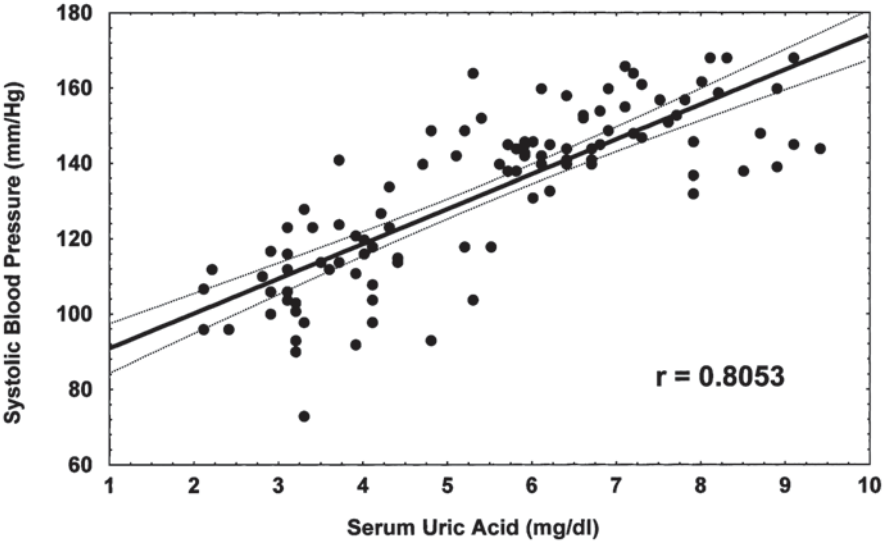

Fig. 12.3 Linear relation between serum uric acid and blood pressure. Serum uric acid is plotted against systolic BP for children with normal BP (controls) and primary hypertension. *Solid* and *dotted lines* in both panels represent the best fit and 95% confidence intervals, respectively, and demonstrate the linear relation between uric acid concentration and systolic BP. Pearson correlation coefficients are $r = 0.8053$ ($P = 0.000004$) for systolic BP. *BP* blood pressure. (Reprinted from [18]. With permission from Wolters Kluwer Health)

Lowering uric acid with either allopurinol or probenecid has also been reported to reduce BP markedly in pilot studies conducted in adolescents with hypertension or prehypertension [19, 20]. In a randomized, double-blind, placebo-controlled, crossover study involving newly diagnosed adolescents with stage 1 essential hypertension and uric acid levels >6 mg/dL, subjects were treated with allopurinol or placebo. Treatment with allopurinol resulted in normalization of BP in two-thirds of the subjects compared to one participant in the placebo group. Another recent study of prehypertensive obese adolescents reproduced similar results and provided direct evidence that uric acid increases BP in adolescents and that this effect can be mitigated by lowering uric acid. In this randomized, double-blind, placebo-controlled study, 60 children (aged 11–17) with prehypertension and uric acid 5 mg/dl were treated with either allopurinol, probenecid, or placebo for 8 weeks. Based on the clinic and 24-h ambulatory BP measurements, patients in the active treatment groups with allopurinol and probenecid experienced marked reduction in systolic BP (average 10 mmHg) and diastolic BP (average 7 mmHg). An interesting observation in this study was the effect of therapy on weight gain. Patients in the treatment arm had stable weight during the 3-month study period compared to the placebo group which gained ~1 kg per month. Similar observations were noted in another study which showed increased BP, weight, and metabolic syndrome in young adult men taking a high-fructose diet (which raises uric acid levels), and these effects were

mitigated by allopurinol [21]. Epidemiologic studies have also shown that uric acid can predict weight gain [22]. All these striking findings strongly highlight the role of uric acid in hypertension and other features of metabolic syndrome like obesity.

The beneficial effects of lowering uric acid in adults are less marked, consistent with the findings in animal studies that once the injury has occurred, hypertension persists irrespective of uric acid levels [23].

The Link Between Uric Acid and Hypertension May Begin in the Intrauterine Environment

The importance of the intrauterine environment in influencing BP during adult life was first reported by Barker et al. who showed an inverse relationship between birth weight and systolic BP [24]. Recent studies suggest that serum uric acid may have a role in both causing low birth weights and increasing the risk for development of hypertension later on in life [25]. Elevated uric acid levels seen during normotensive pregnancy [26] or with preeclampsia predict low birth weight [27] and may have a negative effect on fetal growth and kidney development by blocking endothelial cell proliferation and function [25, 28, 29]. Studies examining children with a history of low birth weight show impaired endothelial function and increased BP and serum uric acid levels [30, 31]. While it is not known if the relationship of elevated uric acid in the mother and child reflects genetic factors, epigenetic factors, or diet, existing data clearly suggest a strong relationship of uric acid with birth weight and the risk for development of hypertension as an adult.

Proposed Mechanism for Uric Acid-Induced Hypertension

The mechanism by which serum uric acid may have a role in driving hypertension is complex. Serum uric acid reflects extracellular uric acid and is directly linked with gout, which results from extracellular deposition of urate crystals in joints and tissues. However, the vascular and renal effects of uric acid are likely mediated by intracellular uric acid levels. While an elevated serum uric acid usually translates into increased intracellular levels due to uptake in cells via organic anion transporters such as URAT1, it remains possible that alterations in urate transport mechanisms might alter this relationship.

A key aspect of the dichotomy between intracellular and extracellular uric acid is the relationship with oxidative stress. Outside the cell, uric acid appears to function as an antioxidant, and is capable of inactivating superoxide anion and hydroxyl radicals. However, inside the cell, uric acid acts as a prooxidant, and this stimulates the release of inflammatory mediators, vasoconstrictors, growth factors, and oxidants [11, 13, 29, 32–35]. The oxidative burst is mediated by an increase in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and causes mitochondrial dysfunction [36, 37]. Within the vasculature, this leads to endothelial

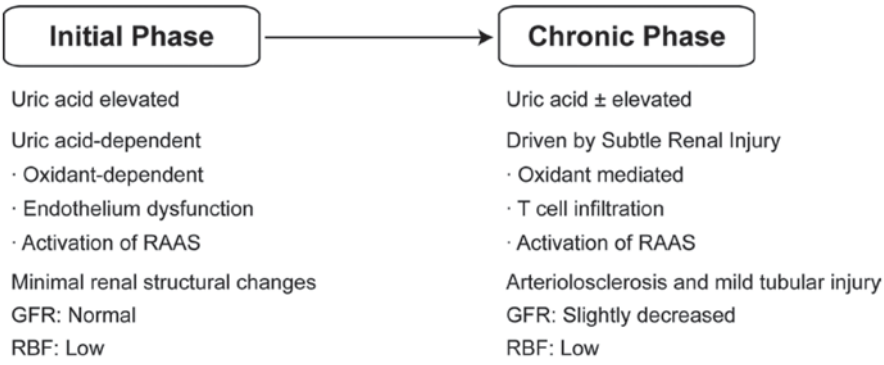

Fig. 12.4 Proposed mechanism of uric acid-induced hypertension. Uric acid is proposed to induce hypertension via two phases. The initial phase is mediated by renal vasoconstriction mediated by uric acid-induced oxidative stress, endothelial dysfunction, and activation of the renin angiotensin system. During this time, there is minimal structural injury to the kidney, and the hypertension tends to be salt resistant. Over time, microvascular disease and tubulointerstitial injury develop, resulting in intrarenal mechanisms that drive salt sensitivity independent of the serum uric acid level. These factors include the role of T cells, oxidative stress, and intrarenal activation of the renin angiotensin system. *RAAS* renin–angiotensin–aldosterone system, *GFR* glomerular filtration rate, *RBF* renal blood flow

dysfunction, arteriolopathy, impaired autoregulation, and increased systemic and glomerular hydrostatic pressure [38]. Low-grade tubular injury and renal inflammation also occur, which may also contribute to salt-sensitive hypertension through pathways involving T cell infiltration and the release of oxidants and angiotensin II [39]. An overall proposed mechanism for hypertension is shown in Fig. 12.4.

Other Effects of Uric Acid

While much attention has been focused on the role of uric acid in hypertension via its action on the vasculature, there is also increasing evidence that uric acid may have direct effects on adipocytes [36], hepatocytes [37], pancreatic islet cells [40], and renal tubular cells [41] that may play a role in obesity, fatty liver, islet dysfunction, acute and chronic renal injury, and metabolic syndrome. There is also increasing evidence that uric acid may have neural effects leading to increased response time and impulsivity [42]. Thus, we have gone a long way since the 1950s when uric acid was simply viewed as an inert biological waste product [43].

Limitations

While there is increasing evidence that uric acid may have a role in hypertension and metabolic syndrome, we are still lacking large, well-controlled, prospective randomized trials that document a benefit of lowering uric acid in these conditions.

It therefore seems premature to empirically treat subjects with allopurinol, given that it can rarely result in serious allergic reactions, such as the Stevens–Johnson syndrome. In addition, other concerns have been raised, especially from genome-wide association studies (GWAS), in which genetic polymorphisms of various genes have been linked with elevated serum uric acid and gout, but not with hypertension or cardiovascular disease [44]. However, most of the polymorphisms responsible for the association of uric acid with gout relate to genes involved in the transport of uric acid into and out of the cell, and hence might act to dissociate serum uric acid from intracellular levels where the vascular and renal effects of uric acid occur. Hence, more studies are needed before we can be definitively sure that uric acid is an important modifiable risk factor in the management of subjects with hypertension and kidney disease.

Summary

Hypertension is a complex disease with multifactorial etiologies. Uric acid may be one of the modifiable risk factors contributing to susceptibility to disease in adult life. Based on the available experimental and clinical studies, intracellular uric acid likely plays a role in early hypertension. Our current strategy of treating BP when microvascular changes have already occurred clearly needs rethinking. The key would be to identify and treat risk factors like uric acid in the prehypertension or early hypertension stage so as to prevent its multitude downstream effects.

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Chapter 13
Preeclampsia: Angiogenic Factors, Blood Pressure, and the Kidney

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Introduction

Preeclampsia (PE) is considered a pregnancy-specific syndrome that is diagnosed when new-onset hypertension and proteinuria occur after 20 weeks of gestation [1–3]. PE can progress rapidly to more severe complications such as seizures (eclampsia) and hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, which can lead to cerebral hemorrhage, organ failure, and death [1–3]. PE is estimated to affect 5–7% of all pregnancies. Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of PE have not been fully elucidated. Hypertension associated with PE develops during pregnancy and remits after delivery, implicating the placenta as a central culprit in the pathogenic process [1–3]. PE affects the vasculature of many target organs including the brain, liver, and kidney [1–3]. Indeed, glomerular endotheliosis is considered an important characteristic lesion of women with PE [1–3].

Although numerous factors including genetic, behavioral, and environmental factors have been implicated in the pathogenesis of PE, an important initiating event for the development of PE is thought to be placental ischemia/hypoxia ([1–3]; see Fig. 13.1). The hypoxic placenta, in turn, releases a variety of soluble factors that have profound effects on the peripheral vasculature and arterial pressure regulation. These factors include a host of molecules such as the soluble vascular endothelial growth factor (VEGF) receptor-1 (sFlt-1), the angiotensin II type 1 receptor autoantibody (AT1-AA), and inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), which in turn generate widespread dysfunction of the maternal vascular endothelium. This dysfunction manifests as enhanced formation of factors such as endothelin, reactive oxygen species (ROS), and augmented vascular sensitivity to angiotensin II. In addition, PE is also associated with decreased formation of

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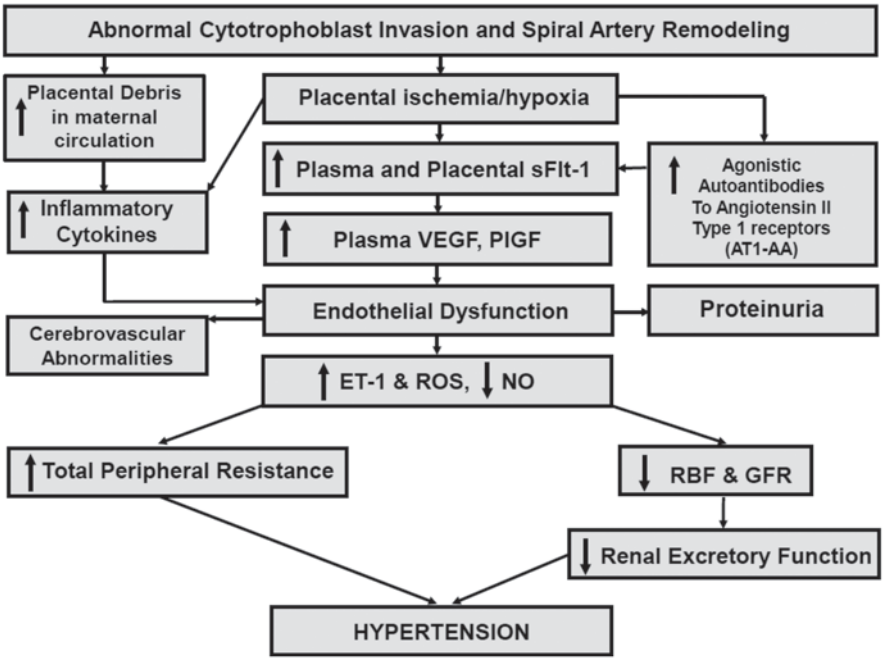

Fig. 13.1 Hypothetical scheme depicting how abnormal cytotrophoblast invasion and subsequent reductions in spiral artery remodeling results in endothelial dysfunction and hypertension in PE

vasodilators such as nitric oxide (NO). These alterations in vascular function not only lead to hypertension but multiorgan dysfunction including the brain, kidneys, and liver as well. Since PE remains to be one of the leading causes of maternal death and perinatal morbidity, identifying the mechanisms underlying abnormal placentation and the factors that link placental hypoxia and maternal cardiovascular and renal abnormalities remain important areas of investigation.

Abnormal Spiral Artery Remodeling and Placental Hypoxia in PE

During normal pregnancy, fetally derived cytotrophoblasts migrate to the uterine tissue in an orchestrated manner to invade and remodel the maternal uterine spiral arteries to ensure adequate oxygen and nutrient delivery to the developing uteroplacental unit [1–5]. This complex migration and invasion process results in the conversion of the high-resistance, small-diameter spiral arteries into high-capacitance, low-resistance vessels [4, 5]. It is believed that poor cytotrophoblast migration and/or vascular invasion during PE, leads to abnormal spiral artery remodeling and inadequate oxygen delivery to the developing uteroplacental unit [4, 5].

While the exact mechanisms responsible for the abnormal placental trophoblast migration/invasion and vascular remodeling in PE are unclear, results from a recent study by Hunkapiller et al. found that the absence of Notch2 in mice is associated with reduced vessel diameter and placental perfusion [6]. Additional findings that perivascular and endovascular cytotrophoblast often fail to express the Notch ligand, JAG1, in PE provides further evidence that defects in Notch signaling may be important in the pathogenesis of this pregnancy syndrome. Another recently described molecular pathway implicated in placental vascular development is the transcription factor storkhead box 1 (STOX1), a member of the winged helix transcription factor family [7]. Transgenic overexpression of STOX1 in the mouse leads to a phenotype that mimics PE in several key ways, most notably an increase in systolic blood pressure during gestation and elevated maternal circulating levels of soluble fms-like tyrosine kinase (sFlt)-1 and soluble endoglin [7]. While data from these recent studies are intriguing, much work remains to be done to elucidate the role of factors in mediating abnormal spiral artery remodeling in PE.

Factors Linking Placental Ischemia/Hypoxia with the Maternal Hypertension

Angiogenic Factors

One of the most intensely studied pathways in the pathophysiology of PE is that related to VEGF signaling [1–3, 8–11]. VEGF and the placental growth factor (PlGF-1) are also critically important in the maintenance of proper endothelial cell function in adult animals [8–11]. The VEGF signaling pathway came to prominence with the discovery of elevated circulating and placental levels of the soluble form of the VEGF receptor, fms-related tyrosine kinases-1 (sFlt-1) in preeclamptic women, especially in late gestation [8–11]. sFlt-1 is a circulating soluble receptor for both VEGF and PlGF, which when increased in maternal plasma leads to less circulating free-VEGF and free-PlGF, thus preventing their availability to maintain maternal endothelial integrity. In the kidney, this inactivation of free VEGF is believed to cause endotheliosis and proteinuria [12]. Subsequent studies of the regulation of sFlt-1 in cell culture and placental tissue in vitro have demonstrated that sFlt-1 is released from placental villi and trophoblast cells in response to reduced oxygen tensions similar to that seen in an ischemic placenta [1–3]. While sFlt-1 production appears to be regulated by hypoxia inducible factor-1, other factors such as TNF and the agonistic autoantibody to the AT1-AA also appear to be involved [1–3, 13].

Several lines of evidence support a role for angiogenic factors in the pathogenesis of hypertension during PE. Several clinical studies have reported that sFlt-1 levels are strongly correlated with the severity of the PE [8–11]. In addition, chronic intravenous administration or adenovirus delivery of sFlt-1 to pregnant rats, to

mimic plasma concentrations of sFlt-1 observed in preeclamptic women, decreases free VEGF and PlGF and produces hypertension and proteinuria [9, 14]. Moreover, a promising pilot study recently demonstrated that sFlt-1 could be removed from the maternal circulation of preeclamptic women by apheresis safely, and that this therapy reduced both blood pressure and proteinuria, with a trend toward increased gestational duration [15].

In addition to playing a pathogenic role in PE, angiogenic factors have been proposed as diagnostic markers for the syndrome. Several clinical studies were designed over the past decade to determine the potential of angiogenic factors as prediction tests in PE [1, 11]. While their accuracy fell short of sensitivities and likelihood ratios required for clinical use, prediction was much more reliable for early-onset PE. Ohkuchi et al. recently found that the sFlt-1 to PlGF ratio was a useful component for the prediction of PE when measured at 26–31 weeks of gestation [16]. Likewise, Perni et al. examined angiogenic factors in patients who had preexisting hypertension with superimposed PE, and found higher circulating levels of sFlt-1 prior to the 20th week of gestation in these patients versus pregnant women who had preexisting hypertension but did not develop PE [17]. These studies, along with other recent work, suggest that angiogenic balance could be a reliable marker of PE and allow detection prior to the onset of patient symptoms [11, 18]. Rana and colleagues recently suggested that angiogenic proteins alone account for the disease's major phenotypes and therefore are extremely specific for both diagnosis and prognosis [11]. They also suggested that future screening studies should focus on prediction of the angiogenic form of PE rather than disease diagnosis based on nonspecific clinical criteria [11].

Immune Factors and Inflammation

The pathophysiology of PE is also thought to involve immune system abnormalities and inflammation [18–20]. Redman and colleagues proposed that fragments shed from the placental surface include pro-inflammatory proteins that may contribute to the systemic inflammatory response in normal pregnancy and the exaggerated inflammatory response in PE [19]. Supporting this concept are findings that pro-inflammatory cytokines, such as IL-6 and TNF-α, are elevated in preeclamptic women and placental ischemic rat models [18]. Moreover, infusion of proinflammatory cytokines into pregnant animals produces significant elevations in blood pressure [3, 18].

Maternal immune tolerance mechanisms are also implicated in the pathophysiology of PE. This maternal immune tolerance involves crucial interactions between regulatory CD4+ T cells and uterine natural killer cells recognizing and accepting the fetal antigens and facilitating placental growth. Partial failure of this interaction is thought to lead to poor placentation and dysfunctional placental perfusion and chronic immune activation originating from the placenta. Preeclamptic women have a decrease in circulating regulatory CD4+ T cells. Moreover, placental ischemic rats have a 47% decrease in regulatory CD4+ T cells in the peripheral circulation when

compared to normal pregnant rats [19]. T helper 17 cells, which are upregulated in a variety of autoimmune disorders, are also increased in preeclamptic women, and in placental ischemic rats [20]. While these data support the hypothesis that hypertension in response to placental ischemia represents a shift from the normal anti-inflammatory state of pregnancy to a pro-inflammatory state, the quantitative importance of CD4+ T cells and T helper 17 cells in the pathophysiology of PE remains to be determined [18].

A number of recent studies have also indicated that women with PE produce a novel agonistic autoantibody to the angiotensin II type I receptor [20–23]. Dechend and colleagues reported that sera from preeclamptic women contain an IgG (type 3) autoantibody that reacts with the AT1 receptor [22]. The binding of the AT1-AA to the seven amino acid stretch of the second extracellular loop of the angiotensin II type 1 receptor stimulates a chronotropic response from rat neonatal cardiomyocytes which can be attenuated with administration of an AT1 receptor antagonist. The is the basis of the bioassay primarily used for the detection of the autoantibody. These autoantibodies, isolated over a decade ago in preeclamptic women, have been studied more intensively recently, including their identification in the circulation of rats undergoing placental ischemia [3, 18, 24]. While infusion of the AT1-AA directly into pregnant animals results in moderate hypertension, the pathogenic importance of these antibodies remains to be fully elucidated, as their presence has been noted postpartum in a subset of preeclamptic patients even after the symptoms were resolved. Further studies are needed including determining how these unique antibodies are produced and how they interact with the other pathogenic agents in PE to produce the clinical phenotype.

Endothelin

There is growing evidence to suggest an important role for endothelin-1 (ET-1) in the pathophysiology of PE [25, 26]. Multiple studies have examined circulating levels of ET-1 in normal pregnant and preeclamptic cohorts, and found elevated levels of plasma ET-1 in the preeclamptic group, with some studies indicating that the level of circulating ET-1 correlates with the severity of the disease symptoms, though this is not a universal finding [25]. ET-1, however, is produced locally and plasma levels typically do not reflect tissue levels of the peptide. Animal studies have shown that a myriad of experimental models of PE (placental ischemia, sFlt-1 infusion, TNF-α infusion, and AT1-AA infusion) are associated with elevated tissue levels of ET-1 [2, 3, 25, 26]. A recent report also indicated increased vascular contractility to big ET-1 in the reduced uteroplacental perfusion pressure rat model of PE, an effect that was attributed to a greater contribution of matrix metalloproteinases to cleave bET-1 to ET-1 [27]. Finally, the fact that hypertension in pregnant rats, induced by placental ischemia or chronic infusion of sFlt-1, TNF-α, or AT1-AA [25, 26] can be completely attenuated by ET_A receptor antagonism, strongly suggests that ET-1 is a final common pathway linking factors produced during placental ischemia to elevations in maternal blood pressure.

Nitric Oxide

Studies have suggested important roles for NO as a regulator of arterial pressure under various physiological and pathophysiological conditions [28–30]. NO is synthesized endogenously from L-arginine, oxygen, and nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) by various NO synthase (NOS) enzymes. NO production is elevated in normal pregnancy and these increments appear to play an important role in the vasodilatation that occurs in healthy pregnancy [28–30]. Thus, it was postulated that NO deficiency during PE might be involved in the disease process. Whether there is a reduction in NO production during PE is controversial. Much of the uncertainty originates from the difficulty in directly assessing the activity of the NO system in a clinical setting. Assessment of whole body NO production via measurement of 24-hour nitrate/nitrite excretion has yielded variable results, likely due to difficulties in controlling for factors such as nitrate intake and excretion [2–3]. Thus, the relative importance of NO deficiency in the pathogenesis of PE has yet to be fully elucidated.

In support of a role for NO deficiency in the pathogenesis of PE are reports from several laboratories that chronic NOS inhibition in pregnant rats produces hypertension associated with peripheral and renal vasoconstriction, proteinuria, intrauterine growth restriction, and increased fetal morbidity, a pattern resembling the findings of PE [28–30]. Placental ischemia has been reported to result in endothelial dysfunction and reduced NO production in some but not all vascular beds [29]. Moreover, L-arginine supplementation in animal models and in women with PE reduces blood pressure and improves pregnancy outcomes in some but not all studies [29]. Finally, hypertension induced by sFlt-1 in pregnant animal models is associated with significant reductions in NO synthesis [14].

Endoplasmic Reticulum and Oxidative Stress

Endoplasmic reticulum stress activates a number of signaling pathways aimed at restoring homeostasis. Burton and colleagues proposed that this mechanism to restore homeostasis fails and apoptotic pathways are activated to alter placental function in women who develop PE [31]. In addition, chronic, low levels of endoplasmic reticulum stress during the second and third trimesters may result in a growth-restricted phenotype. They also propose that higher levels of endoplasmic reticulum stress lead to activation of pro-inflammatory pathways that may contribute to maternal endothelial cell activation [31]. While endoplasmic reticulum stress is known to occur in PE, the importance of this abnormality in the pathophysiology has yet to be fully elucidated.

Oxidative stress has also been implicated in PE, as increased concentration of several oxidative stress markers have been reported systemically in preeclamptic women, among these peroxynitrite [32, 33]. Peroxynitrite concentrations in vascular

endothelium were much higher in preeclamptic women versus normal gestation, concurrent with decreased levels of superoxide disumutase (SOD) and NOS [32, 33]. There is also evidence of increased oxidative stress during gestation in the placental ischemic rat hypertensive model, suggesting a link between placental ischemia/hypoxia and the production of reactive oxygen species [2, 3]. For example, the SOD-mimetic drug tempol, led to significant attenuation of the hypertensive response [2, 3]. In a related study, administration of the NADPH oxidase inhibitor apocynin also significantly attenuated placental ischemia-induced gestational hypertension, implicating the enzyme as an important source of pathogenic ROS in the reduced uterine perfusion pressure (RUPP) animal [2, 3]. Failure of the drug to fully normalize blood pressure, however, leaves open the possibility that alternative ROS production pathways are at work in the RUPP model. Further studies into the mechanism of ROS production in animal models of PE should help shed light into the importance of oxidative stress in the pathophysiology of PE and perhaps allow the identification of useful antioxidant strategies. It remains to be seen whether ROS production is a primary or secondary cause of PE pathophysiology, and how effective manipulation of the system will be in the search for effective therapies.

The Kidney and PE

PE is associated with decreases in renal blood flow and glomerular filtration rate and increases in protein excretion [1–3]. While the kidneys are an important target organ in PE, the pathophysiological mechanisms underlying the reduction in renal hemodynamics and proteinuria in PE has yet to be fully elucidated. VEGF is important to maintain endothelial cell function especially for the fenestrated endothelium found in glomeruli of the kidney, the brain, and liver. VEGF and VEGF receptors are highly expressed in the kidney. VEGF is expressed in podocytes in the glomerulus, and VEGF receptors are present on endothelial, mesangial, and peritubular capillary cells [1–3, 12]. Signaling between endothelial cells and podocytes is thought to be important for maintenance of the filtration function of the glomerulus and inhibitors of VEGF signaling have been shown to result in alterations in glomerular structure and function (see Fig. 13.2). In addition, ablation of VEGF-A from endothelial cells results in progressive endothelial degeneration and sudden death of mutant animals [12].

Because the endothelium is a major target organ for the actions of VEGF, it is likely that decreases in the production of endothelium-derived relaxing factors such as NO and enhanced production of vasoconstricting factors such as endothelin play a role in mediating the changes in renal hemodynamics in PE. (see Fig. 13.2) In support of this concept are studies demonstrating that inhibition of VEGF signaling with sFlt-1 or antibodies is associated with significant reductions in the expression of endothelial and neuronal NOS in the kidney [34]. Another potential mechanism whereby VEGF blockade could reduce renal hemodynamics and increase blood

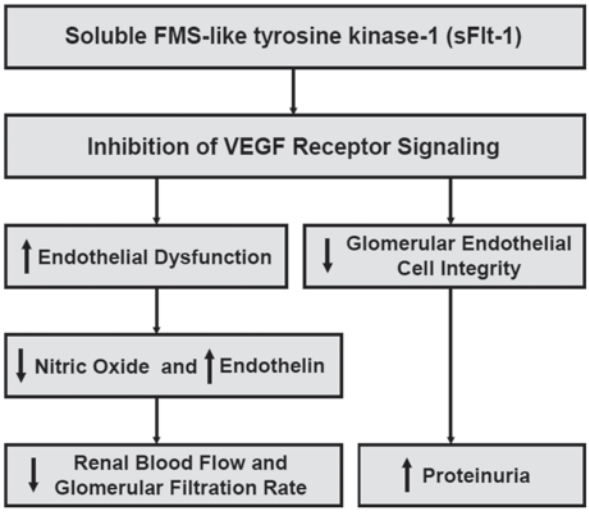

Fig. 13.2 Potential mechanisms whereby placental ischemia leads to changes in renal hemodynamics and proteinuria

pressure is by enhancing ET-1 synthesis. Indeed, renal endothelin levels are increased in placental ischemic rats and in pregnant rats infused with sFlt-1 [14]. In addition, ET_A receptor antagonist significantly attenuates the vascular responses to placental ischemia or chronic infusion of sFlt-1 in pregnant animals [14].

The Brain and PE

Cerebrovascular abnormalities play a significant role in the pathogenesis of PE/eclampsia [35, 36]. Neurological symptoms such as headaches, blurred vision, nausea, drowsiness, and seizures are commonly reported in preeclamptic patients [1, 35–38]. Furthermore, the risk of developing a stroke during pregnancy and the postpartum year is increased in women with PE/eclampsia [39]. Approximately 40 % of all PE/eclampsia deaths are due to cerebrovascular events with cerebral hemorrhage contributing to 35 %, cerebral edema 3 %, and cerebral embolus 1 % of PE-related deaths [35–38].

Magnetic resonance imaging and computed tomography scans of the brain reveal abnormalities consistent with edema in preeclamptic patients [35–38]. Edema forms either from increased water transport into cells (cytotoxic edema) or through the disruption of the blood–brain barrier (BBB; vasogenic edema) [39]. The BBB, formed by the close association of endothelial cells, smooth muscle cells or pericytes (capillaries), and astrocytes, regulates the transport of substances between the blood and the brain tissue. Increased permeability of the cerebral vessels has been reported in both normal pregnancy and PE. For example, plasma from normal pregnant and even more so from preeclamptic women increases permeability of cerebral

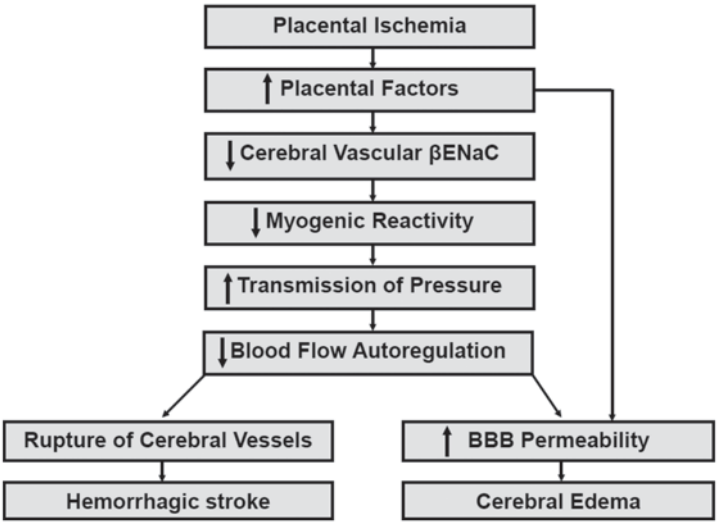

Fig. 13.3 Proposed mechanisms whereby placental ischemia leads to cerebrovascular abnormalities

vessels in an ex vivo model [40]. These and other studies suggest that pregnancy itself induces changes in the cerebral vasculature, which may be exacerbated in the presence of increased arterial pressure, characteristic of PE.

Abnormalities in cerebral blood flow autoregulation may also contribute to cerebral dysfunction in PE (see Fig. 13.3). Cerebral blood flow is highly regulated and kept relatively constant even with fluctuations in blood pressure. Acute increases in blood pressure activate the vascular myogenic response, protecting neuronal tissue from damage. Women with severe PE have increased cerebral blood flow and perfusion pressure [41], and a recent study demonstrated impaired myogenic tone in the middle cerebral arteries and cerebral edema in placental ischemic rats [42]. Janzarik and colleagues recently reported that a history of previous PE is associated with poorer dynamic cerebral autoregulation values in subsequent pregnancies [43]. These conditions of increased cerebral blood flow and impaired myogenic reactivity render preeclamptic patients susceptible to neurological complications with acute increases in blood pressure. This concept is supported by studies demonstrating that during acute hypertension, pregnancy decreases vascular resistance and increases cerebral blood flow, resulting in a rightward shift in the autoregulatory curve, and cerebral edema.

Summary

Despite being one of the leading causes of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of PE have yet to be fully elucidated. PE affects the vasculature of many target

maternal organs including the brain, liver, and kidney. Growing evidence supports the concept that the placenta plays a central role in the pathogenesis of PE and that reduced uteroplacental perfusion, which develops as a result of abnormal cytotrophoblast invasion of spiral arterioles, triggers the cascade of events leading to the maternal disorder (see Fig. 13.1). The hypoxic placenta in turn releases a variety of soluble factors such as sFlt-1, AT1-AA, and inflammatory cytokines such as TNF-α which that generate widespread dysfunction of the maternal vascular endothelium. This dysfunction manifests as enhanced formation of factors such as endothelin, reactive oxygen species, and augmented vascular sensitivity to angiotensin II. In addition, PE is also associated with decreased formation of vasodilators such as NO. The full elucidation of the molecular and cellular mechanisms involved in various stages of the disease process will hopefully lead to a more complete understanding of the etiology of PE and eventually lead to successful therapeutic intervention through the targeted disruption of new and novel pathways.

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Chapter 14
Inflammation and Hypertension

Paolo Pauletto and Marcello Rattazzi

Introduction

Clinical and experimental data collected in the past two decades significantly highlight the relevance of inflammatory processes during cardiovascular disease (CVD) progression [1, 2]. In fact, circulatory levels of inflammatory mediators, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have not only been shown to predict the risk of future CV events but, together with specific immune cell subpopulations, can actively be involved in the generation of vascular damage, including endothelial dysfunction and atherosclerosis [2]. Hypertension is a major risk factor for CVD events in different clinical settings, including chronic kidney disease (CKD). Moreover, it has been clearly demonstrated that low blood pressure is followed by significant reduction of cardiovascular (CV) organ damage and prevention of future CV events. Clinical data collected in the past few years have suggested the association between the presence of low-grade systemic inflammation and hypertension [3], but it is not yet known whether the two are correlated. In fact, it is well demonstrated that hypertensive damage is frequently characterized by activation of inflammatory process within different organs (including the arterial wall, heart, kidney, and the brain). Nevertheless, recent data showed that the participation of inflammatory mediators and immune cells in the onset of high blood pressure is more relevant than previously thought [4–6]. In particular, a number of studies demonstrated the active participation of innate immunity (such as macrophages) and adaptive immunity (mainly different lymphocytes subsets) in the pathogenesis of hypertension [4–6]. In the present chapter, we summarize the evidence of these concepts.

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Epidemiological Data

As mentioned above, a number of epidemiological studies, including both cross-sectional and prospective investigations, suggested that hypertension and inflammation could be linked. In particular, some of these studies showed not only that circulating inflammatory molecules are high in hypertensive subjects but also that their plasma levels can predict the future onset of high blood pressure. In this context, it has been shown that serum levels of inflammatory markers (such as CRP), cytokines (such as tumor necrosis factor-α (TNF-α), and IL-6), chemokines (such as monocyte chemoattractant protein, MCP-1), and adhesion molecules (such as P-selectin and soluble intercellular adhesion molecule-1, sICAM-1) are increased in patients with essential hypertension without history of CVD, compared to normotensives subjects [7–9]. A similar association has been described among patients with prehypertension, that in fact displayed higher plasma levels of high-sensitivity CRP (hs-CRP), TNF-α, amyloid-A, homocysteine, and leukocytes as compared to control individuals [10]. Some authors also showed that hypertensive patients exhibit increased inflammatory activation of circulating blood elements compared to normotensive subjects. In particular, it has been observed that circulating blood monocytes from patients with essential hypertension harbor a pre-activated state and release higher levels of cytokines (such as IL-6, IL-1β, and TNF-α) after stimulation with pro-inflammatory mediators [11]. Other investigators also reported that patients with essential hypertension have increased plasma-soluble CD40L level and elevated CD40/CD40L expression on platelets [12].

Data arising from prospective studies are of relevance in this context as they can help to demonstrate whether this low-grade chronic inflammatory status observed in hypertensive is the cause of hypertension or is instead the consequence of high blood pressure. In addition, prospective data can also help to clarify whether the presence of inflammation could predict the future development of hypertension. Data collected from 1790 healthy normotensive men showed that elevated plasma levels of fibrinogen, α1-antitrypsin, aptoglobin, ceruloplasmin, and orosomucoid were associated with the increased risk of becoming hypertensive [13]. In particular, the risk of future hypertension was higher among subjects with the concomitant elevation of more than three proteins, underlining the importance of the level of inflammation, more than the effect attributable to a single molecule. Similar findings were obtained in the female cohort of the Women's Health Study, where increased levels of hs-CRP have been shown to predict the development of hypertension after 10 years follow-up [3, 14]. This association was independent of baseline levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) values and was seen even among subjects showing very low levels of blood pressure at the beginning of the follow-up. Moreover, when the predictive value for hypertension development was compared between markers of inflammation (such as IL-6, IL-1β, TNF receptor 2), markers of endothelial activation (such as sICAM-1), and hs-CRP, only the latter remained strongly associated with the risk of becoming hypertensive [14, 15]. Nevertheless, although the predictive value of hs-CRP for the development of hypertension has been confirmed by studies conducted in other populations [16],

some of these investigations showed that this association was weakened upon adjustment for body mass index (BMI) and waist circumference [15, 17]. This observation is of particular relevance if we consider that several epidemiological studies clearly demonstrated the presence of a co-clustering of inflammation and hypertension in patients with metabolic syndrome (MetS). In fact, subjects affected by MetS, hypertension, atherogenic dyslipidemia, insulin resistance, and central obesity are frequently accompanied by increased circulating levels of inflammatory mediators (mainly hs-CRP itself). A similar association has been observed among subjects with moderate to severe CKD. Even in cases of renal function decline, body fat percentage has been shown to be highly associated with the markers of inflammation and oxidative stress [18]. On the whole, these findings underscore the ongoing complexity of the interrelationship between inflammation and central adiposity in the development of high blood pressure and point towards the conduction of additional investigation to understand whether the inflammatory status induced by the adipose tissue actively contributes in generating future hypertension.

Despite these epidemiological data, the nature of the link between hypertension and inflammation in humans is still elusive [19]. Although it cannot be excluded that they represent two independent phenomena, basic science evidence obtained in the past few years allowed depicting a whole new scenario. In particular if, on one side, hypertension could be the inducer of inflammatory organ damage, on the other, inflammatory processes could actively contribute to the pathogenesis of high blood pressure. On these bases, a hypothetical vicious cycle between hypertension and inflammation can be proposed. This is especially the case for those clinical conditions, such as CKD, that harbor a relevant increase in vascular and systemic inflammation.

Does Hypertension Induce Inflammation?

A lot of evidence clearly demonstrated that hypertension acts as a major determinant of endothelial dysfunction and vascular wall damage, mainly through the inflammatory activation of endothelial cells (EC), recruitment of immune cells within the arteries and the proliferative-profibrotic activation of vascular resident elements (mainly smooth muscle cells (SMC) and adventitial myofibroblasts; Fig. 14.1). Studies conducted by using different experimental models of hypertension (such as salt-sensitive, angiotensin II (AngII), aldosterone, and hypertensive rodent models) clearly demonstrated that high blood pressure is accompanied by the activation of both innate and adaptive immune system within the kidney and the vascular wall. This process is mainly characterized by the expression of cytokines (such as IL-6, IL-1β, TNFα), chemokines (such as MCP-1), adhesion molecules (such as ICAM-1, VCAM-1), and has been linked to nuclear factor-kappaB (NF-kB) system activation [20–22]. Mechanisms leading to this inflammatory response have not been fully elucidated and can be ascribed both to mechanical stress of the arterial wall and the pro-inflammatory effects of humoral factors, such as AngII, aldosterone, reactive

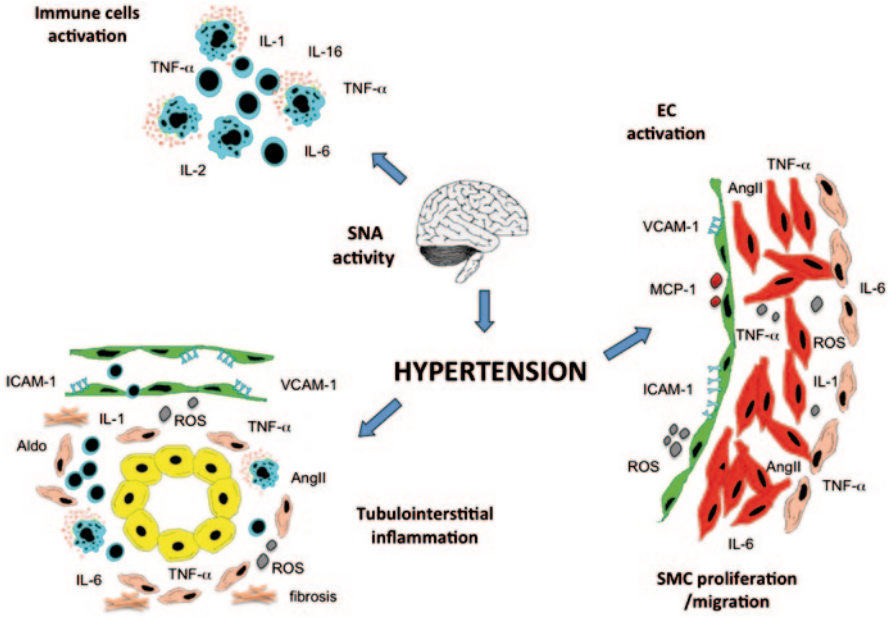

Fig. 14.1 Hypertension induces inflammatory processes. Hypertension can promote inflammatory events within the vascular wall and the kidney. Increased sympathetic nerve activity (*SNA*) can drive both hypertension and immune cells activation. *EC* endothelial cells, *SMC* smooth muscle cells, *ROS* reactive oxygen species, *Aldo* aldosterone, *AngII* angiotensin II

oxygen species (ROS), and cytokines itself [4]. An elegant study performed by using an in vitro organ culture model of the whole vessel showed that arteries exposed to high intraluminal pressure exhibited an increased expression of adhesion molecules and cytokines by both EC and SMC. This inflammatory activation induced by the stretching of the vascular wall is mainly driven by NF-kB pathway activation and is also followed by increased monocyte adhesion to the vessels [23]. These data, collected in the absence of external hormonal factors, clearly demonstrated that high blood pressure is sufficient to induce per se chemokine and adhesion molecule expression by vascular cells and thus promotes the initial steps of immune cell recruitment within the arterial wall [23].

Accumulating evidence from basic science research and clinical studies extensively demonstrated that AngII, besides regulating the vascular tone, could exert pro-inflammatory effects within the arterial wall and other organs. AngII, in fact, induces NF-kB activation by triggering the production of inflammatory cytokines, promotes the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is followed by the release of ROS, and impairs endothelium-dependent vasodilatation by reducing nitric oxide (NO) generation [24]. Some of the hypertensive effects of AngII can be also driven by the modulation of the immune/inflammatory response. For example, it has been demonstrated in mice that lack the production of IL-17 (IL-17(−/−)) that the rise in blood pressure induced by

AngII infusion was less sustained compared to wild-type animals. Moreover, the vessels of IL-17(−/−) mice showed preserved vascular function, lower superoxide production, and less T cell infiltration within the arterial wall as compared to control animals [25]. As mentioned above, inflammatory processes including immune cell recruitment, cytokine release, and ROS production are commonly observed within the kidneys of experimental model of hypertension. These processes can actively contribute to local tissue damage and induce progressive impairment of renal hemodynamic and tubular function [26]. In this context, a central role can be played by intrarenal AngII, whose expression has been found to be correlated with the severity of hypertension and the level of immune cell infiltration in the kidney [27]. In fact, locally activated renin–angiotensin system (RAS) can contribute to the pathogenesis of renal damage, thus driving the recruitment and inflammatory activation of immune cells [28]. In addition, treatment of animal models of hypertension with RAS blockade have been shown to reduce the renal inflammatory infiltration mainly through reduction of chemokines, cytokines, and adhesion molecules expression [28]. Similar effects have been observed within the arterial wall, where the RAS inhibition was able to reverse most of the detrimental effects of AngII on endothelial function and to reduce the level of inflammatory activation in the vessels [20, 24]. This basic science data found some confirmation in clinical studies showing that treatment with AT-1 receptor blockers can lower the circulating levels of some inflammatory mediators (such as IL-6, TNFα, MCP-1, hs-CRP, and CD40L) [29–31]. Also, aldosterone, an important component of the RAS system, has been shown to actively contribute to vascular and kidney damage, by inducing oxidative stress, endothelial dysfunction, fibrosis, and inflammation [32]. In addition, aldosterone inhibits NO synthase thereby reducing NO production both within the kidney and vessels [33]. As for AngII, also the pharmacological blockade of aldosterone has been proved to reduce pro-inflammatory and pro-fibrotic vascular damage independently from the effects on blood pressure. For instance, despite similar blood pressure reduction, treatment with mineralcorticoid receptor (MR) blockade resulted more efficiently than treatment with atenolol in reducing vascular stiffness and systemic inflammation among hypertensive subjects [34]. Of interest, the expression of MR has also been demonstrated in immune cells (mainly monocytes/macrophages) suggesting a role for aldosterone in promoting vascular damage through inflammatory activation of this cell type. In addition, it has been shown that macrophages, through MR receptor, could also mediate some of the hypertensive effects of aldosterone. In fact, data obtained in the deoxycorticosterone acetate (DOCA)-salt-hypertension mouse model demonstrated that the selective lack of MR expression in monocytes is followed by no increase in either cardiac fibrosis or blood pressure level [35]. Several pieces of evidence arising from animal models and clinical studies also showed that MR blockade with either eplerenone or spironolactone is accompanied by reduction in renal inflammation, oxidative stress, proteinuria, and glomerular and tubular injury [36]. Nevertheless, the safety as well as the renal and CV outcomes of treatment with low-dose MR antagonists of CKD patients is still uncertain, and large prospective studies are needed to clarify this aspect.

Mechanical stress and humoral factors are also considered as important stimuli for the activation of medial and adventitial vascular cells. In this context, a pivotal role is played by vascular SMC, which harbor remarkable plasticity in terms of differentiation, proliferation, and motility. We and others observed that specific immature type of SMC populations can be found within the arterial wall, and that these cells are actively involved in the vascular remodeling associated with hypertension [37]. Both medial SMC and adventitial myofibroblasts exposed to mechanical forces and growth factors could undergo a phenotypic dedifferentiation towards the acquisition of a "synthetic" profile [38]. Following this transition the vascular cells exhibit an increase in ability to migrate towards the intima layer, higher secretion of inflammatory mediators, and higher capacity of extracellular matrix (ECM) remodeling [38, 39]. These cellular modifications are influenced both by hemodynamic and bioumoral factors (including ROS, AngII, and aldosterone) and lead to the generation of pro-fibrotic vascular damage. In addition, together with endothelial dysfunction and inflammatory cells recruitment, vascular cells proliferation/migration within the neointima represent initial steps of atherogenesis and certainly represent a pathophysiological connection between hypertension and atherosclerosis development. The amplification of the inflammatory response associated with the hypertensive damage of the arteries could increase the circulating levels of inflammatory molecules, and partly accounts for the low-grade inflammatory status observed in hypertensive subjects.

It is well established that the sympathetic nerve activity (SNA) plays a crucial role in the regulation of blood pressure mainly through the modulation of peripheral arterial tone and cardiac output. In particular, data in humans suggest that a neurogenic component can be observed in 40–65 % of hypertensive patients [40]. Growing evidence suggest that SNA could significantly interplay with the immune system. Lymphoid organs are highly innervated by the sympathetic nerves and stress hormones such as catecholamines have been shown to possess immunomodulatory properties [41]. In particular, early studies suggested that stress hormones may exert immunosuppressive effects through the inhibition of the T helper lymphocyte 1 (Th1) pro-inflammatory activities, as well as the induction of Th2 anti-inflammatory cytokines production. However, more recent findings indicate that in certain conditions, the hyperactive stress system might instead exert pro-inflammatory effects, thus influencing the onset of several human immune-related diseases, including vascular disease progression [41]. Cerebral infusion of AngII has been shown to increase SNA, which in turn increases the expression of inflammatory cytokines (such as IL-1, IL-2, IL-6, IL-16) in splenocytes. This inflammatory activation of the cells was blunted by splenic sympathectomy [42]. Data are available showing that immune cells possess both adrenergic and cholinergic receptors and that these receptors significantly impact on their function. For example, T cells possess both α- and β-adrenergic receptors which have been shown to be actively involved in cell proliferation, Th1/Th2 polarization, and change of surface markers [43]. In addition, expression of α1- and β1-adrenergic receptors have been demonstrated on the surface of monocytes and macrophages and its stimulation with adrenergic receptor agonists significantly enhance the pro-inflammatory cytokine production

by the cells in response to toll-like receptor (TLR) agonists [44, 45]. Additional investigations showed that monocyte and macrophages express α7-nicotinic receptors and its activation suppress cytokine production [46, 47]. Thus, it is plausible that an increase in SNA often observed in hypertensive patients might contribute to the overall low-grade inflammatory state also through its immunomodulatory effects. On the other hand, the immune system could represent an important mediator of SNA contribution of hypertension.

Does Inflammation Promote Hypertension?

Evidence so far collected does not clearly establish whether or not inflammation per se could induce structural/functional changes of the arterial wall which lead to the development of hypertension. Nevertheless, several lines of research on this topic have been developed in the past few years and novel theories are now under intense investigation (Fig. 14.2). As a first hypothesis, it could be postulated that, independently from their source, inflammatory circulating molecules might significantly impact

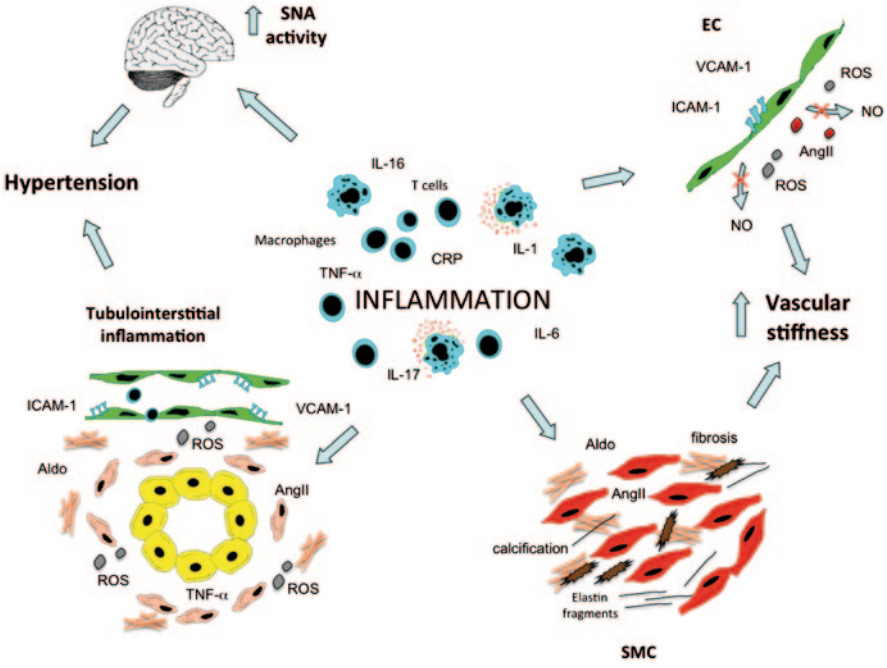

Fig. 14.2 Inflammation can induce hypertension. Inflammatory processes within the arterial wall can induce endothelial cell (*EC*) dysfunction and smooth muscle cell (*SMC*) activation, which both lead to increase of vascular stiffness. Moreover, also inflammatory events involving the kidney and the central nervous system can promote hypertension. *SNA* sympathetic nerve activity, *ROS* reactive oxygen species, *Aldo* aldosterone, *AngII* angiotensin II, *NO* nitric oxide

on mechanisms of arterial tone regulation. In particular, it has been shown that inflammatory molecules (such as IL-6, IL-1, TNFα, CRP, and others) can produce detrimental effects on the vascular wall, including EC dysfunction with reduced NO bioavailability, an increased expression of adhesion molecules, and release of ROS [48]. Some of these cytokines have been also shown to mediate AngII hypertensive and pro-atherogenic effects. For instance, in mice it has been shown that IL-6 deficiency protects against AngII-induced increases in superoxide, EC dysfunction, and vascular hypertrophy [49]. Of note, the knockdown of IL-6 was also able to blunt the AngII-driven rise in blood pressure [50]. A similar effect and interaction with AngII have also been described for TNFα. In particular, it has been shown that the use of etanercept, a TNFα antagonist, prevented hypertension induced by fructose feeding and AngII infusion [51, 52]. Both IL-6 and TNFα together with other cytokines are increased in the kidneys of animal models of hypertension, suggesting that they can be important mediators in the link between renal injury and blood pressure elevation. In line with this possibility, it has been demonstrated that inhibition of both TNFα (with etanercept) and IL-6 (with small hairpin RNA) attenuated both the inflammatory damage of the kidney and the development of hypertension [53, 54]. Together with pro-inflammatory cytokines some studies have been conducted to dissect the role played by anti-inflammatory cytokines (such as IL-10) during hypertension development. Of interest, data obtained from IL-10-deficient mice showed that this cytokine is able to prevent the vascular dysfunction induced by AngII [55]. Moreover, it has also been observed that IL-10 infusion was able to reduce blood pressure, endothelial dysfunction, and urinary protein excretion in a pregnancy hypertension model [56]. Also, chemokines, important mediators of immune cells infiltration within the vessels, can be actively involved in the pathogenesis of hypertension. For instance, data are available showing that pharmacological blockade of chemotactic cytokine receptor-2 (CCR2; main receptor of the chemokine monocyte chemoattractant protein-1, MCP-1) attenuated both macrophages aortic infiltration and hypertension development in the DOCA-salt animal model [57]. Some of these pro-hypertensive effects of cytokines and chemokines could also be ascribed to their role in modulating proliferation, migration, and synthetic behavior of vascular SMC [58]. In fact, evidence available shows that exposure of vascular SMC to IL-6, TNFα, CRP, and other cytokines is followed by cellular inflammatory activation with increase proliferation/migration and enhanced capacity of ECM remodeling (mainly through the secretion of metalloproteinases and collagen synthesis) [59, 60]. As mentioned above, these pathological processes are mainly characterized by the involvement of SMC harboring an immature/synthetic phenotype. We previously observed that arterioles obtained from hypertensive patients displayed higher amount of immature SMC compared to those obtained from normotensive subjects [61]. Additional investigations are needed to establish whether, besides modulating SMC phenotype during atherogenesis, inflammatory mediators can also impact on the morphological and functional behavior of SMC resident within the resistance arterioles.

Inflammatory activation of both EC and SMC can also be associated with significant changes in large vessels structure, mainly increase in arterial stiffness and reduction in vascular resilience. The rise in SBP, the fall in DBP and the resulting increase in pulse pressure are now considered as a manifestation of the presence of central arterial stiffening. The development of this blood pressure pattern,

which is commonly observed with aging, is accelerated among subjects with advanced stages of CKD and diabetes. Moreover, several epidemiological investigations demonstrated the negative prognostic value of arterial stiffness for future CV events [62]. Stiffening of the arteries is mainly characterized by fracturing of elastin together with increase of collagen and calcium accumulation. Traditional view interprets reduced elasticity of the arteries as a consequence of hypertension. However, some recent studies underline the possibility that arterial stiffening might not only precede the development of hypertension [63] but also drive, at the later stages, the development of systolic hypertension [64]. Of note, pulse wave velocity (PWV), a measure of large vessels stiffness, has been directly associated with the circulating levels of some inflammatory mediators (such as CRP, IL-6, and TNFα) [65–67] suggesting that inflammation may contribute to arterial stiffness, maybe through induction of EC dysfunction and SMC activation. Vascular calcification is now identified as a major determinant of arterial stiffening especially among patients with advanced stages of CKD, and its presence has been linked to the increased CV mortality observed in this group of subjects [68]. Growing evidence suggested that calcium accumulation within the arterial walls and the heart valve leaflets cannot be considered just a passive phenomenon [64, 69, 70]. Osteoblast/chondrocytes-like cells have been identified in vivo within pathological vascular tissue of humans and animal models of atherosclerosis. In addition, the expression of osteogenic markers has been shown to significantly increase within the arteries of patients with advanced stages of renal failure [71]. A number of in vitro experiments demonstrated that both valve cells and vascular SMC exposed to inorganic phosphate [72], uremic factors, and inflammatory mediators (such as TNFα and IL-6) [73] can acquire an osteogenic phenotype and deposit calcium [74]. More recently, AngII has been implicated in the pro-calcific differentiation of vascular cells and its effect seems to be driven by the induction of receptor activator of nuclear factor kappa-B ligand (RANKL) which prevents the anti-calcific effects of osteoprotegerin [75]. It is plausible that all these humoral and inflammatory factors can synergically participate within the pathological vessel in promoting elastin damage, collagen/calcium deposition and thus leading to arterial stiffness. The latter is then associated with worsening of blood pressure levels and favors the onset of future CV events.

Monocytes/macrophages are known to be major contributors to cytokines/chemokines release during vascular and kidney disease progression. These cells are also the source of ROS, metalloproteinases, and other factors that induce tissue damage and promote vascular remodeling which in turn leads to increased vasoconstriction and arterial stiffness through the mechanisms listed above. Recent data showed that selective deletion of circulating monocytes is able to attenuate AngII-induced blood pressure elevation and vascular dysfunction, including the induction of vascular adhesion molecules and ROS generation [76].

Growing evidence collected in the past few years underscored that beside the role played by elements belonging to the innate immunity response (such as cytokines, chemokines, and monocytes/macrophages), components of the adaptive immunity might also be actively involved in the pathogenesis of hypertension. Early data obtained from animal models showed that transfer of lymph node cells, splenocytes, and lymphocytes obtained from hypertensive rats were able to raise the blood

pressure in the normotensive recipients [77–79]. Moreover, the removal of thymus was followed by blood pressure reduction in rats with renal hypertension [80]. More recently, it has been clearly shown that lymphocytes play a causative role in the rise of blood pressure observed in different animal models [4]. For instance, AngII-induced blood pressure rise was significantly blunted in RAG-1-deficient mice, which lacks both T and B cells. These animals also displayed a significant reduction of vascular dysfunction induced by AngII, including ROS production. Of interest, only the adoptive transfer of T lymphocytes, and not the B cells, was able to restore the AngII-induced hypertension [51]. Similar findings were confirmed by using other models of animal hypertension (such as the norepinephrine and DOCA-salt mice) [81] and immunodeficiency (such as the severe combined immunodeficiency (SCID) mice) [82]. An opposite, protective effect has been instead recently proposed for regulatory T cells (Tregs), an immunosuppressant subset of T cells, that are thought to be protective against vascular disease progression. Interestingly, it has been shown that Tregs are reduced in the renal cortex during AngII-induced hypertension and that adoptive transfer of these cells is able to ameliorate AngII effects on blood pressure, renal inflammation, and cardiac damage [83, 84].

As mentioned above, evidence obtained from animal models of hypertension showed that an inflammatory infiltration by immune cells occurs in the kidney. Of interest, this renal tubulointerstitial inflammation is observed at a young age of the animals and seems to precede the onset of hypertension [85], thus suggesting a causative role of kidney inflammation in hypertension generation. Early studies showed that the immune cells recruitment in the kidney can be prevented by blocking NF-kB activation, a master transcription factor controlling inflammatory responses. Of note, NF-kB inhibition was accompanied by complete abrogation of hypertension development in spontaneously hypertensive rats [86]. In line with this finding, data are available demonstrating that immune cell infiltration is actively involved in the pathogenesis of hypertension in Dahl salt-sensitive rats. In fact, immunosuppressive therapy with mycophenolate mofetil in this animal model was accompanied by reduced T and B recruitment in the kidney, and significantly attenuated the development of hypertension [87, 88]. Further studies also suggested that the detrimental effects of T lymphocytes on hypertension and kidney damage are due to local release of AngII and increased production of ROS [5]. Thus, it could be assumed that the infiltration of immune cells, and the associated increase in inflammatory cytokines and oxidative stress within the renal interstitium, can have a prominent role in the pathogenesis of hypertension. Nevertheless, we do not actually know if this phenomenon has some relevance on humans.

Sympathetic overdrive is actively contributing in generating essential hypertension and in particular the so-called neurogenic hypertension. Interestingly, vascular inflammation affecting the cerebral vasculature and, in particular, the brainstem CV control areas has been recently implicated in the generation of this form of hypertension [89]. In particular, it has been demonstrated that the microvasculature in the nucleus of the solitary tract (NTS) of hypertensive animals expresses higher level of pro-inflammatory molecules (such as JAM-1 and LTB4 12-HD) as compared to normotensive animals [89]. Moreover, overexpression and injection of these molecules in normotensive rats was followed by increased arterial pressure. It is known that

RAS is involved, within the NTS, in the CV regulation. Of note, evidence has been collected and shows that the central actions of AngII in modulating SNA are mediated by inflammatory molecules. For instance, it has been shown in rat infused with AngII that the intracerebroventricular administration of minocycline (an anti-inflammatory antibiotic) is followed by a significant reduction of IL-6, IL-1β, TNFα, and an increase of IL-10 in the microglia of the brain. This concomitant attenuation in pro-inflammatory cytokines and increase in anti-inflammatory molecules is followed by significant reduction in blood pressure, cardiac hypertrophy, and plasma levels of norepinephrine [90]. These findings coupled with the observations reported above allow depicting a vicious cycle scenario, with inflammatory mechanisms controlling SNA in the brain, and sympathetic activity modulating immune responses in the periphery with subsequent induction of vascular inflammation/dysfunction.

Conclusions

Data collected from clinical and basic science studies showed a complex mosaic of interplay between local and systemic inflammation, central nervous system, and vascular cells. It appears that effectors of inflammation (immune cells, cytokines, chemokines) and hypertension could interact with each other in a bidirectional manner and that numerous feedback loops probably exist between these two conditions (Fig. 14.3). Of note, the inflammatory processes taking place in the kidney appear to

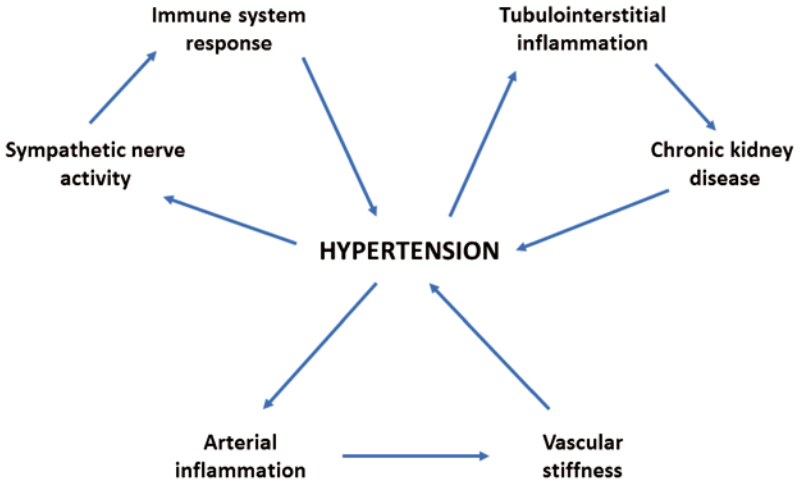

Fig. 14.3 Hypothetical interplay between hypertension and inflammation. Inflammatory processes induced by high blood pressure can be observed both within the kidney and the arteries. The resulting reduction in renal function and increase in vascular stiffness are then followed by further elevation in blood pressure levels. The increase of sympathetic nerve activity that is often observed in hypertensive subjects has been shown to induce pro-inflammatory activation of the immune system. Moreover, both innate and adaptive immune responses can actively contribute in the pathogenesis of hypertension (see the text for details)

play a central role not only during CKD progression but also in the pathogenesis of systemic hypertension. Further investigations are needed to clearly identify factors initiating these pathological events and the mechanisms driving the interplay between vascular/renal inflammation and sympathetic system activity. Data collected from such studies could offer the opportunity to identify novel therapeutic targets for the treatment of hypertension and its CV complications.

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Chapter 15
Genome-Wide Association Studies (Gwas) of Blood Pressure in Different Populations

Srividya Kidambi and Theodore A. Kotchen

Introduction

Hypertension (HTN), affecting up to one third of the population globally, is a major risk factor for cardiovascular disease (CVD), left ventricular hypertrophy, congestive heart failure, cerebrovascular disease, and renal insufficiency. Adoption, twin, and family studies document a significant genetic component to blood pressure (BP) levels and HTN [1–3] and indicate that the heritability of BP is in the range of 15–35 % [4, 5]. HTN < 55 years of age occurs 3.8 times more frequently among persons with a positive family history of HTN [6]. While the heritable nature of the BP trait is well established, to date < 2 % of the interindividual BP variation can be explained by common genetic variants [7, 8].

When the candidate-gene approach and quantitative trait locus mapping failed to identify the underlying gene or locus despite the considerable knowledge of the pathways that contribute to the regulation of BP, attention turned to genome-wide association studies (GWAS). GWAS test whether a particular genetic marker or a trait (single-nucleotide polymorphism, SNP) co-occurs with phenotypes more often than expected by chance and are typically conducted in unrelated subjects. This strategy has been facilitated by unraveling of the human genome, the HapMap project, and the availability of dense computer chips for genetic sequencing. In GWAS, one human DNA sample can be queried for millions of genetic variants simultaneously, and the whole genome can be compared between different subjects. In addition, GWAS offer the potential to identify novel mechanisms in the pathophysiology of HTN. Since 2007, several GWAS and meta-analyses of GWAS have been conducted but have failed to identify consistent gene variants for HTN among different populations [7–11]. This chapter reviews the GWAS of BP and

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HTN published to date (Table 15.1 and Fig. 15.1); studies using candidate-gene and genome-wide linkage approaches are beyond the scope of this chapter.

GWAS of HTN Among Populations of European Origin

The first GWAS on HTN, published on the Framingham Heart Study population in 2007 (Table 15.1), found that there were no SNP associations with systolic BP (SBP) or diastolic BP (DBP) [12] that achieved genome-wide significance (GWS; $P \leq 4.4 \times 10^{-8}$). However, at a more modest level of stringency ($P < 10^{-5}$), there were seven associations for SBP or DBP. However, none of these were in previously identified candidate-gene loci. A larger-scale GWAS for HTN was performed by the *Wellcome Trust Case Control Consortium* (WTCCC) using a case-control design, and this study too failed to identify SNPs with GWS ($P < 10^{-7}$) [9]. Even the most strongly associated SNPs did not identify genes from physiological systems previously implicated by clinical or genetic studies in HTN. The authors contend some of these common susceptibility variants of large effect size, e.g., promoter of the WNK lysine-deficient protein kinase 1 (*WNK1*) gene, [13, 14] were not well tagged by the Affymetrix chip they used. In addition, HTN may have fewer common risk alleles of larger effect sizes than some of the other complex phenotypes, in which case identification of susceptibility variants for HTN will need synthesis of findings from multiple large-scale studies. Further, BP is an imperfect trait and may have resulted in misclassification due to inclusion of hypertensive subjects within the control samples. In a replication study, Ehret et al. attempted to replicate six top-associated SNPs from WTCCC in the *Family BP Program* cohort [15] with very discrepant results. In a GWAS on subjects with type 2 diabetes mellitus (T2DM) and euglycemic controls, Saxena et al. evaluated 18 traits including BP and found no genome-wide associations for BP [16].

The observation that BP variation, in the general population, is due to multiple variants with small effects led to the formation of large consortia, e.g., Cohorts for Heart and Aging Research in Genome Epidemiology (CHARGE) and Global BPgen consortium to identify common generic variation associated with complex traits (Table 15.1). The CHARGE consortium consisted of a large number of participants of European descent [7] and identified 13 SNPs for SBP, 20 for DBP, and 10 for HTN ($P < 4 \times 10^{-7}$), some of which were common among different BP traits. Mean BP and prevalence of HTN increased in relation to the number of risk alleles carried. When ten CHARGE SNPs for each trait were included in a joint meta-analysis with the Global BPgen consortium (replication sample, another GWAS consortium of similar size), four CHARGE loci attained GWS ($P < 5 \times 10^{-8}$) for SBP (*ATP2B1*, *CYP17A1*, *PLEKHA7*, *SH2B3*; Table 15.1), six for DBP (*ATP2B1*, *CACNB2*, *CSK-ULK3*, *SH2B3*, *TBX3-TBX5*, *ULK4*), and one for HTN (*ATP2B1*; Table 15.1), with considerable concordance among top loci across all three phenotypes. Of note, rs1004467, a common intronic variant in *CYP17A1*, a gene associated with a rare Mendelian form of HTN, emerged as a genome-wide significant

Table 15.1 Overview of GWAS of hypertension, systolic and diastolic blood pressure based on ancestry

Study/year/platform with SNPs passing QC	Initial sample size and population	Replication sample size and population	Top SNPs (with closest gene if known in parentheses) identified in that cohort		
			SBP	DBP	HTN
	Subjects of European descent				
Levy et al./2007/Affymetrix (70,897) [12]	1300 European descent subjects	NR	–	–	–
The Wellcome Trust Case Control Consortium/2007/Affymetrix (469,557) [9]	2000 British cases 3000 British controls	NR	–	–	–
Saxena et al./2007/ Affymetrix (386,731) [16]	1464 T2DM cases 1467 controls (Finnish and Swedish)	NR	–	–	–
Levy et al./2009/ Affymetrix and Illumina (2,533,153; imputed) [53]	29,136 CHARGE and Global BPgen consortia meta-analysis/European descent subjects	34,433 European descent subjects	rs1004467 (*CYP17A1*) rs381815 (*PLEKHA7*) rs2681492 (*ATP2B1*) rs3184504 (*SH2B3*)	rs2681492 (*ATP2B1*) rs11014166 (*CACNB2*) rs6495122 (*CSK-ULK3*) rs3184504 (*SH2B3*) rs2384550 (*TBX3-TBX5*) rs9815354 (*ULK4*)	rs2681492 (ATP2B1)
Newton-Cheh et al./2009/Affymetrix and Illumina (2,497,993; imputed) [8]	34,433 European descent subjects	17 GWAS studies 71,225 European subjects 12,889 (LOLIPOP study with Indian Asians)	rs11191548 (*NT5C2*) rs17367504 (*MTHFR*) rs12946454 (*PLCD3*)	rs16998073 (*FGF5*) rs1530440 (c10orf107) rs653178 (*ATXN2*) rs1378942 (*CSK*) rs16948048 (*ZNF652*)	rs11191548 (*NT5C2*) rs17367504 (*MTHFR*) rs12946454 (*PLCD3*) rs16998073 (*FGF5*) rs1530440 (c10orf107) rs653178 (*ATXN2*) rs1378942 (*CSK*) rs16948048 (*ZNF652*)
Wang et al./2009/ Affymetrix (79,447) [17]	542 Amish subjects	6583 Amish and non-Amish subjects of European descent	rs6749447 (*STK39*) rs3754777 (*STK39*)	rs6749447 (*STK39*) rs3754777 (*STK39*)	
Sabatti et al./2009/Illumina [18]	4763 Finnish subjects	NR	–	–	–

Table 15.1 (continued)

Study/year/platform with SNPs passing QC	Initial sample size and population	Replication sample size and population	Top SNPs (with closest gene if known in parentheses) identified in that cohort		
			SBP	DBP	HTN
	Subjects of European descent				
Org. et al./2009/Affymetrix (395,912) [19]	1644 German descent	1830 Germans 1823 Estonians 4370 British cases and controls	rs11646213 (*CDH13*)	rs11646213 (*CDH13*)	rs11646213 (*CDH13*)
Padmanabhan et al./2010/Illumina (521,220) [10]	1621 Swedish cases, 1699 Swedish controls	19,845 European ancestry cases, 16,541 European ancestry controls			rs13333226 (*UMOD*)
Kraja et al./2011/ Affymetrix and Illumina (~2.5 million) (imputed) [25]	22,161 European ancestry subjects	NR	BP defined as one of the three, SBP or DBP ≥130/85 mmHg or antihypertensive medication use		
			rs780093 (*GCKR*) [BP-TG] rs116131468 (*BUD13*) [BP-TG] rs11823543 (*ZNF259*) [BP-TG] rs15285 (*LPL*) [BP-TG] rs2266788 (*APOA5*) [BP-TG] rs2954033 (*TR1B1*) [BP-TG] rs3764261 (CETP) [BP-HDL] rs1387153 (LOC100128354) [BP-GLUCOSE]		
Ehret et al./2011/ Affymetrix and Illumina (~2.5 million) (imputed) [21]	69,395 European Ancestry subjects	133,661 European Ancestry subjects	rs2932538 (*MOV10*) rs419076 (*MECOM*) rs13107325 (*SLC39A8*) rs1173771 (*NPR3*-C5orf23) rs11953630 (*EBF1*) rs1799945 (*HFE*) rs805303 (*BAG6*) *rs4373814 (CACNB2(5')* rs932764 (*PLCE1*)	rs2932538 (*MOV10*) rs13082711 (*SLC4A7*) rs419076 (*MECOM*) rs13107325 (*SLC39A8*) rs13139571 (*GUCY1A3-GUCY1B3*) rs1173771 (*NPR3*-C5orf23) rs11953630 (*EBF1*)	rs1173771 (NPR3-C5orf23) rs11953630 (*EBF1*) rs1799945 (*HFE*) rs805303 (*BAG6*) rs633185 (*FLJ32810-TMEM133*) rs6015450 (*GNAS-EDN3*)

Table 15.1 (continued)

Study/year/platform with SNPs passing QC	Initial sample size and population	Replication sample size and population	Top SNPs (with closest gene if known in parentheses) identified in that cohort		
			SBP	DBP	HTN
	Subjects of European descent				
			rs7129220 (*ADM*) rs633185 (*ARHGAP42*) rs2521501 (*FURIN-FES*) rs17608766 (*GOSR2*) rs6015450 (*GNAS-EDN3*) *rs17367504 (MTHFR)* *rs1458038 (FGF5)* *rs1813353 (CACNB2 (3'))* *rs4590817 (c10orf107)* *rs11191548 (CYP17A1-NT5C2)* *rs381815 (PLEKHA7)* *rs17249754 (ATP2B1)* *rs3184504 (SH2B3)* *rs1084504 (TBX5-TBX3)* *rs1378942 (CSK)* *rs12940887 (ZNF652)*	rs1799945 (*HFE*) rs805303 (*BAG6*) *rs4373814 (CACNB2(5')* rs633185 (*ARHGAP42*) rs2521501 (*FURIN-FES*) rs1327235 (*JAG1*) rs6015450 (*GNAS-EDN3*) *rs17367504 (MTHFR)* *rs3774372 (ULK4)* *rs1458038 (FGF5)* *rs1813353 (CACNB2 (3'))* *rs4590817 (c10orf107)* *rs11191548 (CYP17A1-NT5C2)* *rs381815 (PLEKHA7)* *rs17249754 (ATP2B1)* *rs3184504 (SH2B3)* *rs1084504 11 (TBX5-TBx3)* *rs1378942 (CSK)* *rs12940887 (ZNF652)*	*rs17367504 (MTHFR-NPPB)* *rs1813353 (CACNB2 (3')* *rs4530817 (c10orf107)* *rs17249754 (ATP2B1)*

Table 15.1 (continued)

Study/year/platform with SNPs passing QC	Initial sample size and population	Replication sample size and population	Top SNPs (with closest gene if known in parentheses) identified in that cohort		
			SBP	DBP	HTN
	Subjects of European descent				
Slavin et al./2011/ Affymetrix (405,022) [20]	2000 cases 3000 controls of European ancestry (British)	NR	–	–	rs10496288-rs10496289 rs13420028-rs10188442 (*GPR39*) rs7735940-rs12522034 (*RANBP3L*) rs6452524–rs6887846 (*XRCC4*) rs3798440–rs9350602 (MYO6) rs2469997–rs6469823 (*NOV*) rs7827545–rs1372662 (*ZFAT*) rs7960483–rs10785581 (AN06) rs200752–rs200759 (*MACROD2*)
Das et al./2012/ (~500,000) [26]	500 European ancestry males, 477 European ancestry females	NR	–	–	–
Salvi et al./2012/Illumina [27]	1865 European ancestry cases, 1750 European ancestry controls	1385 cases 1246 controls 21,714 (all of European descent)	–	–	rs3918226 (eNOS)
Kristiansson et al./2012/ Illumina [24]	2637 cases of MS, 7927 controls (Finnish)	NR	rs782590 (*SMEK2*) rs1084522 (*SMEK2*)	–	–
Ganesh et al./2013 [51]	61,619 European descent subjects		rs347591 (*HRH1*) rs2014408 (*SOX6*)	rs2169137 (*MDM4*)	

Table 15.1 (continued)

Study/year/platform with SNPs passing QC	Initial sample size and population	Replication sample size and population	Top SNPs (with closest gene if known in parentheses) identified in that cohort		
			SBP	DBP	HTN
	Subjects of African descent				
Adeyemo et al./2009/ Affymetrix (808,465) [32]	1017 (509 African American cases, 508 African American controls)	980 (366 West African cases, 614 West African controls)	rs5743185 (*PMS1*) rs3751664 (*CACNA1H*) rs11160059 (*SLC24A4*) rs17365948 (*YWHAZ*) rs12279202 (*IPO7*) rs1687730 (pseudogene)		
Fox et. al./2011/ Affymetrix (2.5 million; imputed) [34]	7473 African American subjects	11,882 African American subjects	rs2258119 (C21orf91)	rs1047346 (*SETD3*)	
	Subjects of Asian descent				
Kato et al./2008/Affymetrix [36]	188 Japanese cases and 752 Japanese controls	752 cases and 752 controls, 619 cases and 1406 controls	–	–	rs3755351 (*ADD2*)
Yang et. Al./2009/ Affymetrix (91,713) [38]	175 Han Chinese cases, 175 Han Chinese controls	1008 Han Chinese cases, 1008 Han Chinese controls	–	–	Young onset hypertension rs9308945-rs6711736-rs6729869-rs10495809
Cho et al./2009/Affymetrix (38,364) [37]	8842 Korean subjects	NR	–	–	*rs17249754 (ATP2B1)*
Lowe et al./2009/ Affymetrix [43]	2,906 subjects from Island of Kosrae	NR	–	–	–
Hiura et al./2010/Illumina (368,274) [45]	936 Japanese subjects	6123 Japanese subjects	–	–	–
Zabaneh et al./2010/Illumina (317,968) [44]	2700 Asian Indian men	NR	–	–	–

Table 15.1 (continued)

Study/year/platform with SNPs passing QC	Initial sample size and population	Replication sample size and population	Top SNPs (with closest gene if known in parentheses) identified in that cohort		
			SBP	DBP	HTN
	Subjects of Asian descent				
Kato et al./2011/ Affymetrix and Illumina (1.7 million; imputed) [39]	19,608 (17,089 East Asian ancestry subjects, 2519 Malay ancestry subjects)	10,518 20,247 East Asian ancestry subjects	rs16849225 (*FIGN*) rs1173766 (*NPR3*) rs11066280 (*HECTD4*)	rs17030613 (*CAPZA1*) rs6825911 (*ENPEP*) rs11066280 (*RPL6*) rs35444 (*TBX3*) rs880315 (*CASZ1*)	–
Hong et al./2011 [40]	7551 Korean subjects	3703 Korean subjects	rs11638762 (*AKAP−13*)	rs11638762 (*AKAP−13*)	–
Guo et al./2012/Illumina (503,984) [42]	328 Hong Kong Chinese subjects from 111 families	None	–	–	rs6596140 (*FSTL4*)
Yang et al./2012/Illumina (475,157) [41]	Han Chinese 400 cases 400 controls	315 Han Chinese, 1999 European ancestry cases, 3004 European ancestry controls	–	–	*IGF1* *SLC4A4* *WWOX* *SFMBT1*
Kim et al./2012/Affymetrix (334,450) [46]	4965 Korean ancestry subjects	None	–	–	rs6691577 (*LRRC7*) rs2226284 (*LRRC7*) rs12756253 (*LRRC7*)

Probable action has been provided only for the genes in which a SNP association was identified in the intronic or exonic regions
SNP single-nucleotide polymorphism, *NR* not replicated, *rs* reference SNP number, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HTN* hypertension *QC* quality control, *T2DM* type 2 diabetes mellitus

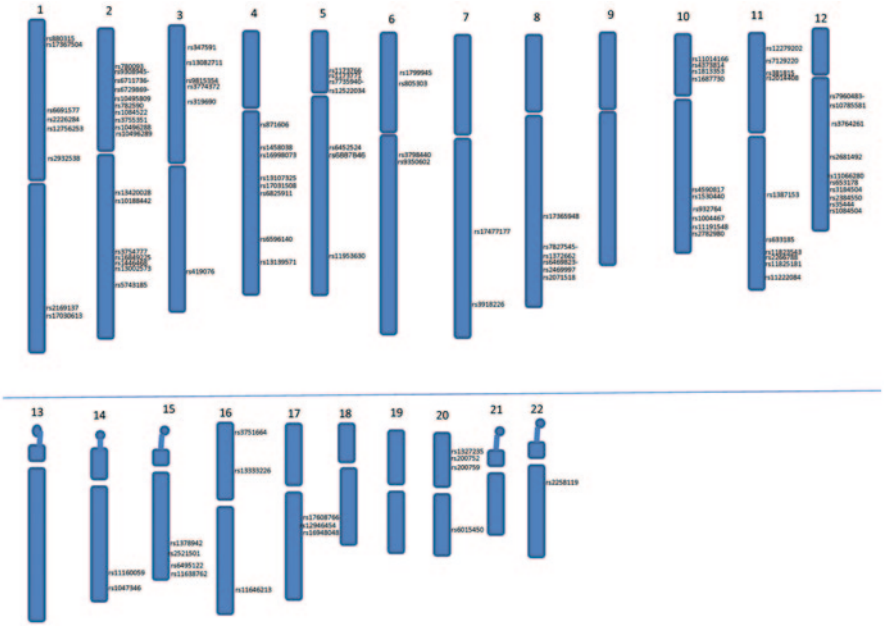

Fig. 15.1 Reference SNP associations for HTN, SBP, and DBP plotted by chromosomal location. *SNP* single-nucleotide polymorphism, *HTN* hypertension, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

locus in the meta-analysis of results from both consortia. In a similar large study, Newton-Cheh et al. also tested ~100,000 subjects (including replication study) and identified associations between SBP or DBP and common variants in eight regions near the *CYP17A1*, *CYP1A2*, *FGF5*, *SH2B3*, *MTHFR*, c10orf107, *ZNF652*, and *PLCD3* ($P \leq 1 \times 10^{-8}$) genes [8]. All variants associated with BP were also associated with dichotomous HTN. These landmark studies, which identified 13 novel BP loci, paved the way for a number of studies in different populations; however, each study reported new findings and often failed to confirm previous GWAS.

Using the concept that limited genetic and environmental diversity and reduced allelic heterogeneity observed in isolated founder populations could facilitate discovery of loci contributing to both Mendelian and complex diseases, Wang et al. carried out a GWAS of SBP and DBP in Amish subjects from Amish Family Diabetes Study [17]. Strong association signals with several common variants in a serine/threonine kinase gene (*STK39*) were found, and they confirmed these associations in an independent Amish and four non-Amish Caucasian samples including the Diabetes Genetics Initiative, Framingham Heart Study, GenNet, and Hutterites ($P < 10^{-6}$). Two SNPs (rs6749447 and rs3754777) accounted for an estimated allelic effect size of 2 mmHg SBP and 1 mmHg DBP. In a similar effort, Sabatti et al. conducted GWAS for SBP and DBP in Northern Finland Birth Cohort 1966 (NFBC1966) members, drawn from the most genetically isolated Finnish regions; however, no individual locus achieved GWS [18].

Org et al. used Kooperative Gesundheitsforschung in der Region Augsburg (KORA) S3 cohort ($n=1644$) recruited from the general population in southern Germany, [19] and identified an association between BP traits and common variants upstream of the *CDH13* gene. The initial associations with HTN and DBP were confirmed in two other European population-based cohorts: KORA S4 (Germans) and HYPEST (Estonians). Carriers of the minor allele A had a decreased risk of HTN. A nonsignificant trend for association was also detected with severe family-based HTN in the BRIGHT sample (British). Using an extreme case-control design, Padmanabhan et al. identified a locus on Uromodulin gene ($P=3.6\times10^{-11}$) [10]. The minor G allele was associated with a lower risk of HTN (OR, 95%CI: 0.87, 0.84–0.91), reduced urinary uromodulin excretion, better renal function; and each copy of the G allele is associated with a 7.7% reduction in risk of CVD events after adjusting for age, sex, BMI, and smoking status (H.R. = 0.923, 95%CI: 0.860–0.991; $P=0.027$). In another subset of 13,446 subjects, they showed that rs13333226 was independently associated with HTN (OR, CI: 0.890.83–0.96, $P=0.004$) [10]. Similarly, using another novel two-marker method, Slavin et al. reexamined WTCCC dataset, and detected SNP pairs in five genes associated with HTN: *GPR39*, *XRCC4*, *MYO6*, *ZFAT*, and *MACROD2* along with four other SNP pair regions that were at least 70 kb from any known gene [20].

In 2011, a large meta-analysis of GWAS of European population, using a multistage design in 200,000 subjects [21], identified 29 independent SNPs at 28 loci which were significantly associated with SBP, DBP, or both ($P<5\times10^{-9}$). Sixteen of these 29 associations were novel loci: Six of these loci contained genes previously known or suspected to regulate BP (*GUCY1A3–GUCY1B3*, *NPR3*–C5orf23, *ADM*, *FURIN–FES*, *GOSR2*, and *GNAS–EDN3*); the other ten provided new clues to BP physiology [21]. They further evaluated whether the BP variants identified in Europeans were associated with BP in subjects of East Asian ($N=29{,}719$), South Asian ($N=23{,}977$), and African ($N=19{,}775$) ancestries. They found significant associations in subjects of East Asian ancestry for SNPs at nine loci (rs1173771, rs633185, rs2521501, rs1327235, rs381815, rs1458038, rs11191548, rs1378942, and rs17249754) and in subjects of South-Asian ancestry for SNPs at six loci (rs2932538, rs1327235, rs6015450, rs1458038, rs11191548, and rs17249754). The authors attributed the lack of association of BP with some SNPs to small sample size in non-European cohorts, and created a genetic risk scores for SBP and DBP involving all 29 BP variants weighted according to the effect sizes observed in the European samples. In each non-European ancestry group, risk scores were strongly associated with SBP ($P=1.1\times10^{-40}$ in East Asian, $P=2.9\times10^{-13}$ in South Asian, $P=9.8\times10^{-4}$ in African ancestry subjects) and DBP ($P=2.9\times10^{-48}$, $P=9.5\times10^{-15}$, and $P=5.3\times10^{-5}$, respectively). In an independent sample of 23,294 women [22], the authors found one SD increase in the genetic risk score was associated with a 21% increase in the odds of HTN (95%CI19%–28%). Among subjects in the top decile of the risk score, the prevalence of HTN was 29% compared with 16% in the bottom decile (OR: 2.09, 95%CI: 1.86–2.36). In another independent HTN case-control sample, subjects in the top compared to bottom quintiles of genetic risk

score differed by 4.6 mmHg SBP and 3.0 mmHg DBP, differences that approach population-averaged BP treatment effects for a single antihypertensive agent [23]. A risk score derived from 29 variants was also significantly associated with CVD, but not kidney disease.

In a relatively smaller GWAS in four Finnish cohorts consisting of metabolic syndrome (MS) cases and controls, both free of T2DM, Kristiansson et al. identified *SMEK2* gene locus SNPs to be associated with SBP ($P=4.02\times10^{-8}$ and $P=4.25\times10^{-8}$) [24]. In a similar attempt, Kraja et al. studied subjects of European descent from SNP Typing for Association with Multiple Phenotypes from Existing Epidemiologic Data (STAMPEED) consortium, eight unique SNPs were identified for bivariate traits (BP being one of the traits) based on NCEP definition of MS (Table 15.1). None of these SNPs demonstrated a significant association ($P<0.05$) with BP alone [25], although some of the SNPs were associated with MS. Using a slightly different model of considering a bivariate response, Das et al. detected eight SNPs for males and seven for females from Framingham Heart Study which are most significant in controlling BP [26].

Few investigators investigated genetic association with related BP phenotypes including mean arterial pressure (MAP), and pulse pressure (PP). Ganesh et al. investigated genetic associations with SBP, DBP, MAP, and PP among subjects of European ancestry by genotyping 50,000 SNPs in 2100 candidate genes for cardiovascular phenotypes and identified two novel associations for SBP and DBP, and confirmed ten previously known loci (Table 15.1).

In an attempt to overcome earlier problems with misclassification of cases as controls, HYPERGENES project investigators excluded controls that developed HTN at a later age. These subjects were followed for 5–10 years after DNA collection. In a two-stage study of cases and controls from different European regions [27], SNP rs3918226 was associated with HTN in whites ($P=2.58\times10^{-13}$ and OR of 1.54; 95%CI: 1.37–1.73) under an additive model. This SNP mapped to a new HTN susceptibility locus in the promoter region of the endothelial NO synthase gene. This finding was further confirmed in a meta-analysis of genotyping data for 21,714 subjects (Anglo-Scandinavian Cardiac Outcomes Trial/AIBIII/NBS, BRIGHT, EPIC-Turin, HYPEST, and NORDIL/MDC samples), resulting in an overall OR of 1.34 (95%CI: 1.25–1.44; $P=1.032\times10^{-14}$). The quantitative effect of rs3918226 was also estimated in continuous BP phenotypes, resulting in a β-coefficient of 1.91 for SBP and 1.40 for DBP, despite the low *P*-values of the regression probably because of the low sample size. This is the first GWAS that points to eNOS regulation, though the authors point to the use of Ilumina 1M array as rs3918226 is not present in other commercial arrays and the high rate of recombination in this region resulting in low linkage disequilibrium. Seven additional SNPs within the eNOS gene showed significant *P*-values, but did not reach GWS. Previously, candidate-gene studies had inconsistently pointed to the association of eNOS with HTN with positive associations in Asian cohorts [28–30], whereas the majority of studies among whites were negative [31].

GWAS of HTN Among Populations of African Origin

African Americans (AA) are disproportionately affected by HTN and associated complications. Adeyemo et al. undertook the first GWAS for BP and HTN among AA from the Washington DC area who were all participants of Howard University Family Study (HUFS) and replicated some of the significant SNPs in a sample of West Africans [32]. They identified multiple SNPs reaching GWS ($P \leq 0.05$) for SBP in or near the genes: *PMS1*, *SLC24A4*, *YWHA7*, *IPO7*, and *CACANA1H*. No variant reached GWS for association with DBP or with HTN as a binary trait. In addition, they attempted to replicate significant SNPs in *STK39* and *CDH13* genes identified in Amish and German populations and found that variants in both these genes were also associated with SBP among AA. These findings were not confirmed in a separate AA sample from Milwaukee, WI. A subsequent large GWAS for BP was performed among AA recruited in the Candidate Gene Association Resource (CARe) consortium which failed to identify any major loci associated with HTN [33, 34]. However, in a related meta-analysis, two novel loci were identified that reached statistical significance: rs2258119 on chromosome 21 with SBP and rs10474346 on chromosome 5 with DBP. However, neither of these associations was replicated in independent AA samples, again highlighting the difficulty in extending the findings of GWAS to independent populations [35].

GWAS of HTN Among Populations of Asian Origin

In the first high-density association study of HTN among Japanese subjects [36], investigators observed association with rs3755351 ($P = 1.7 \times 10^{-5}$) in ADD2. Cho et al. described an intergenic SNP near the *ATP2B1* gene ($P = 1.3 \times 10^{-7}$) with an effect size of -1.309 ± 0.266 mmHg in GWAS among Korean subjects [37].

To increase the genetic contribution and homogeneity of the study trait, Yang et al. focused on young-onset HTN and performed GWAS. They identified an SNP quartet s9308945-rs6711736-rs6729869-rs10495809 located on chromosome 2p22.3. The quartet was 219, 322, 457, and 495 kb downstream of *LOC344371* (hypothetical gene), *MYADML* (pseudo gene), *FAM98* A (hypothetical protein), and *RASGRP3*, respectively [38]. These genes are novel HTN targets identified in this first GWAS of the Han Chinese population.

The Asian Genetic Epidemiology Network BP (AGEN-BP) working group was established to facilitate the identification of genetic variants influencing BP among populations of East Asian ancestry (including Japanese, Han Chinese, Korean, and Malay) [39]. In combined analyses of a three-stage study, six loci reached GWS ($P < 5 \times 0^{-8}$; Table 15.1). One SNP rs3544 (located near *TBX3-TBX5*) showed some evidence of allelic heterogeneity in relation to BP. In addition, rs880315 (CASZ1), previously identified in European population was associated with DBP ($P = 3.1 \times 10^{-10}$). Of the 13 other variants in GWAS meta-analyses in subjects of

European descent, 7 of the 13 loci (54 %) showed nominally significant associations of the reported lead SNPs in East Asians. These data suggest that although some interpopulation differences may exist in the pathways involved in the BP elevation (or HTN) between Europeans and East Asians, the majority of pathways are common. In addition, SNP rs3544 and BP were associated with a nonsynonymous SNP (rs671) in *ALDH2*, which determines an individual's tolerance to alcohol intake and has pleiotropic effects on other metabolic traits and CAD, highlighting the importance of fine-mapping efforts to pinpoint causal variants and causal genes, thereby providing new insights into the physiology of complex diseases. This association was not noted in populations of European descent and appears to be specific to East Asians.

Among other GWAS findings in Asian populations include *AKAP13* gene association in a Korean population [40]; *IGF1*, *SLC4A4*, *WWOX*; *SFMBT1* gene associations a Han-Chinese population [41]; and *FSTL4* in another population of Chinese ancestry [42]. Among the GWAS in which no SNP reached GWS ($P < 5 \times 10^{-7)}$ were studies on genetically isolated founder population of the Pacific island of Kosrae [43], Indian-Asian men [44], and Japanese subjects [45].

Among other studies in Asian populations, one study, prospectively investigated the incidence of HTN in subjects with short sleep duration over a 6-year follow-up period in a GWAS (Table 15.1) [46]. They identified three genetic variants associated with an increased risk of incident HTN only in premenopausal women (adjusted hazard ratio 2.43, 95 % CI = 1.36–4.35). Some investigators have also studied other BP related phenotypes in Asian populations. Wain et al. reported GWAS of PP and MAP in discovery and follow-up studies and identified four new PP loci near *CHIC2*, near *PIK3CG*—in *NOV*—and near *ADAMTS8*, and two new MAP loci (in *MAP4* and near *ADRB1*) and one locus associated with both of these traits (near *FIGN*) that has also recently been associated with SBP in East Asians ($P < 2.7 \times 10^{-8}$; Table 15.2) [47]. Zhang et al. carried out GWAS for pulse pressure on 63 middle-aged dizygotic twin pairs using high-density markers [48] and detected a suggestive association (rs17031508, $P < 8.3 \times 10^{-8}$; Table 15.2).

Table 15.2 Overview of GWAS of mean arterial pressure and pulse pressure

Study/year/platform with SNPs passing QC	Initial sample size and population	Replication sample size and population	Top SNPs (with closest gene if known in parentheses) identified in that cohort	
			MAP	PP
			Subjects of European descent	
Wain et al./2011/Affymetrix, Illumina, and Perlegen [NR; imputed) [47]	74,064 European Ancestry subjects	48,607 European ancestry subjects	rs319690 (*MAP4*) rs2782980 (*ADRB1*) rs1446468(*FIGN*)	rs871606(*RPLP21P44*) rs17477177(*PIK3CG*) rs2071518(NOV) rs11222084(*ADAMTS8*) rs13002573(*FIGN*)
Zhang et. al./2012/Affymetrix (~900,000) [48]	Chinese: 63 dizygotic twin pairs	NR	rs17031508 (*BANK1*)	

SNP single-nucleotide polymorphism, *NR* not replicated, *rs* reference SNP number, *MAP* mean arterial pressure, *PP* pulse pressure, *QC* quality control

Shortcomings of GWAS

Despite successes with robust associations found in some GWAS with BPs and HTN, each SNP explains only a small proportion of BP variance ~1.0 mmHg per allele. Even the pooled results of meta-analysis from large individual GWAS identified only a few gene variants, each associated with a small risk of HTN. The small-discovered effect sizes could in part be because of the effect of misclassification, sample selection bias, inappropriate phenotyping of cases and controls, and inadequate sample size.

A total of 110 SNPs in and around 86 genes have been identified; however, many of them are in intronic or intergenic regions (Table 15.3). In addition, GWAS failed to identify and replicate consistently gene variants of HTN [9], and very few genes have shown associations in more than one study (e.g., *PLEKA7*, *ATP2B1*, *SH2B3*, *TBX3-TBX5*, *ULK4*, *NT5C2*, *MTHFR*, *FGF5*, c10orf107, *CSK*, *ZNF652*, and CACBN2). The tendency of these variants to localize within noncoding regions has also complicated the interpretation of GWAS results and the formation of hypotheses that aim to address the functional relevance of top association signals. SNPs in noncoding regions are purported to have important regulatory roles in the nearby genes if they are in strong linkage disequilibrium with other regulatory SNPs in relatively close regions. Many of these associations also fail biological plausibility test and are in genes that are associated with BP pathophysiology with some exceptions (e.g., *CACNB2*, ENOS, and *CACNA1H*).

Some of what ails GWAS techniques and findings can be remedied by defining more rigorous selection criteria and case definition, recruitment of hypernormal controls, very large sample sizes (with collaborative ventures), and assignment of appropriate levels of statistical significance [49, 50]. While each individual SNP has small effects, their aggregate effect on BP is significant, and are able to produce meaningful population changes in risk. An important and positive message resulting from meta-analyses published thus far is that there are many more common variants associated with BP that remain to be discovered.

New Approaches

Although GWAS have only been recently developed, large-scale SNP genotyping in the context of GWASs may soon be superseded by the next generation of high throughput DNA sequencing. This technology allows for rapid, efficient, and targeted sequencing of candidate genes and GWAS-identified loci for variant analysis [51, 52]. Novel strategies also include the concept that differential regulation of gene expression may not be coded in their DNA sequence—but in epigenetic modifications. Techniques focusing on epigenetic regulation, including microRNAs (miRNAs), histone modification, and methylation will add significantly to our knowledge of what keys our genetic code hold in answering questions about complex disease causation.

Table 15.3 Genes associated with SNPs identified in GWAS for blood pressure-related phenotypes

SNP	Closest Gene/ genes	Location	Associated role/pathway
rs1004467 [21, 53]	*CYP17A1*	Intronic/Chr. 10q24.2	Cytochrome P450, family 17, subfamily A. polypeptide; involved in steroid synthesis pathway
rs381815 [21, 53]	*PLEKHA7*	Intronic/Chr. 11p15.1	Plexkstrin homology domain containing, family A member 7; involved in stabilization and expansion of the E-cadherin adherens junction
rs2681492 [53] rs17249754[a] [21, 37]	*ATP2B1*	Intronic/Chr. 12q21.33 Intergenic/Chr. 12q21.33	ATPase, Ca^{2+} transporting, plasma membrane 1; catalyzes the hydrolysis of ATP coupled with the transport of calcium out of the cell
rs3184504 [21, 53]	*SH2B3*	Exonic/Chr. 12q24.13	SH2B adaptor protein 3; key negative regulator of cytokine signaling and plays a critical role in hematopoiesis
rs11014166 [53] rs4373814[a] [21] rs1813353 [21]	*CACNB2*	Intronic/Chr. 10p12.31 Intergenic/Chr. 10p12.31 Intronic/Chr. 10p12.31	Calcium channel, voltage-dependent, β-2 subunit; contributes to the function of the Ca^{2+}channel by increasing peak Ca^{2+} current, shifting the voltage dependencies of activation and inactivation, modulating G protein inhibition and controlling the α-1 subunit membrane targeting
rs6495122[a][53]	*CSK-ULK3**	Intergenic/Chr. 15q24.1	C-Src tyrosine kinase and Unc-51-like kinase 3
rs2384550[a][53] rs1084504[a][21]	*TBX3-TBX5*	Intergenic/Chr.12q24.21 Intergenic/Chr.12q24.21	T-Box protein 3 and T-Box protein 5
rs9815354 [53] rs3774372 [21]	*ULK4*	Intronic/Chr. 3p22.1 Exonic/Chr. 3p22.1	Unc-51-like kinase 4 No known function
rs11191548[a][8]	*NT5C2*	Intergenic/Chr. 10q24.2	5′-nucleotidase, cytosolic II
rs17367504 [8, 21]	*MTHFR*	Intronic/Chr. 1p36.1	Methylenetetrahydrofolate reductase Catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine
rs12946454 [8]	*PLCD3*	Intronic/Chr.17q21.32	Phospholipase C, delta 3 Hydrolyzes the phosphatidylinositol 4,5-bisphosphate (PIP2) to generate 2 s messenger molecules diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3)
rs16998073[a][8] rs1458038[a][21]	*FGF5*	Intergenic/Chr.4q21.21 Intergenic/Chr.4q21.21	Fibroblast growth factor 5
rs1530440 [8] rs4590817 [21]	c10orf107	Intronic/Chr. 10q21.2 Intronic/Chr. 10q21.2	Chromosome 10 open reading frame 107

Table 15.3 (continued)

SNP	Closest Gene/ genes	Location	Associated role/pathway
rs653178 [8]	*ATXN2*	Intronic/Chr. 12q24.13	Ataxin 2 Involved in EGFR trafficking, acting as negative regulator of endocytic EGFR internalization at the plasma membrane
rs1378942 [8, 21]	*CSK*	Intronic/Chr. 15q24.1	C-Src tyrosine kinase Phosphorylates tyrosine residues
rs16948048[a][8] rs12940887 [21]	*ZNF652*	Intergenic/Chr. 17q21.33 Intronic/Chr. 17q21.33	Zinc finger protein 652 Functions as a transcriptional repressor
rs6749447 [17] rs3754777 [17]	*STK39*	Intronic/Chr. 2q24.3	Serine threonine kinase 39; may act as mediator of cellular stress activated signals
rs11646213[a][19]	*CDH13*	Intergenic/Chr. 16q23.3	Cadherin 13, H-Cadherin
rs13333226[a][10]	*UMOD*	Intergenic/Chr. 16p12.3	Uromodulin
rs2932538[a] [21]	*MOV10*	Intergenic/Chr. 1p13.2	Moloney leukemia virus 10
rs419076 [21]	*MECOM*	Intronic/Chr. 3q26.2	MDS1 and EVI1 complex locus Functions as a transcriptional regulator and oncoprotein that may be involved in hematopoiesis, apoptosis, development, and cell differentiation and proliferation
rs13107325 [21]	*SLC39A8*	Exonic/Chr. 4q24	Solute carrier family 39 (Zinc Transporter), member 8 Functions in cellular import of zinc at the onset of inflammation
rs1173771[a][21]	*NPR3-C5orf23*	Intergenic/Chr. 5p13.3	Natriuretic peptide receptor C/guanylate cyclase C and chromosome 5 open reading frame 23
rs11953630[a][21]	*EBF-1*	Intergenic/Chr. 5q33.3	Early B-cell factor 1
rs1799945 [21]	*HFE*	Exonic/Chr. 6p22.1	Hereditary hemochromatosis protein Regulates iron absorption by regulating the interaction of the transferrin receptor with transferrin
rs805303 [21]	*BAG6*	Intronic/Chr. 6p21.3	BCL2-associated athanogene 6 Implicated in the control of apoptosis, forms a complex with E1A binding protein p300, and is required for the acetylation of p53 in response to DNA damage
rs932764 [21]	*PLCE1*	Intronic/Chr. 10q23.33	Phospholipase C, Epsilon 1 Catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate to generate two second messengers: inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG)

Table 15.3 (continued)

SNP	Closest Gene/ genes	Location	Associated role/pathway
rs7129220[a][21]	*ADM*	Intergenic/Chr. 11p15.4	Adrenomedullin
rs633185 [21]	*ARHGAP42*	Intronic/Chr. 11q22.1	Rho GTPase activating protein 42 May act as a GTPase activator
rs2521501 [21]	*FES*	Intronic/Chr. 15q26.1	Feline sarcoma oncogene It has tyrosine-specific protein kinase activity and that activity is required for maintenance of cellular transformation
rs17608766 [21]	*GOSR2*	? location in the gene/Chr. 17q21.32	Golgi SNAP receptor complex member 2 A trafficking membrane protein which transports proteins among the medial- and trans-Golgi compartments
rs6015450[a] [21]	*GNAS-EDN3*	Intergenic/Chr. 20q13.3	GNAS complex locus and endothelin 3
rs13082711[a] [21]	*SLC4A7*	Intergenic/Chr. 3p24.1	Solute carrier family 4 (Sodium Bicarbonate Cotransporter), member 7
rs13139571 [21]	*GUCY1A3*	Intronic/Chr. 4q32.1	Guanylate cyclase 1, soluble, alpha 3 Catalyzes conversion of GTP to cGMP
rs1327235[a] [21]	*JAG1*	Intergenic/Chr. 20p12.2	Jagged 1
rs10496288–rs10496289[a] [20]	–	Intergenic/Chr. 2p11.2	–
rs13420028–rs10188442 [20]	*GPR39*	Intronic/Chr. 2q21.2	G-Protein coupled receptor 39 Activates a phosphatidylinositol-calcium second messenger system
rs7735940–rs12522034[a] [20]	*RANBP3L*	Intergenic/Chr. 5p13.2	RAN binding protein 3-like
rs6452524–rs6887846 [20]	*XRCC4*	Intronic/Chr.5q14.2	X-ray repair complementing defective repair in Chinese hamster cells 4 Helps in repair of DNA double-strand break
rs3798440–rs9350602 [20]	*MYO6*	Intronic/Chr. 6q14.1	Myosin VI Involved intracellular vesicle and organelle transport, especially in the hair cell of the inner ear
rs2469997–rs6469823[a] [20]	*NOV*	Intergenic/Chr. 8q24.12	Nephroblastoma overexpressed
rs7827545–rs1372662 [20]	*ZFAT*	Intronic/Chr. 8q24.22	Zinc finger and AT hook domain containing Likely binds DNA and functions as a transcriptional regulator involved in apoptosis and cell survival

Table 15.3 (continued)

SNP	Closest Gene/ genes	Location	Associated role/pathway
rs7960483–rs10785581[a] [20]	*ANO6*	Intergenic/Chr. 12q12	Anoctamin 6
rs200752–rs200759 [20]	*MACROD2*	Intronic/Chr. 20p12.1	MACRO domain containing 2 Deacetylates O-acetyl-ADP ribose, a signaling molecule generated by the deacetylation of acetylated lysine residues in histones and other proteins
rs3918226 [27]	*NOS3* (ENOS)	Intronic/Chr. 7q36.1	Nitric oxide synthase 3 (endothelial cell) Produces nitric oxide (NO) which is implicated in vascular smooth muscle relaxation through a cGMP-mediated signal transduction pathway
rs782590 [24] rs1084522 [24]	*SMEK2*	Intronic/Chr. 2p16.1	SMEK homolog 2, suppressor Of Mek1 (Dictyostelium) Associated with centrosomal microtubule organizing centers
rs347591 [51]	*HRH1*	Intronic/Chr. 3p25.3	Histamine Receptor H1 Mediates the contraction of smooth muscles, the increase in capillary permeability due to contraction of terminal venules, the release of catecholamine from adrenal medulla, and neurotransmission in the central nervous system
rs2014408[51]	*SOX6*	Intronic/Chr. 11p15.1	SRY (sex determining region Y)-box 6 Transcriptional activator. Binds specifically to the DNA sequence 5′-AACAAT-3′ Plays a key role in several developmental processes, including neurogenesis and skeleton formation
rs2169137[51]	*MDM4*	Intronic/Chr. 1q32.1	Mdm4 P53 binding protein homolog (mouse) Inhibits p53/TP53- and TP73/p73-mediated cell cycle arrest and apoptosis by binding its transcriptional activation domain. Inhibits degradation of MDM2. Can reverse MDM2-targeted degradation of TP53 while maintaining suppression of TP53 transactivation and apoptotic functions
rs5743185 [32]	*PMS1*	Intronic/Chr. 2q32.2	Post meiotic segregation increased 1 Probably involved in the repair of mismatches in DNA
rs3751664[32]	*CACNA1H*	Exonic/Chr. 16p13.3	Calcium channel, voltage-dependent, T type, alpha 1H subunit These channels mediate the entry of calcium ions into excitable cells and are also involved in a variety of calcium-dependent processes, including muscle contraction, hormone or neurotransmitter release, gene expression, cell motility, cell division and cell death

Table 15.3 (continued)

SNP	Closest Gene/ genes	Location	Associated role/pathway
rs11160059[32]	*SLC24A4*	Intronic/Chr. 14q32.12	Solute carrier family 24 (sodium/potassium exchanger), member 4 Transports 1 Ca(2+) and 1 K(+) in exchange for 4 Na(+)
rs17365948[32]	*YWHAZ*	Intronic/Chr. 8q22.3	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide Adapter protein implicated in the regulation of a large spectrum of both general and specialized signaling pathways
rs12279202[32]	*IPO7*	Intronic/Chr. 11p15.4	Importin 7; functions in nuclear protein import, either by acting as autonomous nuclear transport receptor or as an adapter-like protein in association with the importin-beta subunit KPNB1
rs1687730[a] [32]	*MKX*	Intergenic/Chr. 10p12.1	Mohawk homebox
rs2258119 [34]	*C21orf91*	Intronic/Chr. 21q21.1	Chromosome 21 open reading frame 91 Unknown function
rs1047346[34]	*SETD3*	Intronic/Chr. 14q32.2	SET domain containing Histone methyltransferase that methylates "Lys−36" of histone H3 (H3K36me). H3 "Lys−36" methylation represents a specific tag for epigenetic transcriptional activation
rs3755351 [39]	*ADD2*	Intronic/Chr. 2p13.3	Adducin 2 (β) Promotes the assembly of the spectrin-actin network
rs16849225[a][39] rs1446468[a] [47] rs13002573[a] [47]	*FIGN*	Intergenic/Chr. 2q24.3	Fidgetin
rs1173766[a] [39]	*NPR3*	Intergenic/Chr. 5p13.3	Natriuretic peptide receptor C/guanylate cyclase C
rs11066280[39]	*HECTD4*	Intronic/Chr. 12q24.13	HECT domain containing E3 ubiquitin protein ligase 4 E3 ubiquitin-protein ligase which accepts ubiquitin from an E2 ubiquitin-conjugating enzyme in the form of a thioester and then directly transfers the ubiquitin to targeted substrates
rs17030613[39]	*CAPZA1*	Intronic/Chr. 1p13.2	Capping protein (actin filament) muscle Z-line, alpha 1 Regulates growth of the actin filament by capping the barbed end of growing actin filaments.
rs6825911[a] [39]	*ENPEP*	Intergenic/Chr. 4q25	Glutamyl aminopeptidase

Table 15.3 (continued)

SNP	Closest Gene/ genes	Location	Associated role/pathway
rs35444[a] [39]	*TBX3*	Intergenic/Chr. 1q24.21	T-Box 3
rs880315[39]	*CASZ1*	Intronic/Chr. 1p36.22	Castor zinc finger 1 Probable transcription factor
rs11638762 [40]	*AKAP-13*	Intronic/Chr. 15q25.3	A kinase (PRKA) anchor protein 13 Anchors cAMP-dependent protein kinase (PKA) and acts as an adapter protein to selectively couple G alpha-13 and Rho. Augments gene activation by the estrogen receptor in an element-specific and ligand-dependent manner. Activates estrogen receptor beta by a p38 MAPK-dependent pathway. Stimulates exchange activity on Rho proteins in vitro, but not on CDC42, Ras or Rac and may bind calcium ions
rs6596140[a] [42]	*FSTL4*	Intergenic/Chr. 5q31.1	Follistatin-like 4
rs319690[47]	*MAP4*	Intronic/Chr. 3p21.31	Microtubule-associated protein 4 Promotes microtubule assembly
rs2782980[a] [47]	*ADRB1*	Intergenic/Chr. 10q25.3	Adrenoceptor beta 1
rs871606[a] [47]	*RPL21P44*	Intergenic/Chr. 4q12	Ribosomal protein L21 pseudogene 44
rs17477177[a] [47]	*PIK3CG*	Intergenic/Chr. 7q22.3	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma
rs2071518 [47]	*NOV*	Intronic/Chr. 8q24.12	Nephroblastoma overexpressed Immediate-early protein likely to play a role in cell growth regulation
rs11222084[47]	*ADAMTS8*	Intergenic/Chr. 11q24.3	ADAM metallopeptidase with thrombospondin Type 1 Motif, 8 Has an anti-angiogenic property
rs17031508[a] [48]	*BANK1*	Intergenic/Chr. 4q24	B-cell Scaffold protein with Ankyrin repeats 1
rs6691577 [46] rs2226284 [46] rs12756253 [46]	*LRRC7*	Intronic/Chr. 1p31.1	Leucine rich repeat containing 7 Required for normal synaptic spine architecture and function
rs780093[25]	*GCKR*	Intronic/Chr. 2p23.3	Glucokinase (hexokinase 4) regulator Inhibits glucokinase by forming an inactive complex with this enzyme
rs1387153[a] [25]	*MTNR1B*	Intergenic/Chr. 11q21	Melatonin receptor 1B
rs3764261[a] [25]	*CETP*	Intergenic/Chr. 16q12.2	Cholesteryl ester transfer protein, plasma
rs2954033[a] [25]	*TRIB1*	Intergenic/Chr. 8q24.13	Tribbles homolog 1 (Drosophila)
rs2266788[a] [25]	*APOA5*	Intergenic/Chr. 11.q23.3	Apolipoprotein A-V

Table 15.3 (continued)

SNP	Closest Gene/ genes	Location	Associated role/pathway
rs15285 [25]	*LPL*	Intronic/Chr. 8p21.3	Lipoprotein lipase Hydrolysis of triglycerides of circulating chylomicrons and very low density lipoproteins (VLDL)
rs11823543 [25]	*ZNF259*	Intronic/Chr. 11q23.3	Zinc finger protein 259 May be a signaling molecule that communicates mitogenic signals from the cytoplasm to the nucleus
rs11825181[25]	*BUD13*	Intronic/Chr. 11q23.3	BUD13 homolog Unknown function
rs9308945– rs6711736– rs6729869– rs10495809[a] [38]	*SLC25A5P2* *MYADML* *FAM98A* *RASGRP3*	Intergenic/Chr. 2p22.3	Solute carrier family 25 (mitochondrial carrier; adenine nucleotide translocator), member 5 pseudogene 2 Myeloid-associated differentiation marker-like (pseudogene) Family with sequence similarity 98, member A RAS guanyl releasing protein 3 (calcium and DAG-regulated)

SNP single-nucleotide polymorphism, *rs* reference SNP number, *Chr* Chromosome
[a]SNPs in intergenic region

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Chapter 16
Endocrine Hypertension and Chronic Kidney Disease

Christian A. Koch, Christina Pamporaki and Vitaly Kantorovich

Introduction

Endocrine forms of secondary hypertension (HTN) have traditionally included syndromes of mineralocorticoid excess with primary aldosteronism (PA) representing the most common etiology, followed by Cushing's syndrome (CS), and pheochromocytoma. Besides these conditions of hormonal excess, there are also other rare conditions such as congenital adrenal hyperplasia (11β-hydroxylase, 17α-hydroxylase deficiency), apparent mineralocorticoid excess, Geller syndrome (mineralocorticoid receptor (MR) activation), Liddle syndrome, pseudohypoaldosteronism type 2, and Chrousos syndrome that can cause HTN [1–4] (see Fig. 16.1).

When considering the current obesity epidemic, with its many hormonal derangements (e.g., deficiencies of testosterone, vitamin D, growth hormone), the hitherto estimated prevalence rates of approximately 10% for endocrine HTN are likely to be an underestimate. Potential nonadrenal causes of endocrine HTN include excess production of growth hormone (acromegaly), thyroid hormone, and parathyroid hormone, as well as insulin resistance, hypothyroidism, and overstimulation of central MRs [1, 5–40]. These "nontraditional" forms of endocrine HTN will not be discussed in detail in this chapter.

Cutoffs of systolic and diastolic blood pressure (BP) for defining HTN along with reference ranges for hormonal assays among various patient populations are

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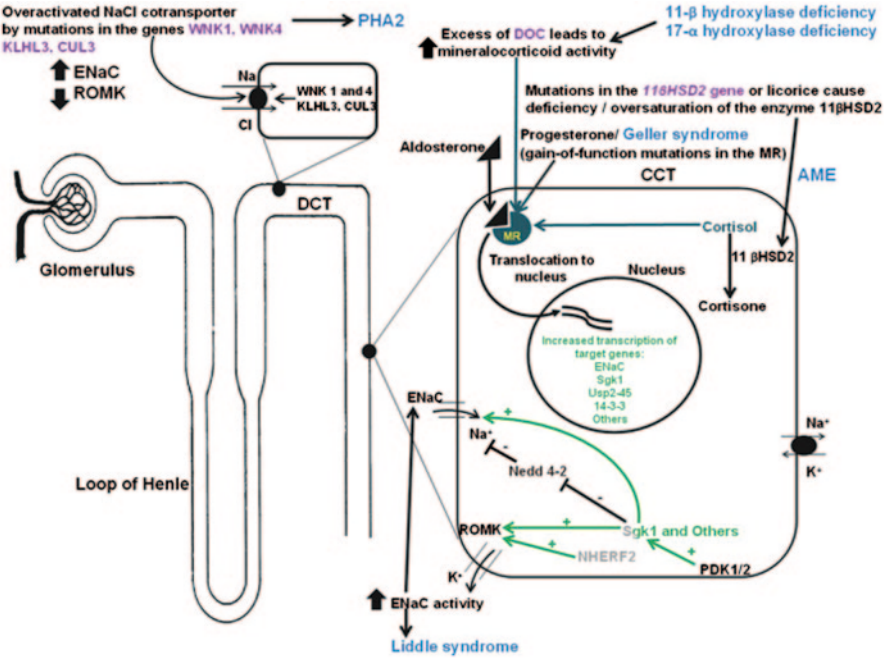

Fig. 16.1 Inherited endocrine condition related to mineralocorticoid excess. The picture shows the molecular pathways involved in dysregulation of NaCl homeostasis located in the distalrenal tubules. *AME* apparent mineralocorticoid excess; *GRA* glucocorticoid-remediable aldosteronism; *PHA2* pseudohypoaldosteronism type 2; *MR* mineralocorticoid receptor; *WNK* with-no-lysine (*K*) kinase 1,4; *ROMK* renal outer medullary potassium channel; *ENaC* epithelial sodium channel; *KLHL3* kelch-like 3; *CUL3* cullin 3; *Sgk1* serum glucocorticoid kinase 1; *Nedd4–2* ubiquitin-protein ligase; deubiquitylating enzyme Usp2–45; 14–3-3 proteins; *NHERF2* Na^+/H^+ exchange regulating factor 2; *PDK1, 2* phosphoinositide-dependent kinases 1 and 2; + activation; − inhibition. (Reprinted from Melcescu and Koch [1])

all important to consider when applying existing or emerging data to clinical patient scenarios. HTN guidelines by various societies have been recently revisited [41–46]. The American Society of Hypertension/International Society of Hypertension (ASH/ISH) guidelines reaffirm the traditional threshold of 140/90 mmHg as a cutoff for defining an elevated BP and state that individuals with a BP of 140–159/90–99 mmHg and no other risk factors are considered at low risk. On the other hand, the Joint National Committee (JNC 8) suggests a systolic blood pressure (SBP) of 150 mmHg as a worrisome threshold, especially for those 80 years and older. For the diastolic BP goal, both the ASH/ISH and JNC 8 guidelines view 90 mmHg as the cutoff; the exception are diabetic hypertensives for whom the cutoff is 85 mmHg. From epidemiologic studies and drug trials, there appears no sound evidence to continue recommending a BP of 140/90 mmHg as the cutoff to initiate antihypertensive treatment; moreover, any increased benefit from additional antihypertensive medications can be nonexistent or negligible, particularly in the face of increased likelihood of adverse effects.

Nevertheless, both the JNC 8 panel and ASH/ISH group recommended a treatment threshold of 140/90 mmHg for adults with diabetes or chronic kidney disease (CKD), based on expert opinion due to lack of randomized controlled evidence. For initial HTN therapy, a thiazide-type diuretic or calcium channel blocker was recommended, and in nonblack patients, the use of an angiotensin-converting-enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). The latter recommendation is based on the large-scale ALLHAT (antihypertensive and lipid-lowering treatment to prevent heart attack trial). In the era of patient-centered medicine, it is important to remain flexible with these guidelines and use them on an individualized basis. Hopefully, future data (2018 and later) from more randomized trials such as the systolic blood pressure intervention trial (SPRINT) will clarify whether a BP of less than 140 mmHg or less than 120 mmHg is more beneficial for nondiabetic adults of age 50 years and older.

Case Finding and Screening

Resistant HTN represents an important case finding feature for endocrine HTN that is often associated with obesity, sleep apnea, and reduced renal function among other conditions. With the current obesity epidemic, approaching an endocrine assessment of HTN can be difficult [47]. There are many (neuro)endocrine alterations in obese patients with and without sleep apnea, including an increase in leptin, cortisol, insulin, and aldosterone levels and a decrease in growth hormone, prolactin, and testosterone [48]. Among National Health and Nutrition Examination Survey (NHANES) participants with CKD, only 37% had a BP < 130/80 mmHg, leaving 63% with a BP higher than 130/80 mmHg. In ALLHAT, 34% of patients taking at least two antihypertensive drugs continued to have uncontrolled HTN after 5 years of follow-up [49]. For patients with truly resistant HTN, the new recommendations include withdrawing medications that do not lower BP, and consideration of a mineralocorticoid antagonist, amiloride, or doxazosin as alternatives. Furthermore, renal denervation or baroreceptor stimulation should be considered if optimal drug therapy is deemed ineffective. These invasive approaches should be reserved for patients with clinic values > 160 mmHg SBP or > 110 mmHg and with BP elevation confirmed by ambulatory BP monitoring. In treating resistant hypertensive patients, renal nerve ablation is associated with a decrease in plasma noradrenaline but not in renin [50].

Of note, the exact prevalence of resistant HTN in patients with CKD remains unknown, but may reach to 30% of all patients with uncontrolled HTN in the USA [51, 52]. Large-scale population-based studies such as the US NHANES suggest that 12% cases of HTN are resistant to pharmacological therapy [53]. Importantly, apparent treatment resistance is often related to poor adherence to antihypertensive therapy, which is reflected by findings that about 40% of patients with newly diagnosed HTN discontinue their treatment during the first year [52]. In all patients with an albumin excretion rate of > 30 mg/24 h, the use of an ACE inhibitor or ARB is

recommended [54]. A recent review of the evidence on the role of dietary salt and potassium intake in cardiovascular health and disease revealed that modest salt restriction while increasing potassium intake serves as a strategy to prevent or control HTN and decrease cardiovascular morbidity and mortality [55].

CKD affects approximately 15% of the adult population, and intensive BP lowering apparently can protect against kidney failure events in patients with CKD, especially among those with proteinuria [56]. A systematic review and meta-analysis suggest that a 10 mmHg reduction in SBP might result in an overall reduction of 22% in the risk of kidney failure [56].

One important question in this regard is when to screen for secondary causes of HTN, including endocrine HTN. HTN in young patients and refractory HTN (characterized by poorly controlled BP on >3 antihypertensive drugs) should alert the physician to screen for secondary causes. The clinician should carefully screen for cardinal signs and symptoms of CS, hyper- or hypothyroidism, acromegaly, or pheochromocytoma. The importance of endocrine-mediated HTN resides in the fact that, in most cases, the cause is clear and can be traced to the actions of a hormone, often produced in excess by a tumor such as an aldosteronoma in a patient with HTN due to PA. More importantly, once the diagnosis is made, a disease-specific targeted antihypertensive therapy can be implemented, and in some cases, surgical intervention may result in complete cure, obviating the need for lifelong antihypertensive treatment.

Clinical Diagnosis of Endocrine Hypertension

A detailed medical history and review of systems should be obtained. The onset of HTN and the response to previous antihypertensive treatment should be determined. Consideration should be given to compliance to prescribed antihypertensive regimen. A history of target organ damage (i.e., retinopathy, nephropathy, claudication, heart disease, abdominal or carotid artery disease) and the overall cardiovascular risk status should also be explored in detail.

As in other causes of HTN, the clinician should question the patient about dietary habits (salt intake, etc.); weight fluctuations (recording exact dry weights, etc., in patients with chronic renal disease); and use of over-the-counter drugs and health supplements, including teas and herbal preparations, recreational drugs, and oral contraceptives. Moreover, a detailed family history may provide valuable insights into familial forms of endocrine HTN. The review of systems should include disease-specific questions. Most patients with HTN due to pheochromocytoma are also symptomatic. Symptoms may include headaches, palpitations, anxiety-like attacks, and profuse sweating, similar to symptoms of hyperthyroidism. Pheochromocytoma, CS, and other endocrine conditions may represent secondary causes of diabetes mellitus [57].

Patients with CS often complain of weight gain, insomnia, depression, easy bruising, and fatigue. Acne and hirsutism (in women) can also be observed. The challenge these days is to recognize patients with evolving CS among the many

obese and often poorly controlled diabetic individuals. Primary hyperaldosteronism is manifested by mild to severe HTN [58–60]. Hypokalemia can be present but it is not a universal finding, and there is normokalemic PA. Polyuria, myopathy, myoglobinuric acute renal failure, and cardiac dysrhythmias may occur in cases of severe hypokalemia [61]. Hypokalemia is associated with kidney function impairment in patients with PA [62, 63], because chronic hypokalemia could induce chronic renal failure through characteristic tubulointerstitial damage consisting of vacuolization of epithelial tubular cells and interstitial fibrosis [64]. In the study of Takanobu and colleagues [65], however, preoperative serum potassium levels did not differ significantly among untreated PA patients. This result suggests that excretion of potassium could have already declined in patients with progressive renal damage, such as epidermal growth factor receptor (eGFR) < 60 mL/min/1.73 m^2.

Many adrenal tumors are today being discovered incidentally during imaging procedures. The challenge for health-care providers is to identify those lesions that may be potentially harmful by either excessive hormone secretion, compressive effects on other structures adjacent to the adrenal glands, or spreading metastases. When caring for a patient with impaired renal function and an incidentally discovered adrenal tumor, screening for excessive hormone secretion from the tumor may be challenging, as many of our contemporary hormonal cutoff values, including stimulation and suppression tests, are based on patient populations with normal renal function. (Fig. 16.2) In both patient groups, those with and those without normal renal function, the transition from normal to subclinical and to finally full-blown clinical hormonal oversecretion often is difficult to recognize. When evaluating a patient with impaired renal function and an adrenal incidentaloma, one should attend to unexplained hypokalemia, typical cushingoid features, signs of

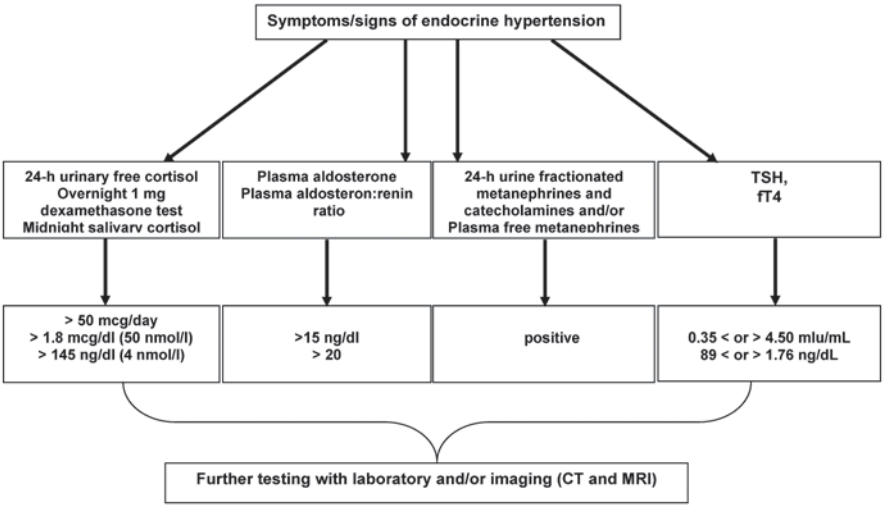

Fig. 16.2 Testing algorithm for endocrine hypertension. (Reprinted with permission from the App "Endocrine hypertension," June 2014, by Melcescu and Koch, of www.endotext.org, the FREE online comprehensive, authoritative, constantly updated web-based Endocrinology Textbook)

Table 16.1 Tests for diagnosing the most prevalent forms of endocrine hypertension

Cushing's syndrome
1 mg dexamethasone suppression test Midnight salivary cortisol, diurnal rhythm ACTH-dependent (5–10 %; ACTH > 20 ng/l) High-dose DST or CRH test If *positive,* then pituitary MRI and/or BIPSS If *negative,* then chest/abd MRI and/or somatostatin scan ACTH-independent (90–95 %; ACTH < 10 ng/l) Adrenal CT or MRI
Hyperaldosteronism
Plasma aldosterone and direct renin Salt suppression test *Positive* if aldosterone excretion > 12–14 µg/day while urine Na > 200 mEq/day Adrenal CT or MRI Adrenal vein sampling
Pheochromocytoma
Plasma-free and/or urine-fractionated metanephrines Anatomic imaging (CT/MRI): a. abd/pelvis if *negative* then b. chest/head and neck Functional imaging: [123/131]Iodine-MIBG Specific PET ([18F]FDA, [18F]FDOPA) Nonspecific PET ([18F]FDG) Genetic testing

ACTH adrenocorticotropic hormone, *DST* dexamethasone suppression test, *CRH* corticotropin-releasing hormone, *MRI* magnetic resonance imaging, *BIPSS* bilateral inferior petrosal sinus sampling, *CT* computed tomography, *MIBG* metaiodobenzyl-guanidine, *PET* positron emission tomography, *FDA* fluorodopamine, *FDOPA* fluorodihydroxyphenylalanine, *FDG* fluorodeoxyglucose

hyperandrogenism, spells including headaches, palpitations, sweats, severe or refractory HTN, and familial syndromes that are associated with adrenal tumors (e.g., von Hippel–Lindau (VHL) syndrome, multiple endocrine neoplasias).

In patients with a positive screening test, subsequent confirmation by various testing modalities is necessary. The most used investigations are listed in Table 16.1.

Primary Aldosteronism

PA has first been described in a Polish patient with HTN and hypokalemia who experienced normotension and normokalemia after removal of an adrenocortical adenoma [66]. In patients with HTN and adrenal incidentaloma, the median prevalence of PA is estimated to be 2 %. In patients with resistant HTN, the estimated prevalence of PA is between 17 and 23 % [67]. After applying the aldosterone-to-renin ratio (ARR) not only to hypokalemic but also normokalemic hypertensives, the diagnosis of PA increased up to 15-fold [68].

The ARR, commonly used to screen for PA, has also been viewed as an index for salt sensitivity and recently has been linked to the development of CKD in a longitudinal, observational study of 698 Japanese individuals. The mean follow-up in that study was 9 years, and those people with a higher ARR more frequently developed CKD [69]. In the German Diabetes and Dialysis Study, including 1255 diabetic hemodialysis patients, the combined presence of high plasma aldosterone >200 pg/ml and high serum cortisol >21 mcg/dl increased the risk of sudden cardiac death as well as all-cause mortality compared to patients with an aldosterone level less than 15 pg/ml and a cortisol value less than 16.8 mcg/dl [70].

Although PA has long been viewed as a relatively benign form of HTN [71, 72], recent studies suggest that long-term exposure to high aldosterone levels might lead to cardiovascular and renal structural damage that seems to occur independent of the BP level [73, 74]. Furthermore, significant histological damage to the kidney was noted in PA patients [63, 75].

Animal Studies

Animal studies support the role of aldosterone in the progression of renal vascular disease [76–79]. In desoxycorticosterone acetate (DOCA)-salt rats, micropuncture studies have demonstrated glomerular hyperfiltration, reflecting increased glomerular blood flow consequent upon vasodilation of both afferent and efferent arterioles, and ascribed to volume expansion [80]. This renal vasodilation may be in large part via a direct mineralocorticoid effect on the vessel wall [81] and is in sharp contrast to the vasoconstrictor response to increased renal perfusion pressure in essential HTN. Studies in dogs indicate that an increase in renal artery pressure, which raises glomerular filtration rate and fractional sodium excretion, is essential in allowing the kidneys to escape from the chronic sodium-retaining action of aldosterone and to achieve sodium balance and a stable level of arterial pressure without severe volume expansion and ascites [82]. Preclinical studies in animal models clearly show that inappropriate aldosterone levels for sodium status can produce extensive renal damage [83].

Clinical Trials

Although preclinical studies indicate that aldosterone per se might cause important renal damage [76, 78], the clinical evidence supporting a direct role of this hormone as a potential contributor to renal dysfunction is limited.

Cross-sectional studies on renal function in PA have shown a high degree of variability in the prevalence of clinically relevant renal damage [84–86]. In fact, the majority of initial reports indicated that PA is less likely to cause overt renal damage [71, 72, 87, 88].

Two recent studies, a short-term [89] and a long-term follow-up [90], demonstrated that the renal dysfunction of PA is closely related with the hemodynamic adaptation of the kidney to the effect of aldosterone excess. In particular, the long-term follow-up study has shown that the condition is characterized by partially reversible renal dysfunction, in that glomerular hyperfiltration is corrected and urinary albumin excretion significantly reduced after either surgical or medical treatment of PA [89]. In agreement with the findings of studies that were conducted in more experimental settings [80–82], longitudinal studies consistently demonstrate that the hallmark of renal dysfunction in PA is reversible glomerular hyperfiltration that contributes to increase urinary albumin losses.

In a short-term study of adrenal adenoma patients after adrenalectomy, the evidence favors a major hemodynamic driver for the increased albuminuria of PA [89]. Patients with proteinuria have lower preoperative serum potassium levels than those without proteinuria [91].

This contrasts with the partial response in terms of BP and albuminuria seen in patients with higher pretreatment plasma renin levels, a possible marker for more severe renal structural damage [89].

Patients with an aldosteronoma are heterogeneous concerning mechanisms for impaired eGFR: those whose eGFR improved after adrenalectomy had lower preoperative plasma renin than those with decreased eGFR after the operation. In those patients with decreased eGFR after removal of the aldosteronoma, preoperative plasma renin was higher and not completely suppressed by the elevated aldosterone. This suggests the coexistence of a high aldosterone state due to the adenoma and an additional nonsuppressible renin state from other causes such as essential HTN. This nonsuppressible renin state would result in additional kidney damage that cannot be reversed by adrenalectomy [91, 92].

Correct interpretation of renal function in patients can be difficult using conventional eGFR before surgery, because in patients at an early stage, subtle kidney impairment might be masked by the glomerular hyperfiltration peculiar to PA preoperatively [93]. Recent studies have shown that many PA patients show a significant decline in eGFR within 6 months of follow-up without any further decrease or increase later on, because the glomerular hyperfiltration state has disappeared after treatment [62].

The occurrence of hypoaldosteronism after unilateral adrenalectomy can be a potential risk factor for postoperative development of CKD, because low aldosterone with improving HTN might decrease growth factor receptor (GFR) and lead to renal impairment [94].

Cardiac and Renal Outcomes

Excessive production of aldosterone in PA patients has been noted to lead to a higher frequency of cardiovascular events, as compared with patients suffering from essential HTN [95]. Furthermore, CKD itself has been suggested to show a significant association with risks of death, cardiovascular events, and hospitalization [96].

Patients with aldosteronoma and left ventricular hypertrophy had lower eGFR compared to those without left ventricular hypertrophy [91]. The dysfunction of both heart and kidneys may be more closely related to other mechanisms, such as generalized endothelial dysfunction and increased oxidative stress [97, 98]. Renal damage might be underestimated in PA patients preoperatively. In the study of Takanobu, all patients with manifested CKD showed a preoperative eGFR of 60–89 mL/min/1.73 m^2. Patients with preoperative eGFR of 90 mL/min/1.73 m^2 did not progress to an eGFR of 60 mL/min/1.73 m^2 because of higher baseline eGFR.

Utsumi et al. [99] found that the previous presence of dyslipidemia is an independent predictor for the postoperative development of CKD. Additional factors, such as older age, lower diastolic BP, and lower estimated GFR, also influence the development of CKD. In particular, aging is closely associated with declining renal function [100, 101]. Furthermore, older age might affect lower diastolic BP in patients with manifested CKD, as a result of the fall in diastolic BP after approximately 50 years of age [102].

Diagnosis

The ARR is useful to screen for PA in patients in whom there is an expected high prevalence of PA. Such patient groups are those with resistant HTN, HTN and adrenal incidentaloma, HTN grade 2 or 3, HTN and spontaneous or diuretic-induced hypokalemia, HTN and a family history or early-onset HTN or cerebrovascular accident younger than age 40, and all hypertensive first-degree relatives of patients with PA [67]. As there is no general consensus on the ARR cutoff, sensitivity and specificity vary widely. The ARR has good within-patient reproducibility and an accuracy of 80 % for identifying patients with an aldosterone-secreting adenoma [68].

Antihypertensive drugs are the most confounding factor affecting the measurement of aldosterone and renin. Especially, MR antagonists, such as spironolactone, eplerenone, and canrenone, should be discontinued 4–6 weeks prior to screening for PA and prior to adrenal vein sampling (AVS), because these agents can lead to an increase in renin secretion and subsequently aldosterone secretion from the unaffected side (if only one adrenal gland was oversecreting aldosterone). Only half of the patients (PA or essential HTN) can be studied drug-free or on medication with minimal influence on the ARR, with approximately 20 % of patients switching antihypertensive drugs experiencing an increase in BP and several patients suffering serious adverse events requiring hospitalization [103].

In 27 uremic patients on a chronic dialysis program, there was no correlation between BP and renin. After dialysis, renin activity rose significantly [104]. In such patients on chronic hemodialysis, the renin–angiotensin system apparently still functions regarding circulatory homeostasis with challenges by volume loss or loading, as demonstrated with 1.5–2 l of intravenous saline infusion that resulted in an increase in plasma volume by 0.4 l and BP by 10–15 mmHg, but in a decrease in plasma renin activity (PRA) by 40 % [105]. In hyperkalemic patients with chronic renal failure and mild azotemia, PRA and aldosterone levels usually

Drug	Class	Usual dose	Comments
Verapamil slow-release	Non-dihydropyridine calcium channel antagonist	90–120 mg twice daily	Use singly or in combination with the other agents listed in this table.
Hydralazine	Vasodilator	10–12.5 mg twice daily, increasing as required	Commence verapamil slow release first to prevent reflex tachycardia. Commencement at low doses reduces risk of side effects (including headaches, flushing, and palpitations).
Prazosin hydrochloride	α-Adrenergic blocker	0.5–1 mg two to three times daily, increasing as required	Monitor for postural hypotension
Doxazosin mesylate	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension
Terazosin hydrochloride	α-Adrenergic blocker	1–2 mg once daily, increasing as required	Monitor for postural hypotension

Fig. 16.3 Medications that have minimal effects on plasma aldosterone levels and can be used to control hypertension during case finding and confirmatory testing for PA. (Reprinted from Funder et al. [67], with permission from The Endocrine Society)

are lower compared to patients with normokalemia [106]. In some patients with PA and end-stage renal disease (ESRD), aldosterone excess exists for many years, if hypokalemia is "masked" by normokalemia in the setting of chronic renal failure which may become unmasked after hemodialysis when hypokalemia due to PA can develop [107]. When interpreting the ARR, one should consider the specific patient population, as elderly and/or black patients often have low PRA values which can result in high ARR while plasma aldosterone levels are rather low. Also, black individuals are more sensitive to aldosterone regarding BP elevation than white people [108]. Most individuals with a plasma aldosterone concentration less than 9 ng/dl have normal suppression after administration of fludrocortisone [109]. When assessing the ARR, direct active renin is rarely measured and standardized/compared to the traditional plasma renin activity [110, 111]. Before measuring the ARR, certain factors should be considered, as mentioned in the Endocrine Society Practice guidelines [67]. Such factors include to correct hypokalemia, to collect blood midmorning, avoiding stasis and hemolysis, maintaining the sample at room temperature and not on ice, separating plasma from cells within 30 min of collection, considering age, the levels of potassium and creatinine, the intake of estrogen-containing medications, as estrogens can increase angiotensinogen synthesis by the liver, and considering other medications that can affect the ARR. Among drugs that have minimal effects on plasma aldosterone levels are the ones listed in Fig. 16.3.

It is recommended to withdraw these medications at least 4 weeks before screening: spironolactone, eplerenone, amiloride, triamterene, potassium-wasting diuretics, licorice-containing products. This clearly may represent a challenge in patients with chronic renal failure and HTN.

After screening for PA with the ARR, patients should typically undergo a confirmatory test for which various procedures exist, including oral sodium loading, saline infusion, fludrocortisone suppression, and a captopril challenge. Depending on the degree of chronic renal failure and HTN, such tests may not be safe to be performed in an individual patient. This becomes especially an issue when considering the lack of data in such patient groups. In patients without PA and normal or only slightly impaired renal function, plasma aldosterone usually suppresses to less than 6 ng/dl after 2 l of intravenous saline infusion. Assessing urinary aldosterone levels is also an option in patients with normal renal function who are suspected to

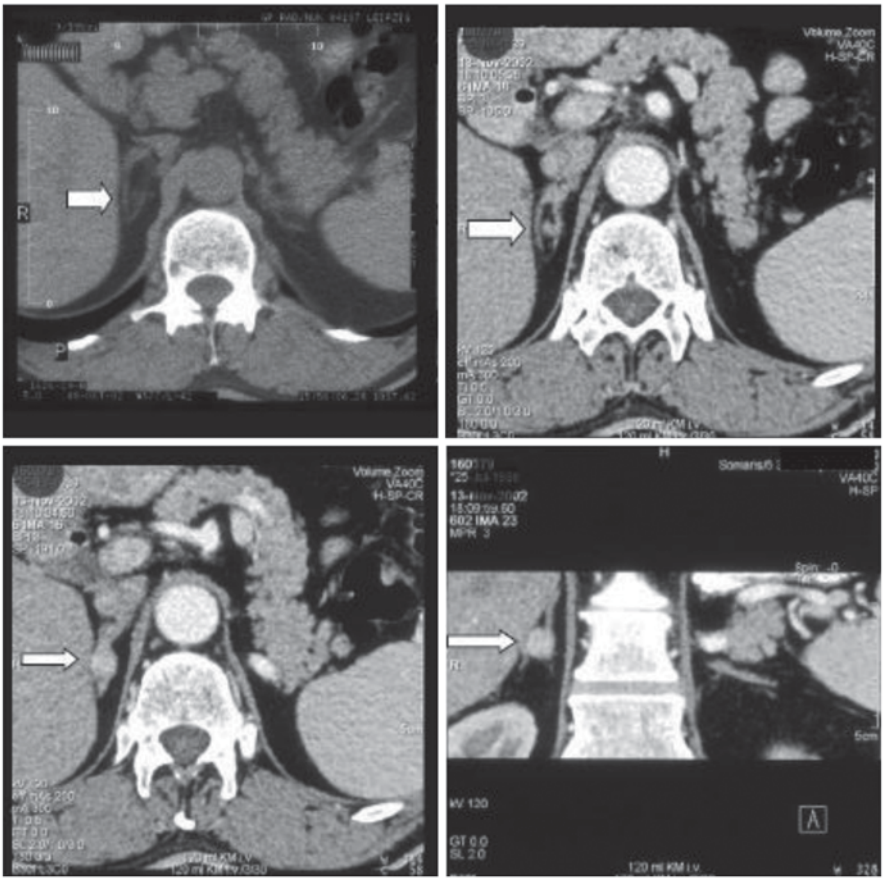

Fig. 16.4 Computed tomography scan of the adrenal glands. *Left upper*: without contrast, all other images with contrast, *right lower image*: coronary section. The *white arrow* points to the right adrenal adenoma in between the adrenal limbs. (Reprinted with permission from Chap. 26 "Overview of Endocrine hypertension," December 2009, by Koch CA, Wofford MA, Ayala AR, Pacak K, of www.endotext.org, the FREE online comprehensive, authoritative, constantly updated web-based Endocrinology Textbook)

have PA [67]. After oral sodium loading, the urinary aldosterone should be less than 10 mcg/day.

Imaging can be performed by computed tomography (CT) or magnetic resonance imaging (MRI). A typical aldosteronoma is shown in Fig. 16.4.

AVS should be performed in patients with PA who are considered for adrenalectomy, unless they are younger than 40 years with marked PA and have a clear unilateral adrenal adenoma, have an unacceptable high risk of adrenal surgery, are suspected to have adrenal cancer, or are proven to have familial hyperaldosteronism type 1 (glucocorticoid (GC) remediable) or type 3 (often due to germline mutations in the KCNJ5 potassium channel gene and treated with bilateral adrenalectomy).

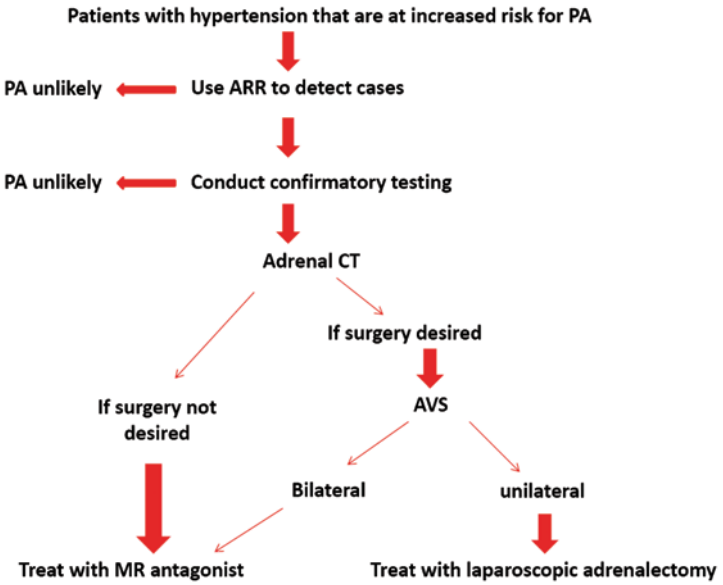

Fig. 16.5 Algorithm for the detection, confirmation, subtype testing, and treatment of PA. (Reprinted from Funder et al. [67], with permission from The Endocrine Society)

MR antagonists or amiloride should be discontinued 4–6 weeks before AVS, and AVS should best be performed in the morning, if cosyntropin stimulation is not used [112]. The selectivity index cutoff value (difference between affected and unaffected sides) should be greater than 2.0 under unstimulated conditions and greater than 3.0 during cosyntropin stimulation. In patients with PA and CKD stage III, stage IV, and stage V, AVS could be performed safely with acute kidney injury occurring in two patients [113] (see Fig. 16.5).

Genetic Aspects of Primary Aldosteronism

Deciphering the human genome has helped identify several disease-causing genes, including some being involved in PA, i.e., in the K-channel gene KCNJ5, encoding Kir3.4, a member of the inwardly rectifying K^+ channel family [114]. The presence of these mutations in the KCNJ5 gene alter the K^+ conductance/selectivity of this channel and consequently increase the Na^+ conductivity (influx) with a further impact on voltage-gated calcium channels, leading to cellular proliferation in the adrenal cortex [115]. The recurrent somatic mutations (G151R, L168R) in the adrenal potassium channel KCNJ5 have been related to benign aldosterone-producing adenomas (APAs) with initial estimates, reporting almost half of APAs being associated with these mutations [115–118]. Subjects with the KCNJ5 G151E mutation have no features of APAs and hyperplasia, a different clinical course (not progressive), and excellent control of BP with spironolactone.

We now know of familial aldosteronism type 1, type 2, and type 3, although the precise molecular pathogenesis of aldosteronomas still needs to be elucidated [119–122]. FH−1 is caused by adrenocorticotropic hormone (ACTH)-dependent aldosterone secretion, GC remediable, and therefore treated with dexamethasone and/or MR antagonists, whereas FH−2 is non-GC remediable and indistinguishable from sporadic PA. FH−3 is resistant to pharmacotherapy and therefore treated with bilateral adrenalectomy. Given the heterogeneity of tumors not only between but also within one individual, it may be more prudent to analyze family members with a known gene defect and identical tumors in a whole genome- and exome-wide sequencing project for targeted genes known to be involved in cell growth regulation. Some of these patients with familial aldosteronism (overall less than 5 % of patients with PA) may require bilateral adrenalectomy to control their HTN which can occur at young age (sometimes in childhood). Exome sequencing of aldosterone-secreting adenomas has revealed somatic hotspot mutations in the ATP1A1 (encoding an $Na(^{+})/K(^{+})$ATPase alpha subunit) and ATP2B3 (encoding a $Ca(2^{+})$ATPase) genes [123, 124] in a small subset of tumors. Similarly, somatic mutations in CACNA1D, encoding a voltage-gated calcium channel, potentially causing increased calcium influx with subsequent aldosterone production and cell proliferation in adrenal glomerulosa cells, have been identified in less than 10 % of aldosteronomas [125].

Therapy

Prevention of Kidney Damage by Treating Primary Aldosteronism

Appropriate management of this endocrine condition results in effective prevention of cardiovascular and renal damage with evidence that applies to both surgical and medical treatment [126–128].

Adrenalectomy

Unilateral adrenalectomy can lead to a decrease in GFR as a release from the hyperfiltration state, which has to be considered a specific functional response to treatment in PA [62]. Adrenalectomy itself does not worsen kidney function, but shows the masked renal damage in PA patients postoperatively.

In animal models, MR blockade by eplerenone prevents the development of the glomerular, interstitial, and renal vascular damage caused by inappropriate mineralocorticoid-salt excess status [129, 130]. Clinically, Epstein and colleagues [131] showed MR blockade to be superior to ACE inhibition in lowering levels of proteinuria, with the combination better than either alone. In ESRD patients on hemodialysis, small pilot studies have shown that spironolactone therapy did not result in higher hyperkalemia rates [132].

The Endocrine Society Practice guidelines recommend medical management with a MR antagonist for patients who do not undergo adrenalectomy [67]. Spironolactone is a nonselective MR antagonist with an incidence of gynecomastia of approximately 7% for doses at 50 mg/day and of more than 50% for doses higher than 150 mg/day. Matsuda and colleagues [133] found that fecal potassium excretion in an anuric patient with PA and hypokalemia decreased while serum potassium increased after administration of spironolactone 50 mg/day. Eplerenone is a selective MR antagonist with 60% of the potency of spironolactone and a shorter half-life but similar antihypertensive efficacy [134]. Amiloride has also antihypertensive effects in patients with PA and can be used in combination with other antihypertensives to achieve BP control. Patients with unilateral aldosteronomas should be offered unilateral laparoscopic adrenalectomy, as their HTN is cured in around 50% of cases with many others experiencing reduction of BP values and subsequently the number of antihypertensive medications and costs [68].

Cushing's Syndrome

Introduction

Most cases of CS are caused by exogenous GCs. Endogenous overproduction of GCs by the adrenal cortex can be the result of an ACTH-secreting pituitary tumor (approximately 80% of cases of endogenous CS), ACTH- or corticotropin-releasing hormone (CRH)-secreting nonpituitary neuroendocrine tumor (approximately 10% of cases of endogeneous CS), or ACTH-independent adrenal tumor [135].

HTN is a common complication of CS. HTN has a prevalence of approximately 55–80% in adult Cushing's patients and 50% in children and adolescents [136–138]. GCs have a myriad of actions on multiple organ systems. GC-induced HTN results from many interacting pathophysiological pathways, which ultimately lead to an increased cardiac output (CO), total peripheral resistance (TPR) and renal vascular resistance (RVR) [136]. GCs may also influence vascular tone, BP, and electrolyte homeostasis through their mineralocorticoid activity. Indeed, free cortisol binds not only to glucocorticoid receptors (GRs) but also to MRs, and its activity at the tissue level is mediated by the microsomal enzyme 11-β-hydroxysteroid dehydrogenase (11β-HSD).

The renin–angiotensin–aldosterone system is also stimulated by GCs through increased hepatic synthesis of angiotensinogen and increased angiotensin II receptor type 1 concentrations in peripheral tissues [139, 140]. Nonetheless, patients with endogenous CS have normal or suppressed PRA [141, 142].

In patients on hemodialysis, the cortisol-to-cortisone ratio is increased due to reduced activity of 11-β-hydroxysteroid dehydrogenase [143]. Renal 11β-HSD2 expression is reduced in patients with impaired renal function, potentially causing the MR be occupied by GCs such as cortisol which may contribute to increased sodium retention in such patients [144]. Therefore, some investigators suggest making the analysis of urinary 5α-tetrahydrocortisol, 5β-tetrahydrocortisol, and

tetrahydrocortisone part of the routine workup of patients with CKD and HTN [145]. Hypokalemia in obese anuric patients on chronic hemodialysis can point to CS from an adrenal tumor [146]. In this context, one should also consider the rare occurrence of apparent mineralocorticoid excess syndrome in which affected patients homozygous for missense mutations in the HSD11B2 gene, encoding 11β-HSD, have an increased ratio of urine-free cortisol to cortisone, often requiring treatment with potassium supplements and spironolactone [147].

GCs are associated with occlusive vascular disease in humans, which occurs through a myriad of effects on vascular smooth muscle, endothelial cells, myocardium and macrophages, as well as their link with obesity, HTN, dyslipidemia, and insulin resistance.

HTN is caused by GC-induced insulin resistance [148, 149], increased vascular resistance [150, 151], and sodium retention. Malignant HTN, a potentially fatal disorder if left untreated, accompanied by Cushing's disease has been rarely reported [152, 153].

Changes in Glomerular Function

In patients with adrenal insufficiency, sodium and mineralocorticoid replacement and volume expansion were insufficient to correct the fall in renal blood flow and GFR [154, 155]. This result reflects the essential role of cortisol in the maintenance of normal renal blood flow and GFR [156].

Short-term administration of ACTH or GCs increases GFR in humans, rats, sheep, and dogs [157–159].

As most GCs exhibit some mineralocorticoid effects, it has been suggested that plasma volume expansion due to sodium retention might lead to an increased GFR. However, GFR remained elevated in studies using GCs almost completely devoid of mineralocorticoid activity as well as in animal experiments with low or zero sodium intake. Thus, the GC-induced rise in GFR was not solely volume dependent [158, 160, 161].

Studies examining GC effects on glomerular vasculature are conflicting. In dogs, rats, and sheep, GCs increase renal blood flow, but this outcome is not always the case in humans [159, 161–163].

Although acute effects of synthetic or endogenous GCs increase the GFR in laboratory animals, dogs, and humans, long-term effects of CS in humans may decrease GFR as shown in the study by Haentjens and coworkers [164]. Most of the patients included in the latter study had been cured of CS, and had a decreased GFR compared to matched controls. Interestingly, the strongest predictor of GFR was duration of active disease and 4 of 18 Cushing's patients were identified with CKD. Permanent alterations of vessel remodeling due to the chronic endogenous state of excess cortisol may have contributed to a lower GFR in these patients [164]. Two other studies demonstrated a lower creatinine clearance in Cushing's patients with active and cured disease compared with controls [165, 166].

Serum creatinine is often used as an indirect measurement of GFR. Because muscle mass is the main source of serum creatinine and urinary creatinine elimination

is constant over time, diseases affecting muscle mass influence the serum creatinine level [167, 168]. Both muscular atrophy and truncal obesity are features of CS in humans and dogs, and they have been shown to result in a decreased creatinine production rate that may be compensated by muscular hypertrophy associated with obesity [169]. In people with CS, both increased and reference range serum creatinine levels have been reported [164, 166, 169]. Patients receiving prednisone showed a rise in plasma creatinine and urinary creatinine excretion, which was probably due a catabolic effect [170]. Serum creatinine in dogs with CS was usually within or lower than the reference range [171, 172].

Effects of Glucocorticoids on Fetal Renal Development

GCs have a direct effect on growth and differentiation of a wide range of fetal tissues, especially close to term [173]. In addition, GCs can program tissues in utero and mediate effects of environmental or nutritional challenges during pregnancy, which leads to long-term consequences in later life [174, 175]. Administration of GCs affects renal function. In the fetal kidney, GCs stimulate angiotensin II, vasopressin, ACTH, and leptin receptor function, as well as metabolic enzymes, epithelial Na^+ channels, Na^+/K^+ ATPase and Na^+/H^+ ion transporters and aquaporins [176, 177]. Several studies have shown that the main effect of prenatal GCs was a reduced number of nephrons, which was commonly associated with the development of HTN in later life [178, 179].

Effects of Glucocorticoids on Renal Function

Proteinuria

Urinary albumin is increased in humans, dogs, and rats treated with GCs as well as canine Cushing's patients [180–183]. Reports on proteinuria in people with naturally occurring CS are very rare, but one study described increased urinary albumin excretion in more than 80% of patients before treatment, which was almost completely resolved after successful therapy [184]. This finding was corroborated in a second report, which mainly involved cured subjects without an increase in microalbuminuria [164]. In general, renal proteinuria may be caused by increased glomerular filtration resulting from higher intraglomerular pressure, damage to the glomerular barrier, or decreased tubular reabsorption [185].

Chronic Kidney Disease

Excess GCs have many detrimental effects on kidney function, but whether people or dogs with CS are at risk for developing CKD is an essential issue that warrants further investigation.

In humans, the combination of Cushing's disease and renal failure is considered to be very rare [186, 187]. However, one case-control study reported a decreased GFR in a group Cushing's patients mainly with cured disease; 4 out of 18 patients had CKD, which was defined as a GFR < 60 mL/min/1.73 m^2. The authors concluded that follow-up of renal function after treatment for CS was important because a decreased GFR may have implications for medication dosages [164].

Creatinine clearance was also lower in patients with active and cured CS compared with controls in two other studies, although these differences were not statistically significant [165, 166]. In addition, a highly significant correlation between endogenous GC production and the progression rate of chronic renal failure has been described [188].

Nephrolithiasis

Compared to the general population of industrialized countries, nephrolithiasis is remarkably common in human Cushing's patients. Indeed, studies have shown that there is a prevalence of approximately 50 % in patients with active disease and 17–27.3 % in cured patients [164, 166]. Importantly, subjects who have been cured of Cushing's disease for a long time still maintain a higher risk for the development of kidney stones compared with controls, which is also associated with a persistence of metabolic syndrome and HTN, despite the normalization of cortisol levels. Hypercalciuria, hypocitraturia, and increased urinary excretion of phosphorus, oxalate, potassium, and cystine, mainly systemic HTN and excess urinary excretion of uric acid, seem to play a crucial role in kidney stone formation in patients with Cushing's disease [166].

In CS, systemic HTN, which leads to an increased capillary hydrostatic pressure, and additional hemodynamic effects, which cause hyperfiltration, may eventually result in proteinuria and glomerulosclerosis. Glomerulosclerosis has been documented in humans and dogs with CS and in dogs treated with prednisone [183, 189–192].

Diagnosis

One of the largest challenges remains to timely identify patients with CS. In the current society of obese individuals, one may have to consider establishing new reference ranges for various hormones. For instance, norm values for urinary-free cortisol adapted to obese children may help avoid unnecessary dexamethasone suppression or other testing for possible CS [193]. This may even be difficult in full-blown CS, as the sensitivity and specificity of clinical signs and symptoms of CS vary widely. For instance, the occurrence of ecchymoses may have a specificity of 94 % for CS, while its sensitivity varies between 60 and 68 %. Stretch marks wider than 1 cm and of purple color have a sensitivity of 50–64 % and a specificity of 78 %. Increased fatigue and weight gain have a sensitivity of nearly 100 % but are not

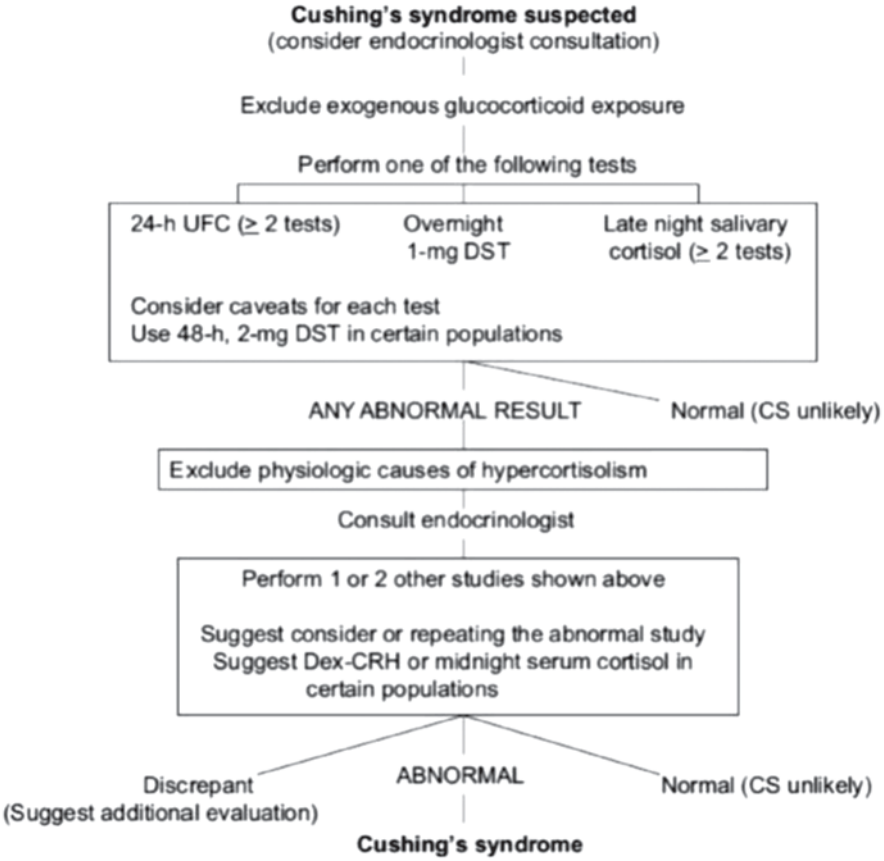

Fig. 16.6 Cushing's syndrome algorithm. (Reprinted from Nieman et al. [195], with permission from The Endocrine Society)

very specific [194]. This poses the question who should be screened for CS. First, patients with signs that are most suggestive of hypercortisolism, including wide (>1 cm) purple striae, excessive bruising, proximal muscle weakness, abnormal fat distribution (temporal fossae and supraclavicular), and failure of linear growth with continued weight gain in children. Second, anyone with unusual features for their age group, including HTN and/or nontraumatic fractures in young individuals, or anyone with multiple clinical features that are progressive over time. The Endocrine Society has published guidelines on this topic in 2008 and the algorithm is shown in Fig. 16.6 [195].

Biochemical assessment for CS in patients with chronic renal impairment is difficult. Obviously, assessing 24-h urinary-free cortisol excretion largely depends on how precisely an individual patient collects urine and on her/his renal function. Plasma binding protein concentrations and dexamethasone clearance can be significantly altered with decreased renal function [143, 196, 197]. Recent studies have

shown a disrupted circadian cortisol rhythm in patients with ESRD, whereas previous studies showed normal rhythms [197–200]. C-reactive protein is increased in patients with ESRD [201]. Some authors report that patients with chronic renal failure generally have normal plasma levels of cortisol, depending on the assay used [202, 203], whereas ACTH levels may be increased [204]. Spuriously, low urinary-free cortisol levels can occur in patients with a GFR less than 30 ml/min [205]. Ovine CRH may not appropriately stimulate ACTH and cortisol in patients with chronic renal failure except for those on continuous ambulatory peritoneal dialysis [206]. The oral absorption of dexamethasone can be altered (reduced) in some patients, but the metabolism of dexamethasone usually is normal in chronic renal failure. Normal suppression of cortisol after 1 mg of overnight dexamethasone is uncommon [207]. The use of the dexamethasone suppression test in the diagnosis of CS has recently been critically reviewed [208]. Even if plasma dexamethasone levels are measured, the interpretation of what a normal cortisol suppression is for each individual patient assessed for possible CS remains challenging, as there are patients with Cushing's disease with slightly or moderately elevated basal plasma cortisol levels and post dexamethasone plasma cortisol levels that are interpreted as normal [209]. In addition, there are many medications that can alter the metabolism of dexamethasone. Recently, topiramate, a frequently used contemporary medication, has been reported to cause a false positive overnight 1-mg dexamethasone suppression test [210].

Alternatively, salivary cortisol has been regarded as a reliable parameter for the diagnosis of severe hypercortisolism, even in women during pregnancy or taking oral contraceptive pills [211]. Obtaining two samples improves the diagnostic accuracy of measuring late-night salivary cortisol for CS [212]. A study of 16 patients on daytime chronic hemodialysis and controls showed that ESRD subjects have increased late-night plasma and salivary cortisol and plasma ACTH levels, with late-night salivary cortisol being a reliable index of plasma cortisol in ESRD patients [213]. In that study, the authors suggest that ESRD may represent a state of ACTH-dependent hypercortisolism but not CS per se, similar to previous studies in poorly controlled diabetics [214]. Raff and Trivedi [213] measured late-night salivary cortisol levels as high as 15 nmol/l in ESRD patients (reference range, <4 nmol/l or 145 ng/dl, ref. [195]) and concluded that a "normal" late-night salivary cortisol value rules out CS in patients with ESRD.

Interestingly, ACTH-stimulated salivary cortisol represents an accurate biomarker for the diagnosis of adrenal insufficiency in hypotensive patients with ESRD, whereas neither basal salivary nor serum cortisol do [215].

Genetic Aspects of Cushing's Syndrome

We here will not review the molecular pathogenesis of ACTH-secreting pituitary tumors, ectopic ACTH-secreting neuroendocrine tumors, or adrenal tumors. However, a few statements based on more recent findings should be made. In general,

the molecular pathogenesis of ACTH-independent macronodular adrenal hyperplasia and sporadic cortisol-secreting adenomas has recently been elucidated. Exome sequencing or tumor–normal pairs revealed gain of function mutations in the CTNNB1 (β-catenin) or GNAS (Galphas) genes or somatic mutations in the PRKACA (protein kinase A catalytic subunit) gene with protein kinase activity inducing cortisol production and cell proliferation of affected adrenal cells [216]. Germline duplications of the PRKACA gene result in bilateral adrenal hyperplasia, whereas somatic mutations in this gene cause unilateral cortisol-producing adrenal adenomas [217]. A subset of ACTH-independent macronodular adrenal hyperplasia contains inactivating mutations in armadillo repeat containing 5 (ARMC5), a putative tumor-suppressor gene [218]. Regarding ACTH in the pituitary, most of such tumors occur sporadically with altered gene expression, somatic mutations in various genes, epigenetic changes, and abnormal microRNAs. Their pathogenesis remains largely unknown [219]. Whole exome sequencing of pituitary adenomas reveals different oncogenic mutations in each individual tumor, making it probable that there is no common oncogenic denominator but an abnormal stem cell that leads to abnormal localized proliferation. Nevertheless, there are familial pituitary tumor syndromes, including multiple endocrine neoplasia type 1, Carney complex, familial isolated pituitary adenomas, and others. The pathogenesis of ectopic ACTH-secreting neuroendocrine tumors is largely unknown, although some familial syndromes in which an ACTH-secreting neuroendocrine tumor is part of helped elucidate the biology of these neoplasms. For instance, neuroendocrine tumors of the pancreas in patients with VHL syndrome usually are nonfunctional but can secrete ACTH [220]. VHL syndrome is caused by germline mutations in the VHL gene and subsequent molecular events [221]. Neuroendocrine tumors of the thyroid usually are medullary thyroid cancer and often are caused by germline mutations in the rearranged during transfection (RET) proto-oncogene [222]. Many other organs can harbor ACTH-secreting neuroendocrine tumors, and for each organ, for instance, the prostate, pancreas, adrenal medulla/pheochromocytoma, one would have to consider the respective pathogenesis [223–225].

Therapy

In patients with a cortisol-producing adrenal tumor, laparoscopic adrenalectomy should be performed to normalize cortisol production. If bilateral adrenalectomy is necessary, proper adrenal hormone replacement should be commenced. For instance, most individuals can be managed by taking oral hydrocortisone, 10 mg in the morning and 5–10 mg late afternoon, in addition to fludrocortisone 50–100 mcg/day [226]. Adrenal function should be assessed in patients with ESRD in order to unmask adrenal insufficient states [227].

In patients with an ACTH-secreting pituitary tumor, transsphenoidal or transcranial surgical removal should be performed, if possible. Postsurgically, transient or permanent adrenal insufficiency can occur and should be handled, as aforementioned.

Long-term follow-up is necessary even in patients with initial and long-term remission [228]. In patients with nonpituitary ACTH-dependent CS, ideally the primary neuroendocrine tumor should be found and removed, although surgical resection of metastases might result in short-term remission of CS [60]. For patients who are not or poor surgical candidates, medical therapy of hypercortisolism should be initiated. Depending on country-specific regulations and availability of drugs, one can choose among the following arsenal with each one to be revisited for mild or more impaired renal and/or liver function with respective dose adjustments: metyrapone, ketoconazole, mifepristone RU486, cabergoline, pasireotide, octreotide, etomidate, and mitotane [195, 229–232].

Pheochromocytoma

Pheochromocytoma is a neuroendocrine tumor that arises from the adrenal gland, while paraganglioma originates from sympathetic or parasympathetic paraganglia. Pheochromocytoma and sympathetic paraganglioma can produce, store, metabolize, and secrete catecholamines and metanephrines (MNs). Parasympathetic head and neck paraganglioma are typically biochemically silent [233, 234]. With an annual incidence of around 2–8 cases per million people, pheochromocytoma is a less common cause of endocrine HTN than PA [235].

Clinical Symptoms and Signs

Among 2585 hypertensive patients, headaches, palpitations, and sweating attacks were most frequently associated with pheochromocytoma [236]. However, only 6.5% of these 2585 patients reported all three symptoms which then had a specificity of 93.8%, a sensitivity of 90.9%, and an exclusion value of 99.9% for the diagnosis of pheochromocytoma. In the absence of this classic triad, the probability of pheochromocytoma has been viewed as inferior to 1 in 1000. In a recent German cohort of 201 pheochromocytoma patients, less than 10% had this classic triad and most tumors had been detected incidentally, underscoring that certain imaging features combined with biochemical analyses are important in establishing the diagnosis of pheochromocytoma/paraganglioma [237]. Performing a biopsy of pheochromocytomas and paragangliomas without prior biochemical testing can lead to serious complications, including hemorrhage, pain, severe HTN, difficult surgical resection, and others [238].

Patients with pheochromocytoma have a higher rate of cardiovascular events than patients with essential HTN, most likely related to prolonged exposure to hypercatecholaminemia [239]. Although HTN is the most common clinical finding in patients with pheochromocytoma, it may not be uniformly present in all patients. In a study conducted at Mayo Clinic on 76 patients with pheochromocytoma, 20%

of the patients with paroxysmal HTN and 30% with persistent HTN had fasting hyperglycemia [240]. Insulin sensitivity often improves after removal of pheochromocytoma [241]. In children, HTN due to pheochromocytoma tends to be more severe and refractory than in adults [242]. The patients presenting with pheochromocytoma crisis may have extremely varied manifestations, ranging from severe HTN to circulatory failure and shock [243].

Case finding strategies may include considering possible pheochromocytoma/paraganglioma in patients with:

- Resistant HTN
- Familial syndrome that predisposes to pheochromocytoma
- Family history of pheochromocytoma
- Incidentally discovered adrenal mass
- Hyperadrenergic spells
- HTN and diabetes
- Onset of HTN at young age (<20 years)
- Pressor response during anesthesia, surgery, or angiography
- History of gastric stromal tumor or pulmonary chondroma
- Idiopathic dilated cardiomyopathy

Physical exam findings can be associated with a genetic pheochromocytoma/paraganglioma syndrome and may include retinal angiomas (VHL syndrome), marfanoid body habitus, café au lait spots (neurofibromatosis type 1), axillary freckling, mucsoal neuromas on eyelids/tongue (multiple endocrine neoplasia type 2), thyroid mass (MEN2), and others [234, 244, 245].

CKD has been described as a complication of pheochromocytoma. In particular, in patients with episodes of paroxysmal HTN, suggestive of pheochromocytoma, persistent HTN could have contributed to the development of chronic renal insufficiency [246, 247].

In severe cases of glomerulonephropathy in rats, associated with disturbed calcium/phosphorous homeostasis, there might be chronic stimulation of the chromaffin cells toward proliferation, which may eventually lead to hyperplasia and neoplasia. A study from 1999 in rats showed a positive correlation between the severity of chronic progressive glomerulonephropathy and the incidence of adrenal pheochromocytoma. In particular, the incidence of adrenal pheochromocytoma was consistently higher in animals with more severe glomerulonephropathy [248].

If a pheochromocytoma is located at the renal hilum, it can cause renovascular HTN via several mechanisms. Besides producing catecholamines, this topography can cause transient or fixed renal artery stenosis with subsequent HTN.

Mechanisms of renal artery stenosis secondary to pheochromocytoma include direct compression of the tumor on the renal artery or its branches, fibromuscular dysplasia, and fibrous bands emanating from the tumor [249, 250]. Although extrinsic pressure on the renal artery is the most common, long-term pressure causes myointimal proliferation needing reconstruction. The attenuation in the caliber of the renal artery may not necessarily be caused by mechanical causes but can be caused by catecholamine- induced vasospasm. Catecholamine-induced vasospasm

is generally termed *pseudostenosis* because it is a pharmacologically reversible cause of renal artery stenosis [251]. It is most likely a result of local seepage of vasoactive amines from an adjacent pheochromocytoma into the renal hilum.

Indeed, stenosis of the renal artery and concomitant pheochromocytoma, although a seemingly rare combination, has been reported in more than 25 publications. In a large survey of world literature, over 100 cases have been reported, of which only about 14% occurred in children [252, 253].

Diagnostic Difficulties in Patients with Pheochromocytoma and Renal Dysfunction

As a chameleon, pheochromocytoma can be disguised in various forms of clinical presentation with or without impaired renal function [235]. Besides searching for signs and symptoms typical for pheochromocytoma, other steps are critical in establishing the diagnosis. Among these, biochemical analyses are of utmost importance. Of course, the interpretation of biochemical results depends on the assay analysis used, for instance, whether liquid chromatography/mass spectroscopy or LC-MS/MS has been utilized. Recent Endocrine Society guidelines suggest measurement of plasma free or urinary fractionated MNs [244]. The role of catecholamines had decreased because of episodic secretion. On the other hand, pheochromocytoma/paragangliomas with less differentiated features such as those seen in the succinate dehydrogenase (SDHx) mutation-related syndromes possess less advanced enzymatic machinery. This results in a mostly dopaminergic secretory profile, which can be detected by assessing either dopamine or methoxytyramine levels. Methoxytyramine is a dopamine metabolite. Measuring plasma-free (in particular deconjugated) MNs may be compromised by increased sympathetic outflow or dependence of catecholamine metabolite levels on clearance by the kidneys [254, 255]. These problems are particularly acute in ESRD, when patients are functionally anephric and on dialysis and may have several-fold elevations of plasma norepinephrine and dopamine concentrations without having a pheochromocytoma [256–260]. In such patients with renal failure, there are at least twofold higher plasma concentrations of catecholamines and free MNs [261–263]. Of note, there are several medications that may cause falsely elevated tests results for plasma and urinary MNs, as shown in Fig. 16.7.

We propose a flow chart as shown in Fig. 16.8 for diagnosing pheochromocytoma/paraganglioma.

VHL syndrome is one example where there is a high risk of both pheochromocytoma and kidney cancer, and where the former tumor may often need to be considered in the setting of mildly to severely impaired renal function [264, 265]. In screening such patients for pheochromocytoma, one third may not have any symptoms, normal BP, and normal catecholamine testing [266].

In hemodialysis patients, few reports of pheochromocytoma exist in the literature [267–269]. Clinical signs may be neglected because HTN, headache, and

	Plasma		Urine	
	NMN	MN	NMN	MN
Acetaminophen[a]	++	−	++	−
Labetalol[a]	−	−	++	++
Sotalol[a]	−	−	++	++
α-Methyldopa[a]	++	−	++	−
Tricyclic antidepressants[b]	++	−	++	−
Buspirone[a]	−	++	−	++
Phenoxybenzamine[b]	++	−	++	−
MAO-inhibitors[b]	++	++	++	++
Sympathomimetics[b]	+	+	+	+
Cocaine[b]	++	+	++	+
Sulphasalazine[a]	++	−	++	−
Levodopa[c]	+	+	++	+

Abbreviations: MAO, monoamine oxidase; MN, metanephrine; NMN, normetanephrine; ++, clear increase; +, mild increase; −, no increase.

[a] Analytical interference for some but not all methods employing LC-ECD.

[b] Pharmacodynamic interference leading to increased levels affecting all analytical methods.

[c] Analytical interference with some LC-ECD assays, and also pharmacodynamic interference increase the dopamine metabolite 3-methoxytyramine affecting all analytical methods.

Fig. 16.7 Major medications that may cause falsely elevated test results for plasma and urinary metanephrines. (Reprinted from Lenders et al. [244], with permission from The Endocrine Society)

palpitations occur frequently in these patients. Normal values of plasma catecholamines in hemodialysis patients may be similar or slightly elevated as compared to patients with normal renal function [270]. Plasma noradrenaline levels are extremely high in some of these patients [268]. In fact, it has been proposed that in a patient on long-term hemodialysis, a plasma noradrenaline concentration of greater than a threefold elevation compared with normal controls should raise the suspicion of pheochromocytoma. Measurement of urinary excretion rates of noradrenaline and MN has been advocated by some authors as the best criterion for the diagnosis [271]. HTN due to pheochromocytoma can be masked by excessive reduction of intravascular volume by preoperative hemodialysis. In a hemodialyzed patient harboring pheochromocytoma who undergoes a surgical procedure unrelated to adrenalectomy, preoperative alpha-adrenergic blockade and subsequent intravascular volume expansion by increasing dry weight is required to avoid severe intraoperative hypotension. It is well known that many patients on long-term hemodialysis treatment suffer from hypotension. Daul et al. [272] reported that increased plasma noradrenaline levels with longer duration of hemodialysis may induce alpha-adrenoceptor downregulation, and the resulting reduction in alpha-adrenoceptor responsiveness to adrenergic stimuli might be an important cause of arterial hypotension in patients on long-term hemodialysis treatment.

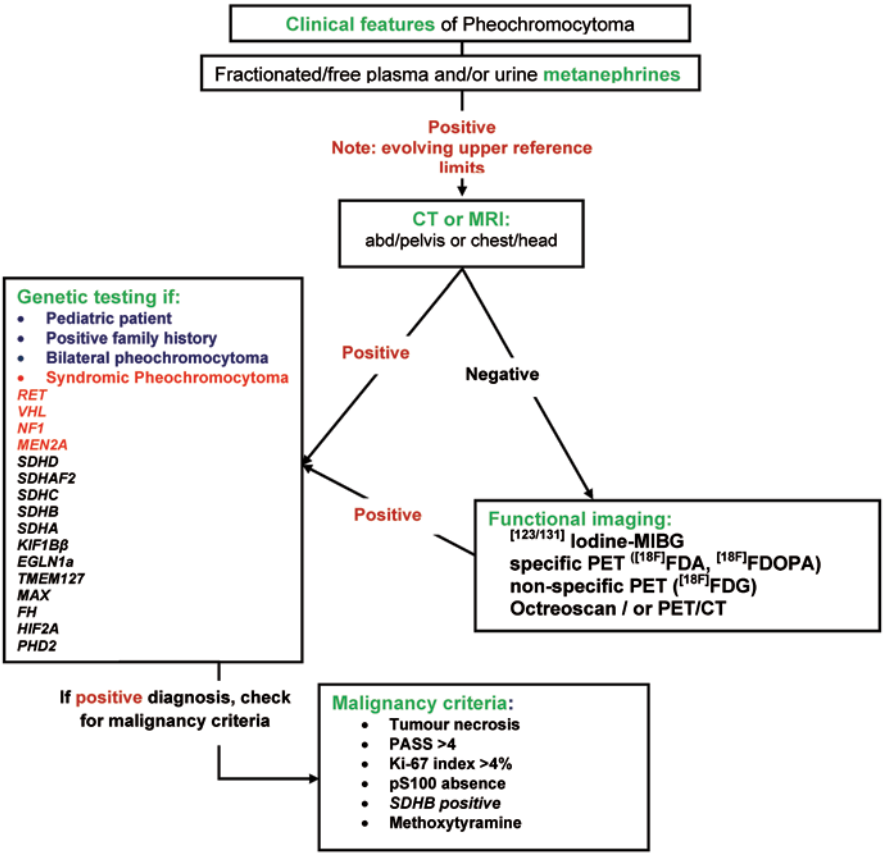

Fig. 16.8 Diagnosing pheochromocytoma/paraganglioma flowchart. (Reprinted with permission from Chap. 7 "Testing for Endocrine hypertension," June 2012, by Melcescu and Koch, of www.endotext.org, the FREE online comprehensive, authoritative, constantly updated web-based Endocrinology Textbook)

Patients with renal failure (with and without dialysis) may have up to twofold higher plasma concentrations of catecholamines and free MNs, and more than 12-fold higher plasma concentrations of deconjugated MNs than comparison groups consisting of patients with VHL syndrome, essential HTN, and normotensive volunteers [261]. For instance, the 95% confidence intervals for free normetanephrines (NMNs) in patients on dialysis, with renal insufficiency, essential HTN, normotensive volunteers, and VHL syndrome had been 26–410 pg/ml, 29–307 pg/ml, 24–148 pg/ml, 18–119 pg/ml, and 26–137 pg/ml, respectively. In addition, one may have to consider adjustment of urinary and/or plasma MN reference ranges for patients after uni- and bilateral adrenalectomy [273]. In the latter study, concentrations of NMN were increased after uni- and bilateral adrenalectomy, whereas levels of MN were decreased. Follow-up for these biochemical parameters usually is recommended 2–3 months postoperatively, annually during the first 5 years, and thereafter every 2 years, as tumor recurrence rates are reported in up to 16% of patients within 10

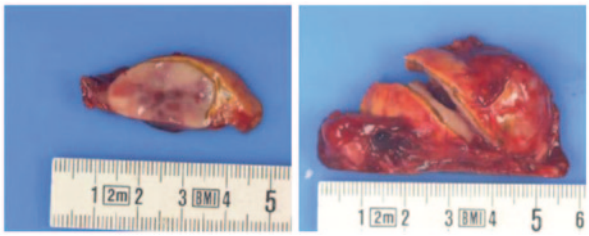

Fig. 16.9 Koch unpublished observation in a patient with MEN2-related bilateral pheochromocytomas and unilateral tumor recurrence 11 years after bilateral adrenalectomy. (Reprinted with permission from Chap. 26 "Overview of Endocrine hypertension," December 2009, by Koch CA, of www.endotext.org, the FREE online comprehensive, authoritative, constantly updated webertens Endocrinology Textbook)

years postsurgically, but even after 15 years [274–276]. Although generally cortical-sparing adrenalectomy has been performed in pheochromocytoma/paraganglioma patients, microscopic intermingling of adrenomedullary cells with the adrenal cortex can become ground for tumor recurrence, especially in patients with hereditary pheochromocytoma/paraganglioma syndromes [244, 277] (see Fig. 16.9).

In addition to plasma-free MNs, plasma methoxytyramine has recently been proposed as a novel biomarker for metastatic pheochromocytoma and paragangliomas (PPGLs) that together with succinate dehydrogenase subunit B (SDHB) gene mutation status, tumor size, and location provide useful information to assess the likelihood of malignancy and manage affected patients if measured supine under fasting conditions [278, 279].

Plasma chromogranin A has clinical utility in the diagnosis of SDHx-related paragangliomas and adrenal pheochromocytomas [280, 281]. However, the circulatory clearance of chromogranin A depends on renal elimination, so that serum levels of chromogranin A in patients with renal failure are increased well into the range usually observed in patients with pheochromocytoma [282, 283]. Plasma levels of vanillylmandelic acid (VMA), a catecholamine metabolite more commonly measured in urine, are increased about 15-fold in patients with renal failure compared to those with normal kidney function [284].

Imaging features of pheochromocytoma on conventional MRI and CT can assist in the diagnosis. Most pheochromocytomas are heterogeneous. High T2 signal intensity on MRI is found in approximately one third of solid tumors. Most pheochromocytomas are less enhancing than the spleen on CT and MRI scans [285]. CT and MRI have high sensitivity (90–100 %) and specificity (70–90 %) for the anatomical localization of pheochromocytoma. Radionuclide imaging modalities such as metaiodobenzyl-guanidine (MIBG) scintigraphy, positron emission tomography, and single photon emission CT are useful in assessing functionality of these tumors and in localizing metastatic or multifocal disease [286]. The Endocrine Society guidelines propose the following decisional algorithm for functional imaging in patients with proven pheochromocytoma/paraganglioma (see Fig. 16.10).

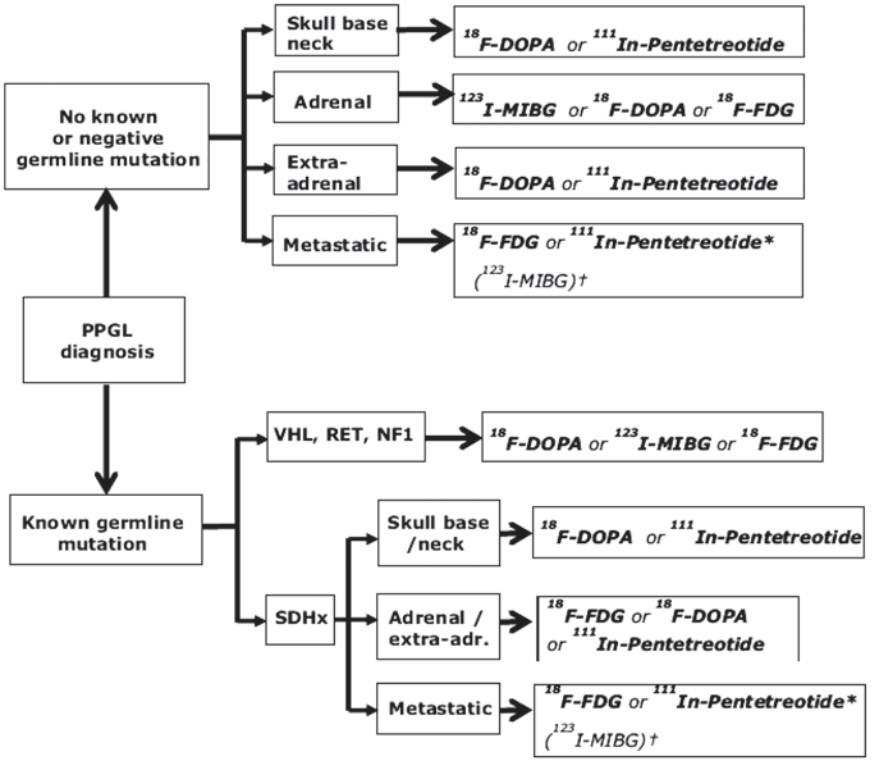

Fig. 16.10 Decisional algorithm for functional imaging in patients with proven pheochromocytoma/paraganglioma. *Asteriks* indicate when treatment with radiolabeled somatostatin analogs is considered; *dagger symbols* indicate when treatment with 131I-MIBG is considered. (Reprinted from Lenders et al. [244], with permission from The Endocrine Society)

Genetic Aspects of Pheochromocytoma/Paraganglioma

The molecular pathogenesis of pheochromocytoma/paraganglioma has greatly been elucidated over the last 20 years [234, 245, 287–291]. We now know that at least one third of all patients with paragangliomas/pheochromocytomas have disease-causing germline mutations. Therefore, genetic testing is recommended for all patients presenting with pheochromocytoma/paraganglioma [244, 245]. Identifying the molecular cause to an individual patient's pheochromocytoma/paraganglioma assists in predicting future tumor risk and risk of malignancy not only for such a patient but also for the patient's family members, especially for hereditary tumor syndromes with autosomal dominant transmission. Germline mutations associated with pheochromocytoma/paraganglioma known to date include at least 14 different susceptibility genes: *VHL* at chromosomal location 3p25, *SDHA* at 5q15, encoding SDHx subunit A, *SDHB* at 1p36.1, *SDHC* at 1q23.3, *SDHD* at 11q23.1, *SDH5/SDHAF2* at 11q12.2, the neurofibromatosis gene NF1 at 17q11.2, the RET

proto-oncogene at 10q11.2, *TMEM127* at 2q11.2, *MAX* at 14q23, and more recently the genes IDH1, FH at 1q43, HIF2 A at 2p21, EGLN1/PHD2 at 1q42.2, and KIF1B at 1p36.22. Current knowledge estimates the risk for metastatic pheochromocytoma/paraganglioma to be highest for patients with germline mutations in the SDHB gene (approximately 40 %). It is recommended to perform a thorough physical examination and history, including a three-generation family history of each patient, presenting with pheochromocytoma/paraganglioma, acknowledging that to date there is no consensus to guide genetic testing in such patients, mainly due to lack of long-term studies validating one particular approach in surveillance and/or therapy. Immunohistochemical analysis (negative results suggest presence of a mutation in one of the SDHx genes) of SDHB of pheochromocytoma/paraganglioma (or other tumors) in order to identify patients who are germline carriers of *SDHB*, *SDHC*, or *SDHD* mutations may represent a cost-effective screen, especially considering the high risk of metastatic disease in *SDHB* carriers [292]. One important point to consider in that regard and annual or biannual imaging surveillance, especially with scans from the skull base to the pelvis in individuals with germline mutations in *SDHx, TMEM127, MAX, PHD2, HIF2A*, is the cumulative amount of radiation exposure and risks of cancer development from that analogous to the benefits and potential harms of mammography screening programs [293, 294]. The Endocrine Society guidelines propose this decisional algorithm for genetic testing in patients with proven pheochromocytoma/paraganglioma (see Fig. 16.11).

Therapy

After diagnosing and localizing pheochromocytoma/paraganglioma, perioperative considerations should be made, including genetic aspects. For instance, a patient may have a 2 cm large adrenal pheochromocytoma and an additional paraganglioma located at the L1 spine area. This likely would make an open surgical approach necessary instead of a laparoscopic (adrenocortical function preserving) adrenalectomy. Generally, for large pheochromocytomas or retroperitoneal paragangliomas, an open total adrenalectomy/paraganglioma resection is recommended, whereas small, presumably benign tumors can be endoscopically removed (to preserve adrenocortical function if it is an adrenal pheochromocytoma). For head and neck paragangliomas, one can take a wait and see approach in elderly patients with slowly growing tumors or hereditary multiple very small (< 1 cm) tumors [295]. Radiation therapy can be utilized in elderly patients with inoperable paragangliomas, tumors with extensive skull/intracranial involvement, jugular tumors, recurrent tumors, or contralateral paragangliomas. Small (> 1 cm), unilateral, malignant, functioning, and tympanic paragangliomas should primarily be removed surgically. Preoperatively, an alpha-1 blocker should be used for at least 7 days prior to the scheduled procedure to control HTN, heart rate, and volume. Options include competitive alpha-1 antagonists such as doxazosin (half-life 22 h, dosing: start 2 mg/day up to 32 mg/day) and terazosin (half-life 12 h) or the noncompetitive, nonselective

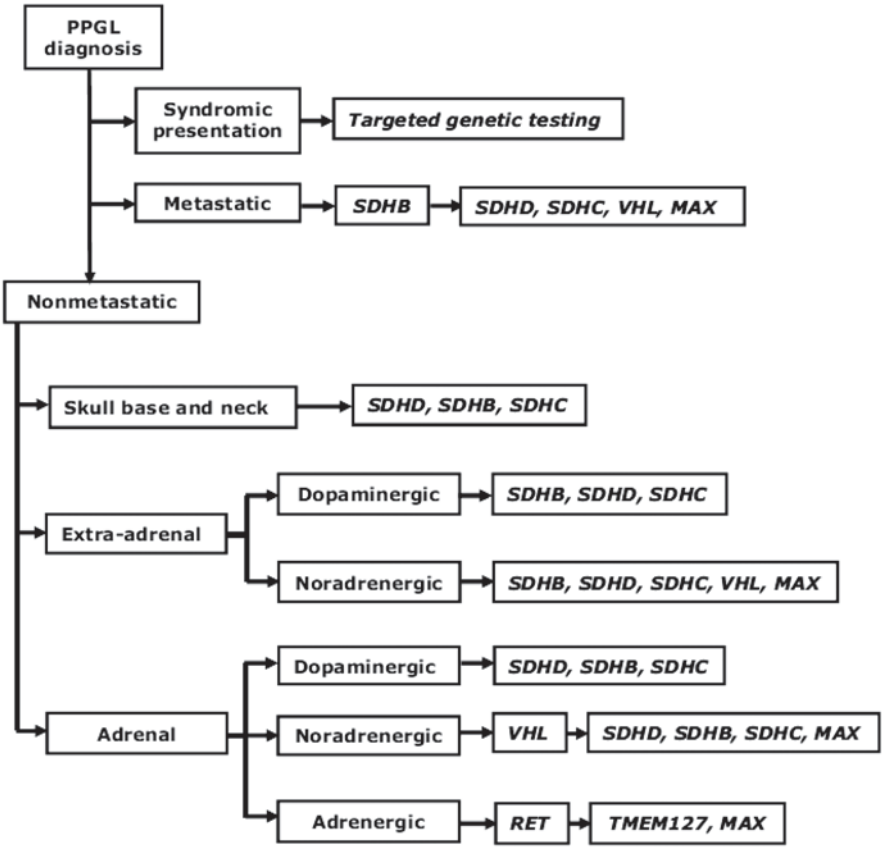

Fig. 16.11 Decisional algorithm for genetic testing in patients with proven pheochromocytoma/paraganglioma. (Reprinted from Lenders et al. [244], with permission from The Endocrine Society)

alpha-1/2 antagonist phenoxybenzamine (half-life > 24 h, dosing: start 10 mg twice daily, up to 1 mg/kg/day), all of which may cause tachycardia, orthostatic hypotension, nasal stiffness, as side effects. All agents are titrated based on BP response. Depending on the individual "baseline" BP, the target BP varies, but generally, should be less than 130/80 mmHg while seated without causing significant orthostatic hypotension and greater than 90 mmHg systolic while standing, considering that patients with renal impairment have significant volume changes, especially when undergoing dialysis. This will limit the usual recommendation to administer a high salt diet 3 days prior to tumor removal, in order to restore diminished blood volume and reduce the risk of postsurgical hypotension from diffuse vasodilation. For developing tachycardia preoperatively, first volume status should be assessed and then the administration of a beta blocker considered (propranolol 20 mg three times daily up to 40 mg three times daily; atenolol 25 –50 mg/day). Patients with uncontrolled HTN may need metyrosine (250 mg/8 h, up to 2 g/day) which inhibits

tyrosine hydroxylase, the rate-limiting step in catecholamine synthesis. Usually, the last dose of phenoxybenzamine or other alpha blocker (and metyrosine, if needed) are given at midnight before surgery. As mentioned above, postsurgically, glucose and BP should be monitored, as removal of the tumor causing catecholamine excess might now lead to hypoglycemia and hypotension, especially if vasoconstriction cannot yet ensue because of ongoing blockade of adrenergic receptors [244].

Surveillance should be performed by annual biochemical testing and period imaging studies in selected cases. Estimated recurrence rates for VHL patients are 10–15% over 10 years and the cumulative recurrence rate for MEN2 patients is 38.5% at 10 years after adrenal-sparing surgery [244].

Malignant pheochromocytomas/paragangliomas are difficult to treat with the first option being surgical debulking next to radiation and chemotherapy [296–299].

Pheochromocytoma Crisis

A pheochromocytoma/paraganglioma can present as hypertensive crisis, although one has to distinguish hypertensive urgency (BP > 180/110 mmHg + symptoms such as headache) from emergency (BP > 220/140 mmHg + acute target organ damage, i.e., heart failure, acute myocardial infarction, aortic aneurysm, stroke, encephalopathy). This distinction is often difficult, and many patients with chronic renal failure have BPs that are elevated in the range of such a crisis but without having any symptoms. Typically, patients on hemodialysis experience higher BP on nondialysis days than during dialysis, because of blood volume changes. Useful medications for hypertensive emergencies, including those caused by pheochromocytoma/paraganglioma, include sodium nitroprusside, a nonselective arterial and venous vasodilator that acts within 30 s and should be utilized as first line medication to control intraoperative crisis; nicardipine, an intravenous dihydropyridine calcium channel blocker that can prevent catecholamine-induced coronary vasospasm; phentolamine, an intravenous nonselective alpha adrenergic receptor antagonist which is given as bolus of 5–15 mg and then infused; and esmolol, a short acting beta-1 adrenergic antagonist administered as an infusion.

Conclusion

In patients with chronic renal impairment, a single cause of endocrine HTN is difficult to diagnose and treat, as such patients often have multiple hormonal imbalances simultaneously and varying degrees of renal dysfunction, depending on the glomerular filtration rates. Many of these patients have HTN which, in some cases, is aggravated and/or caused by PA, the most common form of endocrine HTN.

Screening for PA includes watching for unusual hypokalemia or normokalemia in patients with chronic renal impairment, measuring plasma aldosterone and direct renin or PRA concentrations, followed by confirmatory testing, including saline loading, if possible in the respective renal patient. Imaging studies including adrenal CT or MRI may detect incidentalomas, necessitating AVS for definitive diagnosis of aldosterone excess from one or both adrenal glands. Reducing aldosterone excess will reduce the BP in many of these patients. In nonsurgical candidates, mineralocorticoid antagonists such as spironolactone can be utilized if careful attention is directed at the individual patient's potassium levels.

Diagnosing GC excess in patients with chronic kidney dysfunction can also represent challenges, as reference ranges for many tests typically used in the diagnosis are not (well) established and many clinical symptoms and signs are not very sensitive or specific. Obviously, the use of 24-h urinary-free cortisol excretion is limited with impaired renal function. Interpreting salivary cortisol levels or dexamethasone suppression test results in these patients also is challenging. Nevertheless, a "normal" late-night salivary cortisol level or early morning serum cortisol concentrations after 1 mg of dexamethasone at midnight rules out CS in patients with ESRD.

Pheochromocytoma or paraganglioma are rare neuroendocrine tumors that can cause resistant HTN. Often, these tumors are found incidentally in patients with chronic renal impairment. A high index of suspicion should exist for patients with a familial syndrome that predisposes to pheochromocytoma, a family history of pheochromocytoma, onset of HTN at young age, pressor response during anesthesia, surgery, or angiography, idiopathic dilated cardiomyopathy, hyperadrenergic spells, and HTN and diabetes mellitus (many people suffer from that). Although biochemical assessment is hindered by impaired renal function (different reference ranges), plasma-free MNs and methoxytyramine are helpful in diagnosing pheochromocytoma/paraganglioma. Conventional imaging can be performed with CT and/or MRI (cave: nephrogenic systemic fibrosis) to localize the tumor which should then be surgically removed after treating the respective patient at least for 1 week with an alpha-1 blocker to achieve a BP of less than 130/80 mmHg seated without orthostatic hypotension. Tumor manipulation can induce a hypertensive crisis which is treated according to the hypertensive urgency/ emergency protocol, utilizing sodium nitroprusside, nicardipine, phentolamine, and other antihypertensive drugs. After pheochromocytoma/paraganglioma removal, hypoglycemia and hypotension may occur. Therefore, careful postoperative monitoring of glucose values, BP, and volume status is necessary.

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Chapter 17
Hypertension in Children with Chronic Kidney Disease

Douglas L. Blowey and Bradley A. Warady

Elevated blood pressure (BP) is a common clinical issue in adults and children with chronic kidney disease (CKD). In adults, hypertension (HTN) is an independent risk factor for stroke, myocardial infarction, congestive heart failure, aneurysms, and peripheral artery disease [1]. HTN is also a common cause of CKD in adults and is associated with a shortened life expectancy [2]. Fortunately, the long-term cardiovascular effects of HTN are not often realized during childhood, but there is substantial evidence that the pathological processes leading to cardiovascular disease are present and more advanced in children with CKD who are hypertensive [3, 4]. Young adults with childhood-onset CKD have an excessive prevalence of arteriopathy demonstrated by an increase in coronary artery calcifications and intima-media thickness of the carotid arteries (cIMT) [5]. In children with more advanced renal disease requiring renal replacement therapy, the cardiovascular mortality rates are 1000-fold higher than the general population [6]. In addition to traditional risk factors for cardiovascular disease such as HTN, dyslipidemia, altered glucose tolerance, and obesity, the risk for cardiovascular disease may be amplified in children with CKD due to a high prevalence of other possible risk factors that include hyperparathyroidism, hyperhomocysteinemia, hyperuricemia, calcium phosphate overload, and micro-inflammation [3, 4, 7]. This chapter focuses on the epidemiology, clinical manifestations, pathophysiology, and management of HTN in children with CKD.

Epidemiology

Accurate BP measurement in children with CKD is crucial to providing optimal clinical care and conducting meaningful research related to the impact of BP on targeted outcomes. The measurement of BP in children is influenced by many

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factors including the method of measurement (e.g., auscultation versus oscillometric), the protocol employed during BP measurement, and numerous patient-related variables including age, gender, height, and activity. Reference values for casual BP and ambulatory blood pressure monitoring (ABPM) are based on the distribution of BP readings obtained from large cohorts of normal children [8, 9] rather than BP targets based on clinically relevant outcomes. Casual BP normative data have been issued by the National High Blood Pressure Education Program and are based on BP measurements obtained by auscultation [8]. Although convenient, oscillometric devices significantly overestimate both systolic blood pressure (SBP) and diastolic blood pressure (DBP) in children with CKD with a bias of approximately 9 mmHg for SBP and 6 mmHg for DBP [10]. This upward bias in oscillometric BP readings can potentially lead to a misclassification of the HTN status of children with CKD. Thus, the preferred method for casual BP measurement in children with CKD is auscultation. Any elevated BP measurement obtained by an oscillometric device should be confirmed by a BP measurement obtained by auscultation.

HTN as defined by casual BP measurement is present in more than 50% of children with CKD [11, 12]. A retrospective analysis of BP obtained at baseline in the 3834 children enrolled in the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) found that 48% of children with CKD had HTN when defined as an SBP and/or DBP that exceeded the 95th percentile for age, gender, and height [12]. Of the 1847 children with HTN, 51% were not prescribed any antihypertensive medication while the remaining 49% reported the use of antihypertensive medication, highlighting the frequent uncontrolled nature of the disorder. The longitudinal, observational Chronic Kidney Disease in Children (CKiD) study noted that 54% of children with CKD enrolled in the study had HTN when defined as a casual BP measured by auscultation that was ≥95th percentile or self-reported HTN with concurrent use of antihypertensive medication [11]. Consistent with the NAPRTCS finding that elevated BP in children with CKD is often underdiagnosed and not effectively treated, the analysis of the CKiD group showed that 49% of children receiving antihypertensive medication did not have adequately controlled BP when defined as an SBP or DBP measured by auscultation that was <90th percentile.

ABPM is a technique that delivers an expanded representation of BP by providing a picture of the child's BP profile for 24 h, or longer, while the child goes about their normal activity. ABPM provides an estimate of the "true," or mean BP values, characterization of the diurnal rhythm of BP, and provides an estimate of BP variability (e.g., BP load) [9]. In adults with CKD, ABPM is superior to casual BP measurements in predicting future cardiovascular events and the progression of kidney disease [13]. In children with CKD, ABPM appears to predict a similar predisposition to cardiovascular disease, when cardiovascular disease is defined using surrogate markers such as an increased in cIMT or left ventricular hypertrophy (LVH). An abnormal ABPM study, defined as either an elevated mean BP and/or elevated BP load (≥25% of BP readings exceeding the 95th percentile), was observed in 49% ($n=332$) of children in the CKiD study who successfully completed an ABPM study 1 year after study entry [14]. Of the 164 children with an abnormal ABPM, 71% were classified as having masked HTN. Masked HTN is characterized

by a normal casual BP assessment and an abnormal ABPM study and in adults is more strongly correlated with cardiovascular events than other BP measures [15]. In the CKiD study, the vast majority of cases of masked HTN were due to an alteration in the normal diurnal BP pattern and manifested as an altered sleep BP profile, a parameter not assessed by casual BP monitoring. Among the children with masked HTN, approximately one fourth were not prescribed antihypertensive medication and the remainder who reported taking antihypertensive medication were misclassified by casual BP monitoring as having controlled BP. Although BP management based on ABPM-derived BP targets have not been endorsed by recent guidelines (i.e., Kidney Disease Improving Global Outcomes (KDIGO) [16]), in part due to cost and accessibility, the fact that ABPM provides a more accurate BP profile in children with CKD, including an assessment of masked HTN which may provide an improved risk assessment for future cardiovascular disease, suggests that ABPM should be employed whenever possible to help guide optimal BP management and cardiovascular disease risk reduction.

Clinical Manifestations

Observational studies of children with CKD have found that elevated BP is associated with significant sequelae including decreased performance on neurocognitive testing [17], increased cIMT [18, 19], LVH [3, 20–24], and a more rapid decline in glomerular filtration rate (GFR) [17, 21, 24, 25]. In the cohort followed by the CKiD study, increased casual BP measurements were associated with lower neurocognitive test scores related to nonverbal abilities that are generally linked to perceptual organization [26]. The authors reported that these deficits could contribute to problems involving spatially based math and science skills, directionality, reading maps, graphs, and charts.

Increased cIMT and LVH, both markers of target organ damage and predictors of future cardiovascular events in adults [27, 28], are prevalent in the CKD population. The CKiD study [18] and others [19] have observed an association between BP and cIMT in children with CKD. A significant increase in cIMT was observed in 101 children with CKD enrolled in the CKiD study when compared to aged-matched healthy children with a median cIMT difference of 0.02 mm (95th confidence interval (CI) 0.01–0.05). Of the cardiovascular risk factors assessed, only HTN, defined as a casual BP ≥95th percentile and dyslipidemia were significantly associated with an increased cIMT. LVH, defined as a left ventricular mass that is >95th percentile when measured by echocardiogram and normalized for height in meters raised to the allometric power of 2.7 (e.g., $g/m^{2.7}$), is observed in 16–49% of children with CKD [3, 20–24]. Both eccentric and concentric geometric patterns of LVH are observed in children with CKD, and there is a strong association between BP and the presence of LVH in these patients [21, 24]. The CKiD study analyzed the BP and echocardiogram characteristics of 366 children with CKD [21]. After adjustment for multiple factors, the presence of LVH was observed more frequently in children with

confirmed (abnormal casual BP and abnormal APBM) and masked HTN (normal casual BP and abnormal ABPM). Highlighting the frequent occurrence of unrecognized HTN, 38 % of the children were found to have masked HTN. The odds ratio for the presence of LVH was 4.13 (95 % CI 1.26–13.56) for children with masked HTN and 4.30 (95 % CI 1.01–18.26) for children with confirmed HTN. A smaller, single-center study of 52 children with CKD noted a high prevalence of LVH in children with clinic BP measurements that were well below the 95 %. The finding suggests a continuous relationship between BP and LVH where the "optimal" level of BP control may be well below the traditional definitions for HTN [20].

Elevated BP in children with CKD is also associated with a faster decline in kidney function. A randomized prospective trial designed to assess the impact of protein restriction on the progression of CKD in children [29] concluded that although a low-protein diet did not affect the rate of decline in kidney function, the presence of marked proteinuria (≥ 50 mg/kg/day) and elevated BP, defined as an SBP ≥ 120 mmHg, were independently associated with a faster decline in kidney function. The observation that the correlation between BP and the decrease in kidney function persisted even in the setting of normal BP led to the creation of the prospective *Effect of Strict Blood Pressure Control and ACE-Inhibition on Progression of Chronic Renal Failure in Pediatric Patients* (ESCAPE) trial in which the impact of aggressive BP management versus standard BP control were compared [26] (vide infra). Two separate analyses of the NAPRTCS database came to the similar conclusion that HTN, defined as an SBP or DBP ≥ 95th percentile, was an independent predictor of CKD progression in children [12, 25].

Pathogenesis

Although the etiology of HTN in children with CKD may be due to primary or secondary causes not directly related to the underlying CKD (Table 17.1), and should be considered during the evaluation process, most HTN in children with CKD is presumed to be a result of CKD-associated perturbations in the normal processes that control cardiac output and/or total peripheral resistance [30]. The alterations may arise directly from pathology related to the disease process itself (e.g., vasculitis, renal scarring), physiologic changes associated with CKD, or to the treatment of the underlying cause of CKD (e.g., corticosteroids, calcineurin inhibitors). Sodium retention and fluid overload are well-recognized complications of CKD that can increase BP through an increase in cardiac output. HTN ensues only when the increased cardiac output is not accompanied by a fall in peripheral vascular resistance, a process that may be impaired in children with CKD. In CKD, peripheral vascular resistance may be sustained or increased due to enhanced activity of the renin–angiotensin–aldosterone system (RAAS), sympathetic system, or vascular endothelial cell dysfunction [30]. In view of the central role that the RAAS plays in the regulation of BP, activation of the RAAS likely plays a key role in the development of HTN in children with CKD [31]. Local activation of the RAAS

Table 17.1 Etiology of HTN in children with chronic kidney disease

Traditional factors
Family history (essential HTN)
Obesity
Tumor (e.g., pheochromocytoma, Wilms, neuroblastoma)
Neurologic (e.g., dysautonomia)
Cardiovascular (coarctation, renal artery stenosis, middle aortic syndrome)
Chronic lung disease, obstructive sleep apnea
Endocrine (e.g., pheochromocytoma, primary aldosteronism, Cushings)
Factors related to chronic kidney disease
Activation of renin–angiotensin–aldosterone system
Activation of sympathetic nervous system
Vascular endothelial dysfunction
Medications (e.g., corticosteroids, calcineurin inhibitors)

HTN hypertension

may result from poorly perfused segments of the kidney caused by inflammation, scars, or cysts. RAAS activation leads to angiotensin II-induced vasoconstriction and aldosterone-mediated sodium retention. The activation of the RAAS also induces inflammation and fibrosis through the effects of aldosterone and may help explain the renoprotective effect observed with drugs that block the RAAS that is independent of the BP-lowering effect [15]. Independent of the RAAS and fluid overload, increased sympathetic activity, possibly related to renal ischemia or other undefined mechanisms, leads to an increase in vascular resistance. The vascular endothelial cell dysfunction that is observed in children with CKD [32] may impair compensatory vasodilatation and further promote increased vascular resistance. Impaired nitric oxide synthesis appears to play a role in the observed vascular endothelial cell dysfunction and may be related to hyperparathyrodism or alterations in asymmetric dimethylarginine [33].

Management

Because HTN is very common in children with CKD and associated with target organ damage, monitoring of BP should be a routine part of clinical care. In turn, when elevated BP is identified, treatment should be aggressively pursued. In children with mild CKD (e.g., stage I–II) and a past history of BP measurements that are <90th percentile, a BP assessment every 3–6 months is reasonable. In children with more advanced CKD (e.g., stage III–V), or a prior history of BP measurements that have exceeded the 90th percentile, more frequent monitoring is recommended. In view of the high prevalence of masked HTN in children with CKD, an ABPM study should be considered in any child with moderate-severe CKD or in any child with CKD regardless of casual BP readings with findings of LVH, increased cIMT,

or proteinuria. While the optimal model for the use of ABPM remains to be determined, one possible plan in children with CKD is to obtain an ABPM every 1–2 years. Additional ABPM studies can be completed 1–2 months after a change in antihypertensive therapy, especially in children where the medication changes were made to address masked HTN.

The treatment of elevated BP is important in children with CKD to protect against the development or advancement of cardiovascular disease and the progressive loss of kidney function. Although prior guidelines [8, 34] have recommended that the target BP for children with CKD should be <90th percentile, or <130/80 mmHg, whichever is lower, more recent guidelines have suggested lower BP goals. The KDIGO *Clinical Practice Guidelines for the Management of Blood Pressure in Chronic Kidney Disease* published in 2012 [16] recommends that BP-lowering therapy in children with CKD be initiated when the BP exceeds the 90th percentile and suggests that the target BP is a SBP and DBP ≤50th percentile. Because some children with CKD, particularly those prone to salt and water loss (e.g., dysplasia), may be prone to hypotension, BP targets should be individualized and more conventional BP targets may be appropriate. The rationale for lower BP goals stem primarily from the results of the ESCAPE trial [26]. This landmark study randomized 385 children with CKD to either intensified BP control or conventional BP control. All children received the angiotensin-converting enzyme (ACE) inhibitor, ramapril, at a dose of 6 mg/m^2 and additional antihypertensive agents (excluding drugs that were antagonist of the RAAS) were prescribed to achieve the target BP. A 24-h mean arterial pressure below the 50th percentile was the BP target for the intensified group, whereas the BP target for the conventional group was a 24-h mean arterial pressure between the 50th and 90th percentile. After 5 years, the number of children who had a >50% decline in the GFR or reached end-stage renal disease was significantly less in children who were randomized to the intensified BP group. There was no difference in the type or incidence of adverse events and the benefit of improved outcome persisted despite a loss of the effect on a reduction in the urinary protein excretion during the longitudinal follow-up.

Achieving BP goals often requires lifestyle modifications, specifically sodium restriction, and antihypertensive medications. While it is unlikely that a child with CKD will achieve their target BP solely with lifestyle modifications, these efforts should not be ignored, as the modifications may enhance the effect of many antihypertensive drugs and may help decrease the prevalence of other risk factors for cardiovascular disease. Nonpharmacologic treatment of HTN encompasses increased exercise and decreased sedentary time, weight loss in overweight children, stress reduction, incorporation of a Dietary Approaches to Stop Hypertension (DASH)-type diet, and sodium restriction. In children with CKD, dietary modifications may be challenging, or not possible, due to the requirement to limit potassium and phosphorus intake and should be implemented after consultation with a knowledgeable dietitian [35]. Likewise, sodium restriction may be contraindicated in children with diagnoses associated with urinary salt and water loss.

Almost all children with HTN complicating CKD require antihypertensive medications and often require multiple medications to achieve BP goals [17]. While the

Step 1	ACE inhibitor or ARB
If BP not controlled, add ↓	
Step 2	Calcium Channel Blocker and/or Diuretic
If BP not controlled, add ↓	
Step 3	Mineralocorticoid receptor antagonist α/β blocker Vasodilator α blocker β blocker Central acting agents

Fig. 17.1 Algorithm for treatment of hypertension in children with CKD

choice of the antihypertensive agent depends in part on whether the patient displays proteinuria, ACE inhibitors or angiotensin receptor blockers (ARBs) are the preferred agents in children with CKD as shown in Fig. 17.1. These drugs are preferred because of their ability to safely and effectively lower BP in adults and children with CKD and their benefit in preserving kidney function through anti-proteinuric, anti-fibrotic, and anti-inflammatory properties. The recommendation for the use of ACE inhibitors and ARBs is supported by the findings of the CKiD study where children who received ACE inhibitors or ARBs were less likely to have LVH [21] and more likely to have controlled BP [11] compared to children with CKD receiving other classes of antihypertensive agents. The BP-lowering effectiveness of ACE inhibitors was also observed in the ESCAPE study [17] where more than 50% of children in the standard BP control group (target mean BP 50–95th percentile) were able to achieve BP control solely with aggressive dosing of the ACE inhibitor, ramapril (6 mg/m^2). When proteinuria is absent or an ACE inhibitor/ARB is contraindicated, a long-acting dihydropyridine calcium channel blocker (e.g., amlodipine) can be considered for initial therapy. In children with CKD, especially those with edema, diuretics may be helpful in BP control. Thiazide-like diuretics can be used when the GFR is more than 30–40 ml/min/1.73 m^2 but are not effective in children with a lower GFR. Due to a prolonged duration of action, chlorthalidone may provide improved BP control and cardiovascular risk reduction when compared to

Table 17.2 Suggested oral dosing of common antihypertensive medications

Drug	Pediatric dosing
ACE inhibitors	
Enalapril	Initial: 0.08 mg/kg QD Max: 0.6 mg/kg/day (40 mg)
Lisinopril	Initial: 0.07 mg/kg QD Max: 0.6 mg/kg/day (40 mg)
ARBs	
Losartan	Initial: >6 y/o 0.7 mg/kg QD (>25 kg: 25 mg, >50 kg: 50 mg) Max: (>25 kg: 50 mg, >50 kg: 100 mg)
Calcium channel blockers	
Amlodipine	Initial: 0.1–0.2 mg/kg QD (2.5–5 mg) Max: 0.6 mg/kg/day (10 mg)
Diuretics	
Chlorthalidone	Initial: 0.3 mg/kg QD (15 mg) Max: 2 mg/kg/day (50 mg)
Hydrochlorothiazide	Initial: 1–2 mg/kg ÷ QD/QOD Max: <2 y/o 37.5 mg/day; >2 y/o 50 mg/day
Spironolactone	Initial: 1 mg/kg ÷ QD/BID (50 mg) Max: 3 mg/kg/day (200 mg)
Other	
Hydralazine	Initial: 0.7–1 mg/kg ÷ BID/QID Max: 7.5 mg/kg/day (100 mg)
Labetalol	Initial: 1–3 mg/kg/day ÷ BID Max: 10–20 mg/kg (1200 mg)
Minoxidil	Initial: 0.1–0.2 mg/kg ÷ QD/BID (5 mg) Max: 50 mg/day

ACE angiotensin-converting enzyme, *ARBs* angiotensin receptor blockers

other thiazide-like diuretics [36, 37]. In children with more advanced CKD, loop diuretics may be required. There are no clear guidelines on the preference or order of additional antihypertensive drugs that can be added to the regimen after maximizing combination therapy with ACE/ARB, calcium channel blockers, and diuretics. In view of the impressive BP-lowering results in adults with resistant HTN receiving mineralocorticoid receptor antagonist [38], a trial of an aldosterone antagonist (e.g., spironolactone, eplerenone) can be considered in those patients with good control of potassium homeostasis. Other antihypertensive drugs such as combined alpha/beta blockers, vasodilators, centrally acting agents, and alpha blockers can be added as necessary in children with CKD who have resistant HTN. Suggested oral doses for common antihypertensive medications are displayed in Table 17.2. Treatment of resistant HTN with renal denervation and baroreflex activation remain experimental at this time.

Common side effects of medications that antagonize the RAAS include hyperkalemia and acute decline in kidney function. These agents are contraindicated throughout pregnancy and the pregnancy-related risks should be discussed with adolescent/young adult girls prior to and during therapy. The fear of hyperkalemia with advancing CKD should not preclude the use of ACE inhibitors or ARBs as

the incidence of significant hyperkalemia is low and can often be managed with dietary adjustments or the addition of a diuretic. Peripheral edema is the most common adverse effect noted with the dihydropyridine calcium channel blockers. The edema is usually dose related and not responsive to diuretics as the edema is due to increase in capillary fluid efflux (due to preferential arteriolar vasodilation) and not volume overload.

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Chapter 18
Obesity/OSA/Metabolic Syndrome in Patients with CKD and Hypertension: The Missing Link?

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Introduction

Chronic kidney disease (CKD) patient's exhibit elevated rates of deaths compared to the general population [1], with almost similar increase in proportion of cardiovascular (CV) and non-CV deaths [1]; however, the CV mortality risk in patients starting dialysis is much higher compared to the general population (unstandardized CV risk—15-fold higher/age-standardized CV risk—almost 9-fold higher than in matched individuals from the general population) [1]. This huge mortality risk is not determined by the same classical, traditional risk factors; indeed, classical atherosclerotic disease is not the most important and common cause of death in a modern dialysis population. Analysis traditional CV risk factor (like hypertension (HTN), diabetes, or lipids) interventions in CKD has been disappointing. Over the past decade, numerous nontraditional risk factors have been investigated: left ventricular hypertrophy, anemia, mineral metabolism disturbance (phosphate, calcium, vascular calcification or FGF-23), inflammation, electrolyte shifts during hemodialysis (HD) or abnormalities in myocardial ultrastructure and function, including endothelial dysfunction, interstitial fibrosis, impaired coronary flow reserve, and diminished ischemia tolerance, but the results were equally disappointing [2]. In 2013, we still have an enormous mortality rate.

In this context, a new approach would be interesting to be considered. We summarize what is so special about CKD patients and then discuss how these particularities can be used for improving the enormous morbidity and mortality risk.

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A "typical" CKD patient has:

a. HTN—gradually increasing with the severity of CKD (35.8 % in CKD stage 1, 48.1 % in CKD stage 2, 59.9 % in CKD stage 3, and 84.1 % in CKD stage 4–5)
b. Resistant HTN
c. High prevalence of nondipping HTN even in patients with early impairment of GFR
d. Overhydration, subclinical in almost 25 % of the cases, secondary volume-dependent HTN, left ventricular hypertrophy and death
e. Autonomous dysfunction associated with impaired heart rate variability, resting tachycardia, exercise intolerance, abnormal blood pressure regulation and orthostatic hypotension
f. High prevalence of arrhythmias and sudden cardiac death
g. High prevalence of sleep apnea syndrome

Coming back to the issue, the best-characterized CKD model patient has HTN, infraclinic overhydration, obesity, and frequently apnea sleep syndrome.

Obesity and Metabolic Syndrome in CKD

Obesity is an extremely important problem in 2014, with an increasing trend in prevalence; in 2008, more than 1.4 billion adults of age 20 years and older were overweight, and the number is still growing [3]. In CKD patients, obesity is common [4]. The appropriate methodology used for correct classification of obesity is still debated [5]; although body mass index (BMI) is used by almost all nutritional guidelines, it provides an inadequate estimation of true fat mass, especially in patients with gross imbalances of fluid balance, such as kidney disease patients. The waist to hip ratio (WHR) and skinfold thickness seem to be better methods for a correct estimation of obesity [5].

The consensus definition for metabolic syndrome (MetS) encloses *central obesity, elevated BP, dyslipidemia* (low levels of high-density lipoprotein (HDL) cholesterol and elevated serum triglycerides), and *elevated fasting glucose* (impaired fasting glucose or type 2 diabetes).

Obesity/MetS and CKD Stage 3–5

In predialysis CKD population, MetS is highly prevalent (60–65 %) [6], most probably secondary to a higher prevalence of the individual risk factors for metabolic syndrome in these patients.

MetS was independently associated with proteinuria and CKD progression in numerous observational studies. However, this evidence is still controversial. In the secondary analysis of the African American Study of Kidney Disease and Hypertension Trial [7], MetS was associated with a 31 % of increased risk of CKD

progression to end-stage renal disease (ESRD), but this risk was no longer significant when adjusted for baseline proteinuria. In another recent study, Lee et al. [8] found that the influence of MetS on CKD progression was major only in nondiabetic early stage (1–3) CKD subjects, and became nonsignificant in late-stage CKD and in diabetic (early or late) CKD patients. More recently, Navaethan et al. found in a large and retrospective observational study including 25,868 patients with stage 3–4 CKD an independent association between MetS and ESRD [9]; the subgroup analysis showed that the association between MetS and ESRD was attenuated and no longer statistically significant with adjustment for proteinuria. In this context, in a recent editorial comment, Lea J. suggests that proteinuria could play a central role in the potential impact of MetS on CKD progression [9].

The individual components of MetS were also associated with CKD progression. High-grade obesity is a well-recognized risk factor; this association appears to be stronger in females; the effect could be a direct one, obesity causing glomerular hyperfiltration, activation of the renin–angiotensin system, insulin resistance, and direct lipotoxicity or indirectly, obesity leading to comorbidities, such as type 2 diabetes, HTN, and atherosclerosis, which in turn may accelerate progression of CKD [10]. Even in dialysis patients, obesity was associated with the loss of the residual renal function.

The relationship between obesity and survival is a subject of controversy. In a large study [9], MetS was not linked with an increased risk of death in CKD stage 3–5 patients (individual components, such as low HDL cholesterol level and impaired glucose metabolism, were related with an increased risk for death, whereas obesity and HTN were related with a lower risk for death). No significant association between survival and BMI was shown in modification of diet in renal disease (MDRD) study [11]. Often, the different methods used for obesity assessment might have generated these different results. Elsayed et al. analyzed 1669 participants with CKD from two cohorts and found no significant connection between overweight or obesity and cardiac events compared with an ideal BMI (20–24.9 kg/m^2). However, using WHR, they reported a 36 % greater relative risk of cardiac events in the group with the highest WHR ($\geq$1.02 and $\geq$0.96 in men and women, respectively) [12].

Obesity/MetS and Dialysis

The prevalence of MetS in HD which varies between 60 and 80 % [13] is increasing with age and is more frequent in women. In peritoneal dialysis, the prevalence is even higher; these patients have an increased risk of metabolic disturbances (hyperglycemia, dyslipidemia, or weight gain), leading to oxidative stress, systemic inflammation, and endothelial dysfunction and finally, to increase risk of CV events and death. Moreover, the definition of MetS is not appropriate: The plasma glucose is complicated to standardize because of the inherent continuous absorption of glucose from dialysate; the measurement of waist circumference is also difficult—as it can fluctuate in relation to the intraperitoneal dialysate volume or residual volume after dialysate drainage [14]. Recently, dual-energy X-ray absorptiometry,

bioelectric impedance analysis, or abdominal fat computed tomography has been used in clinical studies involving PD patients.

Surprisingly, MetS was associated with a better nutritional status, but not with CVD or all-cause mortality in dialysis patients. The role of obesity, a central part of the MetS represents a complicated dilemma. Numerous studies [15, 16], with a short median period of follow-up (2 years) revealed substantial and significant advantage in overall and CV survival in the group of patients with BMI of 25 kg/m^2 or greater, including the highest BMI category ($\geq$37 kg/m^2) compared to patients with BMI less than 22 kg/m^2. However, several studies with an extended follow-up (5–10 years), a baseline BMI of 30 kg/m^2 or greater was associated with an increased risk of mortality compared to patients with ideal BMI [17, 18].

In the same line, truncal fat mass and abdominal obesity were associated with inflammation (IL-6 and CRP). Truncal fat mass is associated with an adipokine imbalance; an increase of leptin, resistin, tumor necrosis factor-α (TNF-α), and IL-6; and a decrease of adiponectin, and thereby, it may contribute to endothelial dysfunction, inflammation, oxidative stress, vascular calcification, and CV events.

Obstructive Sleep Apnea

Disturbed sleep patterns can be a disease-generating condition. Obstructive sleep apnea (OSA) is one of these conditions, being a high-priority health problem because it disrupts sleep and reduces quality of life. It is caused by a cessation of airflow caused by occlusion of the oropharyngeal tract. The main clinical features include sleepiness, fatigue, or poor concentration, signs of disturbed sleep, such as snoring, restlessness, and last but not least hypopnea or even long periods apnea terminated by loud snorts or snoring. The physical exam can be normal, although obesity, elevated blood pressure, a narrow airway, and a large neck circumference are common.

Definite risk factors for OSA include obesity, craniofacial abnormalities, and upper airway soft tissue abnormalities. Potential risk factors include heredity, smoking, and nasal congestion.

The diagnosis is mainly based upon the presence of the mentioned symptoms as well as the frequency of respiratory events during sleep. Polysomnography is the gold standard method for the diagnosis of OSA, which is defined as an intermittent interruption of airflow at the level of nose and mouth during sleep. Episodes of apnea are considered clinically relevant if they persist for longer than 10 s, but in some cases they may last as long as 2 min.

OSA is associated with obesity, HTN, especially resistant HTN, congestive heart failure, diabetes, mild pulmonary HTN; patients with severe OSA being at risk for high CV complications and death. Additionally, some patients with OSA may present proteinuria, associated with focal segmental glomerulosclerosis, hypercapnia, or nocturnal cardiac arrhythmias including bradycardia or atrial fibrillation triggered by persistent hypoxemia.

The presence of OSA may be even more relevant in nephrology because some of the factors involved in the pathogenesis of renal disease like HTN, diabetes, and obesity are the same that cause, or are associated with, OSA in the general population. However, so far, only a few studies assesed the presence of OSA in CKD patients with a minor degree of renal dysfunction, OSA being mainly suggested from questionnaires related to specific symptoms (daytime somnolence or snoring) and not assessed by polysomnographic examinations.

Several epidemiologic studies provided evidence that obesity is strongly associated with CKD, closing the triangle between OSA, obesity, and CKD [19, 20]. It appears that OSA is one of the most important triggers of sympathetic activity induced by the decreased arterial oxygenation which in turn raises blood pressure, particularly during nighttime. The high sympathetic activity engenders three intermediate mechanisms: chronic HTN, left ventricular hypertrophy, and arrhythmias, particularly atrial fibrillation, which eventually leads to CV complications and death. Another mechanism in the pathogenesis of renal damage in OSA patients is impairment of renal hemodynamics as measured by an increased renal resistance index (RRI) [21]. This can be of great importance since changes of renal blood flow may identify OSA patients at high risk for declining renal function. Furthermore, renal perfusion assessed by RRI is improved with an effective treatment of OSA [22].

OSA is significantly more common in ESRD patients and it has been related with markers of CV disease and poorer survival. Unlike the general population, the usual risk factors for OSA (such as obesity, craniofacial abnormalities, nasal congestion, and smoking) do not usually apply to dialysis patients. Potential mechanisms implicated with higher prevalence of OSA in ESRD patients include the desensitizing effects of uremia or metabolic acidosis on higher respiratory control centers. These assumptions came from observational studies that showed improvement of OSA after correction of biochemical abnormalities, by increasing ultrafiltration or after kidney transplantation. The high prevalence of OSA in ESRD patients can also be the result of fluid overload and more precisely by the increased amount of fluid displaced from the legs into the neck overnight, which can eventually compress the upper airway [23].

In conclusion, OSA seems to be a more frequent disorder even in minor renal dysfunction than previously thought. Given the high risk associated with OSA and CKD, clinical trials would be warranted in the attempt to reduce the burden of morbidity and mortality linked to respiratory disorders in renal diseases [19].

Competing Risk: OSA–MetS–Obesity: A Possible Link?

The relation between MetS, obesity, and OSA is complex. Obesity is one of the most important risk factors for OSA. Even mild to moderate obesity has been associated with increased sleep apnea prevalence. In a community of moderately overweight men, OSA had a prevalence of approximately 40 % [24], which increased to 90 % in

patients with severe obesity (BMI >40 kg/m^2). Changes in body weight determine an increasing risk for OSA; two important studies, the Wisconsin Sleep Cohort Study and the Sleep Heart Health Study, showed that more than 10 kg weight gain over a 5-year period determines a fivefold increased risk in men and 2.5-fold increase in the severity of OSA [25–27]. Additionally, weight loss is associated with a parallel decrease in apnea frequency. Being the only modifiable risk factor of OSA, numerous studies, using both surgically and medically methods for losing weight investigated and founded that weight loss can improve obesity-related OSA [28, 29].

The mechanisms of this relationship are still uncertain, and may include: (1) fat deposition on airway anatomy; (2) changes in the central mechanisms regulating airway tone or ventilatory control stability. The particularly strong association seems to be between visceral fat deposition and OSA; recent studies described neck circumference as a positive predictor of OSA, associated with the severity of OSA independently of visceral obesity [30].

Inversely, OSA may predispose to obesity. It has been assumed that OSA induces neurohormonal changes: a stress reaction activating the hypothalamic–pituitary–adrenal axis leading to release of cortisol and other hormones may trigger mechanisms generating insulin resistance and preferential abdominal fat accumulation [31]. Moreover, hypoxia may generate inflammation in obesity. Adipose tissue contains numerous pro-inflammatory adipocytokines which may support endothelial dysfunction, insulin resistance, and lipid peroxidation.

Even more complex, a link between OSA and MetS, independent of obesity can be described [32]. Many of the individual components of MetS are associated with OSA. The possible mechanisms underlying OSA–MetS–obesity relationship may include the determinant role of intermittent hypoxia and sleep fragmentation who may determine: (1) the release of reactive oxygen species and oxidative stress; (2) inflammation and impaired insulin action in peripheral tissues, associated with insulin resistance, dyslipidaemia, and HTN; (3) release of adipocyte-generated hormones, like adiponectin, leptin, or adipocyte-fatty acid-binding protein. Prospective longitudinal cohort studies and interventional trials are needed to establish a definite direction of the relationship between OSA and MS or its components.

OSA–MetS–Autonomic Dysfunction–HTN

HTN is frequently found in patients with MetS (BP in the high–normal or frankly HTN range was found in more than 80 % of individuals with MetS) [33]. One of the most incriminate mechanisms is autonomic dysfunction.

Several experimental and human studies reported autonomic dysfunction as one of the mechanism for HTN in patients with MetS; it is associated with increased heart rate and cardiac output, increased peripheral vascular resistance, increased tubular sodium reabsorption in the kidney, and consequent elevation of systemic blood pressure. At the same time, abdominal visceral fat is associated with sympathetic

neural activation in humans. Experimental studies suggest a regional sympathetic activation in various types of human obesity, in the absence of other comorbidities; obesity can be associated with an increase in sympathetic activity in the kidney [34, 35]. In addition, the insulin resistance typically found in MetS increases plasma leptin levels, and leptin has been reported to elevate sympathetic nervous activity, suggesting that leptin-dependent sympathetic nervous activation may contribute to an obesity-associated HTN.

Treatment

Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation has been reported to be effective for improving OSA in resistant hypertensive patients, in randomized clinical trials [19, 36, 37] but, despite advances in technology and easiness of application, this technique is either not accepted or refused by many patients. In such cases, pharmacological treatment of sympathetic overactivity remains the sole treatment available to counteract the high risk of this condition.

Intensification of Ultrafiltration

In dialyzed patients, as noted above, fluid overload plays an important role in the pathogenesis of OSA. Many trials have assessed this issue, intensive dialysis or even better nocturnal dialysis having good results in improving OSA in patients with severe sleep-disordered breathing [19, 38, 39]. Additionally, ultrafiltration guided by bioimpedance or ultrasound lung comets may provide a practical method for reaching true patient euvolemia. Renal transplantation is in theory the ideal way for correcting OSA, since it eliminates all uremic toxicity. In a case-control study [40], the prevalence of OSA was almost identical in renal transplant patients as compared to age-, sex-, and BMI-matched healthy subjects, supporting the hypothesis that renal transplantation reverses OSA.

Bariatric Surgery

As noted above, obesity is a risk factor for developing CKD that may be improved with bariatric surgical weight reduction. Bariatric surgical procedures affect weight loss through two fundamental mechanisms: malabsorption and restriction. The main indications are patients who failed previous nonsurgical weight loss methods with BMI >40 or >35 in the setting of other comorbidities like diabetes or sleep apnea.

The goal of surgery is to reduce the morbidity and mortality associated with obesity, and to improve metabolic and organ function all along with reduction of hospitalization periods, medication costs, and improving quality of life [41, 42].

Among the positive effects of bariatric surgery we note:

- A reduction of 50% in incidence of diabetic nephropathy 5 years following bariatric surgery
- An improvement in microalbuminuria in the early postoperative period
- Hyperlipidemia improved in 70% or more of patients
- HTN resolved in 62% and resolved or improved in 79% of patients
- Obstructive sleep apnea resolved or improved in 84%
- A reduction of 29% in mortality [3, 41, 43]

Although there have been dramatic improvements in the safety of bariatric procedures in the past decade, bariatric surgery is not without serious risks, including significant perioperative complications and mortality. The presence and severity of CKD is associated with a higher risk of complications among patients undergoing bariatric surgery [44].

Physical Exercise

A healthy lifestyle facilitated by participation in a regular exercise regimen may prevent or retard conditions commonly associated with CKD, including HTN, hyperlipidemia, and diabetes [45].

Although proteinuria is augmented immediately after exercise, the effect of long-term exercise on proteinuria at rest is less clear. Data from a recent systematic review showed that intentional weight loss after physical exercise is associated with decreased proteinuria and microalbuminuria. Exercise was defined as moderate to intense physical activity with at least 1.8 metabolic equivalents for a minimum duration of 15 min/day for at least 2 days/week for a minimum of 1 month [46].

Physical exercise was suggested as a useful approach to diminish impaired oxidative defense mechanisms, which is very important in the setting of CKD. In a recent study on rats, physical training prevented superoxide production, and decreased the oxidative damage in the CKD group. Furthermore, physical training before induction of a renal lesion is capable of improving oxidative damage parameters and oxidant production, without altering renal function and the antioxidant defense system [47].

Hypolipemiant Treatment

Abnormalities in lipid metabolism occur in patients with all stages of CKD and may contribute to the higher risk of CV disease in this population.

Studies in predialysis are inconclusive as they fail to draw firm conclusions. Some studies in patients with CKD show a positive relation between higher cholesterol levels and mortality risk, while other studies have found that low serum cholesterol is associated with increased mortality. This may reflect the profound adverse effect of malnutrition and chronic inflammation upon mortality, resulting in the so-called reverse epidemiology.

In CKD stage 1–3 patients with dyslipidemia, the available data suggest that statin therapy is associated with a relative reduction in the risk of major CV events. Beyond CKD stage 3, the benefits from statin treatment are less clear, more randomized studies with predefined CV end points being needed to make the correct decisions.

In dialysis patients, the statin therapy is not recommended currently. This approach is supported by three large randomized, controlled studies: 4D, SHARP, and AURORA. In those studies, the statins failed to demonstrate a significant effect of statins in CV or all-cause mortality [48–50].

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Erratum

Front Matter in: M.R. Weir, E.V. Lerma, Chronic Kidney Disease and Hypertension

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The Front Matter has been revised. It now includes a Foreword by the book series editor.

FOREWORD

The importance of hypertension as it relates to chronic kidney disease and end stage renal disease (ESRD) has been greatly appreciated by physicians and scientists for more than 60 years and reinforced during the clinical trials that followed in the 1990s and the first decade of this century. This appreciation of the severity of the complications of this common disorder, particularly in patients with comorbidities such as diabetes mellitus, has led to improvement in the rates of ESRD and kidney-related mortality over the past 30 years. Nevertheless, there is ample room for improvement and chronic kidney disease associated with hypertension and other vascular disorders remain an extremely important problem in clinical medicine. Drs. Weir and Lerma's volume on Chronic Kidney Disease and Hypertension is a highly relevant contribution in the area of clinical nephrology – this book brings together the pathophysiologic, epidemiologic, diagnostic, and therapeutic advances in the evaluation of hypertension in patients with chronic kidney disease and related disorders.

The editors have organized this volume into areas that cover the general pathophysiology and guideline-based recommendations to managing hypertension, and various means to evaluate blood pressure phenotypes by ambulatory and home/self-monitoring as well as central blood pressure assessment. Pharmacologic and device therapy approaches to the management of resistant hypertension and patients with chronic kidney disease are also given substantial attention in this book. Additionally, there are comprehensive chapters on the neurogenic factors in chronic kidney disease, dual renin-angiotensin inhibition and novel molecules and blood pressure vaccine therapy.

Weir and Lerma have also provided interesting chapters devoted to special problems in clinical hypertension that highlight problems which are of particular concern to hypertension specialists, including white-coat and masked hypertension and special populations such as adolescents, pregnancy, and obstructive sleep apnea. These sections contribute to the uniqueness of this book since the chapters are grounded in clinical investigations that have led to enhanced understanding of the evaluation and treatment of hypertension in these special populations. Important basic or translational chapters involving research in inflammation, the sympathetic

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nervous system, uric acid, and genomics are featured by basic investigators who have spent their careers performing research in these specific areas.

The chapters in Chronic Kidney Disease and Hypertension have been composed by a number of well-known, expert authors who have provided comprehensive, scientifically sound, and clinically appropriate information. As series editor of Clinical Hypertension and Vascular Diseases, I am pleased by the publication of this timely and clinically relevant book and know that Chronic Kidney Disease and Hypertension will become a useful textbook for any specialist in nephrology and vascuiar medicine as well as any physician who take care of patients with severe and resistant hypertension.

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Index

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