Fulminant Myocarditis

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Foreword

In the field of cardiovascular medicine, fulminant myocarditis is dangerous, with a rapid onset and extremely high mortality. Although the application of mechanical circulation support devices has reduced the risk of mortality to a certain extent in recent years, it has not fundamentally solved the issues regarding treatment.

To address this problem, Professor Dao Wen Wang conducted theoretical and clinical research for nearly 10 years with his team members. What is particularly important is that they found answers using the basic sciences and then verified them in clinical practice using the scientist's spirit, not simply going from clinical to clinical. They boldly put forward a new theory that "excessive immune activation and inflammatory storm effect cause severe myocardial damage in patients with fulminant myocarditis" and formulated the "life support-based comprehensive treatment regimen" based on this theory.

The core of this regimen is to lighten the burden on heart by using mechanical circulatory support, instead of applying cardiotonic and vasoactive drugs, including norepinephrine and other hypertensive drugs, which is a strategy aimed at relieving symptoms. Meanwhile, adequate doses of glucocorticoids and immunoglobulins will be used to regulate immunity and treat inflammation in this new strategy for curing the disease. I was intrigued by his report. The cardiovascular and intensive care departments of major domestic hospitals, including Peking Union Medical College Hospital and Fuwai Central China Cardiovascular Hospital in Henan Province, are applying this regimen, in addition to Tongji Hospital. The in-hospital mortality rate of fulminant myocarditis has dropped from 50% to less than 5%. Therefore, on behalf of the Cardiovascular Professional Committee of the Chinese Medical Association, I supported Professor Dao Wen Wang's lead in writing the "Chinese Expert Consensus on the Diagnosis and Treatment of Fulminant Myocarditis in Adults," which was published in the *Chinese Journal of Cardiovascular Disease* in 2017. The consensus has aroused strong repercussions and positive reactions across the country, and numerous practical feedback results have proven the effectiveness of the regimen. The long-term follow-up results of patients with fulminant myocarditis were recently released and I am very happy to learn that after discharge from the hospital, they were significantly better than those of patients from Western countries, which makes me more confident about this regimen, as it not only reduces the mortality rate during hospitalization but also has a better long-term effect.

I am proud of this achievement as this represents the level of treatment for fulminant myocarditis in our country and our contribution to the field of cardiovascular medicine. In recent years, Dao Wen Wang's team and other domestic experts engaged in related clinical and basic research have organized 28 study classes and delivered more than 80 academic conference lectures. More than 18,000 medical staff have been taught, which reflects their benevolence and responsibility as clinicians. They then summarized and wrote this academic monograph *Diagnosis and Treatment of Fulminant Myocarditis*, which, to the best of my knowledge, is the world's first monograph on fulminant myocarditis. This book systematically summarizes the etiology, pathology, pathophysiology and its hypotheses, clinical diagnosis, treatment plan, and theoretical basis of fulminant myocarditis, as well as related basic research. It also uses cases to introduce and comment to guide clinicians on how to approach certain cases, which makes up for the lack of consensus that is limited by space.

A number of challenges regarding fulminant myocarditis should be further explored, such as the small number of patients with chronicity, arrhythmia, and heart failure during follow-up. However, the publication of this book will greatly help colleagues to improve their understanding and treatment of fulminant myocarditis and also promote clinical and basic research on related issues. Therefore, I am very happy to write this preface to congratulate its publication. I also hope that Professor Dao Wen Wang's team will continue to explore this field to solve the remaining problems and add more new results when this book is republished.

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Foreword

Fulminant myocarditis is the sudden/severe diffuse myocardial inflammation caused by various factors. It can lead to myocardial necrosis, edema, cardiogenic shock, fatal ventricular tachycardia arrhythmia, bradycardia arrhythmia, and sudden cardiac death.

According to histological examination, fulminant myocarditis can be divided into three subtypes: lymphocytic, giant cell, and eosinophilic. Among these, giant cell type has the worst prognosis.

This finding suggests that the classification of fulminant myocarditis using myocardial biopsy is helpful in prognostic judgment. As the famous myocarditis pathologist Kenneth L. Baughman emphasized, "If there is no tissue, it will be impossible to understand new pathophysiology, and it will not be possible to help the subject to progress" (Moslehi et al. Fulminant myocarditis: evolving diagnosis, evolving biology, evolving prognosis. J Am Coll Cardiol. 2019;74:312–4). In recent years, cancer treatment has developed by leaps and bounds, including the use of immune checkpoint inhibitors, which has led to an increase in immune checkpoint inhibitor-related myocarditis and fulminant myocarditis.

Compared with non-fulminant myocarditis, fulminant myocarditis has a serious clinical outcome. Almost all cases have left ventricular systolic dysfunction, high cardiac mortality, and high heart transplantation rates, and require the support of mechanically assisted circulatory devices and heart transplantation. Therefore, if the hospital can perform these treatments, the patient has a greater chance of being rescued. The rescue team should preferably include intra-aortic balloon counterpulsation, extracorporeal membrane mechanical circulation support, percutaneous or permanent ventricular assist devices, cardiac surgeons and immunologists for heart transplantation, and experts in the treatment of advanced severe heart failure, cardiothoracic surgeons, cardiologists, immunologists, and infectious disease experts. Early cardiogenic shock is the focus of treatment. In addition, if patients are transferred to hospitals with mechanical support and heart transplantation in a timely manner, successful treatment is likely.

Fulminant myocarditis is a relatively rare disease. Therefore, it is impossible to conduct randomized controlled clinical trials to evaluate the clinical effects of mechanical devices on circulatory support. Regardless of the reason, temporary mechanical circulatory assistance can ensure that the patient's condition is stable for a short period of time, and other important organs can be perfused while waiting for a heart transplant.

Professor Dao Wen Wang team is highly alert with regard to fulminant myocarditis. When encountering a suspicious case, they first judge whether it is fulminant myocarditis and make full use of modern diagnostic tools to achieve early diagnosis and treatment. They have earnestly explored and summarized their experience and put forward the theory that "excessive immune activation and inflammatory storm formation" are the core causes of fulminant myocarditis and therefore formulated the "life support-based comprehensive treatment regimen." This regimen is different from traditional "symptomatic treatment" as it optimizes the advantages of equipment. Early application of mechanical circulatory support maintains the patient's circulatory function, including intra-aortic balloon counterpulsation, oxygenation, and ventilation (extracorporeal membrane lung) capabilities, and maintains the end organ's function to avoid the serious consequences of prolonged hypotension. At the same time, the active use of sufficient doses of hormones and immunoglobulins for immunomodulation and inflammation treatment has changed the prognosis of fulminant myocarditis, reduced the 50% mortality rate of fulminant myocarditis in the past to approximately 3.7% today, and has saved patients' lives.

Professor Dao Wen Wang team combined their experience with advances in fulminant myocarditis worldwide and compiled this book, which will definitely help clinicians save more dying patients. This book can improve our understanding of fulminant myocarditis because most patients are relatively young and healthy, without myocardial ischemia or systemic organ failure. Typical symptoms appear late or after the body reserves are exhausted. To avoid misdiagnosis/missed diagnosis and miss the chance of rescue, the best chance to save lives lies in early diagnosis. When necessary, coronary angiography is performed immediately to rule out myocardial infarction, and the patient needs to be transferred to the appropriate CCU or cardiogenic shock treatment center as soon as possible. First-line doctors should have relevant knowledge and be able to recognize signs and symptoms of impending hemodynamic abnormalities or circulatory failure.

The progress of modern science and technology has brought hope for the individualized treatment of fulminant myocarditis. For example, by using next-generation T cells and their receptor gene sequencing, different causes, different patients, and difference in infiltrated T cells, macrophages, and cardiomyocytes can be recognized. Newly developed tumor immunology technologies, such as the new high-dimensional single-cell technology, provide an unprecedented solution to reveal tissue heterogeneity. Multiple immunofluorescence assay (multiplex immunofluorescence assay) and mass cytometry (mass cytometry, displaying the signal pathway hologram of solid tissue cells) were applied to fulminant myocarditis, which can reveal the subtype characteristics of T cells and bone marrow-like cells, thereby promoting the

development of fulminant myocarditis. Multi-unit and multidisciplinary cooperation, the promotion of endocardial biopsy and direct tissue examination, and the use of molecular technology promote targeted therapy and more individualized treatment and also helps in updating the classification of fulminant myocarditis.

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Foreword

Fulminant myocarditis can be considered as a working term indicating a severe form of myocardial inflammation. Acute myocarditis affects relatively young patients (median age 30–45 years) with a higher male prevalence (60–80%). Patients affected by fulminant myocarditis present with acute heart failure and/or ventricular arrhythmias requiring inotropes and/or temporary mechanical circulatory supports. When an endomyocardial biopsy is performed, diffuse inflammatory infiltrates with cardiomyocyte necrosis are often found, even if it is not always feasible and can have relatively low sensitivity. Mortality or need for heart transplantation is still unacceptably high, with a 28% at 60 days based on a recent international study. Beyond circulatory support, there are no evidence-based specific therapies, and immunosuppression is generally indicated in specific histology (for instance, giant cell myocarditis) and in conditions associated with autoimmune disorders.

Based on that a textbook like this that recapitulates fulminant myocarditis from etiologies to state-of-the-art therapies is needed to guide the management of these complex patients.

This textbook merges the vast personal clinical experience of the Authors and an extensive review of the current literature on this topic. The Editor, Professor Dao Wen Wang from the Tongji Hospital in Wuhan, China, had led the *Chinese Society of Cardiology Expert Consensus Statement on the Diagnosis and Treatment of Adult Fulminant Myocarditis.* Furthermore, he managed to organize one of the main symposiums specifically on fulminant myocarditis in Wuhan in October 2019. International experts around the world, including myself, had the occasion to discuss unanswered issues in the management of these patients like the preferred type of mechanical support, the need for biopsy and viral search on the myocardium, or when immunosuppression is indicated. Key questions, that the Authors have replied to in this textbook. Furthermore, interesting case reports and hints on how nursing patients with fulminant myocarditis enrich this book. Professor Wang and his team had the merit to handle patients with COVID-19, and promptly identify

the inflammatory cytokine storm and overactivated immunoresponse as the driving mechanisms of myocardial injury in COVID-19. They proposed successful therapies to target this uncontrolled inflammatory viral response that improved the prognosis of patients with COVID-19.

Hope the readers can enjoy this reading and enhance their knowledge on this theme.

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Preface

The term "fulminant myocarditis" can be traced back to 1975 in the literature, and it is successively report, but still extremely rare. In PubMed, there are only 6 articles in 1975–1984 and 37 articles in 1985–1994; the number of studies increased slightly after 1995, including research reports and clinical observations. In 2000, the *New England Journal of Medicine* published the first report on the long-term prognosis of this disease although subsequent research reports were inconsistent with its results.

The meaning of fulminant is rapid and sudden, and its implicit meaning includes fierce and severe. Fulminant myocarditis is a severe myocardial inflammatory disease that has a rapid course. Rapid onset refers to the occurrence of severe manifestations within 2 weeks, usually within 1 week, or even as short as 1–2 days after the onset of illness. Autopsy or myocardial tissue biopsy have confirmed that myocardial tissue has a large number of inflammatory cells, especially lymphocytes, as well as macrophage infiltration.

Fulminant myocarditis has a sudden onset and progresses rapidly. Circulatory failure and heart pump failure occurs quickly. Severe arrhythmia and sudden death may also occur, combined with damage to other organs. The early mortality rate is extremely high. According to previous reports, the mortality rate of fulminant myocarditis can be as high as 50% or 70%. These statistics come from large hospitals or medical centers, so the actual total mortality rate should be even higher. Since 2000, the use of circulatory support systems (ECMO, intra-aortic balloon counterpulsation, cardiac assist devices, etc.) has reduced the hospital mortality rate, but it is still as high as 30%.

Traditional treatments for fulminant myocarditis include anti-shock and immunosuppressive therapies, which is widely used in Western countries. Patients usually have pre-infection symptoms, followed by shock and pump failure. Anti-shock treatment is usually carried out according to clinical routines, including supplementation of fluids and use of vasoactive drugs; large doses of norepinephrine are administered when the shock is difficult to treat. Ultrasound imaging often indicates a significant decrease in myocardial contractility and heart failure. Therefore, dopamine or the newer cardiotonic agent-calcium sensitizer levosimendan may be used to enhance myocardial contractility. However, these treatments are not ideal in terms of clinical outcomes and may even promote death. In addition, due to the infiltration of a large number of lymphocytes in the patient's myocardial tissue, mainly T lymphocytes, including NK cells and dendritic cells, some centers have

begun to use immunosuppressants or cytotoxic drugs since 1984 [*J Am Coll Cardiol*. 1984;3(1):63–70]. Although subsequent clinical trials proved that this therapy is ineffective, it is still the mainstay of treatment in clinical practice in Western countries.

Traditional treatment of fulminant myocarditis has poor efficacy or lack of effective treatment mainly due to the lack of basic research and correct understanding of the pathophysiology of the disease, leading to serious issues.

Patients with fulminant myocarditis have a poor prognosis; some even die during our clinical treatment. Traditional treatment has little effect. The death of young and middle-aged patients may be attributed to the challenges with the existing treatment method, resulting from the lack of understanding of the underlying pathophysiological mechanism of the disease.

About 10 years ago, a 28-year-old healthy male patient "caught a cold" 5 days prior. His body temperature was 38 °C, and the fever subsided after the use of phenanthramine tablets, but his bad feeling was not relieved. On the contrary, he felt fatigue, loss of appetite, and listlessness. Four days later, he visited the hospital for chest tightness and shortness of breath. Abnormal ECG was found in the emergency room (QRS amplitude was obviously low voltage, widened QRS wave, and some leads were elevated in the ST segment), heart rate was 110 beats/min, blood pressure was 105/70 mmHg, and cardiac troponin I (cTnI) levels were elevated. He was sent to the catheterization lab via the green channel of the chest pain center. Coronary angiography revealed normal coronary arteries. The patient was transferred to the CCU ward. Echocardiography showed diffuse reduction in movement of the left ventricle, the EF value was 40%, and the cTnI level was 30,000 pg/mL. He was diagnosed with fulminant myocarditis. Soon after the patient's blood pressure dropped to 85/50 mmHg, his breathing was 28 breaths/min. There was slight wet rales heard in both lungs, and blood oxygen saturation was 90%. However, the doctors habitually provided mask oxygen, heart strengthening, vasoactive drugs (dopamine), fluid rehydration, and other treatments; his blood pressure rose briefly, blood oxygen saturation rose to 95%, but his breathing was still rapid. After 12 h, the patient's blood pressure was significantly reduced to 70/50 mmHg, and norepinephrine and levosimendan were administered again. Blood pressure increased, but the condition did not improve. After 24 h, the peripheral ischemia became obvious and worsened, and the patient's heartbeat stopped 4 days later. In fact, we have seen many cases with similar illnesses; some patients improved and were discharged, but most have not been successfully cured. Seeing so many young lives being lost in front of us, I could not help but feel the pain that was hard to describe. What happened to the patient? Did we do it wrong? Or did we do it right? Why is our care and treatment ineffective?

As the director of the Cardiologic Division, I was concerned with such a major clinical problem, which directed my focus on learning and research. I read almost all relevant literature and case reports available at the time, and sometimes even forgot to attend specialist outpatient services. Through in-depth study, I understood the pathology and pathophysiological characteristics of the disease and felt that we did not understand these aspects correctly. Our cardiovascular staff get overconfident about being able to bring the dying

back to life. When encountering these new problems, we seem to be blinded in the dark.

Therefore, how should we treat severely damaged myocardium that has almost lost its blood pumping function? It is well known that Genghis Khan almost conquered the entire Eurasian continent with his cavalry. "All the kung fu in the world can be defeated except fast," Genghis Khan's cavalry marched hundreds of miles a day, and when the horses were exhausted, they changed horses instead of men and continued to fight. At this point, we should understand and apply the same principle. If we hope that the horse can still contribute to the battlefield, then we should not increase the load on this extremely tired horse, but lighten the burden and let it rest.

Is it enough to just let the heart rest? According to reports in Taiwan and abroad, the death risk of ECMO patients has improved, but it is far from ideal. Maintaining circulatory stability is temporary strategy for treating symptoms. A large amount of inflammatory cell infiltration and edema of the heart and systemic problems also require treatment, which is the fundamental principle of our treatment.

I share an unforgettable experience. After an in-depth study, I found a ray of light in the dark. One evening in June 2014, I organized a closed-door meeting with doctors in the cardiology department and shared my learning achievements and discussed related theories, especially the treatment plan. Finally, we proposed the pathogenesis of the disease, that is, the "inflammatory storm caused by excessive immune activation": pathogens (including viruses, bacteria, and fungi) infect or attack the heart and cause myocardial damage. The damaged myocardial tissue and pathogens are released as antigens and quickly stimulate an excessive immune response, leading to the infiltration of inflammatory cells and the rapid production of a large number of cytokines and inflammatory mediators to form an "inflammatory storm," which further severely damage myocardial cells and inhibit heart function, until the patient has pump failure and shock.

From this point of view, we propose that modern treatment strategies should include two aspects: First, actively use mechanical life support to reduce the patient's heart load and maintain the patient's effective circulation, instead of "adding a whip to a sick horse" by using vasoactive drugs, cardiotonic agents, and even respiratory stimulants, which is the treatment of symptoms or a temporary life-saving strategy. Second, rather than "immunosuppressive" therapy, "immunomodulatory" therapy should be administered in a timely manner, including the use of adequate doses of glucocorticoids and immunoglobulins. These constitute the basis of our treatment regimen, which is the core content of our "life support-based comprehensive treatment regimen."

We reached a consensus and implemented the plan. The results proved to be effective, which greatly encouraged us. Therefore, we began to lecture and disclose this treatment regimen to the public after obtaining more positive results and continuous improvement. Professor Hui Rutai from Fuwai Hospital listened carefully and tirelessly to my systematic narration and said that after attending the lecture three times, he understood more about fulminant myocarditis. This also moved me deeply. He urged me to write a

consensus and publish it as soon as possible, which would help save the lives of thousands of young and middle-aged Chinese people every year. Therefore, we started to write a consensus since 2016 and reported our work to Academician Ge Junbo, the chairman of the Chinese College of Cardiovascular Physicians, and Academician Han Yaling, who is in charge of the guidelines. After receiving their encouragement and support, and after the application was approved by the Standing Committee of the Society, we organized three discussions with cardiovascular experts across the country and made changes according to their opinions and suggestions. After submission of the manuscript, Academician Han Yaling et al. reviewed and revised the manuscript word by word. Finally, in September 2017, the consensus of Chinese experts on fulminant myocarditis in adults was published in the Chinese Journal of Cardiovascular Diseases. Once released, this consensus aroused great responses. The academicians of the Chinese Academy of Sciences Ge Junbo, Chen Yihan, Yang Yuejin, Chen Yundai, Xiang Dingcheng, and Xu Dingli provided positive comments. Professor Hu Dayi, an academician at the International Eurasian Academy of Sciences, published a review in the *Chinese Journal of Internal Medicine* to introduce this consensus, and finally pointed out, "This is the expert's consensus in the diagnosis and treatment of fulminant myocarditis with Chinese characteristics. It has important guiding value for improving the clinical diagnosis and treatment of fulminant myocarditis by Chinese medical staff and also provides Chinese regimens for international colleagues." Professor Hui Rutai published a comment in *Science China—Life Science* to introduce this consensus to the world.

Thus, is the "life support-based comprehensive treatment regimen" effective? Clinical practice has proven it to be effective. It reduces the risk of death in hospitals from more than 50% in case of traditional treatment to less than 5%. After the consensus was published, it also received responses from frontline experts and colleagues. Professor Zhang Jing from the CCU of Fuwai Central China Cardiovascular Hospital, Henan Province, and Professor Zhao Yuhua from Dongguan Kanghua Hospital in Guangzhou actively implemented the regimen, which achieved very good results and greatly improved the diagnosis and awareness.

After we further promoted this regimen to the whole country at Peking Union Medical College Hospital, the treatment outcomes of many hospitals at different levels, including the Affiliated Hospital of Xiamen University, Wuhan Central Hospital, and the Affiliated Hospital of Wenzhou Medical University, have proved that as long as this regimen is strictly followed, excellent treatment effects can be obtained. The treatment of fulminant myocarditis requires early identification, early diagnosis, early prediction, and early treatment in order to obtain a good outcome. We conducted a 1-year follow-up of discharged patients with fulminant myocarditis. Although approximately 20% of the patients had arrhythmia, recurrence of inflammation, or enlarged heart and decreased heart function, the treatment results of most patients were very promising, especially in patients likely to die. Ammirati et al. reported the follow-up results of 165 patients with fulminant myocarditis after discharge from 16 tertiary hospitals and found that the rate of heart death and heart transplantation events was 28% at 60 days after

discharge, and 39.4% at 1 year; even for lymphocytic fulminant myocarditis with a good prognosis, heart death and heart transplantation events 60 days and 1 year after discharge were 19.5% and 31.3%, respectively, and our results are in sharp contrast with these.

There may be questions regarding the theory of "inflammation storm caused by excessive immune activation." Our team's systematic pathological research data and international pathological reports have proved that a large number of inflammatory cells infiltrate patient's heart, especially T lymphocytes and macrophages. Inflammatory proteomics analysis of the patient's plasma revealed that more than 50 cytokines and inflammatory mediators were significantly increased, and some were even more than thousand times higher than normal. As the patient gradually recovered, the levels of these inflammatory factors also decreased significantly. Furthermore, after adding 3% patient serum to cultured primary mouse cardiomyocytes, the contractility of a single cardiomyocyte was significantly reduced, and in animal experiments, neutralizing antibodies have obvious therapeutic effects. These evidence indicate the existence of immune activation and inflammatory storms. Our clinical treatment practice also proves that this theory is correct.

Although our treatment has improved, there are still many unanswered questions. Who is the susceptible population? What are the epidemiological characteristics? How do different pathogens cause diseases? How can a more precise and effective treatment be achieved? Why do some patients deteriorate after discharge? These require in-depth clinical and basic research.

Fulminant myocarditis is fatal. It is estimated that fulminant myocarditis has an annual incidence of 30,000–50,000 in adults in our country. If the incidence in children is added, this number should be doubled. Although Professor Zhang Jing's team and our team held 28 study classes and delivered more than 120 lectures nationwide, which enabled awareness in more than 30,000 clinicians, this is far from sufficient. As this dangerous disease presents at all stages, primary healthcare workers are usually the first to be consulted by patients, their awareness needs to be improved urgently. Moreover, there are many questions that require answers, the "life support-based comprehensive treatment regimen" is effective; therefore, we have summarized the practical experience and research results in writing this book, hoping to improve early identification of this disease and save thousands of lives. Lastly, we hope that our colleagues at home and abroad will provide valuable opinions to facilitate the revision and improvement of the next edition.

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Contents

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1 Introduction: Accumulating More Knowledge and Ability in Treating Fulminant Myocarditis to Save More Lives

Dao Wen Wang

Fulminant myocarditis, as the term suggests, is a critical disease with rapid onset and progression, usually resulting in severe inflammatory injury to the myocardium, thereby causing serious systolic and diastolic dysfunction, as well as arrhythmia and eventually sudden death [1, 2]. It involves terrifying clinical processes and a very high mortality rate.

The etiology of fulminant myocarditis primarily includes infection, particularly viral infection [3, 4], autoimmune diseases [5], and drug toxicity [6], among which viral infection is the most common with the low possibility to foresee. Various classes of viruses or microorganisms can trigger fulminant myocarditis, including [7] parainfluenza virus [8], parvovirus [3], various enteroviruses [9], adenovirus, cytomegalovirus, EB virus, hepatitis virus, coronavirus HIV, hemorrhagic fever virus, fungus, and spirochete [10].

Fulminant myocarditis is characterized by a sudden onset and rapid progression. Hemodynamic disruption (pump and circulation failure) and severe arrhythmia are common in fulminant myocarditis and occur in a short time, which may be complicated by respiratory failure and hepatic or renal failure, consequently leading to an extremely high mortality rate in the early period (within a few days after onset) [1, 2, 10, 11]. The in-hospital mortality rate is reported to be as high as 50–70% in Western countries [12]. According to a recent review reported by the Taiwan University Hospital in China, the in-hospital mortality rate among 134 patients at the center was 38%, even after receiving circulation support, such as extracorporeal membrane oxygenation (ECMO) or ventricular assistance device, and heart transplantation, and the transplantation-free survival rate was 54% [13]. No large study regarding fulminant myocarditis has been previously reported in the mainland of China until we reported the multicenter study results with a "life support-based comprehensive treatment regimen [2, 14, 15]." Despite the high mortality rate, patients with fulminant myocarditis will have a good prognosis if they undergo appropriate treatment. Fulminant myocarditis is not common but is also not rare. Nearly 30–50 cases of fulminant myocarditis get admitted to our department annually. However, it is a great pity that no consensus or guideline has been reported worldwide until the release of the *Chinese Society of Cardiology Expert Consensus Statement on the Diagnosis and Treatment of Adult Fulminant Myocarditis* [2]. This might be due to the lack of an efficient and perfect treatment regimen for fulminant myocarditis.

The pathophysiological mechanism of fulminant myocarditis triggered by infection includes direct injury to the myocardium by viruses or

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other pathogens and subsequent inflammatory and immune injury (due to hyper-activated immunity and cytokine secretion inducing an inflammatory or cytokine storm) [10, 16, 17]. After the emergence of precursor symptoms, such as fever, fatigue, stuffy and runny nose, sore throat, and frequent mild cough or diarrhea within 2–5 days, the patients can quickly develop symptoms of myocardial injury, including breathlessness, dyspnea, chest pain, palpitation, dizziness, extreme fatigue, and loss of appetite. Statistics from a single center indicate that 90% of fulminant myocarditis patients were transferred or admitted to Wuhan Tongji Hospital due to severe fatigue, weakness, and dyspnea, and 10% were due to syncope or cardiopulmonary resuscitation [14]. Hemodynamic disorders are an important feature of fulminant myocarditis [18]. Some patients quickly develop acute left heart failure and cardiogenic shock showing symptoms of pulmonary congestion or shock. Further, it may involve other organ and tissue damages, such as liver and kidney damages. Fulminant myocarditis is characterized by the sudden onset of severe hemodynamic disorder of myocardial inflammation. Therefore, it is a clinical diagnosis rather than a histological or pathological diagnosis, indicating that the diagnosis can only be made under full consideration of clinical manifestations and laboratory and imaging examinations [1, 10]. Fulminant myocarditis can be clinically diagnosed with the abrupt occurrence of the disease and obvious prodromal symptoms of viral infection, including malaise, fatigue, and loss of appetite, accompanied by severe hemodynamic disorders. Laboratory tests showing severe myocardial injury (manifested as significant elevation of cardiac troponin I or T and N-terminal pro-brain natriuretic peptide and diffuse and obvious reduction in ventricular wall motion revealed by echocardiography can further support the diagnosis. Electrocardiogram examination reveals various abnormalities; most patients display a reduction in voltage amplitude and QRS wave broadening, and many patients present abnormal changes, very similar to acute myocardial infarction. Coronary angiography should be conducted for rapid identification under these circumstances to differentiate or exclude acute myocardial infarction.

We proposed a "Life Support-Based Comprehensive Treatment Regimen [2]"in accordance with the pathological and pathophysiological characteristics of fulminant myocarditis, international and domestic literature, and preliminary practical experience. The basic principle of this treatment regimen is to fully reduce the heart load of the patient to rest the severely damaged heart. It mainly incorporates: (1) active mechanical circulatory support, including the use of intra-aortic balloon counterpulsation and vena-aortic ECMO to maintain basic circulation as temporary treatment, and active mechanical respiratory therapy if necessary [15], (2) immunomodulation therapy, including the use of sufficient doses of glucocorticoids and intravenous immunoglobulin protein, (3) inhibition of neuraminidases using neuraminidase inhibitors, such as peramivir, oseltamivir phosphate, and zanamivir [19–21], and (4) other treatments, such as strict monitoring of vital signs (including invasive blood pressure) and blood oxygen, along with nutritious supportive treatment. The patient should obtain absolute bed rest and fluid management, and continuous renal replacement therapy. It needs to be emphasized that the chance of giving appropriate and timely treatment is fleeting because of the rapid progress of fulminant myocarditis. Hence, it is necessary to implement "very early identification", "very early diagnosis", "very early prediction", and "very early treatment". When a local hospital does not have the ability or equipment for proper treatment, patients should be promptly transferred to a superior hospital with treatment facilities and experience. Our practice has proven that strict implementation of this treatment regimen can greatly improve the therapeutic effect and reduce the in-hospital mortality rate from more than 50% to less than 5% [14, 15].

Entrusted by the cardiovascular branch of the Chinese Medical Association, Tongji Hospital of Tongji Medical College (where the authors work) wrote and organized nationwide experts in cardiovascular emergency and intensive care fields to discuss the *Chinese Society of Cardiology*

Expert Consensus Statement on the Diagnosis and Treatment of Adult Fulminant Myocarditis based on results of both basic studies and clinical trial. Finally, the statement was published in the Chinese Journal of Cardiology in September 2017 [22]. After that, the *Expert Consensus Statement*, especially the novel treatment regimen of fulminant myocarditis, has been widely practiced in several medical centers in China, and its therapeutic efficacy has been confirmed [15, 23]. Therefore, we are determined to write this book to systemically introduce the pathology, pathophysiology of fulminant myocarditis, pathogens, and hypothesis of mechanisms, particularly our treatment regimen and its efficacy, as well as the clinical outcome of the follow-up. We have also introduced several typical clinical cases and comments to guide readers in entering the clinical state. We hope that all readers will actively practice and explore to accumulate data and experience to improve our expert consensus statement and raise treatment levels to save more lives of patients with fulminant myocarditis worldwide.

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2 The Epidemiology of Fulminant Myocarditis

Chenze Li and Dao Wen Wang

2.1 Introduction

Fulminant myocarditis is the most severe form of acute myocarditis and can contribute to the burden of fatal cardiovascular complications, causing cardiogenic shock, lethal arrhythmia, multi-organ failure, and death. Studies on the incidence of fulminant myocarditis have shown that it is a sporadic, less common, but never rare disease. It varies regionally, but is present worldwide in both developed and developing countries. To date, there has been a substantial absence of epidemiologic data on fulminant myocarditis, because it is difficult to obtain the true morbidity of this disease and many patients die before a clear diagnosis is reached due to its extremely fast disease process. However, there remains to be a few of studies and analyses on this topic in literature. In this chapter we summarize and describe the epidemiology of fulminant myocarditis, mainly based on early data on fatal myocarditis.

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2.2 The Incidence of Fulminant Myocarditis

In a population-based study in Finland, the authors investigated the incidence of fatal myocarditis in the general population [1]. They retrospectively reviewed all myocarditis-related deaths from 1970 to 1998, and included a total of 1,349,824 deaths and 141,438,176 person-years. They found that 639 cases developed fatal myocarditis. Based on the mortality data from this Finnish study, the median age-adjusted incidence of fatal myocarditis was 4.6 per 1000,000 person-years in the general population, and the incidence of death caused by myocarditis was 0.47 per 1000 deaths. In addition, an increase in the incidence of fatal myocarditis was observed from the 1970s to the 1990s. Furthermore, this study investigated the incidence of fatal myocarditis stratified by sex and age. The results showed that the rate of fatal myocarditis was higher in males (5.1 per 1000,000 person-years) than in females (4.2 per 1000,000 person-years), and fatal myocarditis resulted in a higher rate of death in young people (<44 years old: 2.18–6.38 per 1000 deaths) than in those who are older (>55 years old: 0.11–0.39 per 1000 deaths). The incidence of fatal myocarditis in this investigation was further adjusted by histopathologic diagnosis. After adjustment, the corrected incidence of fatal myocarditis was 1.5 per 1000,000 person-years.

In another study involving 672, 672 Finnish men with a mean age of 20 years, the incidence

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of myocarditis was evaluated over a 20-year period. Three forms of myocarditis were recognized in this study: mimicking myocardial infarction, presenting with dilated cardiomyopathy, and sudden death. One myocarditis-related sudden death was observed during follow-up. The calculated incidence of this form of fatal myocarditis was 2 per 1000,000 person-years [2]. Similarly, a nationwide survey conducted to determine the clinicopathologic features of myocarditis from January 1997 to December 2002 reported 169 patients with myocarditis. Of all myocarditis cases, fulminant cases accounted for 37.9%. The imputed incidence of fulminant myocarditis is 1.0 per 1000,000 person-years [3]. Thus, from the existing epidemiologic data on fatal myocarditis, it can be estimated that the incidence of fulminant myocarditis is approximately 1.0 to 2.0 per 1000,000 person-years.

Data on the incidence of fulminant myocarditis can also be indirectly inferred from the published data on all myocarditis worldwide. Accordingly, we systematically reviewed the epidemiology of acute myocarditis and estimated the incidence of fulminant myocarditis from this data. According to data from the Global Burden of Disease Study (GBD) 2013, which systematically evaluates the prevalence of 1160 sequelae of 289 diseases in different parts of the world, the cases of acute myocarditis were 961,000 in 1990 and 1,481,000 in 2013. After adjusting for age, the age-standardized rate was 22.8 per 100,000 persons-years in 1990 and 22.0 per 100,000 persons-years in 2013 [4]. As a part of GBD 2017, the incidence of myocarditis was calculated again [5]. In this report, there were 1.80 million myocarditis cases. The age-standardized incidence of myocarditis in 2017 was 23.2 per 100,000 persons-years, which is similar to the previous GBD statistics. More importantly, the incidence of myocarditis was also reported across different geographic locations. It was shown that approximately 45.6 per 100,000 person-years of myocarditis occurred in the Asia-Pacific region. In China, the incidence of myocarditis ranged from 30 to 40 per 100,000 person-years. Chile had the lowest incidence of myocarditis (10.2 per 100,000 person-years) while Albania had the highest incidence (105.6 per 100,000 person-years). Furthermore, the proportion of fulminant myocarditis among all cases of myocarditis has been reported in various studies. The first nationwide survey on acute or fulminant myocarditis in Japan revealed that 33.5% of all cases developed fulminant myocarditis [6]. In a study comparing the features of fulminant and acute myocarditis, the percentage of fulminant myocarditis accounted for 37.9% of cases. However, in an institution collecting data from 1992 to 2003, the rate of acute myocarditis was 1 in 1000 patients per year, of whom 6% experience a fatal form [7]. If we adopt the minimum proportion of fulminant myocarditis among all cases (6%), the incidence of fulminant myocarditis ranges from 6 to 60 per 1000,000 person-years. The average incidence of fulminant myocarditis is 13 per 1000,000 person-years. In China, the incidence of fulminant myocarditis ranges from 18 to 24 per 1000,000 person-years.

Aside from data on the incidence in the general population, there were also other studies reporting the incidence of fulminant myocarditis in special populations, such as in death patients. According to Japanese national autopsy data, 0.11% of patients (434 of 377,841) were identified to have had myocarditis [8]. Myocarditis can be divided into two forms: fulminant and nonfulminant. Of these, the fulminant form often contributes to sudden death. In a report involving 193 patients with sudden death, 12% was due to myocarditis [9]. Another autopsy series reported that the percentage of fatal myocarditis was 11.6% in all sudden deaths [10]. In cases of sudden death aged 16–29 years, 3.5% of patients died because of fatal myocarditis [11].

Currently, data on the incidence of fulminant myocarditis in the general population are limited worldwide. We expect a high-quality survey to investigate the accurate incidence of fulminant myocarditis in the future.

2.3 The Prognosis of Patients with Fulminant Myocarditis

Myocarditis is a major cause of several life-threatening conditions, such as dilated cardiomyopathy, heart failure, and even sudden death. The prognosis for different forms of myocarditis vary considerably. Notably, fulminant myocarditis is the most treacherous type of myocarditis, described as a state of rapid onset, progressing to hemodynamic disorder and even death quickly, complicated by ventricular lethal arrhythmia or multiple organ failure. Although data on the global burden of fulminant myocarditis are limited, the GBD study provides estimates of the burden of acute myocarditis [5]. Based on the GBD 2017, the global number of deaths attributable to myocarditis was 46,486 (95% uncertainty interval [UI] 39,709–51,824). Moreover, 131,376 (95% UI 90,113–183,001) years lived with disability (YLDs) and 1.26 million (95% UI 1.10–1.42) years of life lost (YLLs) were attributable to myocarditis. In 2017, the age-standardized YLD was 1.7 (95% UI 1.2–2.4) while the YLL was 16.6 (95% UI 14.5–18.5) per 100,000 people for myocarditis.

For the long-term prognosis, the event rate of fulminant myocarditis partly depends on the histological subtype [12]. In a study, the authors found that giant-cell myocarditis had a worse clinical outcome than eosinophilic myocarditis and lymphocytic myocarditis, including a significantly higher incidence of cardiac arrest, sustained ventricular tachycardia and fibrillation, and increased creatinine. At 60 days, the rate of cardiac death or heart transplantation was 62.5% in giant-cell fulminant myocarditis, while it was only 26.3% and 21.0% in patients with eosinophilic fulminant myocarditis and lymphocytic fulminant myocarditis, respectively (log-rank $p < 0.001$). In addition, at 3-year follow-up, a significantly higher rate of cardiac death or heart transplantation was observed in patients with giant-cell fulminant myocarditis (81.3%) than in those with eosinophilic fulminant myocarditis (37.3%) and lymphocytic fulminant myocarditis (39.9%) (log-rank $p < 0.001$).

Although patients with fulminant myocarditis may have a better long-term prognosis than those with non-fulminant myocarditis [13], the in-hospital mortality was significantly higher in patients with fulminant myocarditis. According to a report involving 35 patients who were diagnosed with acute myocarditis, the in-hospital mortality was 45% in the fulminant group, which was higher than that in the non-fulminant group (45% vs. 4%, $p = 0.027$) [14]. Even in patients managed with aggressive pharmacological therapy and mechanical support, the in-hospital mortality rate is considerably high [15]. One report revealed that the death rate in patients on extracorporeal life support was 49%, and transplant-free survival was 56% [16]. In 2017, a Chinese Consensus on fulminant myocarditis drafted by our team was published [17]. In this consensus, a life support-based comprehensive treatment regimen (LSBCTR), involving a combination of mechanical life support (intra-aortic balloon pump [IABP] with or without extracorporeal membrane oxygenation [ECMO]), immunological modulation therapy using sufficient doses of glucocorticoids and immunoglobulins, and neuraminidase inhibitors, was encouraged. In our multicenter study, our team evaluated 169 patients with fulminant myocarditis recruited from four centers in China [18]. The results showed that 44 patients (26.0%) died in hospitals. The in-hospital mortality rate was 3.7% (3 of 81) in the LSBCTR group and 46.6% (41 of 88) in the traditional treatment group ($p < 0.001$). Our data revealed that early application of mechanical life support, neuraminidase inhibitors, and immunomodulation therapy could significantly decrease in-hospital mortality. Moreover, Zhou et al. compared the prognosis of patients who were treated with both temporary mechanical circulatory support (t-MCS) and immunomodulation therapy (IT) to those who did not receive these treatments [19]. Out of 138 patients, the in-hospital mortality rate was 18.8%. The mortality rates were 4.2% (4 of

96) in the t-MCS + IT group and 52.4% (22 of 42) in the control group. The adjusted odds ratio (OR) was 0.11 (95% confidence interval [CI] 0.09–0.46, $p = 0.001$) for the t-MCS + IT group compared with the control group. Notably, patients were more likely to have better blood pressure (BP) and left ventricular ejection fraction (LVEF) following the combined treatment of t-MCS and IT. Meanwhile, data from an international registry comprising of 16 tertiary hospitals in the United States, Europe, and Japan reflected that the rates of cardiac death and heart transplantation were 27.8% at 60 days and 39.4% at 1 year [12]; this was higher than that in our study, proving the superiority of the LSBCTR [19]. Similarly, Ye et al. from Huangzhong and Fuwai Hospital of Zhengzhou University retrospectively evaluated the combined efficacy of mechanical circulatory support devices using clinical data from 37 patients with fulminant myocarditis [20]. In their study, patients were treated with the LSBCTR and were divided into three groups: IABP, ECMO, and IABP+ECMO groups. The findings showed that 34 out of the 37 patients survived, and only three patients died. Among the three groups, the survival rate was similar, supporting the core strategies of the application of mechanical circulatory support devices in the treatment of fulminant myocarditis. In addition, Guangdong Dongguan Hospital investigated the mortality among three different treatments. In the group given conventional treatment, 56.7% patients died. In another group where the patients were managed using IABP and ECMO but without immune modulation, 30% of the patients died. The last group was managed with a combination of IABP, ECMO, and immune modulation; in this group, the mortality rate was only 7.9% [21]. Moreover, the mortality of acute phase in patients with a combination of IABP and ECMO but without immune modulation was 40% [22]. These findings reflect the importance of complete implementation of the LSBCTR, with which the prognosis of patients with fulminant myocarditis can be significantly improved. Furthermore, the patients receiving this treatment have much better longterm outcome during one year follow-up [23].

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3 Pattern Recognition Receptors and Fulminant Myocarditis

Dao Wen Wang and Rongbin Zhou

3.1 Brief Introduction

Human bodies as well as living beings can sensitively sense, recognize and defeat infected microbes, such as bacteria, fungus, virus and others, and also some materials from apoptosis and necrosis. It is a unique and important, and daunting task, which is essential for the survival of human bodies. This is an ability so called innate immune system of vertebrates by innate immune cells mainly including neutrophils, monocytes, macrophages, dendritic cells, natural killer cells, mast cells, eosinophils, and basophils. Furthermore, monocytes and macrophages swallow and manage antigens and transform to lymphocytes to have the adaptive or specific immunity.

Humans and organisms recognize self and non-self (exogenous microorganisms and materials) through pattern recognition receptors (PRRs). PRRs are distributed on both immune cells and non-immune cells, including endothelial cells, fibroblasts, and cardiomyocytes. Pathogen-associated molecular patterns (PAMPs) refer to PRR recognition of exogenous microorganisms and other pathogens, and corresponding damage-associated molecular patterns (DAMPs) refer to the recognition of endogenous molecules by PRRs [1]. Although some controversies exist and many action mechanisms need to be figured out it is widely accepted that both PAMP and DAMP trigger immune responses via the activation of classical and non-classical PRRs, so that PRRs signal to corresponding cells and initiate a series of cascade effects and inflammatory response. Importantly, activating immune cells and tissue cells not only stimulate innate immune and adaptive immune response, but also involve human disorders, even severe disease, such as fulminant myocarditis. In this chapter, we briefly introduce PRRS and pattern associated molecules and pathogen associated molecules, distribution and possible roles of PRRs to help understand pathogeny and pathogenesis of fulminant myocarditis and further is able to handle treatments patients with fulminant myocarditis.

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3.2 Pattern Recognition Receptors (PRRs)

PRRs include five main classes, membrane-bound Toll-like receptors (TLRs) and NOD-like receptors (NLRs), retinoic acid inducible gene

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I (RIG-I)-like receptors (RLRs), C-type lectin receptors (CLRs) and multiple intracellular DNA sensors [1]. In addition, several ion channels, G-protein-coupled receptors (GPCRs), and triggering receptors expressed on myeloid cells (TREMs) can sense DAMPs stimulation and have response although they are put under classical PRRs. Here we list all the PRRs and their roles in Table 3.1 [2].

Table 3.1 Common pattern recognition receptors in human immunity

PRRs	Cell distribution	PAMPs	DAMPs	Pro-inflammatory functions	Signaling pathways
TLRs					Most TLRs: MyD88-dependent pathways; TLR3: TRIF-dependent pathways; TLR4: MyD88-dependent pathways and TRIF-dependent pathways
TLR1 (TLR1–TLR2)	Mo, DC Ma, Eo, Ba	Triacyl lipopeptide Viral proteins			
TLR2 (TLR1–TLR2, TLR2–TLR6)	Ubiquitous, high in DCs, Mo, Ma, N, Ba, CM	Viral proteins, Lipoteichoic acid, Arabinomannan, Peptidoglycan, Zymosan, Lipoprotein, Pore protein	HMGB1, several HSPs, SNAPIN, versican, biglycan, decorin, Eo-derived neurotoxin, surfactant protein A/D, β-defensin 3, histone, SAA, Aβ, β2-glycoprotein I	Promotes the production of pro-inflammatory cytokines and chemokines	
TLR3	Ubiquitous, high in Mφ, DC, NKC, IEC, CM	dsRNA		Promotes the production of pro-inflammatory cytokines, chemokines and IFN-I	
TLR4 (MD-2/CD14)	Mφ, DC, Ma, Eo, CM	LPS,	HMGB1, tenascin-C, several HSPs, S100s, HMGN1, biglycan, decorin, heparin sulfate, hyaluronic acid, fibrinogen, fibronectin, β-defensin 2, surfactant protein A/D, lactoferrin, neutrophil elastase, peroxiredoxin, histone, SAA, ox-LDL	Promotes the production of pro-inflammatory cytokines, chemokines and IFN-I	

Table 3.1 (continued)

PRRs	Cell distribution	PAMPs	DAMPs	Pro-inflammatory functions	Signaling pathways
TLR5	IEC, CM	Flagellin			
TLR6 (TLR2–TLR6)	Mo, DC, Ma, Eo, Ba	Lipoteichoic acid, Peptidoglycan			
TLR7	Ubiquitous, high in pDC, Mo, Mφ, Eo, B-cell, CM	ssRNA, Imidazoquinoline	IgG–ribonucleoprotein complex, microRNAs	Promotes the production of IFNα and other cytokines and hemokines	
TLR8	Mφ, N, DC	ssRNA			
TLR9	Ubiquitous, high in pDC, Mo, Mφ, Eo, Ba, B-cell, CM	Non-methylated CpG DNA	IgG–chromatin complex, mtDNA, HMGB1	Promotes the production of IFNα and other cytokines and chemokines	
TLR10	pDC, Eo, Ba, B-Cell, also in thymus, gastric mucosal tissues, cancer cells, tonsil and lung	dsRNA		1. Antiinflammatory: NF-κB, MAPK, MyD88, and TRIF 2. Proinflammatory: Via IL-8, IL-6, TNF-α, type I, type III IFNs and NF-κB	Co-receptor of many other TLRs
NLRs					
NLRP3	DCs, N, Mo and Ma	LPS	MSU, glucose, cholesterol crystals, Aβ, ATP, oxPAPC, Alu-RNA	Promotes IL-1β and IL-18 secretion and initiates pyroptosis	
RLRs					
RIG-I	Ubiquitous, highly in epithelial cells and myeloid cells	5′-triphosphorylated RNA, shortchain dsRNA	Endogenous 5′ppp RNA	Promotes the production of IFN-I and other cytokines and chemokines	
MDA5	Ubiquitous, highly expressed in epithelial cells and myeloid cells	poly IC, longchain dsRNA	Unedited long self-dsRNA, endogenous retroviral RNA	Promotes the production of IFN-I and other cytokines and chemokines	
LGP2		dsRNA			
CDSs					
cGAS	Ubiquitous, highly expressed in epithelial cells, DCs, monocytes, macrophages and T cells	Cytoplasmic DNA	dsDNA	Promotes the production of IFN-I and other cytokines and chemokines	

(continued)

Table 3.1 (continued)

PRRs	Cell distribution	PAMPs	DAMPs	Pro-inflammatory functions	Signaling pathways
AIM2	Ubiquitous, highly expressed in epithelial cells, DCs, Mo, Ma, B cells and NK cells	Cytoplasmic DNA, damaged DNA in the nucleus		Promotes IL-1β and IL-18 secretion and initiates pyroptosis	
RAGE					
RAGE	Ubiquitous	AGEs, HMGB1, S100s, Aβ, DNA		Promotes the expression of pro-inflammatory genes, as well as cell migration, proliferation and apoptosis	
TREMs					
TREM1	Myeloid cells, epithelial cells, endothelial cells and fibroblasts	HMGB1, HSP70, PGLYRP1, actin		Promotes pro-inflammatory cytokine and chemokine secretion	
TREM2	Myeloid cells, highly expressed in DCs, Mo, Ma and N	PA, PC, PE, PG, PI, PS, CL, SF, SM, APOA1, APOA2, APOB, APOE, APOJ, LDL, HDL, VLDL, Lp(a), HSP60		Modulates cell differentiation, survival, phagocytosis, chemotaxis	
CLRs					
Dectin-1	DC, Mo, Ma, N, mast cells, T and B-cell	N-glycans	β-Glucan	Promotes IRF5-dependent gene expression	Tyrosine kinase-dependent and non-tyrosine kinase dependent pathways
Dectin-2			α-Mannan		
MINCLE	Mo, Ma, DCs, N and B cells	Sin3A-associated protein 130, β-glucosylceramide		Promotes pro-inflammatory cytokine production	
DNGR1	Mainly in DCs	F-actin		Promotes DC antigen crosspresentation, inhibits IL-10 production	
GPCRs					
FPR1	Ubiquitous, high in N, Mo and Ma	N-formylated peptides, cathepsin G, FAM19A4, annexin 1		Promotes chemotaxis of N and Mo/Ma, induces SIRS	
FPR2	Ubiquitous, high in N, Mo and Ma	Aβ42, SAA, oxLDL, LL-37 and other peptides		Promotes chemotaxis of N and Mo/Ma	

Table 3.1 (continued)

PRRs	Cell distribution	PAMPs	DAMPs	Pro-inflammatory functions	Signaling pathways
P2Y2R	Ubiquitous, high in epithelial cells, N, DCs, Mo and Ma	ATP, UTP		Promotes migration and activation of various immune cells	
P2Y6R	Ubiquitous, high in stromal cells, N, Mo, Ma and T cells	UDP		Promotes proliferation and cytokine and chemokine production in stromal cells	
P2Y12R	Mainly in platelets, also in DCs, Mo, Ma and T cells	ADP		Promotes platelet activation and Th17 differentiation	
CaSR	Ubiquitously expressed	Ca2+		Promotes monocyte/ macrophage recruitment and NLRP3 activation	
GPRC6A	Ubiquitous	Ca2+		Promotes NLRP3 activation	
PAFr	Ubiquitous, high in epithelial cells, endothelial cells, CM and astrocytes; Ma and DC	Phosphorylcholine-containing bacterial components		Induces severe pathophysiology and loss of contractility in heart	
Ion channels					
TRPM2	Ubiquitous	ROS		Promotes chemokine production and NLRP3 activation	
Other TRPs	Ubiquitous	ROS		Promotes the production of inflammatory neuropeptides	
P2X7R	Ubiquitous	ATP		Promotes cytokine and chemokine production, NLRP3 inflammasome activation and T cell activation	

Aβ β amyloid, *NLRs* Nucleotide binding oligomerization domain-like receptors, *RLRs* RIG-I-like receptors, *IEC* intestinal epithelial cell, *Dcs* dentritical cells, *CDSs* cytosolic DNA sensors, *cGAS* cyclic GMP–AMP synthase, *PAFr* platelet activating factor receptor, *Mo* monocytes, *Ma* macrophages, *N* neutrophils, *AIM2* absent in melanoma 2, *GPCR* G-protein-coupled receptor, *HMGB1* high-mobility group box 1 protein, *HSPs* heat shock proteins, *oxLDL* oxidized lowdensity lipoprotein, *oxPAPC* oxidized 1-palmitoyl-2-arachidonylsn-glycero-3-phosphocholine, *P2X7R* P2X7 receptor, *P2Y2R* P2Y2 receptor, *PA* phosphatidic acid, *PC* phosphatidylcholine, *PE* phosphatidylethanolamine, *PG* phosphatidylglycerol, *PGLYRP1* peptidoglycan recognition protein 1, *PI* phosphatidylinositol, *PS* phosphatidylserine, *RAGE* receptor for advanced glycation end products, *RIG-I* retinoic acid inducible gene I, *RLRs* RIG-I-like receptors, *FPR1* N-formyl peptide receptor 1, *HSPs* heat shock proteins, *IFN-I* type I interferons, *SAA* serum amyloid A, *SF* sulfatide, *SIRS* systemic inflammatory response syndrome, *TREM1* triggering receptors expressed on myeloid cells 1, *TRPs* transient receptor potentials, *CM* cardiomyocytes

3.2.1 Membrane-Bound TLRs

As one of the earliest PRRs discovered in immune system, Toll-like receptors (TLRs) have numerous family members and are essential in inflammatory responses. Up to date, at least 15 TLRs have been found and identified in mammalian and constitute a big family, of them 12 being mouse TLRs (TLR1–TLR9, TLR11–TLR13), 10 being human TLRs (TLR1–TLR10), and additional 2 discovered recently, respectively, TLR14 in fish species and chicken specific TLR15 [3–5]. PRRs are widely expressed on the cell membrane (TLR1–2, TLR4–6 and TLR10), intracellular compartment membranes (TLR3, TLR7–9) and distributed in the cytoplasm [6].

TLRs consist of three parts, a N-terminal domain (NTD), which located outside the membrane (ligand recognition domain), a middle single helix transmembrane domain, and a C-terminal domain (CTD) towards the cytoplasm (effector domain), respectively [7]. Ligand recognition domain is extracellular region which have leucine-rich repeats (LRRs) in charge of the pattern recognition of Toll/IL-1R (TIR) domain same as IL-1R and TLRs related with signal transduction (Fig. 3.1). Extracellular region specifically recognizes ligands. Once TLRs recognizing and binding with corresponding PAMPs or DAMPs ligands, TIR domain transform signal to cytoplasmic region and results in sequential inflammation in myeloid differentiation factor 88 (MyD88)-dependent and MyD88-independent pathways (including TIR domain-containing adaptor inducing IFN-β (TRIF), TRIF-related adaptor molecule (TRAM), B-cell adaptor for phosphoinositide (BCAP), and Sterile α- and armadillo-motif-containing protein (SARM)) (Fig. 3.2).

3.2.2 TLR1–2 and TLR6

TLR2 recognizes various microbial components including Gram-positive bacteria's peptidoglycan, lipoproteins/lipopeptides and lipoteichoic acid, mycobacteria's lipoarabinomannan, Trypanosoma cruzi's glycosylphosphatidylinositol anchors, Staphylococcus epidermis's phenol-soluble modulin, fungi's zymosan and Treponema maltophilum's glycolipids and also LPS. This phenomenon may arise from the heterophilic dimerization of TLR2 with TLR1/6 and others, which are functionally linked to TLR2. In addition, TLR2 functionally cooperates with dectin-1 that recognize the fungal cell wall component b-glucan.

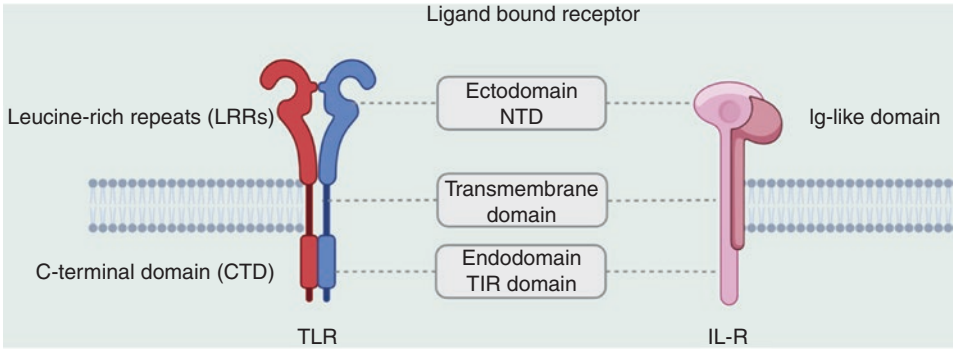

Fig. 3.1 Similar structural features of TLR and IL-R

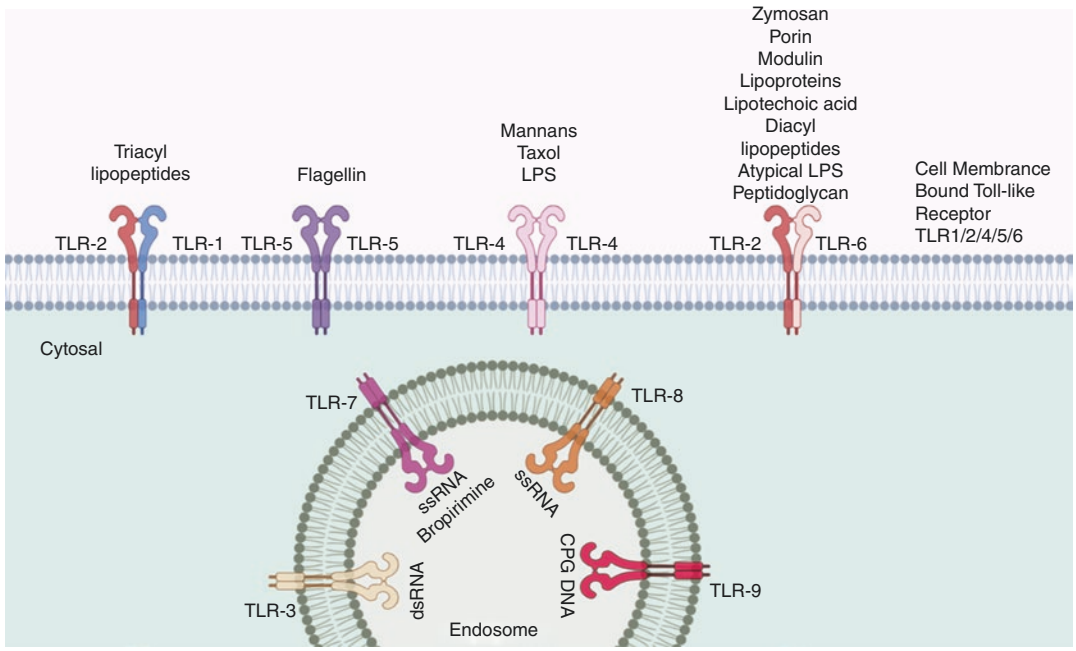

Fig. 3.2 Distribution of TLRs in the cell membrane and endosomal compartments, and detection of various PAMPs by TLRs

3.2.3 TLR4

It is well known that TLR4 is vital for LPS recognition, which is a classic example. TLR4 is also responsible for recognizing DAMPs, endogenous ligands, including the extra domain A of fibronectins, heat shock proteins (HSP60 and HSP70), heparan sulfate, oligosaccharides of hyaluronic acid and fibrinogen which, however, requires very high concentration [8].

3.2.4 TLR5

TLR5 is also located in cell membrane and it expresses in both immune cells and tissue cells (on the basolateral of intestinal epithelium, and subepithelial compartment of intestinal endothelial cells) [9, 10]. TLR5 can recognize flagellin by the interaction of TLR5 and flagellin. Because of its expression location, it can fight microbes via flagellin and dsRNA sensing and stimulation production of proinflammatory cytokines and interferons at the mucosal surface.

3.2.5 TLR3 and TLR7-9

TLR3 and TLR7-9 are known as nucleic acid-sensing TLRs. Because they are located in the endosomal compartment, and host-derived single strand RNAs are generally not delivered to endosomes, they are not aberrantly activated by self-nucleic acids. However, in some cases TLRs are nevertheless activated by internalized self-nucleic acids. TLR3 exists in cytoplasm and responds to double-stranded RNA and then induces cytokine production through a signaling pathway dependent on MyD88 [11]. TLR7/TLR8 recognize the same ligands in some cases, probably because

they are highly conserved in structure [9]. Recent studies suggest that TLR7/TLR8 can recognize single-stranded RNA of viruses (including human immunodeficiency virus, and influenza virus). While TLR9 recognize CpG DNA no matter bacterial CpG DNA or viral-derived CpG DNA. A/D-type and B/K-type are the two major types of CpG DNA. B/K-type CpG DNA induces the release of IL-12 and TNF-α, and other inflammatory cytokines [9]. While A/D-type CpG DNA can effectively induce plasmacytoid dendritic cells to produce IFN-α.

3.2.6 TLR10

As one of the least-known members of TLR family, the TLR10 gene was first cloned 20 years ago [12]. TLR10 is mainly distributed in immune cells including spleen, lymph nodes, thymus, tonsils and lungs, among which the highest expression is in B cells, followed by plasmacytoid dendritic cells. TLR10 also expresses in tissue cells, such as gastric mucosal tissues, cancer cells, TLR10 can recognize dsRNA and recruit MyD88 for signal transduction. In addition, it suppresses the production of type I interferon. Additionally, TLR10 can serve as co-receptor of many other TLRs, for example, it can work together with TLR2/TLR4 to recognize LPS and with TLR2/TLR6 to recognize synthetic diacylated lipoprotein (FSL-1).

3.2.7 NLRs

NLRs belong to intracellular PRRs, a large family of intracellular sensors that investigate the presence of PAMPs and DAMPs in the cytoplasm. NLRs are composed of three domains: (1) the central nucleotide-binding domain (NBD) that is critical in nucleic acid binding and oligomerization of NLRs; (2) the LRR of C-terminus for ligand recognition, and (3) an N-terminal effector domain comprising the caspase activation and recruitment domain and other protein interaction domain [3]. There are five subfamilies of NLRs: the NLRC subfamily, the NLRP subfamily, the NLRB subfamily; the NLRA subfamily; and NLRX subfamily [3, 7, 13]. After NLR oligomerization, pro-caspase-1 is recruited directly or via apoptosis-associated speck-like protein, and promoting the formation of inflammasome [13].

3.2.8 NLRP3 Inflammasome

The NLRP3 inflammasome is activated by a variety of molecules including microbial molecules, environmental stimuli, and many metabolites. The NLRs sense a common intracellular molecule. Many endogenous molecules have been linked mitochondrial damage to NLRP3 inflammasome activation, which recruit NLRP3 and trigger inflammasome. Ion fluctuations may involve NLRP3 inflammasome activation. Thus, the NLRP3 inflammasome is critical in various acute and chronic diseases.

3.2.9 RLRs

As a kind of intracellular PRRs, RLRs has three main members, melanoma differentiation-associated gene 5 (MDA5), RIG-I, and laboratory of genetics and physiology 2 (LGP2) [1, 3, 14]. Similar to TLR7 and TLR9, RLRs have innate antiviral immunity (Fig. 3.3).

RIG-I induces the expression of IFN-β and therefore it has antiviral activity. RIG-I has three parts: the DexD/H helicase domain, RLR family domain with ATPase and helicase activities; The N-terminus with two caspase activation and recruitment domains (CARD) [15]. The C-terminus is composed of the C-terminal domain (CTD) for the recognition of viral RNA,

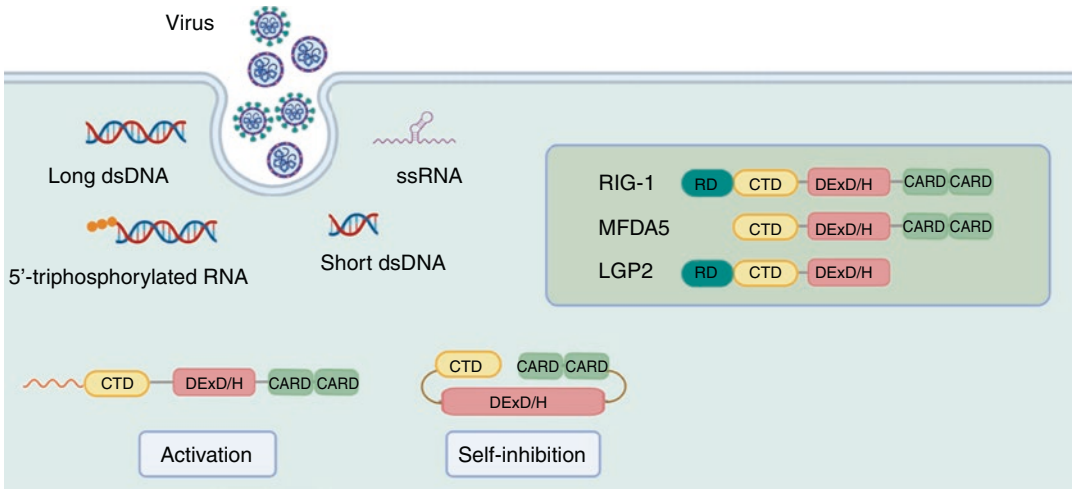

Fig. 3.3 RLRs' structure and ligand recognition. In contrast to RIG-I, MDA5 has no self-inhibitory ability due to the lack of a repressor domain. LGP2 cannot transmit signal because there is no CARD

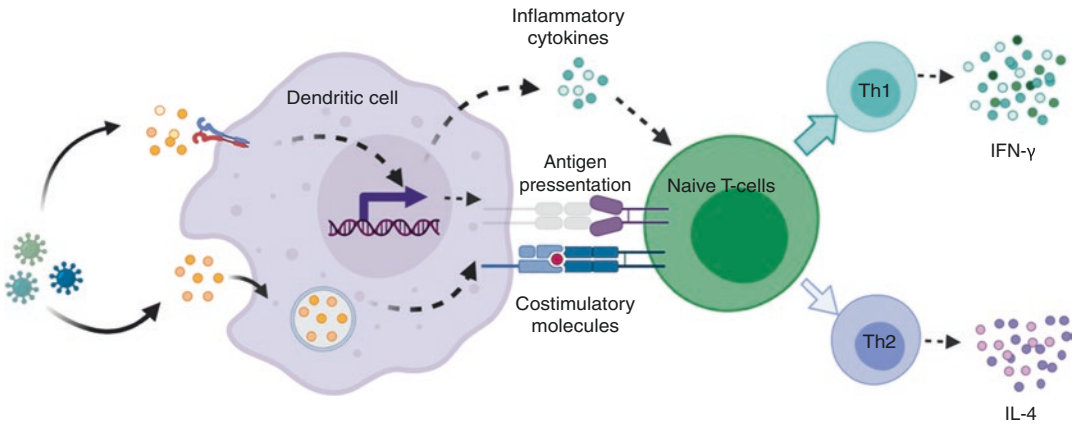

Fig. 3.4 Development of innate and adaptive immunity

and the repressor domain (RD) [3]. MDA5 is similar to RIG-I (Fig. 3.4). Very long double strand RNAs (>300 bp) can efficiently activate MDA5 regardless of the structure of the MDA5 terminus. LGP2 cannot recruit molecules due to the lack of CARD, but it plays a role in regulating the viral nucleic acid's recognition by RIG-I and MDA5 [16]. LGP2 reduces the production of IFN and inflammatory factors by negatively regulating RIG-I-mediated viral dsRNA recognition, ultimately suppressing the antiviral innate immune response.

3.2.10 Cytoplasmic DNA Sensors

Cyclic GMP-AMP synthase (cGAS) and absent in melanoma 2 (AIM2) are the two main DNA sensors, which are critical in antimicrobial immunity. Activation of cGAS or AIM2 by self-DNA resulting from cell damage induces cellular senescence, and promotes cancers and inflammation.

3.2.11 CLRs

CLRs are phagocytic PRRs that are rarely studied and understood. Once CLRs recognizing and binding PAMPs through PRRs, pathogens are eliminated by phagocytosing into cytoplasmic vesicles for digestion.

3.2.12 Non-pattern Recognition Receptors

Non-pattern recognition receptors include TREMs, RAGE, ion channels and GPCRs. They sense DAMPs and PAMPs, and therefore promotes the activation and migration of immune cells after activated.

3.2.13 RAGE

RAGE is expressed in various types of cells and tissues. RAGE can bind a series of endogenous ligands, including advanced glycation end products (AGEs), HMGB1, S100 proteins (S100s) [17]. In turn, these ligands upregulate RAGE expression, forming vicious circle. RAGE activation plays important roles in cardiovascular disease via inducing inflammation and activating NF-κB signaling.

3.2.14 PRMs

Both cellular PRRs and extracellular soluble PRMs belong to PRMs. Extracellular soluble PRMs play a key role in nonspecific humoral immunity [1, 3]. Extracellular soluble PRMs have various family members including pentraxin, collectin, and ficolin. Once the various pathogenic factors are identified, they are eliminated by complement, opsonization, and neutralization of inflammatory regulation activated by extracellular soluble PRMs; in addition, extracellular soluble PRMs interact with and regulate cell-associated PRRs to co-regulate the innate immune response. As typical representatives of pentraxin, liver-produced CRP and serum amyloid P components are nonspecific proteins in systemic inflammatory responses. They bind to phosphorylcholine and bacterial outer membrane protein A of pathogenic microorganisms. Mannose-binding lectin (MBL) is the main part of collectin, and is formed by homotrimer, of which consists of a CRD that recognize sugar structures (mannose, fucose and glucose, an alpha helix, and a backbone formed by collagen and surfactant protein (SP) helices) on the pathogen membranes. Although structurally similar to collectin, ficolin can recognize bacteria with fibrin-prototype carbohydrate recognition structures due to its binding with N-acetylglucosamine and LTA.

3.2.15 Myeloid Cells's Triggering Receptors

There are two classes of TREM, TREM1 and TREM2, both of which are innate immune membrane receptors. TREM1 is mainly distributed in bone marrow cells and non-immune cells; TREM2 is highly expressed by myeloid cell types. Activating antibodies activate TREM1 on neutrophils and monocytes, promote the release of pro-inflammatory cytokine and chemokine, and enhance inflammatory responses. Intracellular proteins, including HMGB1, peptidoglycan recognition protein 1 (PGLYRP1), HSP70, and extracellular actin, are its ligands. A number of endogenous lipids and lipoproteins that bind to and activate TREM2 have been identified, although further identification is required.

3.2.16 G-Protein-Coupled Receptors

N-formyl peptide receptors (FPRs) and P2Y receptors (P2YRs) belonging to GPCRs, bind to various endogenous DAMPs and exogenous PAMPs to promote inflammation. FPR is widely distributed, and in addition to being expressed in leukocytes [18], it is also expressed in a variety of non-immune cells, including hepatocytes, and fibroblasts. Formylated peptides belong to both PAMPs and DAMPs. FPR has many ligands that are structurally and chemically unrelated. Activation of FPR by these ligands elicits distinct cellular responses. Serum amyloid A (SAA) and oxidized LDL participate in the pathogenesis of chronic inflammatory diseases by binding to FPR. Nucleotides such as ATP and UTP released into the extracellular space through necrosis and apoptosis bind to P2 purinergic receptors to trigger pro-inflammatory immune responses. P2Y2R signaling promotes the activation of a variety of immune cells. UDP activates the stromal cell's P2Y6R signaling, whereas ADP-mediated activation of P2Y12R is critically involved in platelet activation and aggregation. P2X7R with seven members promotes immune responses in a number of ways.

3.2.17 Actions of PRRs

PRRs bind their ligands and act through various ways. They can co-act and have crosstalk between receptors.

3.2.18 Phagocytosis and TLRs

The first step in defensing against microorganisms is phagocytosis [9]. Once pathogens are recognized by TLRs, the expression of inflammatory molecules are enhanced, thereby promoting the development of adaptive immunity (Fig. 3.4). After binding to TLRs, pathogens are recognized and devoured by innate immune cells, and then antigenic peptides are presented to naive T cells. Simultaneously binding of antigen to TLRs induces inflammatory cytokines and costimulatory molecules, Naïve T-cells, including Th1 cells are guided to produce adaptive immunity.

3.2.19 TLR Signaling Pathways

The TLR signaling pathway includes a variety of molecules (protein kinases, transcription factors, etc.), all of which converge on canonical signaling pathways.

The NF-kB Signaling: NF-κB, which is composed of p50 and p65, is critically involved in cellular inflammation and immune responses. After TLRs recognize and receive stimulation of antigens, they trigger the expression of proteins in TLR-mediated signaling pathways [9]. The dimerization of TLRs which is formed via TLR1 or TLR6, as well as homodimers is necessary for the recognition of microorganisms. The cytoplasmic TIR domain of dimerized TLRs recruit MyD88, which then induces inflammatory cytokines, such as TNF-α and IL-12 [9]. MyD88 is essential for all TLRs. Different activation of TLRs may results in different profiles. Activation of TLR3-4 and TLR7-9 signaling pathways lead to induction of type I interferon (IFN) in distinct mechanisms, but not TLR2 and TLR5 mediated pathways.

MyD88-dependent signaling pathway plays a key role in TLR1-2 and TLR4, TLR6 signaling. Upon stimulation, IRAK-4, TRIF, TIRAP, and TRAM are recruited to TLRs by MyD88, which subsequently promote nuclear factor κB (NF-κB) and MAPK activation through the IRAK complex and two non-catalytic subunits, and ultimately lead to the production of tumor necrosis factor (TNF), IL-6, IL-1, chemokines and other pro-inflammatory cytokines [9, 19].

MAPKs are a class of serine-threonine protein kinases that respond to a variety of extracellular stimuli. MAPKs are activated by IRAK-1 in a MyD88-dependent pathway of TLRs, activated p38 MAPK leads to the secretion of pro-inflammatory molecules [3].

The TBK1–IRF-3 signaling: IRF-3 is a transcription factor and is critically involved in the

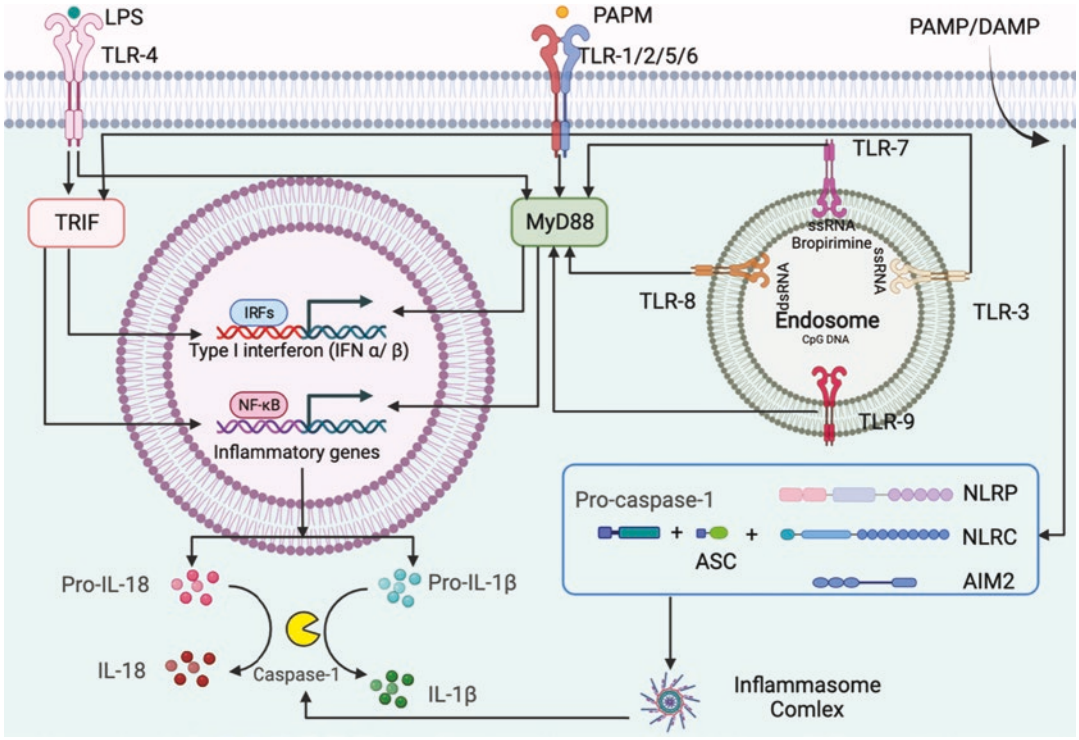

Fig. 3.5 PRR-mediated inflammasome signaling and signal transduction

synthesis of type I IFN. TRIF is the adaptor protein in the MyD88-independent pathway, and promotes the expression of type I interferon, and therefore exerts antiviral effect.

In addition, there is an inflammasome signaling. Inflammasome is a multi-protein complex in the cytoplasm assembled by PRRs. NLRP1, NLRP3, NLRC4, IPAF inflammasome, and AIM2 are inflammasome. After recognition of PAMPs or DAMPs by inflammasome, Caspase-1 is recruited and activated. Then proIL-1β/proIL-18 is spliced into mature cytokines by activated Caspase-1 (Fig. 3.5).

3.3 Pyroptosis and its Pathway

Pyroptosis, Pyroptotic cell death, is controlled by the inflammatory caspases. Caspase 1 is pro-inflammatory and is linked with the secretion of mature IL-1β and IL-18 [20]. Pyroptosis was originally defined as "caspase 1-dependent necrosis" due to its strict requirements for caspase 1 [21]. Further, the inflammasome complex and the non-canonical inflammasome pathway were discovered in 2002 and 2011, respectively. They were identified in pyroptosis in inflammasome-dependent form. After those, there are many advances and importantly it was found that various members of gasdermin family play key roles in pyroptosis processing. Therefore, pyroptosis need redefinition. More recently, it was defined as "gasdermin-induced cell necrosis," a new definition that applies to all gasdermin members that may lead to cell death.

Gasdermin family at least include five classes of members, gasdermin A, B, C, D and E. These gasdermin proteins all involve pyroptosis through pore formation role in cell membrane. Each gasdermin protein has conserved amino- terminal domain (NTD) which has membrane-forming activity, and carboxy-terminal domains. In the quiescent state, the gasdermin protein maintains itself in an autoinhibitory state by binding of NTD with the carboxy-terminal domain (CTD) [22]. However, the aspartic acid residue of

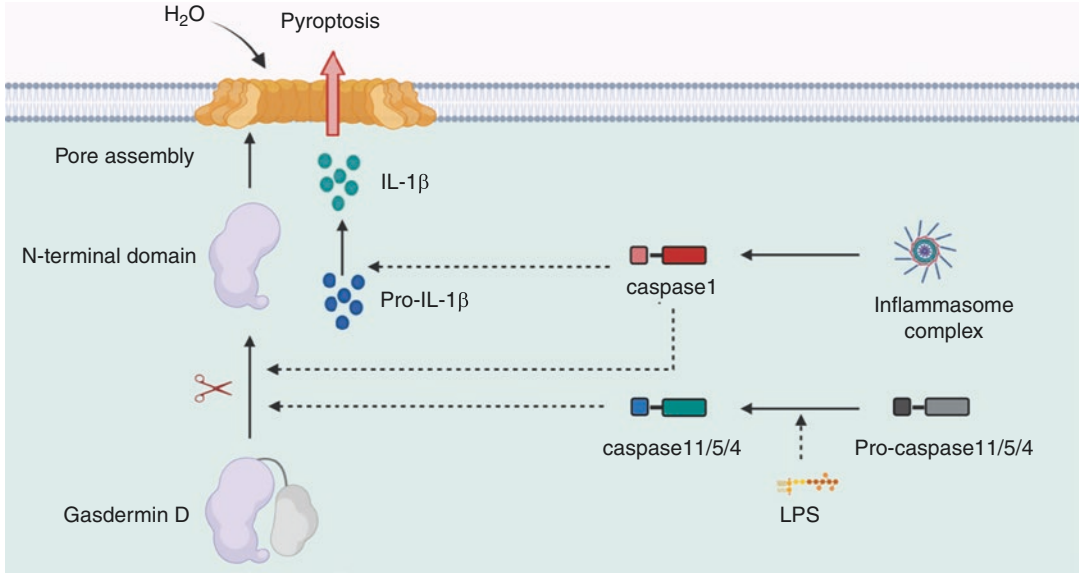

Fig. 3.6 Gasdermin D mechanism to pyroptosis

GSDMD in the linker between NTD and CTD can be recognized and cleaved by activated caspase-1, caspase-4, caspase-5 and caspase-11, and the cleaved NTD is in non-covalent binding state. Due to its high affinity for membrane phospholipids, the NTD of GSDMD translocate to the plasma membrane, induces pyroptotic bubble formation and membrane lysis. Therefore, membrane lysis induced by GSDMD is the final step in LPS-induced pyroptosis mediated by caspase-11, caspase-4 and caspase-5. In fact, NTD of other gasdermins has similar lipid-binding properties and induces intracellular pyroptosis. Following figure shows mechanisms of gasdermin activation and pore formation and pyroptosis occurs [21] (Fig. 3.6).

Gasdermins express in different tissues including the organs in digestive, respiratory, urinary, reproductive, circulatory systems and other tissues. Especially, we note that the heart and artery have expression. Recently, some studies found that in mice with coxsackievirus B3 induced myocarditis, heart levels of GSDMD p30 and IL-1β and HMGB1 were elevated and the inhibition of pyroptosis signaling attenuated myocarditis, which suggest that pyroptosis involves in pathophysiology of myocarditis [23, 24]. Therefore, we have reason to believe, pyroptosis play a vital role in part in fulminant myocarditis.

3.3.1 Expression of PRRs and Responses to Ligands in Heart

Human and mammal heart express almost all PRRs and after the stimulation of ligands the expression of PRRS in whole heart and cardiomyocytes is dramatically upregulated. S. aureus peptidoglycan, E. coli LPS and S. typhimurium flagellin induced chemokine KC production by activating TLR2, TLR4 and TLR5. The IL-6 and MIP2 production mediated by LPS and lagellin, respectively, both significantly reduced by pyrrolidine dithiocarbamate (PDTC), a chemical inhibitor of NF-κB. These indicate that TLRs promotes the expression of proinflammatory cytokines, chemokines and cell surface adhesion molecules by NF-κB signaling [25].

Although the most types of PRRs express in different tissues and cell types in human, their expression patterns are different and different PAMPs and DAMPs or ligands have different tar-

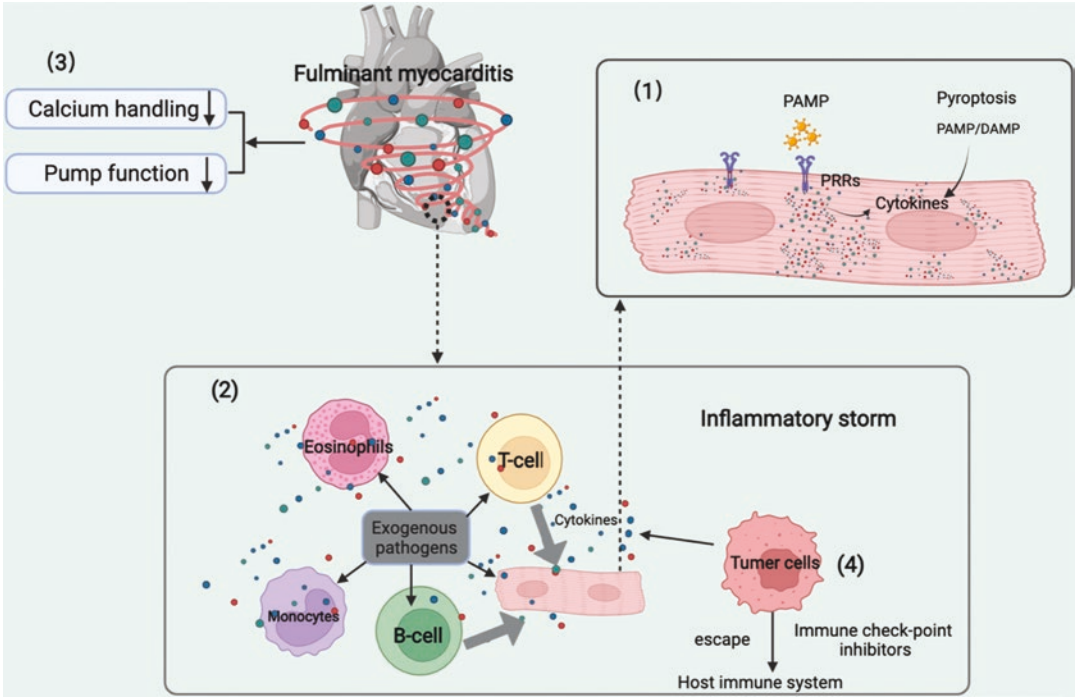

Fig. 3.7 Development of fulminant myocarditis

get PRRs. On the other hand, same PRRs in different cells may have different response to same ligand because some cell may be refractory to some special ligand stimulation, such as platelet-activating factor receptor (PAFr), one of GPCRs, express in cardiomyocytes, endothelial cells and neurons. However, after exposure to phosphocholine-containing bacterial components, three types of cells uptake in a PAFr-dependent manner, but with different pathophysiological consequences. Non-inflammatory manifestations appear in endothelial cells and neurons, while cardiomyocytes rapidly lose contractility and die, because endothelial cells and neurons are refractory to the phosphorylcholine-containing bacterial components and there is no classic-type NF-B response [26]. Therefore, we can meet fulminant myocarditis, fulminant pancreatic, fulminant type I diabetes, fulminant hepatitis and others after exposed to different pathogens and injury in clinic, which may have same or similar pathogenesis and pathophysiological mechanisms.

Finally, we try to raise the proposals for fulminant myocarditis based on our some experiments and clinical practice (Fig. 3.7) [27, 28, 21]. (1) exogenous pathogens, either infection of virus, bacteria, fungus or other microbe, chemicals including proteins, nucleus acids, antibiotics, allopurinol and others such as seafood, or some vaccination, enter the body, as antigens or ligands susceptible to cardiomyocytes, bind to PRRs on cardiomyocytes, either TLRs or others, membrane PRRS or cytoplasm PRRs, sequentially triggering downstream signaling, especially NF-kB pathway. Thus, inflammatory storm form. Importantly, these PAMPs successively or simultaneously activate innate immune cells, monocytes, lymphocytes, neutrophils, eosinophils, and then together with cardiomyocytes produce inflammatory storm; (2) These reactions also induce adaptive immune response, including production of anti-myocardial antibodies by B-lymphocytes and direct attack to heart by toxic T-cells; (3) PAMPs and DAMPs induce pyroptosis and their consequence results in proinflamat-

tory storm. These inflammatory factors can strongly stun the heart, inhibiting calcium handling and pump function; (4) Immune checkpoint inhibitors induced fulminant myocarditis: Programmed cell death protein 1 (PD-1)-mediated and cytotoxic T-lymphocyte antigen 4 (CTLA4)-mediated pathways, and immune checkpoint pathways, are activated by tumor cells to evade recognition by the immune system [23, 29, 30]. Immune check-point inhibitors activate the antitumour immune of T-cells via targeting the molecules of these pathways. However, T-cells targeted antigen may be shared with tumors, heart and muscles and thus, the activated T-cells will attack heart and induce fulminant myocarditis. Additionally, immune check-point inhibitors can activation of cardiac antigen-reactive T cells block antigen-presenting cells.

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4 Etiology and Pathogenesis of Fulminant Myocarditis

Chen Chen and Dao Wen Wang

4.1 Etiology of Fulminant Myocarditis

The etiology of fulminant myocarditis (FM) is similar to that of acute and non-fulminant myocarditis, which includes infectious and non-infectious factors (Table 4.1).

4.1.1 Infectious Factors

Viral infection is the main cause of myocarditis; 1–5% patients with acute viral infection may have symptoms of myocarditis [1]. However, due to the limitations of detection technology and difficulties in the acquisition of samples, only 10–20% patients with viral myocarditis test positive on the myocardial tissue virology test. In a prospective clinical study containing more than 670,000 Finnish men, a total of 98 patients were clinically diagnosed with myocarditis during a 20-year period, and only 4% tested positive for coxsackievirus [1].

In the 1980s and 1990s, it was difficult to isolate and culture infected virus strains from the heart tissue of patients with myocarditis. Through serological examination, enterovirus (including coxsackievirus) and adenovirus have been associated with myocarditis based on the co-occurrence of increased virus titers and acute heart failure performance [2]. With the rapid development of molecular biology techniques, the detection methods of various viruses have constantly improved. Case reports and series have associated myocarditis with more than 20 viruses, including parvovirus and human herpesvirus (HHV) (Fig. 4.1) [3]. Some studies have indicated that enterovirus was the only virus type detected in the hearts of French patients with myocarditis, while several studies have shown that mostly parvovirus B19 (PVB19) and human herpesvirus type 6 (HHV6) only are detected in the hearts of German patients, and coxsackievirus is rarely found [4, 5]. In the United States, adenovirus and enterovirus were the most common pathogenic viruses reported in 2003, while parvovirus was the major pathogenic virus reported in 2010 [6, 7].Currently, it is unclear whether the etiology of myocarditis is regional or epidemic; these differences in the detected virus types may be caused by the diverse epidemic spectrum, the non-specificity of primers and antibodies used for virus detection, different detection schemes, and the limited sample size [3]. Currently, the Center for Disease Control and Prevention (CDC) in several countries is observing the correlation between the outbreak cycle and the region of viral

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Table 4.1 Possible etiology of myocarditis

Infectious factors	
Viruses	Adenovirus, enteroviruses (such as coxsackievirus and poliovirus), arboviruses, cytomegaloviruses, dengue viruses, echoviruses, Epstein-Barr virus, hepatitis C virus, herpes virus, human immunodeficiency virus, influenza virus, coronavirus, mumps virus, parvovirus, rabies virus, rubella virus, varicella virus, varicella zoster virus, hemorrhagic fever virus, yellow fever virus
Bacteria	Brucella, cholera, *clostridium*, *Corynebacterium diphtheriae*, *haemophilus*, *legionella*, *meningococcus*, *Neisseria gonorrhoeae*, *salmonella*, *staphylococcus*, *clostridium tetani*, *tuberculosis*, *Francisella tularensis*
Spirochete	*Leptospira*, Lyme disease spirochete, relapsing fever spirochete, *treponema pallidum*
Fungi	*Actinomycetes*, *aspergillus*, *Blastomyces, Candida*, *Coccidioides*, *cryptococcus*, *histoplasma*, *mucor*, *nocardia*, *Sporothrix*
Rickettsia	Rickettsia burneti, Rickettsiatyphi, rickettsia Prowazeki, rickettsia Mooseri
Protozoa	Trypanosoma, Ameba, Trypanosoma cruzi, leishmania spp., plasmodial, toxoplasma gondii
Helminth	*Ascariasis*, *echinococcosis*, filariasis, *paragonimiasis*, *schistosomiasis*, *strongyloidiasis*, *trichinosis*
Other	*Mycoplasma*
Noninfectious factors	
Systemic diseases	Celiac disease, connective tissue disease, Wegener granuloma disease, Kawasaki disease, eosinophilia, sarcoidosis, thyrotoxicosis
Hypersensitivity	Antibiotics, clozapine, diuretics, insect bites, lithium, snakebite, tetanus toxoid, mesalazine
Cardiotoxic substance	Alcohol, anthracyclines, arsenic, carbon monoxide, catecholamines, cocaine, heavy metals

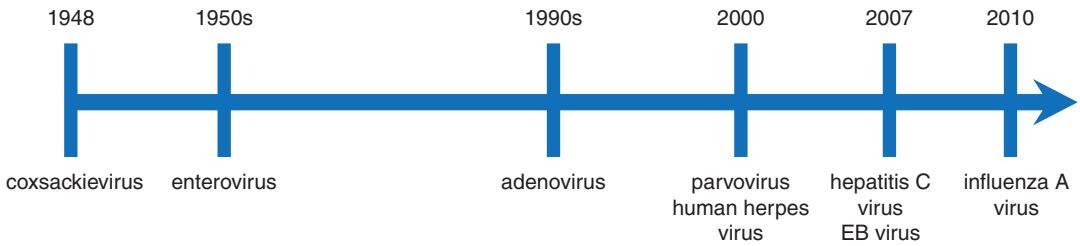

Fig. 4.1 Evolution of major viral causes of myocarditis over time

myocarditis and other viral diseases. In 2006, a Japanese retrospective study found that the detection rate of hepatitis C virus (HCV) in the hearts of 1355 patients with myocarditis was 4.4% [8]. In 2010, influenza A virus was detected for the first time in the hearts of patients with viral myocarditis in the United States at a rate of approximately 10%; the rate in the hearts of patients with FM was approximately 5% [9]. A recent study used nested polymerase chain reaction (PCR) to detect the virus genome (including enterovirus, PVB19, adenovirus, cytomegalovirus, Epstein-Barr virus, and HHV6) in the myocardium of 27 patients with FM from 16 medical centers in the United States, Europe, and Japan. Consequently, PVB19 was only detected in five (18.5%) samples [10]. Recently, Heidecker et al. examined peripheral blood and myocardial tissue samples from 33 patients with myocarditis using virome capture sequencing and identified the following viruses: EB virus, hepatitis G virus, human endogenous retrovirus K, and anaerobic virus. Among them, human endogenous retrovirus K was detected in all the blood and tissue samples from two FM and 13 giant cell myocarditis samples [11]. Cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced FM have also been reported in the recent outbreak of the coronavirus disease (COVID-19) pandemic [12].

These studies have provided partial evidence for the etiology and epidemiological characteristics of viral myocarditis, suggesting that the clinical symptoms of myocarditis caused by different virus types may be heterogeneous. It is important to enhance the understanding of virology, immunology, pathology, and clinical medicine in myocarditis.

4.1.1.1 Enterovirus

Enterovirus, especially coxsackievirus B3 (CVB3), is the primary pathogen of myocarditis. Enteroviruses belong to Picornaviridae, a family of single-strand RNA viruses containing 10 enteroviruses and three rhinoviruses (Fig. 4.2). These viruses are widely distributed and highly pathogenic; they are the causative pathogens of several serious diseases widely prevalent in vertebrates, including humans. Infection with these viruses can lead to either temporary organ dysfunction, persistent irreversible organ function damage, or even death. Enteroviruses are the causes of severe diseases, such as polio, aseptic meningitis, enteroviral encephalitis, and enteroviral vesicular stomatitis, as well as the common cold. Enteroviruses can spread easily from person to person through airway and fecal-oral routes, and infection can also occur by touching items contaminated with enteroviruses. The peak incidence of enterovirus infection occurs mostly in summer. Due to the long asymptomatic incubation period for enterovirus, outbreaks can occur suddenly and are difficult to prevent. Currently, there is no effective drug specific for enterovirus, and treatment is still focused on symptomatic support and symptom control [13].

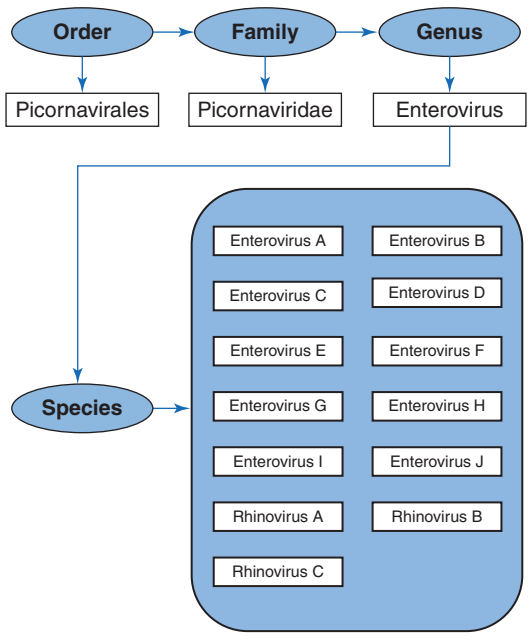

Fig. 4.2 Virological classification of enteroviruses

1. Etiological characteristics: Enterovirus viruses have a single-stranded RNA genome, 15–30 nm icosahedral spherical capsid, and no envelope. When a virus infects a host cell, it first binds to receptors on the cell surface (mainly integrins and immunoglobulin-like proteins) and penetrates the cell membrane. When the virus enters the host cell, viral RNA molecules are released from the capsid to synthesize viral proteins and promote viral replication, which ultimately leads to the death of the host cell. Subsequently, the virus is released from the cytoplasm and can continue to infect other cells [14].

   Enterovirus has a highly recessive infection rate and strong resistance to physical and chemical factors. It can survive for several days at room temperature and can be preserved for a long time at −20 °C. Enterovirus is resistant to ether, acid (pH 3–5), and bile. It can survive in sewage and feces for several weeks, but it is sensitive to heat, drying, and ultraviolet light. It can be inactivated after 30 minutes of treatment at 56 °C. Various oxidants such as potassium permanganate and hydrogen peroxide solution (hydrogen peroxide) can play a role in disinfection. Enterovirus can replicate rapidly and cause pathophysiological changes in host cells within 2–7 days after colonization in suitable host cells.
2. Epidemiology Enteroviruses are transmitted via the fecal–oral route or the respiratory tract. Once infected, enteroviruses can continuously exist in respiratory secretions and feces of patients for 1–3 and 2–8 weeks, respectively.

Enteroviruses are widespread globally. A total of 71 serotypes of enteroviruses have been identified using neutralizing antibodies. The main virus serotypes circulating in various regions are constantly changing, and infection rates far exceed the number of clinically diagnosed cases. Data provided by the National Enterovirus Surveillance System of the CDC showed that from 1970 to 2005, 15 representative enterovirus serotypes accounted for 83.5% of all isolated enterovirus strains provided by public health laboratories at all levels in the U.S. The number of infected cases increases sharply in summer and early autumn and usually reaches its peak in August [15].

4.1.1.2 Adenovirus

Adenoviruses are double-stranded DNA viruses that generally cause mild-to-moderate respiratory and/or gastrointestinal tract infections. They can also induce hemorrhagic cystitis, hepatitis, hemorrhagic colitis, pancreatitis, nephritis, or meningoencephalitis in rare cases. Epidemic adenovirus infection is more likely to occur in children or relatively closed populations, such as individuals in the military. Children are more susceptible to adenovirus because of their underdeveloped humoral immunity. Immunocompromised populations (such as patients undergoing organ transplant and people with HIV) are more susceptible to adenovirus and tend to have more severe symptoms. The mortality rate of severe pneumonia or other organ damage caused by adenoviruses exceeds 50%. At present, more than 50 different serotypes of adenovirus have been discovered. The tissue susceptibility and clinical symptoms induced by different adenovirus serotypes are not entirely similar. The serotypes prevalent in different periods may differ, and the serotypes prevalent in different countries and regions may also vary in the same period. Serotypes 2 and 5 tend to invade the myocardium and cause myocarditis. Due to the lack of prospective randomized controlled clinical trials, the specific treatment regimen for adenovirus infection is controversial. Cidofovir is recommended for the treatment of patients with severe adenovirus infection, but it is not suitable for all patients. The live oral vaccine, which is effective in reducing respiratory adenovirus infections, is routinely used in the US military, but it has not been popularized in the general population [16].

1. **Etiological Characteristics** Human adenoviruses are a group of non-enveloped double-stranded DNA viruses belonging to the mammalian adenoviruses of Adenoviridae. They are icosahedral, 10–100 nm in diameter, and contain seven viruses (HADV-A to HadV-G), the first six of which have caused global outbreaks of human epidemic infections. Fifty-one serotypes (numbered 1–51) have been identified, and more than 70 adenovirus genotypes (including those numbered 52, 53, 54) have been predicted by bioinformatics comparison. Nearly 20 serotypes of adenovirus are pathogenic in humans. Patients and persons with recessive infection are the primary sources of adenovirus, which can be transmitted through the respiratory tract, the fecal–oral route, and contact with contaminated tissues or the blood. The latent period varies among different serotype-induced infections. Adenoviruses can resist various disinfectants, but they are sensitive to 95% ethanol [17].
2. **Epidemiology** Adenoviruses cause epidemics of respiratory diseases, conjunctival pharyngeal fever, keratitis, and gastrointestinal diseases, with a self-limited course in most patients. Severe adenovirus infection occurs most frequently in immunocompromised patients and is rare in individuals with normal immunity. Adenovirus infection can occur round the year without apparent seasonality, but the epidemic period is mostly in winter or early spring. The main route of infection is contact with exposed people and infected objects, including respiratory transmission, conjunctival contact, and the fecal–oral route. The incubation period for adenovirus ranges from 2 days to 2 weeks, and asymptomatic adenovirus carriers can carry the virus for months. Importantly adenoviruses can be dormant for years in other tissues, such as lymphoid tissue and renal parenchyma, and can be reactivated when the host is severely immunosuppressed. Adenovirus can easily spread in closed environments, such as hospi-

tals, public swimming pools, childcare institutions, boarding schools, and long-term care centers [18].

4.1.1.3 Parvovirus

Parvovirus is a non-enveloped virus with a diameter of less than 25 nm and has a linear single-stranded DNA genome of 5–6 kb with hairpins at both ends. Adeno-associated virus (AAV) was the first parvovirus discovered to infect humans, but it is not pathogenic. Subsequently, two kinds of pathogenic parvovirus were discovered—human PVB19 and human Bocavirus (HBoV) 1. PVB19 is highly pathogenic and can induce a series of diseases, including infectious erythema, regenerative disorder crisis in patients with chronic hemolytic anemia, chronic anemia in patients with immunosuppression, pregnancy abortion, stillbirth, and joint disease. Patients with latent infection can carry the virus for a long time without any symptoms. Studies have reported that PVB19 infection is closely associated with acute and chronic myocarditis, and patients with partial dilated cardiomyopathy have higher PVB19 virus titer in the myocardium than healthy person [19]. Other researchers have observed increased neovascularization around inflammatory cells in the hearts of patients with FM caused by PVB19 [20]. HBoV1 infection is an important cause of acute respiratory tract infection, and wheezing is the most common symptom of HBoV1 infection. The clinical significance of other parvovirus infections such as parvovirus 4 (PARV4), HBoV2, HBoV3, and HBoV4 is unclear. Currently, there is no vaccine or specific antiviral drug for parvovirus [21].

1. **Etiological characteristics:** The capsid of parvovirus has icosahedral symmetry with two capsid proteins, VP1 and VP2, of which the is located outside the shell and easily binds to antibodies. In general, PVB19 is particularly cytotropic to human erythrocytes and can grow in fresh human bone marrow cells, peripheral blood cells, fetal liver cells, erythroleukemia cells, and umbilical cord blood cells. However, PVB19 can invade endothelial cells in myocarditis and dilated cardiomyopathy. PVB19 is heat resistant and can survive for 30 minutes at 56 °C [22].
2. **Epidemiology:** Outbreaks of PVB19 infection occur mainly in winter and spring. PVB19 infection is widespread worldwide and its epidemic pattern is regional. Half of all adults have been infected with PVB19. The positive rate of PVB19 antibodies in the population increases with age—2%–20% in children aged under 5 years, 15–40% in adolescents aged 5–18 years, and 40–80% in the adult population. The virus neutralizing immunoglobulin (Ig) G is produced by organisms 2 weeks after PVB19 infection, which can effectively remove the virus from the blood and ensure lifelong resistance by inducing immune response [23–25].

PVB19 is primarily transmitted via the respiratory route, but the prodromal symptoms are mainly fever, fatigue, headache, and myalgia rather than respiratory symptoms. It is unclear how PVB19 travels through the airway epithelial barrier to the bone marrow. PVB19 can also be transmitted through the blood or from mother to child. PVB19 virus DNA can be detected in the airway when prodromal symptoms occur, suggesting a high viral titer in the patient. However, the severity of the acute phase is unrelated to viral load. With remission, the virus titer decreases rapidly and can persist for months, even years.

4.1.1.4 Human Herpes Virus

There are eight species of human herpes viruses (HHV), all belonging to Herbviridae, which can be divided into three subfamilies—α, β, and γ—by genetic analysis of their conserved structural protein gH (Table 4.2) [26]. Herpes viruses of α subfamily have a wide range of hosts. They are a kind of cytolytic viruses with a short replication cycle and fast reproduction rate, mostly lurking in sensory ganglia. The host range of β subfamily herpesviruses is relatively narrow. The infected cells grow and form giant cells. The virus can cause latent infection in lymphocytes as well as secretory glands, the kidneys, or other tissues. γ subfamily herpetic viruses mainly infect B lymphocytes and remain latent for a long time, most of which do not cause cytolytic diseases.

HHV infection can be latent for a long time and cause damage when host immunity is decreased.

Table 4.2 Classification of HHV

Subfamily	Virus	Abbreviation	Adult Infection rate
α	Herpes simplex virus 1	HSV-1	Approx 70%
α	Herpes simplex virus 2	HSV-2	Approx 30%
α	Varicella-zoster virus	VZV (HHV-3)	>95%
γ	EB virus	EBV (HHV-4)	Approx 85%
β	Human cytomegalovirus	HCMV (HHV-5)	Approx 70%
β	Human herpesvirus 6A	HHV-6A	Approx 95%
β	Human herpesvirus 6B	HHV-6B	?
β	Human herpesvirus 7	HHV-7	Approx 85%
γ	Kaposi sarcoma-associated virus	KSHV (HHV-8)	?

Note:? Unknown. approx, approximately

Seventy percent adults have been infected with HSV-1, which usually causes fever and occasionally severe encephalitis. Thirty percent adults have been infected with HSV-2, which usually causes genital herpes and occasionally severe neonatal infections. Almost all adults have been infected with VZV, which causes chickenpox and shingles, and EBV, which is the leading cause of infectious mononucleosis. EB virus can also cause Burkitt lymphoma and nasopharyngeal cancer.

HCMV is also a pathogen that cause infectious mononucleosis, and HCMV infection is an important cause of congenital deafness and intellectual disability. Persistent HCMV infection is also associated with cardiovascular diseases such as coronary heart disease. HHV-6 is a pathogen that cause myocarditis. The pathogenicity of HHV-7 has not been determined, and it may be associated with drug eruption.

Both KSHV and EBV belong to the γ subfamily. KSHV mainly infects lymphocytes of immunodeficient patients, leading to malignant diseases such as Kaposi sarcoma. It is currently the only confirmed carcinogenic human herpes virus. Recently, non-coding RNA expression profiling revealed that KSHV may also be involved in the occurrence and development of myocarditis. KSHV can encode microRNA (miRNA) to increase the susceptibility of model animals to CVB3 infection by inhibiting the body's own defense mechanisms.

1. **Etiological characteristics** Mature virions are approximately 200 nm in diameter. All herpes viruses are composed of three main structures:
   1. Spherical icosahedral stereosymmetric nucleocapsid with a diameter of 90–110 nm and a linear double-stranded DNA genome
   2. The outermost layer is the capsule with glycoprotein spikes
   3. The nucleocapsid and capsule are filled with a protein mixture

   HHV-6 has serological and genetic characteristics that differ from other herpes viruses. Its genomic DNA ranges from 160 to 170 kb, and it can be divided into two types, HHV-6A and HHV-6B, according to its antigenicity. The two types of HHV-6 have similar heritability, but different epidemiological and clinical characteristics [27]. The pathogenicity of HHV-6A is unknown, and HHV-6B can cause herpes and myocarditis in children [28].
2. **Epidemiology**: HHV-6 is widely prevalent worldwide. Most adults in Europe and America have been infected with HHV-6 [29, 30]. It is now believed that HHV-6 infection rates continue to increase between 6 and 18 months after birth due to the gradual depletion of antibodies from the mother, and then slowly decline with age.

   HHV-6 nucleic acid can often be detected in the saliva, suggesting that HHV-6 can be latent in salivary glands. Therefore, the saliva could work as a vehicle for fecal–oral infection.

4.1.2 Non-infectious Factors

Anti-tumor drug-induced myocarditis, especially FM, should not be ignored [31]. In the past 20 years, new approaches to cancer treatment have proliferated, leading to dramatic improvements in the prognosis of some cancers. However, both traditional anti-tumor drugs and various new tumor drugs can cause cardiovascular toxicity, including myocarditis [32]. Anthracyclines have been previously found to cause cardiotoxic effects such as myocarditis–pericarditis syndrome [33]. Recently, myocardial injury, especially myocarditis, caused by novel anti-tumor drugs such as immune checkpoint inhibitors (ICIs) has attracted increasing attention [34]. ICIs are antibody-targeting immune checkpoints that eliminate tumors by inhibiting the immune escape of tumor cells and enhance the immune response of T cells. It is a milestone of progress in tumor therapy in recent years and has greatly improved the prognosis of some patients with cancer. As of 2019, at least seven ICIs have been approved for marketing and many more are in development [35]. However, ICIs can also cause several immune-related adverse reactions, including colitis, dermatitis, pneumonia, and myocarditis [36].

In 2016, Johnson et al. reported two patients with ICI treatment-induced FM for the first time. Both patients presented with malignant arrhythmias and myocarditis, and pathological results suggested massive T cells and macrophages infiltrated in the myocardium [37]. According to statistics, the incidence of myocarditis caused by ICIs is approximately 1%, while programmed cell death protein 1 (PD1) and programmed cell death ligand 1 (PDL1) causes a higher incidence of myocarditis than cytotoxic T lymphocyte antigen 4 (CTLA4) (Table 4.3) [38–41]. A recent study including 101 cases of ICI-induced myocarditis showed that its incidence increased annually. Moreover, the combined use of multiple ICIs significantly increases the incidence of myocarditis, with an average onset time of 27 days after ICI use, while the mortality rate is as high as 46% [42]. Fifty-seven percent patients in the study received anti-PD1 therapy and 27% received anti-CTLA4 combined with anti-PD1 or anti-PDL1 therapy. Among them, 59 patients had detailed medication records; 76% patients developed the disease within 6 weeks of initiating the medication (5–155 days) and 64% patients developed the disease after only one or two doses of medication.

FM accounts for approximately 15% of ICI-induced myocarditis, and the higher the troponin level, the worse the prognosis. Some patients respond well to glucocorticoid treatment [39].

The etiology of FM varies, and the histological appearance of FM caused by different etiologies has a certain tendency. For example, FM caused by various viruses and ICIs is more likely to present as lymphocytic myocarditis; eosinophilic myocarditis is often caused or accompanied by autoimmune diseases. There are also some differences in the treatment of FM caused by different etiologies. Therefore, it is helpful to clarify the etiological diagnosis based on clinical diagnosis for formulating better treatment strategies and improving patient prognosis.

4.2 Pathogenesis of FM

FM is a cardiac inflammatory process that manifests as rapid cardiac functional collapse and even acute heart failure. The underlying pathogenesis of FM is unclear. The lack of comprehensive acknowledgment regarding the pathophysiological mechanisms behind FM has

Table 4.3 ICIs that can cause myocarditis

ICIs	Category	Disease	References
Ipilimumab + navumab	Anti-ctla-4 + anti-PD-1	Melanoma	[37, 43, 44]
Ipilimumab	Anti-CTLA-4	Melanoma	[45]
Pembrolizumab	Anti-PD-1	Melanoma	[46]
Navumab	Anti-PD-1	Melanoma	[47]
Navumab	Anti-PD-1	Non-small cell lung cancer	[48, 49]

largely hindered the development of effective treatment regimens. Previous research has indicated that immune dysfunction and formation of cytokine storms may be the key pathogenesis of FM (Fig. 4.3), but further research is required to elaborately elucidate the detailed mechanisms.

Cytokine storm syndrome (CSS), also named cytokine storm, is a drastic immune attack from abnormally activated immune cells and cytokines on the human body. CSS is not a specific disease, but is a collective name of a pathophysiological phenomenon in different conditions. In rheumatological diseases, such as systemic juvenile idiopathic arthritis (SJIA) and systemic lupus erythematosus, CSS is commonly called macrophage activation syndrome [50]. Immune checkpoint inhibitors and CAR-T-induced CSS is called cytokine release syndrome (CRS) [51]. In inflammatory diseases such as sepsis and severe acute respiratory syndrome coronavirus (SARS-CoV)- or SARS-CoV-2-induced severe pneumonia, the concept of CSS and CRS have commonly been used interchangeably. Generally, CSS that occurs in the pathogenesis of FM is directly called a cytokine or inflammatory storm. The characteristic of CSS is overwhelming inflammation induced by the positive feedback between over-activated immune cells and inflammatory cytokines. The fierce attack of the immune system against pathogens or damaged cells could simultaneously cause extensive self-tissue damage, leading to multiple organ damage and even endanger patients' lives.

Clinically, the diagnosis of CSS primarily relies on the detection of increased cytokines in peripheral blood. Due to diverse etiology and pathogenesis of CSS, the cytokine spectrum varies in different diseases [52] (Table 4.4).

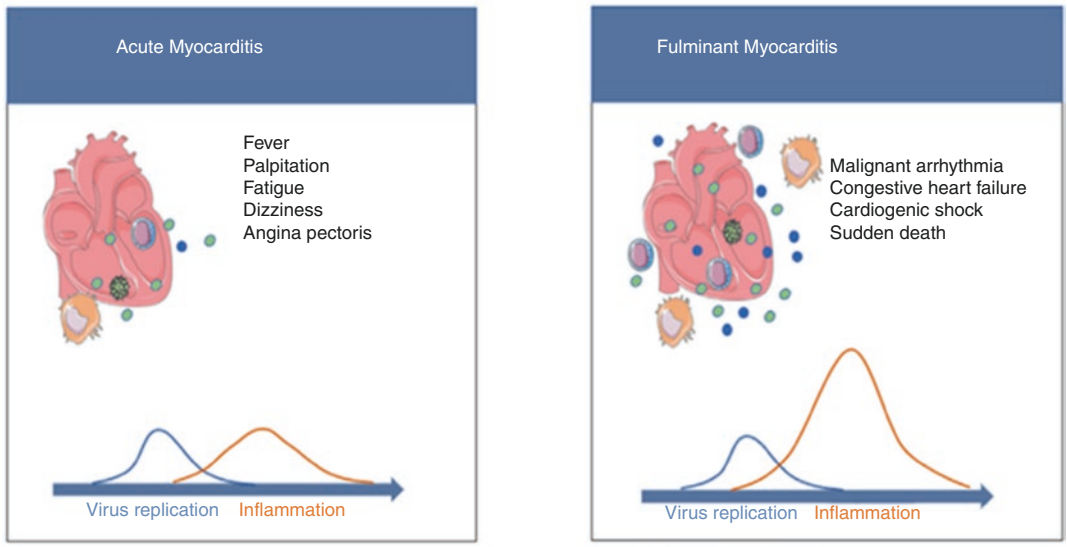

Fig. 4.3 Over-activated immune response and formation of cytokine storms are the main differences between the pathogenesis of FM and AM

Table 4.4 Major cytokines involved in CSS triggered by different etiologies

Etiology	Major cytokines	Reference
CVB3	IL-1β, IL-2, IL-6, TNF-α, IL-1Ra, sTNFR-1, IL-10, IFNs, IL-4, IL-17B	[53, 54]
CAR-T	IFN-γ, IL-2, IL-2Ra, IL-6, sIL-6R, IL-1, IL-10, GM-CSF, IL-12, TNF-α, IFN-α, MCP-1, MIP-1A	[55, 56]
SARS-CoV	IL-1β, IL-6, IL-12, IFN-γ, IP10, MCP-1	[57–59]
MERS-CoV	IFN-γ, TNF-α, IL-15, IL-17	[57, 59]
H1N1	IL-8, IL-9, IL-17, IL-6, TNF-α, IL-12p70 IL-15, IL-6	[60]
Macrophage activation syndrome	IL-1β, IL-6, IL18, TNF-α, IFN-γ	[50, 61]

The roles of the major cytokines in the cytokine storm process of FM are discussed in Chap. 5.

4.3 Laboratory Test

The main laboratory test for FM includes pathogenic detection and cytokine detection.

Pathogenic detection Although both direct cytopathic effects of the pathogen and immune response-mediated myocardial injury were considered to explain the pathogenesis of myocarditis, the detailed mechanisms varied among different pathogens [62–64]. Thus, pathogenic detection may aid in optimizing therapeutic regimens.

4.3.1 Enterovirus

The enterovirus genome is single plus-stranded RNA, which can be used as mRNA to guide viral protein translation. The genome consists of approximately 7500 nucleotides, including (1) the 5′ untranslated region (UTR) length of approximately 750 nucleotides, which forms a secondary structure of RNA and is used to regulate viral replication and translation; (2) an open reading frame length of approximately 6700 nucleotides that encodes a polyprotein; and (3) the 3′ UTR length of approximately 70–100 nucleotides that is used to regulate virus replication (Fig. 4.4). Four structural proteins (VP1, VP2, VP3, and VP4) and seven non-structural proteins (2A, 2B, 2C, 3A, 3B, 3C, and 3D) were cleaved from the multiple proteins encoded by the open reading frame. Among them, 2C, 3C, and 3D proteins are the most conserved in evolution, while 2A, 2B, and 3A usually have high variability and often have different sources in different viruses [65].

The reported detection rate of enterovirus in endocardial biopsy samples of patients with myocarditis is 3–53% [66]. According to the characteristics of the enterovirus genome, the following three detection methods are currently used to diagnose enterovirus infection (Table 4.5).

1. **Nucleic acid detection**: PCR is the most sensitive method for detecting enterovirus nucleic acid in cerebrospinal fluid samples. For samples from cerebrospinal fluid and respiratory secretions, PCR is much more sensitive to enterovirus detection (86%) than virus cultures (30%). Currently, four commercial multiplex PCR kits are available for the detection of enterovirus in nasopharyngeal swab samples. However, the detection of enterovirus by PCR is not practical since stool samples may contain substances that inhibit the PCR reaction.
2. **Virus isolation and culture**: The cerebrospinal fluid, pericardial effusion, the peripheral blood, feces, and various tissues from enterovirus-infected patients could be collected for culture. Enterovirus strains could be isolated from the culture after 2–5 days. After isolation, serotypes of enterovirus can be identified by RNA sequencing. The detection rate of enterovirus can be improved by multi-sampling.

Table 4.5 Detection methods for enterovirus

Detection method	Detection time	Sensitivity	Specificity
Nucleic acid test	1–2 h	100%	97%
Virus culture	3–8 days	80%	100%
Serological test	Several weeks	Limited application	Limited application

Fig. 4.4 Schematic diagram of the enterovirus genome

3. **Serological testing**: Serological testing is limited in acute enterovirus infection due to the following reasons:
   The of antibody titer differs between the acute and convalescent stage
   Cross-reactions may occur between different serotypes
   A lack of highly sensitive IgM assays

The microneutralization method is generally used to detect anti-enterovirus antibodies in patients. However, due to its poor sensitivity, low standardization, and time-consuming characteristics, its application in the routine diagnosis of enterovirus infection is limited.

4.3.2 Adenovirus

The reported detection rate of adenovirus in endocardial biopsy samples of patients with myocarditis is 2–20% [67]. Generally, adenovirus can be detected by immunohistochemistry/fluorescence staining, virus culture, and PCR using samples collected from infected sites (such as nasopharyngeal secretions, pharyngeal swabs, bronchoalveolar lavage, urine, feces, and blood) [68].

1. **Nucleic acid test**: Currently, PCR is the most commonly used method in the clinical diagnosis of adenovirus infection. It is applicable to various clinical samples such as the plasma and urine and is highly sensitive. PCR can also be used to quantify the adenovirus titer and evaluate the therapeutic effect. Some studies have suggested that regular adenovirus detection in the blood and stool samples of high-risk organ transplant recipients can predict adenovirus infection and enable early treatment, but it is unclear whether it should be widely used in patients undergoing organ transplant. Molecular typing of adenovirus by PCR is helpful for the analysis of adenovirus epidemic strains, but since there is no significant difference in the clinical treatment plan for each adenovirus type, detection has not been routinely conducted in clinics.
2. **Virus isolation and culture**: Virus culture is the golden standard for the detection of adenovirus infection, but it is not sensitive to blood samples and may take up to 21 days to detect.
3. **Serological testing**: Serological testing of adenovirus using neutralizing antibodies is cumbersome and time-consuming. Currently, corresponding tests are only conducted in public health laboratories of some countries and regions.
4. **Antigen detection**: After the infected tissue is fixed and embedded, the adenovirus nuclear inclusion body and related antigens can be tested by immunohistochemistry or fluorescence staining.

4.3.3 Parvovirus

The reported detection rates of parvovirus in endocardial biopsy samples of patients with myocarditis is 11–56% [67]. A serum antibody test is the most commonly used method to diagnose PVB19 infection, and a nucleic acid PCR test can further quantify the virus titer. Viral antigen testing is not widely available currently, and PVB19 virus culture is only conducted in research laboratories. Previous and present infections can be distinguished via the detection of IgM and IgG antibodies [69]. At present, HBoV nucleic acid is mainly detected by PCR.

1. Nucleic acid test: One week after PVB19 infection, viral DNA can be detected in the respiratory tract and blood samples of patients. High-titer viremia can last for approximately 1 week, which is then maintained at a low titer level. PCR can be used to diagnose PVB19 infection in the very early stage (before antibody emergence) and is of great value for the diagnosis of PVB19 infection in pregnant women and fetuses. However, low-titer viremia persists after PVB19 infection; thus, viral DNA positivity is not necessarily indicative of present infection. PVB19 virus DNA may also persist in immunocompromised patients. Currently, more than 10^4 viral genomic copies

(vgc)/mL is considered the diagnostic criterion for PVB19 infection. Moreover, the genome of PVB19 has genetic variability, which may affect PCR results.

The first method used to detect PVB19 nucleic acid was dot hybridization, which was gradually replaced by PCR, which is more sensitive. Currently, there are commercially available PCR kits for the diagnosis of PVB19 infection, and the World Health Organization has also established technical standards for nucleic acid amplification of PVB19. In addition to PCR, in situ hybridization can also be used to detect PVB19 DNA in cells or tissues, with a detection sensitivity of about 10^5 vgc/mL.

2. Virus isolation and culture: PVB19 isolation requires special media, such as bone marrow erythroid progenitor cells or embryonic liver cells. Although virus culture is helpful to clarify the infectivity of viruses and study the specific mechanism of virus replication, currently, virus culture is only conducted in laboratory studies due to its finite benefit in clinical diagnosis and treatment and high technical requirements.
3. Serological tests: IgM and IgG antibody tests can be used to diagnose PVB19 infection. However, due to the formation of the antibody–virus complex, serological tests in patients with high-titer viremia may produce false-negative results. Generally, IgM antibodies are produced 7–10 days after PVB19 infection, and IgG antibodies are produced a few days later; positive antibodies can last for 2–4 months. Even if the virus has a genetic mutation, the body's immune response remains; therefore, serological results are unaffected. However, immunocompromised patients may not produce antibodies after infection or may continue to express IgM antibodies without producing IgG antibodies. Even a positive IgG antibody does not rule out passive immunity due to transfusion or intravenous gamma globulin in the active phase of infection.
4. Antigen detection: The detection of virus antigen by immunohistochemistry/fluorescence staining or observation of virus particles through an electron microscope can locate the host cells of the virus, but the sensitivity is relatively low.
5. Bone marrow cytology: Due to the erythrophilic characteristics of PVB19, bone marrow cytology is of great clinical significance. The typical cytological changes of PVB19 infection in bone marrow are erythroid dysplasia resulting from the damage of erythroid precursor cells and emergence of giant erythroid protoblasts containing large eosinophilic nuclear inclusion bodies and cytoplasmic vacuolation.

4.3.4 Human Herpes Virus

The reported detection rate of parvovirus in endocardial biopsy samples of patients with myocarditis is 8–20% [67]. The types of samples currently used to detect HHV-6 infection include the serum/plasma, the cerebrospinal fluid, the alveolar lavage fluid, and various biopsy tissues. The detection methods include the nucleic acid test, virus culture, and serological test. However, due to the prevalence of HHV-6 infection, there is a lack of methods that can be used to identify the incubation period and active period of HHV-6 infection [70].

1. **Nucleic acid detection**: HHV-6 nucleic acid can be detected by PCR or nucleic acid blot hybridization. Southern blot hybridization can be used for the rapid screening of large numbers of samples, but it is not as sensitive as PCR. Currently, PCR primers for different HHV-6 variants are available, which can sensitively identify different virus strains. Due to the high sensitivity of PCR, it is also easy to obtain false-positive results if samples are improperly stored or contaminated.
2. **Virus isolation and culture**: The lymphocytes of patients infected with HHV-6 can be isolated and cultured to obtain virus strains, but this method is time consuming and expensive, has low sensitivity, and is not used for routine diagnosis.

3. **Serological testing**: Currently, there are technical standards for HHV-6 antibody detection, including the anti-complement immunofluorescence method, competitive radioimmunoassay, and the neutralizing antibody method. The disadvantage of serological antibody testing is that HHV-6A cannot be distinguished from HHV-6B infection and may cross-react with HHV-7 to produce false-positive results. In addition, due to the widespread HHV-6 infection, almost all individuals aged over 2 years are positive for HHV-6 IgG antibodies. Typically, a positive IgM antibody indicates a new infection within 5–7 days, but some people do not produce IgM antibodies even if they are infected, which makes it difficult to interpret serological test results.
4. **Antigen detection**: The detection of HHV virus antigens in biopsy tissue samples contributes to observing the changes of tissues at different time points and even the entire infection period. In situ immunohistochemistry/fluorescence tests of infected tissues are often conducted in research laboratories to determine the pathological course of HHV infection rather than as routine clinical diagnostic tests.

Cytokine detection: Cytokine storm plays a significant role in the pathogenesis of FM [71]. The circulating cytokine levels of patients with FM are the primary index that reflects the severity of systemic inflammatory response. The measurement of circulating cytokines would help judge the disease course and assist in the creation of a better treatment plan.

4.3.4.1 Enzyme-Linked Immunosorbent Assay

Principle The assay uses a solid-phase type of enzyme immunoassay to detect the presence of a ligand in a liquid sample using antibodies directed against the protein to be measured. This enzyme-labeled antigen or antibody retains both immune and enzyme activity. Due to the high frequency of enzyme catalysis, it can amplify the reaction effect so that the determination method can reach a high sensitivity.

Advantages Avoids direct labeling with specific antibodies and is cheap.

Disadvantages A large amount of sample is required, only one cytokine can be measured at a time, operation steps and measurement times are very long, and artificial artifacts can be caused by the enzyme-linked reaction.

4.3.4.2 Flow Cytometry

Principle Uses tiny, dispersed particles to capture the liquid analyte and a flow cytometer to detect the fluorescence emitted by the "sandwich" particle–analyte complex to determine the quantity of the analyte.

Advantages Small sample volume required, fast, simple operation, high sensitivity, good repeatability, high efficiency, safe, and close to biological analysis conditions.

Disadvantages Relatively expensive.

4.3.4.3 Liquid Cytokine Chip

Principle This detection method is the combination of enzyme-linked immunosorbent assay and biochip technology based on microplates. It links highly specific capture monoclonal antibodies to different fluorescently labeled magnetic beads and then mixes magnetic beads and suspends them in a microwell plate. Further, a biotin-labeled high-affinity paired detection antibody is added to combine with SA-PE and amplify the signal to achieve the detection of a variety of cytokines simultaneously.

Advantages Small sample volume required, highly flexible panel design, good repeatability, and high efficiency.

Disadvantages Relatively expensive.

4.4 COVID-19 Pandemic-Related Etiology

COVID-19 is caused by SARS-CoV-2, which attacks the respiratory system and other important organs, including the heart [72]. Previous epidemiological data have shown that 7–28% patients have evidence of cardiac injury [73–75]. Although several cases have reported that SARS-CoV-2 could induce myocarditis, relative clinical data is scarce [76–78].

A previous study containing 39 consecutive autopsy cases from Germany indicated that SARS-CoV-2 could be detected in 24 of 39 hearts, with 16 of 39 (41%) having copy numbers higher than 1000 copies/ug RNA [79]. However, there is no direct evidence that SARS-CoV-2 can directly invade cardiomyocytes. Thus, myocardial injury may induce the immune system via hyperactivation characterized by the release of multiple inflammatory mediators [80]. The detailed mechanisms underlying the etiology and pathogenesis of SARS-CoV-2-induced FM requires further exploration.

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5 Pathophysiology and Mechanisms of Fulminant Myocarditis

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5.1 Animal Models of Fulminant Myocarditis

Basic research on fulminant myocarditis (FM) is still in its initial stages, mainly because of the lack of proper animal models. The available animal models for myocarditis research are the acute viral myocarditis mouse model and autoimmune myocarditis mouse model. Viral infection is the most common cause of myocarditis. However, the morbidity of different types of virus-induced myocarditis exhibits regional divergence. Previous research indicated that enteroviruses, especially coxsackievirus B3 (CVB3), is the most common etiology of myocarditis. However, a growing number of studies have shown that parvovirus B19 (PVB19) is gradually becoming the most common etiology of viral myocarditis [1–4]. Moreover, reports indicated that PVB19-induced myocarditis tends to exhibit as FM in children, with a relatively high mortality rate [5]. However, due to sensitivity differences between human and animal models toward PVB19, a PVB19-induced myocarditis mouse model has not yet been developed. At present, the most common animal model is the CVB3-induced myocarditis mouse model.

5.1.1 Mouse Selection

Existing studies have shown that different mouse strains have different susceptibilities to CVB3. The severity of cardiac inflammation response, degree of damage, and disease progression varied among the different mouse strains (Table 5.1) [6]. Factors associated with susceptibility include the major histocompatibility complex (MHC) haplotype [7, 8], differential T helper type 1 (Th1) and Th2 cell response [9, 10], efficacy of dendritic cell antigen presentation [11, 12], mutation of decay-accelerating factor (DAF), and interferon-gamma (IFN-γ)-associated genes [13].

For the building of FM animal models, A/J or C3H/HeJ mice are often used. These two mice strains have a higher sensitivity to CVB3 and a stronger cardiac inflammatory response when inoculated with the same amount of CVB3, which is similar to virus-induced FM in clinical settings. However, a slight difference exists between these two types of FM models. The CVB3-induced C3H/HeJ mice develop severe myocardial lesions while survival is high due to limited systemic response, whereas A/J mice exhibit both severe cardiac and systemic inflammatory responses and have a high mortality rate.

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Table 5.1 Mouse strain susceptibility to the development of viral myocarditis

Author	Species	H-2 haplotype	Susceptibility	Viral elimination
Zaragoza C [14]	129/SvJ	bc	Low	Yes
Chow L.H [15]	C57BL/6	b	Low	Yes
Chow L.H [15]	BALB/c	d	High	Yes
Godeny E.K [16]	CD1	ND	High	Yes
Lee J.K [17]	DBA/2	d	High	Yes
Klingel K [18]	A.BY/SnJ	b	High	No
Klingel K [18]	A.CA/SnJ	f	High	No
Klingel K [18]	DBA/1 J	q	High	No
Klingel K [18]	SWR/J	q	High	No
Chow L.H [15]	A/J	a	Severe	Yes
Chow L.H [15]	C3H/HeJ	k	Severe	Yes

In addition, age, gender, and the general status of mice also influence their sensitivity and tolerance to CVB3. Generally, the susceptibility of mice to CVB3 decreases with age. However, considering the weaning age, 4–8-week old mice are commonly used to build FM models. Mice at this age could live independently and have a high susceptibility to CVB3, making them the optimal choice for building the FM model.

Mice of different genders also have different susceptibilities to CVB3. Under the same conditions, male mice were more sensitive to CVB3 than female mice, and exhibited more severe cardiac damage. The gender differences may be due to differential macrophage polarization [19] and differential T cell response [10, 20].

Macrophages are essential for mediating the innate immune response. Reports indicated that after male BALB/c mice were infected with CVB3, cardiac-infiltrated macrophages were mainly M1 type, which expresses numerous proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1). Conversely, cardiac-infiltrated macrophages in female mice with myocarditis were mainly anti-inflammatory M2 type. In addition, the transfer of M2 macrophages to male mice with myocarditis could alleviate the symptoms, while transfer of M1 macrophages to female mice with myocarditis could exacerbate the symptoms [19]. Another study indicated that increasing the activity of M2 macrophages, Th2 cells, and Treg cells in the local heart through gonadectomy of male BALB/c mice could effectively alleviate the symptoms of myocarditis [21].

T cells are the major components of adaptive immune responses. Huber et al. found that in a CVB3-induced BALB/c mouse model, cardiac-infiltrated T cells were mainly Th1 cells in male mice and Th2 cells in female mice. Furthermore, estrogen treatment could promote the production of IL-2 from Th2 cells in male mice, whereas testosterone treatment could increase Th1 infiltration in female mice hearts [10]. Subsequent studies have indicated that γδ T cells may play a significant role in Th1/Th2 differentiation [20]. In addition, IFN-γ knockout female mice exhibited a higher degree of cardiac damage and viral load than male mice. This indicated that IFN-γ might also play a role in the gender difference in mice with myocarditis [22]. Moreover, selected anti-inflammatory cytokines and TIM-3, IL-4, and Treg cells that are elevated in female mice may also be involved in gender differences in myocarditis [23].

Collectively, the animal model closest to adult FM patients is currently believed to be 4-to-8-weeks old male C3H/HeJ or A/J mice with CVB3 intervention.

5.1.2 Virus Selection

In addition to the mouse species, the degree of cardiac damage is also influenced by the type of virus. At present, the most commonly used virus

for establishing myocarditis animal models is CVB3. In addition, the encephalomyocarditis virus is also being used by some researchers to build myocarditis mouse models, but it is relatively rare and generally only used as a histopathological control for CVB3 virus-induced myocarditis models.

CVB3 virus strains used for myocarditis research include the Nancy, Woodruff (H3), 31-1-93, and PD strains. The latter does not work through chimeric antigen receptors (CARs), but invades cardiomyocytes through heparan sulfate [22, 24]. Different virus strains exhibit slight variations in virulence and mechanisms of action. The CVB3 virus strain used for myocarditis research in China is the standard Nancy strain.

CVB3 is a single-strain RNA virus of the picornavirus family [25]. RNA viruses are prone to mutations, and their mutations are unpredictable. After multiple passages, the affinity of CVB3 to cardiomyocytes may decrease, and the virulence may be weakened or even disappear, resulting in instability of the myocarditis model. Therefore, when using the standard F1 strain for virus passaging, care should be taken to retain as many F2 and/or F3 generation strains as possible. Virus strains with too many passages should not be used continuously. The virus can be re-amplified from the F2 or F3 generations.

The virulence of CVB3 amplified from different batches is also slightly different, and the sensitivity of mice of varying ages to CVB3 may also be different, resulting in the batch effects of the myocarditis model. Therefore, after each batch of virus amplification, it is best to select several experimental mice for pre-experimentation and observe the mortality and cardiac function of the mice before conducting formal experiments. In addition, to maintain the stability of the experimental results, for the same batch of intervened mice it is best to use the same batch of amplified viruses to reduce differences within the group.

5.1.2.1 Modeling Method

CVB3 is from the enterovirus family, and is mainly transmitted through feces or the mouth. After CVB3 orally enters the digestive tract, it infects and proliferates in the Peyer's patch and immune cells of the spleen. The virus is then released into the peripheral blood and colonizes target organs, such as the heart and pancreas. Considering the stability of the model, the current model of myocarditis was mainly induced through the intraperitoneal injection of CVB3.

From the perspective of pathology, the viral myocarditis mouse models (including acute, chronic, and fulminant) induced by CVB3 all belong to lymphocytic myocarditis. Due to undertrained etiology and pathological mechanisms, animal models for other pathological types of myocarditis, such as giant cell and eosinophilic myocarditis, are still lacking. In addition, difficulty in virus isolation and acquisition, and poor susceptibility of animal models to viruses makes it difficult to build the corresponding animal models.

5.1.3 Establishment and Evaluation of Common Animal Models of Fulminant Myocarditis

At present, most researchers use CVB3 to intervene in male A/J or C3H/HeJ mice aged 4–8 weeks to establish animal models of FM.

1. Modeling method: Male A/J mice aged 4–8 weeks (the age of the mice was adjusted according to the actual situation) were subjected to intraperitoneal injection with CVB3. Due to the rapid mutation of CVB3, the Nancy strain has a variety of variants, and the virulence between variants differs. The actual intervention of the virus quantity requires research institutions to conduct preliminary experiments based on the existing literature. For example, 6-to-8-weeks old male A/J mice were injected intraperitoneally with 1×10^4 PFU Nancy strain CVB3 to construct a mouse model of FM [26].
2. Observation content: After virus inoculation, the status of the mice was observed daily; they were examined for signs of viral infection such as loss of appetite, chills, and hair loss,

and their weight change and death were recorded. On the seventh to ninth days after CVB3 inoculation, the heart function of the mice was monitored using ultrasound. The mice were treated, and tissues were taken for testing according to the needs of the experiment. Under normal circumstances, mice can experience loss of appetite and significant weight loss from the second day after inoculation with the virus and maintain a trend of weight loss during the disease course, with an average drop of 0.5–1 g/day. Signs of hair loss and chills began to appear on the fourth day.

3. Mortality: Mice died as early as the second day following viral inoculation, and the peak period of death was approximately after 1 week. The seven-day mortality rate of A/J mice inoculated with 1×10^4 PFU Nancy strain CVB3 virus was nearly 60% (Table 5.2). However, C57BL/6 mice of the same age as A/J mice, inoculated with 1×10^5 PFU of the same Nancy strain CVB3 virus survived for 7 days [26]. This suggests that the course of the myocarditis model of A/J mice is similar to that of FM.
4. Heart function: Compared with normal mice, CVB3 inoculation drastically reduced the heart function of A/J mice. Various cardiac functional indexes, such as cardiac output, stroke volume, and heart rate, decreased significantly.
5. Cardiac inflammatory response: The results of immunohistochemistry indicated significant cardiac inflammatory infiltration of A/J mice 7 days after modeling (Fig. 5.1). Most of the infiltrated inflammatory cells were CD68-positive macrophages and myeloperoxidase (MPO)-positive neutrophils, accompanied by a small amount of T and B lymphocytes. This suggests that cardiomyocyte damage in A/J mice caused by CVB3 is mainly mediated by the innate immune response.

Table 5.2 Cardiac function of control and CVB3 mice

	Control Group	CVB3 Group (Day 8)
CO [ml/min]	9.9 ± 0.6	5.3 ± 0.5
Vol-d [ul]	42.4 ± 1.4	29.1 ± 1.5
Vol-s [ul]	19.7 ± 0.8	14.3 ± 1.1
SV [ul]	22.7 ± 1.2	14.9 ± 1.0
LVEF	53.2 ± 1.8	51.6 ± 2.5
LV-d [mm]	3.6 ± 0.1	3.3 ± 0.1
LV-s [mm]	2.6 ± 0.1	2.5 ± 0.1
IVRT [ms]	16.9 ± 0.6	20.4 ± 0.7
MV_{decel} [ms]	23.5 ± 1.0	31.7 ± 1.5
HR [bpm]	435 ± 12	352 ± 20

It has been noted that A/J mice often undergo heavy systemic reactions after CVB3 inoculation. Thus, mice injected with the viral dose that can cause obvious inflammation in the heart often have a high mortality rate.

There are many causes of FM, but due to the limitations of animal models, current research is mainly focused on CVB3-induced FM. The relative unity and instability of animal models have largely restricted the development of research on FM. Therefore, more animal models of FM are still to be developed.

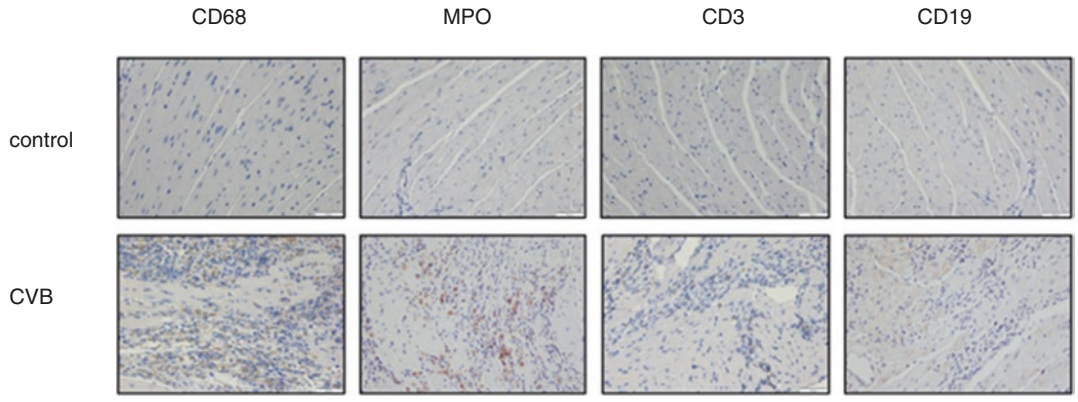

Fig. 5.1 Cardiac inflammatory infiltration of mice with myocarditis

5.2 Cytokine Storm in Fulminant Myocarditis

The dysregulated immune response and the formation of the cytokine storm are thought to play a central role in the development of FM. Several cytokines are thought to be involved in this process.

5.2.1 Interferons

IFNs are a group of low-molecular-weight glycoproteins with similar structures and functions. They are produced by host cells through antiviral immune responses and play a significant role in virus-induced FM. Nearly all cells of the human body can immediately produce IFNs after being infected by the virus. IFNs can be divided into three types based on their origin and physicochemical properties: IFN I, IFN II, and IFN III. IFN I includes IFN-α, IFN-β, IFN-ε, IFN-ω, and IFN-κ, which are predominantly secreted by innate immune cells. IFN II consists of a single gene product, IFN-γ, which is mainly produced by activated natural killer (NK) cells and T cells. IFN III includes several types of IFN-λ with uncertain distribution and function. By activating the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway, IFNs can trigger a signaling cascade, resulting in the activation of several transcription factors and hundreds of IFN-stimulating genes. The gene products exhibit antiviral, antiapoptotic, and immunomodulatory functions.

5.2.1.1 Type I Interferon (IFN I)

As the two most important members of IFN I, IFN-α and IFN-β exert extensive antiviral responses through various pathways (Fig. 5.2). They interfere with viral replication, inhibit cellular protein synthesis, stimulate p53-mediated

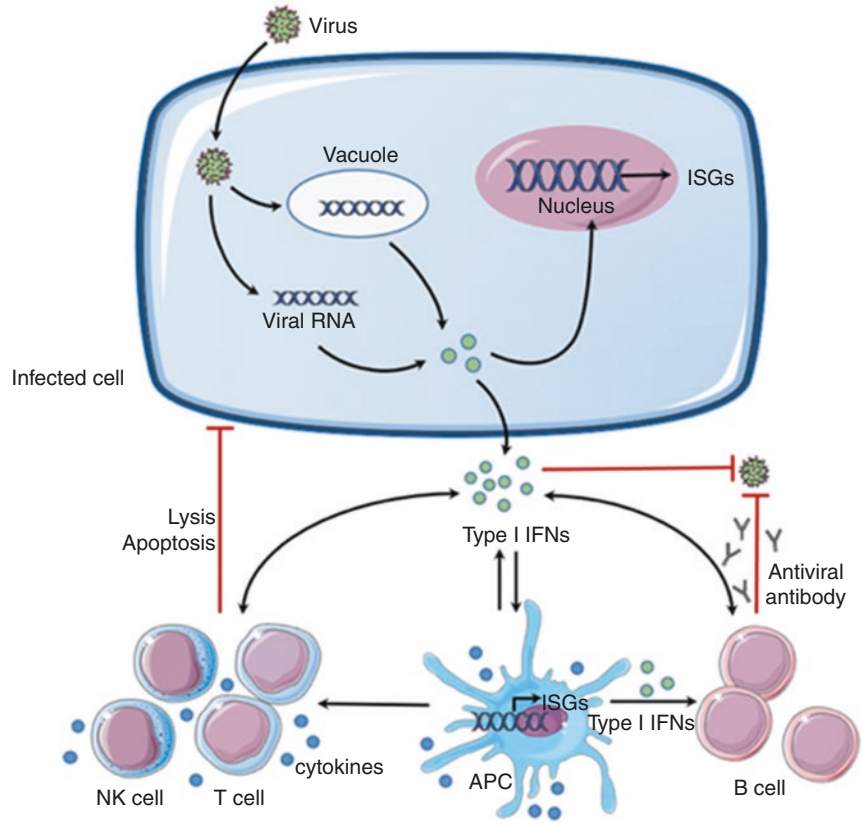

Fig. 5.2 Anti-viral response of type I interferon

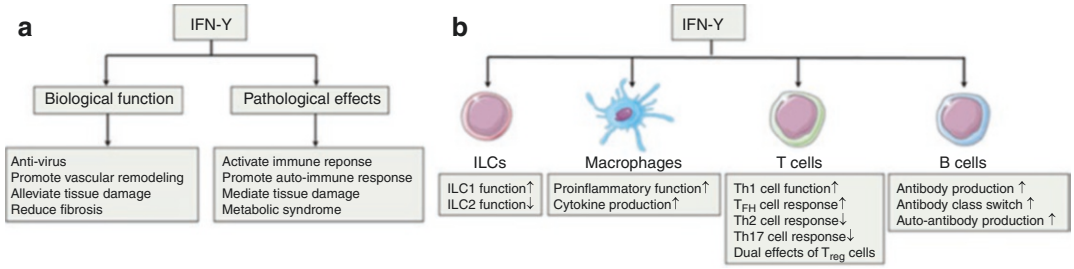

Fig. 5.3 (**a**) the homeostasis regulation and pathological effects of IFN-γ; (**b**) the regulatory effects of IFN-γ to immune cells

cellular apoptosis, and promote inflammasome formation. In addition, they activate macrophages, promote the production of proinflammatory cytokines, enhance the ability of NK cells to eliminate infected cells, promote antibody production, and promote the expression of MHC molecules in cells, facilitating the recognition, adhesion, and killing effects of $CD8^+$ T cells toward infected cells [27, 28].

Previous research indicated that for enterovirus-and adenovirus-induced myocarditis patients, 24 weeks of IFN-β treatment could effectively eliminate the viral genome in the myocardium and improve left ventricular function [29]. However, animal studies have also shown that inhibiting IFN-β during late-stage myocarditis could alleviate symptoms, indicating that the function of IFN-β might be time-dependent [6].

5.2.1.2 Type II Interferon (IFN II)

IFN-γ is mainly produced by $CD4^+$/$CD8^+$ T and NK cells. $CD8^+$ T and NK cells are the major effector cells of the adaptive and innate immune systems, respectively. Thus, IFN-γ is an index used to systemically assess the immune activation status of the human body [30]. Like other members of the IFN family, IFN-γ can inhibit viral replication. However, its principal function is to modulate the adaptive immune response. IFN-γ can act on a broad range of cell types that express IFNγR. It can enhance MHC expression of target cells and facilitate the antigen presentation process, promote Th0 cells to differentiate into Th1 cells and monocyte differentiation into M1 macrophages, and upregulate the release of IL-1, TNF-α, and IL-6 from macrophages. In MAS and cancer therapy-induced cytokine release syndrome (CRS), remarkably high levels of circulating IFN-γ have been reported [31, 32]. In addition, IFN-γ also reduces the attack of T cells at cardiomyocytes by inhibiting the differentiation of Th0 into Th17 cells and enhancing the expression of PD-L1 in cells such as endothelial cells. However, continuous high levels of IFN-γ could also induce cell self-damage and negative inotropic effects by modulating the expression of cytokine receptors (Fig. 5.3) [33].

5.2.2 Interleukins

Interleukins (ILs) are a group of cytokines that exhibit multiple effects. They play a critical role in mediating signal transduction, promoting the activation, proliferation, and differentiation of lymphocytes, modulating the function of various types of immune cells, and are therefore crucial in immune responses.

5.2.2.1 IL-1 Family

The IL-1 family consists of 11 members, including IL-1α, IL-1β, IL-1Ra, IL-18, IL-33, IL-36α, IL-36β, IL-36γ, IL-36Ra, IL-37, and IL-38. Among them, IL-1 and IL-33 were determined to have a close relationship with FM.

IL-1α and IL-1β are different molecular forms of IL-1. They are mainly produced by activated monocytes, macrophages, endothelial cells, and fibroblasts. Other cell types can also produce IL-1 following infection. Although IL-1α and IL-1β are encoded by different genes, they exert

the same biological functions by binding to the same receptor. After binding to its receptor, IL-1 can induce the production of numerous inflammatory mediators, broadly participating in various acute and chronic immune responses [34–36].

IL-1 is closely associated with several cardiovascular diseases. With sepsis, IL-1 is recognized as a "soluble myocardial suppressant molecule." [37, 38] Studies have indicated that IL-1β induces G protein-mediated suppression of L-type Ca^{2+} currents, resulting in contractile abnormalities in cultured rat ventricular myocytes [39]. IL-1 can also promote NO generation, affect mitochondrial ATP production, and affect the re-uptake of calcium ions by cardiomyocytes through the reduction of the mRNA and protein expression of sarcoplasmic reticulum or endoplasmic reticulum calcium-ATPase. These mechanisms collectively influenced the cardiac contractile capability (Fig. 5.4) [40]. In addition, the negative inotropic effects of IL-1β seem to be related to the release and activation of IL-18, but its mechanisms are still unknown [41]. According to previous animal studies, the injection of healthy mice with IL-1β (3 μg/kg) induced reversible cardiac systolic dysfunction and reduced left ventricular contractility reserve [42]. However, pretreatment with IL-1β antibody or IL-1 antagonist significantly improved cardiac dysfunction in mice [43]. IL-1 also plays a critical role in the development of FM. A case report indicated that an IL-1 receptor antagonist (anakinra) was effective in life-threatening PVB19 induced FM [44]. In addition, for ECMO-resistant FM patients and myocarditis-induced end-stage heart failure patients, IL-1 receptor blockade successfully improved cardiac systolic function in 24 hours [45, 46].

Classic activated IL-33, another member of the IL-1 family, functions as an alarmin, which participates in immune modulation by regulating several types of immune cells (Fig. 5.5) [47–49]. It is generally recognized that M2 macrophages exert a protective effect on the progression of myocarditis [19]. IL-33 can promote M2 macrophage polarization by enhancing the expression of IL-4 from cardiac-infiltrated $ST2L^{+}F4/80^{+}$ macrophages and $ST2L^{+}CD4^{+}$ T cells, thereby alleviating the cardiac inflammatory response [50].

ST2, the receptor of IL-33, has two subtypes: transmembrane receptor ST2L and soluble receptor sST2. The former is the functional receptor that activates the downstream signaling pathway, while the latter is commonly recognized as the "bait receptor." [48] Under specific conditions, such as inflammation, IL-33 cannot successfully combine with ST2L; therefore, blocking the

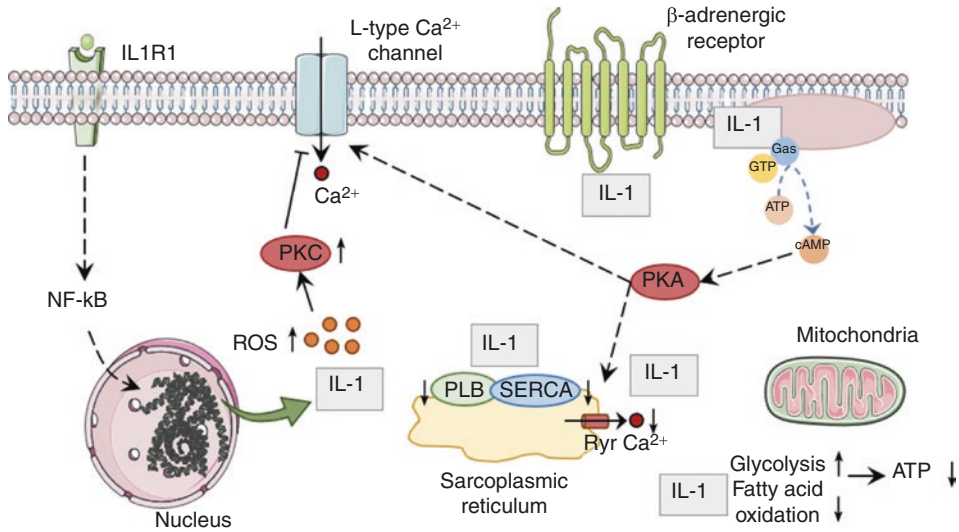

Fig. 5.4 IL-1 and cardiac contractility

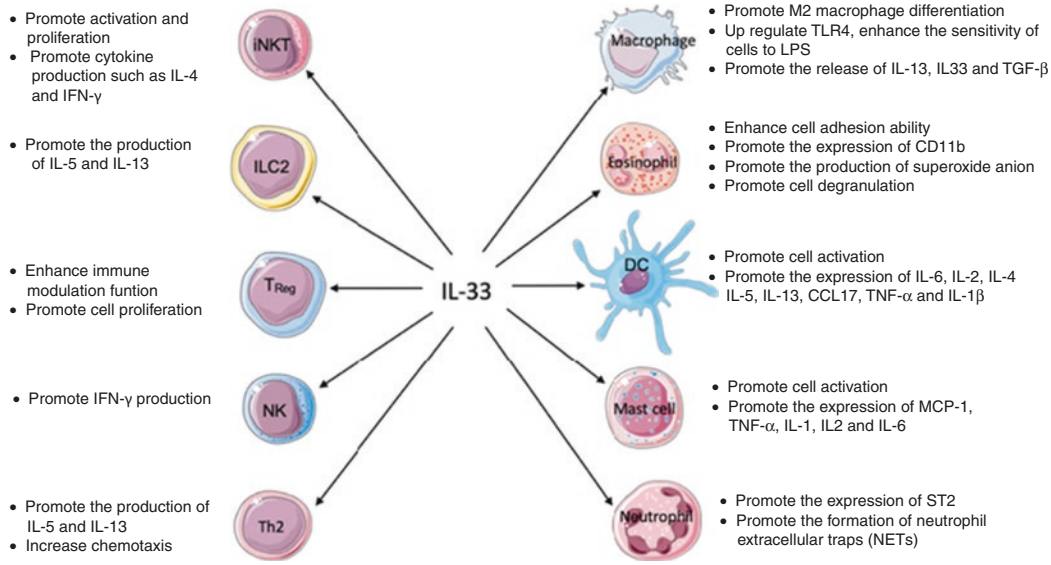

Fig. 5.5 The modulation of IL-33 to immune cells

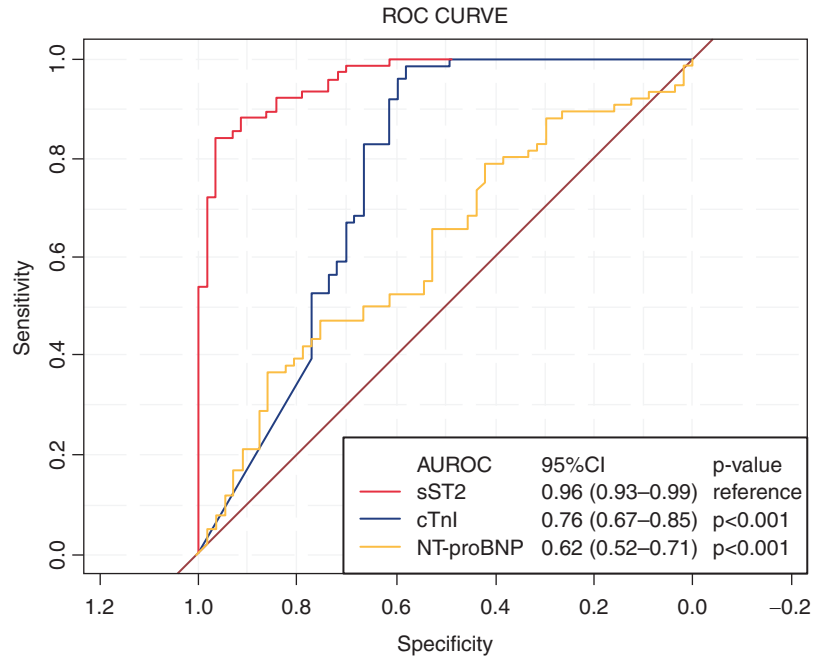

Fig. 5.6 Diagnostic efficiency of sST2 to FM

positive effects of IL-33 on the myocardium, and the level of sST2 increases. Elevated sST2 levels may be a predictor of 1-year mortality in decompensated heart failure [51]. Recent research has shown that plasma sST2 levels are elevated in patients with FM and are related to disease severity in the acute stage. ROC analysis showed that sST2 is more sensitive than cTnI and NT-proBNP for FM diagnosis (Fig. 5.6). Recombinant ST2-treated A/J mice showed impaired cardiac systolic and diastolic functions, with increased cardiomyocyte apoptosis. In addition, ST2 antibody treatment can relieve cardiac decompensation in mice with CVB3-induced FM, alleviate

cardiac inflammation infiltration, and reduce cardiomyocyte apoptosis. Therefore, sST2 may be a biomarker and potential therapeutic target for the diagnosis and treatment of FM.

5.2.2.2 IL-2

IL-2, also known as T cell growth factor (TCGF), is mainly produced by $CD4^+$ T cells, $CD8^+$ T cells, and NK cells [52]. IL-2 is the major growth factor that promotes T cell proliferation, activates T cells, and promotes cytokine production. In addition, IL-2 can also stimulate the proliferation of NK cells, enhance their killing activity and cytokine production ability, activate macrophages, and promote B cell proliferation and antibody production (Fig. 5.7).

Studies have found that in patients with myocarditis and dilated cardiomyopathy, IL-2 and soluble IL-2 receptor levels are significantly elevated, and the elevated levels are closely related to the disease process [53, 54]. The possible mechanism for IL-2-induced myocardial decompensation and inflammatory infiltration is that cytotoxic T cells activated by IL-2 could directly induce extensive tissue damage. In addition, the interaction between activated T cells and endothelial cells could induce capillary leakage and immune cell extravasation, leading to microcirculation disorders, tissue edema, cytotoxic damage, and myocardial cell necrosis [55].

IL-2 can activate T cells and promote the killing of tumor cells by T cells; therefore, it is commonly used in cancer therapy. In clinical settings, several FM cases induced by IL-2 treatment of metastatic melanoma, liver cancer, and other diseases have been reported [56–58].

5.2.2.3 IL-6 Family

The IL-6 family includes IL-6, IL-11, IL-27, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), cardiotrophin 1 (CT-1), cardiotrophin-like cytokine factor 1 (CLCF1), IL-35, and IL-39 [59]. Among them, IL-6 is the most closely related to FM.

IL-6 is a pleiotropic cytokine that exhibits both pro-inflammatory and anti-inflammatory effects.

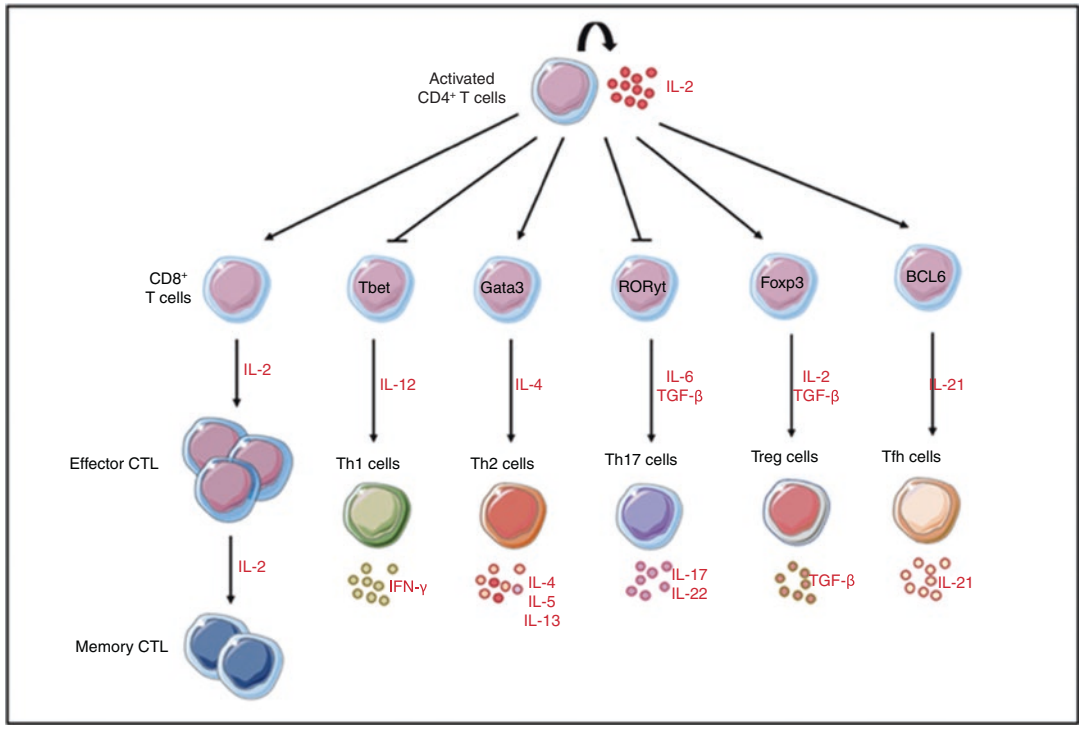

Fig. 5.7 T cell modulation effects of IL-2

It is mainly produced by monocytes, macrophages, Th2 cells, vascular endothelial cells, and fibroblasts. It has traditionally been thought that IL-6 has two signal transduction pathways. In the classic IL-6 signaling pathway, IL-6 directly binds to membrane-bound IL-6 receptor (mIL-6R), that is expressed on the membrane surface of hepatocytes, monocytes, and lymphocytes, and activates the JAK-STAT3 and JAK-mitogen-activated protein kinase (MAPK) signaling pathways under the mediation of gp130 molecules. Thereafter, it exerts a variety of anti-inflammatory biological functions, such as promoting the release of liver proteins in the acute phase. In the cross-signaling pathway, IL-6 forms a circulating complex with soluble IL-6R (sIL-6R) and then binds to gp130 expressed on almost all cell surfaces, thereby expanding the cell types that respond to IL-6. The pro-inflammatory effects of IL-6 are mainly mediated by sIL-6R, making the IL-6/sIL-6R complex an important pro-inflammatory mediator. Recent studies have shown that IL-6 also has a trans-presentation signal transduction pathway. IL-6 first binds to mIL-6R expressed on the surface of dendritic cells and then binds to cells that express gp130 to activate pathological Th17 cells. The trans-presentation pathway plays a vital role in acute respiratory distress syndrome (ARDS) and CRS of viral pneumonia [60].

In the acute phase of the inflammatory response, IL-6 can balance the body's immune response by inhibiting inflammation and protecting the organism. Studies have shown that IL-6 can inhibit virus replication in mice with myocarditis and reduce cardiac inflammation infiltration [60, 61]. However, the continuous high levels of IL-6 promotes B cell activation and differentiation, induces the production of antibodies (especially immunoglobulin M [IgM] and IgG), promotes T cell proliferation, increases the activity of NK cells and macrophages, and promotes the release of cytokines. It can also trigger the automatic aggressive response of the Th17 system, participate in myocardial damage, cardiac dysfunction, multiple organ dysfunction, and disseminated intravascular coagulation by interrupting the balance of the cytokine network, interfering with virus clearance, inducing blood vessel leakage, and promoting the occurrence of thrombosis (Fig. 5.8) [60, 62–64]. Myocardial damage caused by CRS is generally thought to be associated with increased IL-6 [65]. In addition,

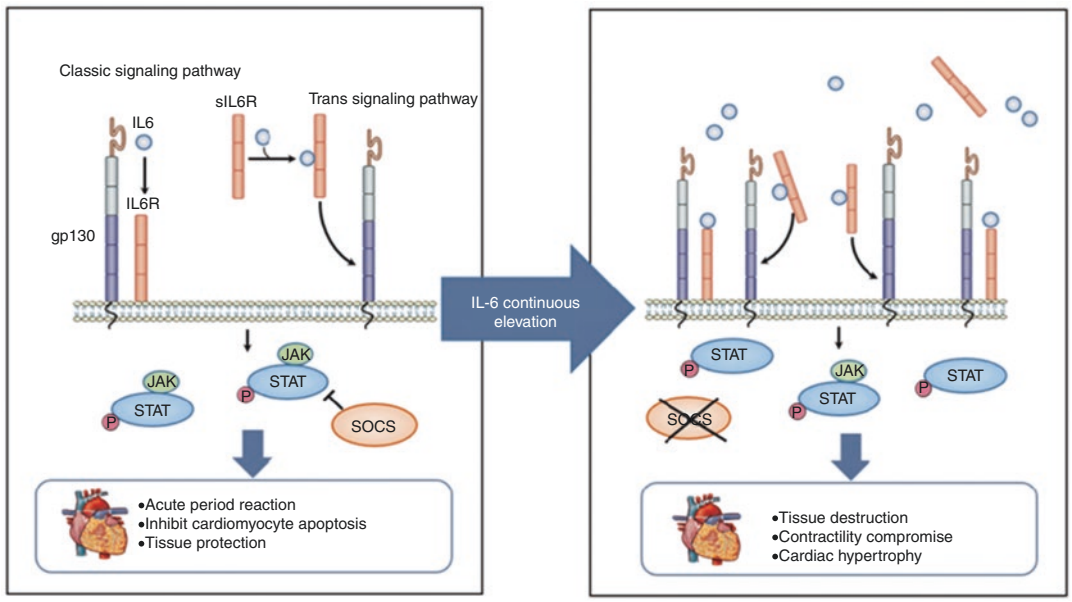

Fig. 5.8 Dual effects of IL-6

since both TNF and IL-1β can stimulate the production of IL-6, IL-6 can indirectly reflect the expression of these two cytokines. The level of peripheral blood IL-6 is often used to assess the systemic cytokine response strength of patients [66]. In myocarditis and congestive heart failure, cautiously increased IL-6 levels usually indicate a poor prognosis [67, 68].

5.2.2.4 IL-10

IL-10 is mainly produced by T cells, monocytes, macrophages, and B cells. Activated dendritic cells and selected NK cell subtypes can also produce IL-10. Generally, IL-10 is thought to be an anti-inflammatory cytokine. It can reduce the intensity of the inflammatory response and inhibit immune overactivation by affecting MHC II expression, negatively regulating inflammatory pathways such as the NF-κB signaling pathway, inhibiting the activation of immune cells, and releasing inflammatory cytokines (Fig. 5.9) [69, 70].

The elevation of IL-10 during the late stage of the cytokine storm indicates the activation of the inflammatory response. This indicates that the organism is trying to repress the activated immune response and represent the functional downregulation of circulating neutrophils and monocytes [71]. Research has indicated that IL-10 treatment downregulates the production of pro-inflammatory cytokines in viral myocarditis, thereby exerting cardioprotective functions [72]. Plasma levels of IL-10 could also be used as a prognostic index in patients with FM. Those with higher IL-10 levels are more likely to be diagnosed with hemodynamic disorder [73, 74].

5.2.3 Chemokines

The chemokine (ChK) family is an extensive cytokine superfamily. Members of the ChK family are low molecular weight proteins that attract various immune cells to damage sites, thereby acting as a 'bridge' in the inflammatory response.

At present, it is generally believed that the major mechanism behind the formation of a cytokine storm is the release of excessive inflammatory mediators by a variety of inflammatory cells in the case of immune regulatory disorders. Thus, the ChKs that guide inflammatory cells to the local infection site play an essential role in the formation of cytokine storms. Therefore, developing drugs targeting ChKs and their receptors may be a feasible strategy to treat a variety of inflammatory reactions, including cytokine storms. At present, a variety of ChK-receptor antagonists have been extensively developed, but due to unsolved problems that exist in clinical trials, the application of these drugs is still limited.

5.2.4 Tumor Necrosis Factor

TNF can be divided into TNF-α and lymphotoxin (LT). The TNF superfamily contains at least 19 members, which exert significant functions by modulating the adaptive immune response, killing target cells, and inducing cellular apoptosis. Among these members, TNF-α was reported to be closely linked to FM. TNF-α can be produced by a variety of immune and non-immune cells. As a pleiotropic pro-inflammatory cytokine,

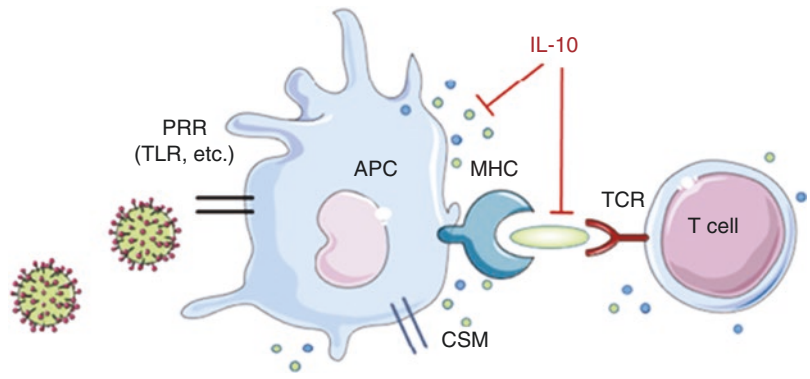

Fig. 5.9 Anti-inflammatory effects of IL-10

TNF-α stimulates the production of various inflammatory cytokines and ChKs.

Previous research has indicated that TNF could affect cardiac function through both immediate and delayed pathways. Increased TNF could inhibit left ventricular function by activating the neutral sphingomyelinase pathway for several minutes. Later, from hours to a few days, TNF could induce negative inotropic effects through NO-mediated β-adrenergic signaling pathway dysregulation. Consistent high levels of TNF can activate matrix metalloproteinases (MMPs), leading to collagen degradation and left ventricular dilation. In addition, it can enhance the sensitivity of fibroblasts to the inflammatory mediators released by mast cells, inducing extracellular matrix degradation and left ventricular dilation, and promoting left ventricular remodeling (Fig. 5.10) [75]. This is consistent with the dilated cardiomyopathy phenotype of cardiac-specific TNF-α overexpression in mice [76]. However, a clinical trial that used a TNF-α antagonist to treat heart failure patients yielded disappointing results [77]. Moreover, there are case reports that administered adalimumab, a TNF-α antagonist, in the treatment of relapsing polychondritis, which could induce eosinophilic myocarditis [78]. Although some research indicated that TNF-α could damage cardiac function by promoting an inflammatory response, evidence also supports that TNF knockout mice with myocarditis exhibited increased myocardial viral load and higher mortality rate, which could be reversed by recombinant TNF. The mechanisms behind this phenomenon could be explained by the fact that the expression of adhesion molecules and ChKs is TNF-α dependent. Thus, TNF-α deficiency induces abnormalities in virus clearance [79]. Collectively, TNF-α may play a dual role in the development of FM.

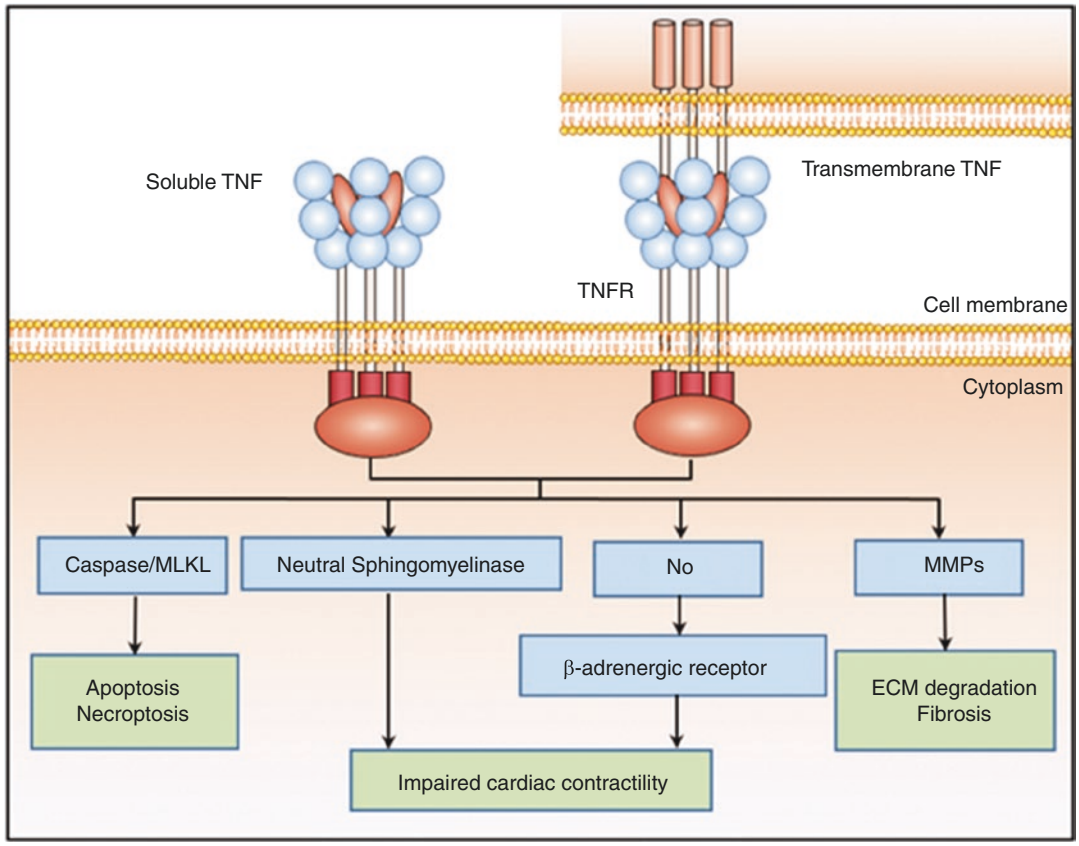

Fig. 5.10 Cardiac inotropic effects of TNF

5.3 Pathogenesis of Cytokine Storm in Fulminant Myocarditis

The inflammatory response is the chief defense mechanism when organisms are damaged or infected. The classical inflammatory response is a self-limited process divided into four stages: recognition, assembly, effector, and recovery. The formation of a cytokine storm is due to the ineffective modulation of the inflammatory process, resulting in a systemic inflammatory response and inducing catastrophic damage to neighboring tissues.

The functions of the cytokine storm varies in different etiologies induced by FM (Fig. 5.11). Although the processes are quite the same, the types of cytokine storms and the types of elevated cytokines are different. In clinical practice, myocarditis is mostly induced by cardiotropic viruses, such as CVB3 and PVB19. However, the pathogenesis of virus-induced cytokine storms remains unclear. The pathogenesis of anti-tumor drugs, such as those that induce immune checkpoint inhibitor-induced cytokine storms, might help us better understand this phenomenon.

Studies have indicated that IL-6, IL-10, and IFN-γ are critical cytokines in anti-tumor immune treatment-induced cytokine storms. After coming into contact with tumor cells, activated T cells release large quantities of IFN-γ and TNF-α, causing fever, shivering, headache, dizziness, and fatigue. IFN-γ also activates immune cells, such as macrophages, and promotes the release of cytokines such as IL-6, TNF-α, and IL-10 from immune cells. These cytokines further promote the release of IFN-γ and TNF-α from T cells, resulting in a positive feedback loop. Significantly elevated IL-6 levels might be the main factor in anti-tumor treatment-induced cytokine storms. Apart from immune cells, endothelial cells may also be involved in the modulation of cytokine storms. In clinical settings, angiotensin-II (Ang-II) and von Willebrand factor (vWF) are commonly elevated in the peripheral blood of patients undergoing cytokine storms. Modulating endothelial expression of sphingosine-1-phosphate receptor 1 (S1P1) through the sphingosine-1-phosphate receptor modulator (S1PS) agonist could reduce the

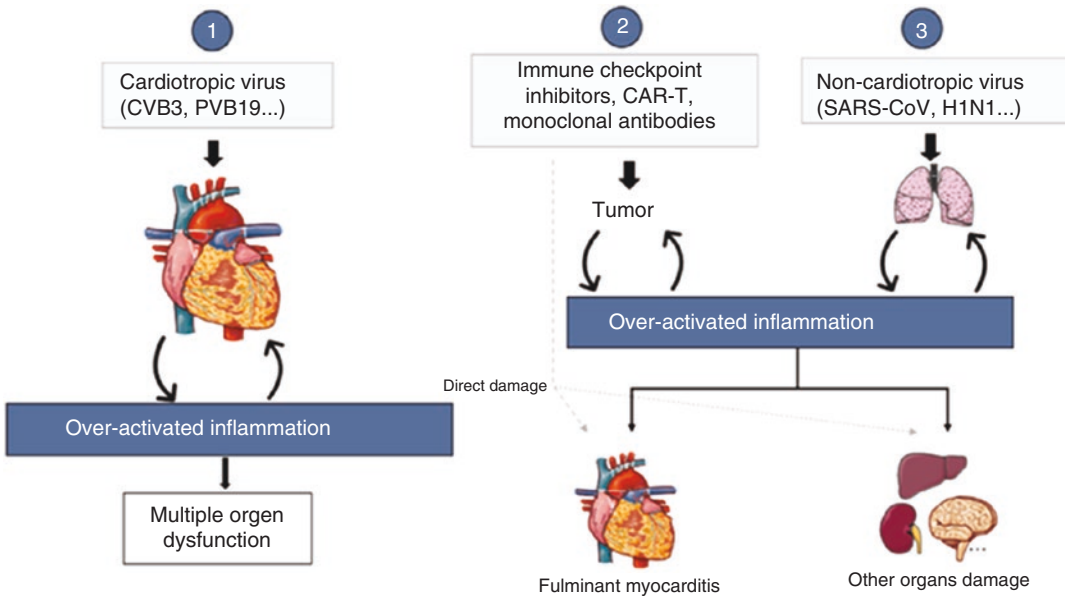

Fig. 5.11 The relationship between common etiologies of FM and over-activated inflammation

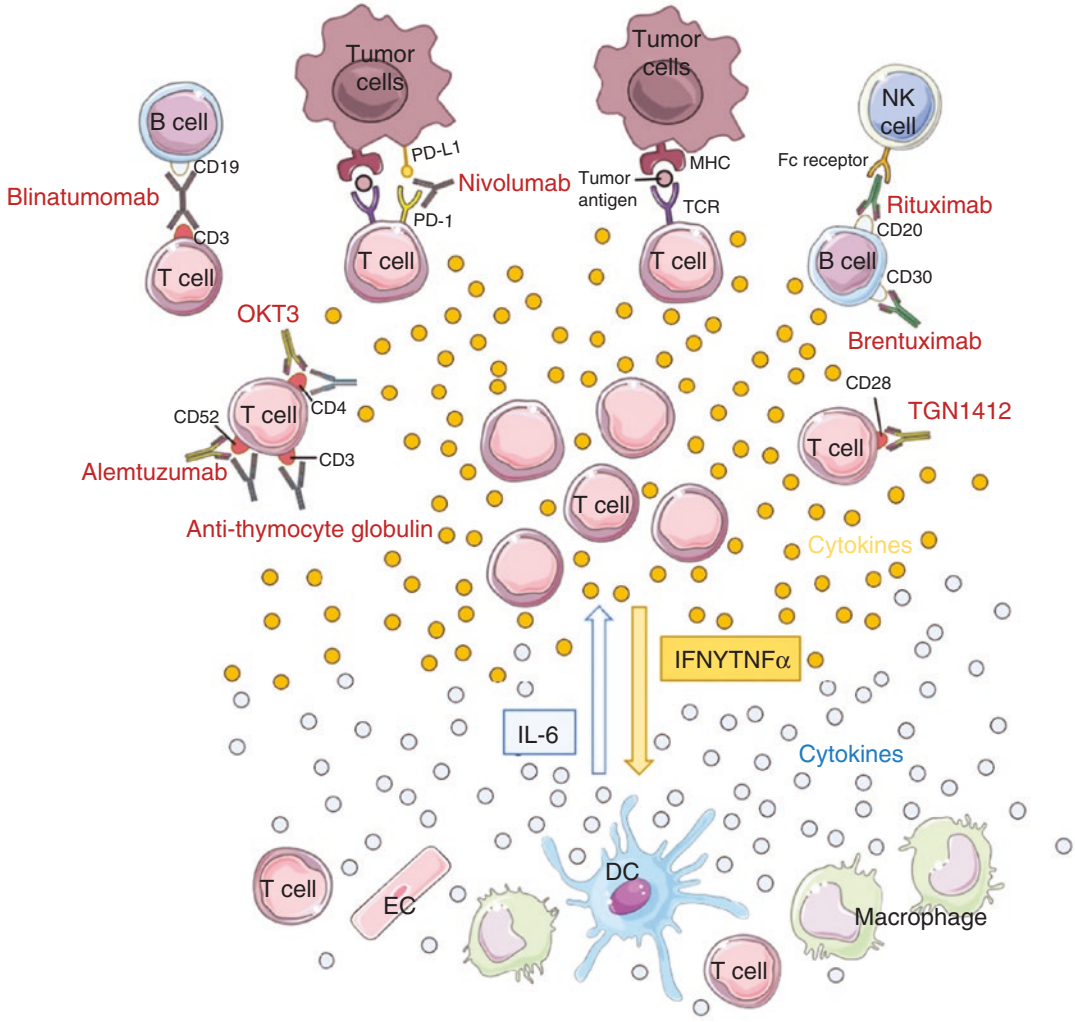

Fig. 5.12 The pathogenesis of anti-tumor therapy-induced cytokine storms

accumulation of innate immune cells in local tissues and prevent the formation and progression of cytokine storms (Fig. 5.12) [80].

The mechanism by which cardiotropic viruses induce cytokine storms require further research. However, the fundamental reason behind the formation of a cytokine storm is the regulatory imbalance between the pro- and anti-inflammatory responses. The positive feedback loop between immune cells, non-immune cells, and cytokines induces the release of excessive cytokines. Our research indicated that several mutually influential cytokines were elevated in the peripheral blood of FM patients (Fig. 5.13).

Among the increased cytokines, it is still unclear which of them plays the most significant role in the formation of cytokine storms. Identifying the key cytokines has tremendous significance in the treatment of FM. In addition, a cytokine storm is the depiction of immune imbalance. In the early stage of inflammation, cells and cytokines form a positive feedback loop to promote the elimination of pathogens. However, this process is controllable and typically does not induce extensive damage to the organism [81]. Therefore, determining how viruses manipulate the immune system and induce immune dysfunction may fundamentally regulate the formation of cytokine storms (Fig. 5.14) [69, 82].

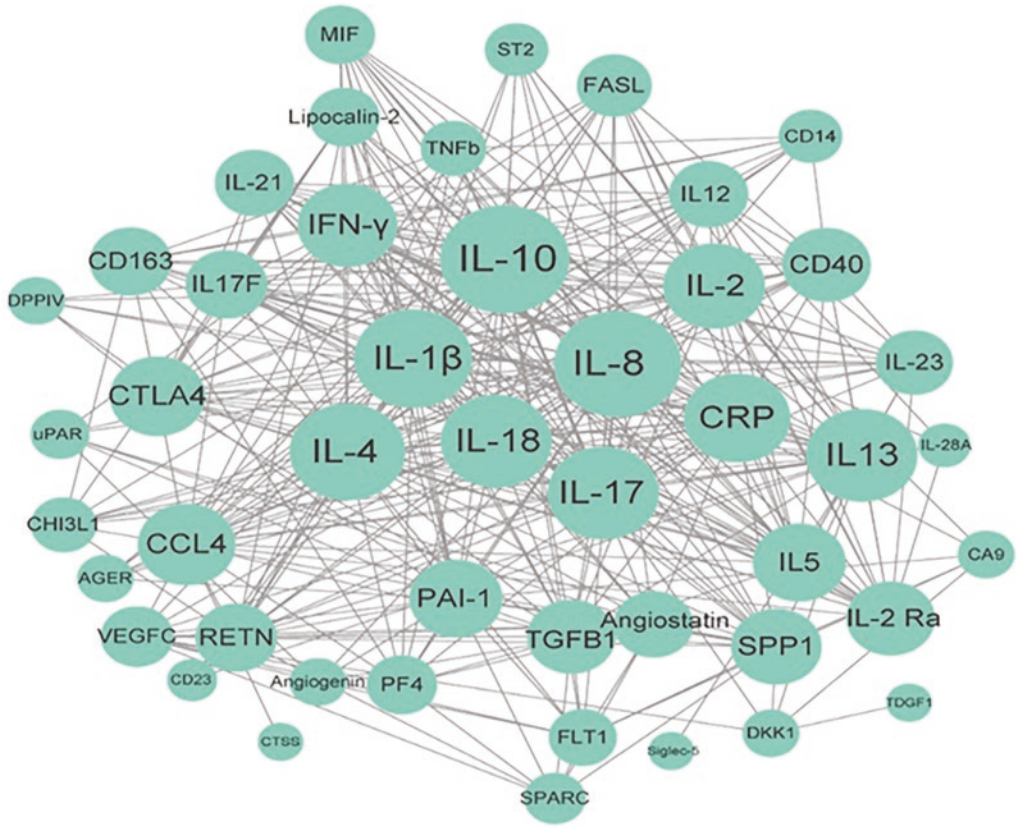

Fig. 5.13 Elevated cytokines in the peripheral blood of FM patients and their interactions

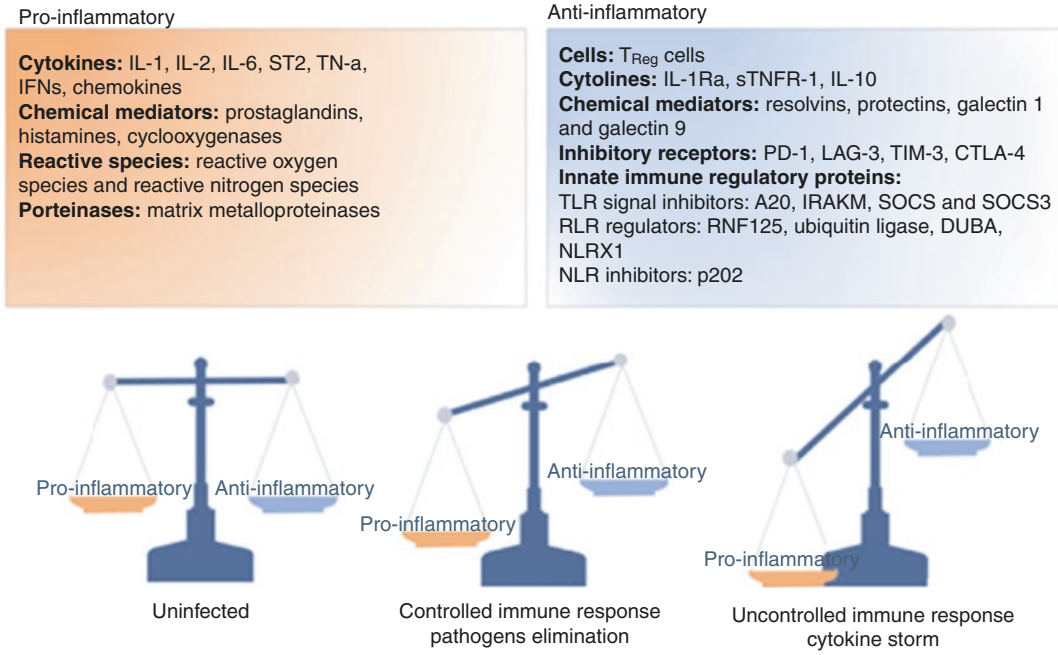

Fig. 5.14 Balance between pro-inflammatory and anti-inflammatory mechanisms during virus infection

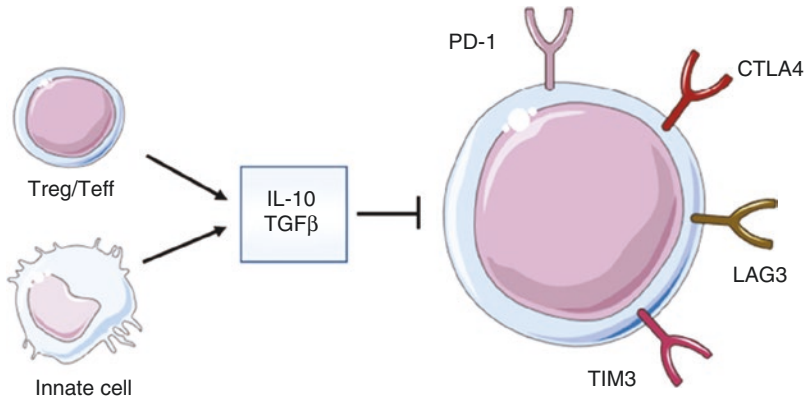

Fig. 5.15 Negative regulatory effects of T cells

5.4 Possible Mechanisms of Cytokine Storm-Induced Cardiac Dysfunction

Extensive T cell infiltration in the myocardium is the most significant depiction of FM patients [83–86]. Excessive activation of T cells induces extensive cardiomyocyte destruction. $CD8^+$ CLT is the primary immune cell that mediates tissue damage. In the local heart of FM patients, abnormally elevated cytokines, such as IL-2, activate T cells and induce tissue injury. Normally, activated T cells are modulated by various negative regulatory signals (Fig. 5.15) [69]. When the negative modulatory system is impaired, over-activated T cells mediate tissue damage.

Cytokines such as TNF-α, IL-1β, IL-6, and IL-18 modulate cardiac contractile ability through multiple signaling pathways. TNF-α also induces myocardial apoptosis, leading to functional cardiac damage.

FM patients, irrespective of etiology, are commonly afflicted by types of arrhythmias, such as atrial or ventricular tachycardia, atrioventricular block, and even cardiac arrest [87–89]. Cytokines such as IL-2, IL-6, IL-17A, and IL-18 prolong the time course of the action potential, TNF-α, IL-1β, and IL-18 affect L-type Ca^{2+} channels, IL-2 inhibits fast Na^+ channels, and IL-17A and VEGF-B exhibit a special function in the K_{ir} channel. The combined function of several cytokines leads to disturbances in electrocardial function and induces arrhythmias in FM patients [90].

In addition, circulating cytokines such as TNF-α, IL-1, IL-6, and IFN stimulate the excretion of platelet agglutinating factor, prostaglandin, peroxide synthetase, leukotrienes, and NO from white blood cells, red blood cells, and platelets. The elevation of these molecules induces the expression of C-reactive proteins, α2 macroglobulin, and fibrinogen, while inhibiting the expression of albumin and transferrin in peripheral blood, leading to the abnormal hemodynamic status of high output and low resistance. In addition, the peripheral blood vessels are dilated, resulting in hypoperfusion of the peripheral organs and microcirculation disturbance.

The above reasons, together with virus-induced damage, lead to rapid cardiac functional deterioration in FM patients. Cancer immune therapy-induced FM is also connected to the above reasons. However, for this type of FM, the accumulation of activated T cells in the local heart is also mediated by drugs. The shared epitopes between tumor cells and cardiomyocytes lead to the direct attack of anti-tumor drugs on the heart (Fig. 5.16) [91]. As for non-cardiotropic viruses, myocardial damage is mainly mediated by reasons 2, 3, and 4. In this type of FM, cardiac infiltration is minimal. However, other organs, especially the lungs, are directly attacked by the virus and usually suffer severe functional dysregulation. Once a cytokine storm is formed, a significant cardiac abnormality can occur, even with few cardiac immune infiltrations.

If patients have a strong immune system or receive treatment prompts, the function of periph-

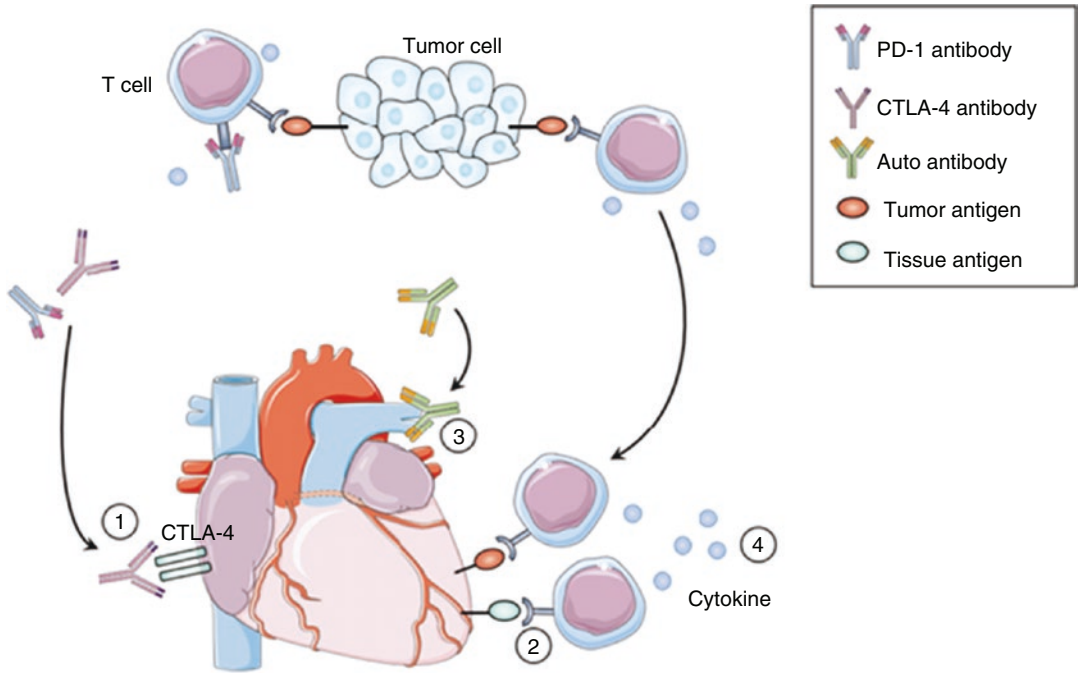

Fig. 5.16 Mechanisms of cancer treatment-induced cardiac damage

eral organs may gradually recover. In contrast, with the combined action of myocardial damage, cardiac contractile dysfunction, and hypoperfusion of peripheral organs, circulatory failure soon occurs and severely endangers the lives of patients.

5.5 In the Future

The specific role of the cytokine storm during the progression of FM has not been fully elucidated, and further research is urgently needed.

The appearance of a cytokine storm is a major cause of death in patients with FM. Therefore, the deep exploration of its pathophysiological mechanism, clinical markers, and treatment methods is of particular importance in reducing the mortality rate of patients. However, the detection of cytokine storms mainly relies on the monitoring of cytokines in the peripheral blood. The short half-life of most cytokines limits their biological effects to autocrine and paracrine effects on local tissues. Only under certain conditions, such as infection, do a few cytokines such as IL-1, IL-6, TNF-α, and IFN increase significantly in peripheral blood, showing an endocrine effect and acting on distant target cells. This discrepancy in cytokine levels between the local heart and peripheral blood makes it difficult to understand the cytokine storm in the heart. In recent years, the development of new technologies such as single-cell sequencing and spatial transcriptomics has provided us with new ideas for further exploring the mysteries of cytokine storms and identifying more accurately the core molecules involved. Cytokine storms play a vital role in the pathophysiology of FM. Therefore, methods of regulating cytokine levels and other immune mechanisms may provide a feasible approach for FM treatment. In the "Chinese society of cardiology expert consensus statement on the diagnosis and treatment of adult fulminant myocarditis," immunomodulatory treatments such as glucocorticoids and human immunoglobulins are recommended to suppress over-activated immune responses by reducing inflammatory cell infiltration, inhibiting the release of inflammatory cytokines, and reducing abnormal antigen-antibody binding. It has been widely used in

clinical practice, and has obtained beneficial clinical results. More targeted cytokine regulation treatment methods remain to be elucidated. It is noteworthy that cytokines are not always detrimental, and blind immunosuppressive therapy is not advisable. Balancing the body's physiological immune response and the occurrence of pathological cytokine storms is an urgent difficulty in the treatment process. In the future, it will be necessary to understand and treat FM using close tracking and testing of clinical samples, combined with more in-depth basic experimental investigations, which will ultimately benefit patients.

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Pathology of Fulminant Myocarditis

6

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Although prominent achievements have been made in the identification, diagnosis, and treatment of myocarditis, the pathological diagnosis of myocarditis is still a difficult problem due to continuous changes of the diagnosis criteria, classification, and pattern of infection. Sobernheim first proposed the diagnosis of myocarditis in 1837. In 1858, the famous German pathologist Virchow popularized the diagnosis of myocarditis. In 1912, Herrick noted the morphological characteristics of ischemic myocardial necrosis. Since then, the diagnosis rates of myocarditis have decreased significantly. The advent of transvenous endomyocardial biopsy (EMB) in 1962 changed the knowledge of the pathophysiology, etiology, and therapeutics of myocarditis. In 1984, eight cardiac pathologists gathered in Dallas, USA, and developed the morphological standards and Dallas Criteria for the diagnosis of myocarditis in EMB samples. Subsequently, the Dallas Criteria was accepted and promoted by the National Institutes of Health, and is still the standard for the identification of myocarditis by pathologists. According to the histological characteristics in EMB and the clinical manifestations, in 1991, Lieberman classified myocarditis into fulminant myocarditis, acute myocarditis, chronic active myocarditis, and chronic persistent myocarditis.

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6.1 Overview of the Pathology of Myocarditis and Fulminant Myocarditis

According to the Dallas Criteria [1], myocarditis can only be diagnosed if myocyte necrosis, degeneration, or both associated with an inflammatory infiltrate adjacent to the degenerating or necrotic myocytes can be demonstrated. However, the morphology of myocardial damage in myocarditis differs from that in ischemic heart disease. According to the types of infiltrated inflammatory cells, myocarditis can be subdivided into lymphocytic, eosinophilic, neutrophilic, giant cell, granulomatous, and mixed cell types. According to the area of inflammatory cell infiltration, myocarditis can be classified into interstitial, perivascular, and endocardial types. According to the severity of cardiac lesions, myocarditis can be divided into slight, mild, moderate, and severe degrees. According to the distribution of inflammatory cell infiltration, myocarditis can be divided into focal, confluent, or diffuse types. Borderline myocarditis refers to a subtype of focal inflammatory cell infiltration

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in the interstitial myocardium, but without obvious myocardial necrosis. According to the Dallas Criteria [1], myocarditis is divided into active, recurrent, rehabilitative, and marginal subtypes, and persistent cardiac viral infection without inflammatory cell infiltration is defined as non-inflammatory viral cardiomyopathy.

Myocarditis is one of the most common causes of sudden cardiac death, especially accounting for sudden deaths in children and young people. Domestic reports stated that the rate of myocarditis detected in autopsies was 2.8%, while in foreign countries it was 4–9%. This rate increased up to 20% in the sudden deaths of children.

Based on etiology, myocarditis is divided into infectious and non-infectious categories. Myocarditis induced by different causes manifest differently in etiologies, pathophysiological mechanisms, and pathological changes(Table 6.1) [2, 3].

6.1.1 Infectious Myocarditis

Infectious myocarditis is caused by an infection of pathogenic microorganisms including viruses, bacteria, fungi, parasites, and so forth. Viral and bacterial myocarditis are the most common types of myocarditis [4]. The main pathogens of infectious myocarditis include the following categories:

1. Viruses. Coxsackie virus, echovirus, adenovirus, cytomegalovirus, varicella-zoster virus, simple herpes virus, Epstein-Barr virus, measles virus, rubella virus, polio virus, influenza virus, acute encephalitis virus, respiratory syncytial virus, arena virus, dengue fever virus, hepatitis virus, human immunodeficiency virus, Junin virus, coronavirus, rabies virus, yellow fever virus, smallpox virus, and so forth.

Table 6.1 The classification and etiology of myocarditis [2, 3]

Types of myocarditis	Etiology	Important examples of myocarditis
Infectious myocarditis	Viruses Pyogenic bacteria Specific bacteria Fungi *Rickettsia* Parasites	Coxsackie viral myocarditis Septic myocarditis Tuberculous myocarditis Diphtheria toxic myocarditis Fungal myocarditis *Rickettsia* myocarditis Chagas myocarditis Toxoplasmosis myocarditis Trichinosis myocarditis
Myocarditis with systemic disease	Collagen-associated vascular disease Acute rheumatic fever Pregnancy	SLE Rheumatic myocarditis Perinatal myocarditis
Granulomatous myocarditis		Sarcoidosis Idiopathic giant cell myocarditis
Drug/toxin-induced myocarditis	Antibiotics, diuretics, antitumor drugs, catecholamines Chemical poisons or heavy metals (phosphine, arsenic, lead, etc.) Biological toxins (venomous snakes, spiders, scorpions, bee bites or stings)	Drug allergic myocarditis
Others	Physical factors (radiation) Transplantation-associated myocarditis	

2. Bacteria. *Streptococcus, Staphylococcus, Pneumococcus, Meningococcus, Mycobacterium, Diphtheria*, Brucella, *Neisseria gonorrhoeae, Haemophilus, Vibrio cholerae,* Listeria, *Actinomycetes, Tularea*, *Salmonella*, Whipple, *Campylobacter*, and so forth.
3. Spirochetes. *Leptospira, Treponema pallidum, Borrelia burgdorferi*, and *Treponema pallidum.*
4. Rickettsia. *Coxiella burnetii*, Rocky Mountain spotted fever, and tsutsugamushi disease.
5. Fungi. *Candida, Mucor, Aspergillosis, Coccidia, Blastomyces, Cryptococcus, Histoplasma*, and so forth.
6. Protozoa/helminth. *Trypanosoma, Toxoplasma, Cysticercosis, Sarcosporidium, Schistosome, Echinococcus, Paragonimus, Trichinella,* Filariasis, roundworms, and so forth.

6.1.2 Non-infectious Myocarditis

1. Systemic disease-associated or immunoreactive myocarditis such as systemic lupus erythematosus (SLE), rheumatism, rheumatoid disease, drug allergic myocarditis, nodular polyarteritis, dermatomyositis, Kawasaki disease, perinatal cardiomyopathy, thrombotic thrombocytopenic purpura, and so forth.
2. Myocarditis caused by physical or chemical factors such as drugs (toxins), heavy metals, biological toxic substances, metabolic disorders (uremia, hypokalemia), and physical injuries.
3. Other types such as sarcoidosis, idiopathic giant cell myocarditis, and so forth.

The clinical manifestations of myocarditis are diverse, ranging from asymptomatic to severe arrhythmia, acute heart failure, cardiogenic shock, and even death. The EMB is the "gold standard" for the clinical diagnosis of myocarditis.

Pathological lesions vary significantly in myocarditis. In some cases, it shows diffuse damage such as myocardial relaxation, lack of elasticity, decreased ventricular tension and compliance, and cardiac enlargement and dilation of the chambers. In other cases, there are myocytic edema, dissolution, necrosis, and interstitial inflammatory infiltration that may lead to acute heart failure, pulmonary edema, cardiogenic shock, or even death. If the disease affects the cardiac conduction system, it can cause various degrees of atrioventricular block, and even ventricular fibrillation which may induce Adam–Stokes syndrome or sudden death.

Myocarditis is usually characterized by myocardial architectural displacement and the presence of focal mononuclear cells and lymphocytes that cause encroachment or scalloping of the sarcolemmal membrane of myocytes, the fragmentation of myocytes with remnants of cytoplasm or bare nuclei, or diffuse infiltration and even the replacement of myocytes by inflammatory cells in severe cases. Extensive myocytolysis and necrosis are rare. The use of Masson's trichrome is helpful in difficult cases because damaged myocytes display a basophilic tinctorial quality [4].

It should be noted that, in terms of pathological diagnosis, the interpretation of myocardial inflammatory cell infiltration must be cautious, because in approximately 5–10% of non-myocarditis deaths (such as mechanical injury, poisoning, etc.), more-or-less focal inflammatory cell infiltrations are present in the myocardial interstitium without myocardial degeneration or necrosis. Only in circumstances where the lesions are severe enough to induce clinical symptoms can the diagnosis of myocarditis be taken into consideration. Under physiological conditions, there are also a few lymphocytes under the endocardium, usually less than 5 cells/mm^2. In 1999, the World Heart Association Consensus Meeting issued a quantitative immunohistopathology standard for myocarditis, which is defined as inflammatory cell infiltration >14/mm^2 [5]. Fulminant or acute progressive myocarditis usually manifests rapid clinical progress and the diffuse infiltration of inflammatory cells in biopsy specimens. The latest diagnostic criteria for fulminant myocarditis was defined as >50/mm^2 inflammatory cell infiltration with obvious myocardial necrosis [6].

The differences between myocarditis and myocardial inflammatory responses, which are two distinct types of pathological changes, should also be noted. In situations such as myocardial infarction or myocardial degeneration, inflammatory responses exist during the clearance of necrotic myocytes, but small focal infarcts usually lie along the coronary arteries. In diseases with systemic leukocytosis such as leukemia and parasitic infections, there are eosinophilia, leukocytosis in the myocardium or small blood vessels, and even scattered or small focal aggregations in the myocardial interstitium, but this is generally not accompanied by myocardial necrosis. In addition, clarifying the pathological characteristics of viral, bacterial, fungal, and parasitic myocarditis in the acute phase, especially pathogen detection in myocardial lesions, will be helpful in the diagnosis and differential diagnosis of myocarditis.

6.2 Pathological Characteristics of Myocarditis of Different Etiologies

6.2.1 Viral Myocarditis

Viral myocarditis is the most common cause of lymphocytic myocarditis. Many viruses can cause different degrees of myocarditis; the most common types are Coxsackie virus groups A and B, echovirus, and adenovirus [2, 4]. The pathogenic mechanism of viral myocarditis includes the direct damage of myocytes by the virus, and through autoimmune responses or inflammatory mediator-induced (such as interleukin-6, interferon, etc.) specific antiviral immune responses. Acute viral myocarditis refers to those who experience a disease course within 3 months.

Pathological Changes A general examination shows that the shape of the heart can be normal or enlarged with dilated chambers (obviously in the left ventricle). The heart weight is slightly increased. No obvious thickening of the ventricular wall is observed, but it shows flattened papillary muscles and trabeculae carneae cordis as well as soft and loose myocardial textures. Faint color and interstitial edema appear in anatomic sections, along with gray-white or gray-yellow spot-like lesions and focal hemorrhages or hemorrhagic necrosis (Fig. 6.1) [7].

Generally, lesions are worse in the left ventricle than in the right, worse in the ventricles than

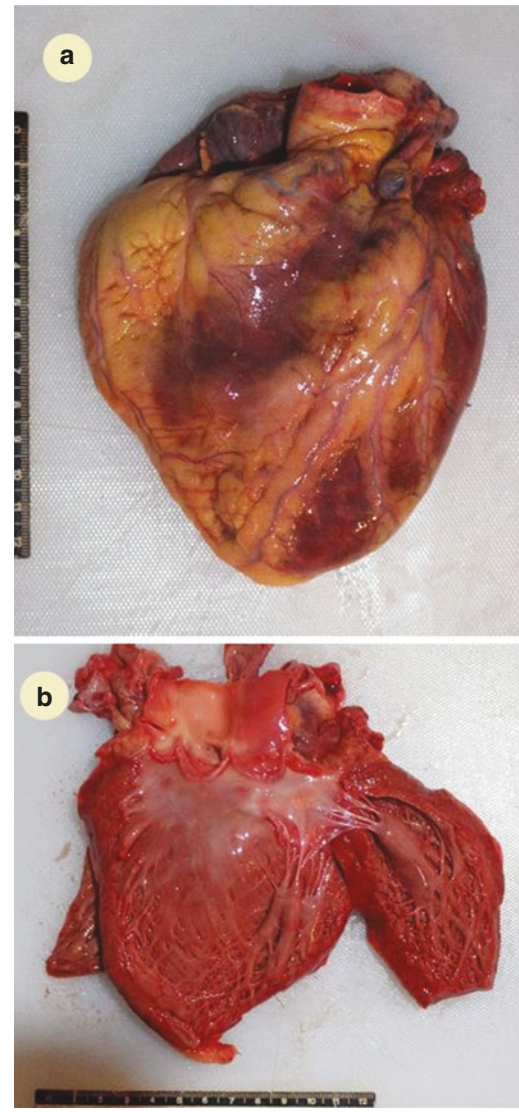

Fig. 6.1 Fulminant myocarditis (female, 30 years old, died 3 days after onset). (**a**) The heart is slightly enlarged (320 g) with a soft texture; (**b**) The section view from panel **a** shows enlargement of the left ventricle, flattened papillary muscles, and trabeculae carneae cordis with light color

in the atriums, and slightly worse in the subendocardial layer than in the outer layer. In most cases, the lesions are widely distributed and diffuse from inside to outside, and are often accompanied by fibrinous pericarditis and exudative pericardial effusion. Auricular or intraventricular thrombosis is uncommon. Compensatory hypertrophy may be present in the chronic phase.

Cardiac Histopathological Examination In the acute phase, degeneration/necrosis occurs in cardiomyocytes, which may involve a single cell or a small group of myocardial fibers. The cardiomyocytes may disintegrate into flakiness or partially dissolve, and even worsen to extensive necrosis, with interstitial and perivascular inflammatory infiltrates predominated in monocytes, lymphocytes, and plasma cells (Fig. 6.2). Neutrophils and eosinophils can be seen occasionally. The chronic phase is manifested by the formation of granulation tissue and interstitial fibrosis (Fig. 6.3), which are mainly concentrated in the muscle bundles and around small blood vessels, and even extended to the endocardium. Scattered small scars may exist (Fig. 6.4). Compensatory cardiomyocyte hypertrophy or degenerative calcification may also be present. In some cases, there may be a few instances of mononuclear, lymphocyte-based inflammatory infiltration. Myocardial necrosis is more obvious and extensive in fulminant myocarditis, with widened myocardial interstitium, edema, and multiple flaky or diffuse inflammatory infiltration.

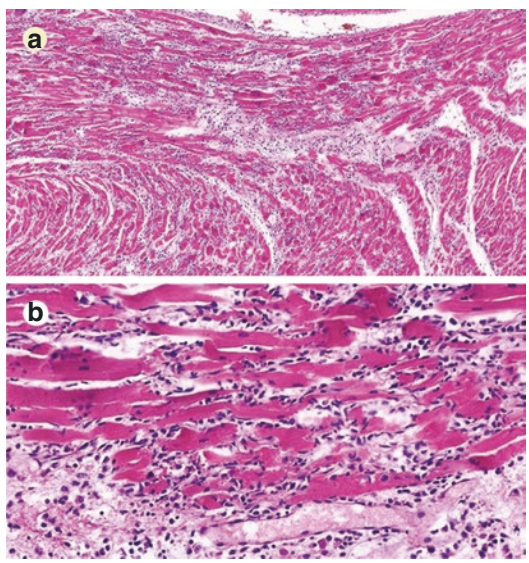

Fig. 6.2 Acute viral myocarditis (male, 13 years old, sudden death). (**a**) Necrosis of myocytes, with extensive infiltrates of monocytes and lymphocytes (HE 40×); (**b**) Necrosis of myocytes, with extensive infiltrates of monocytes and lymphocytes (HE 100×)

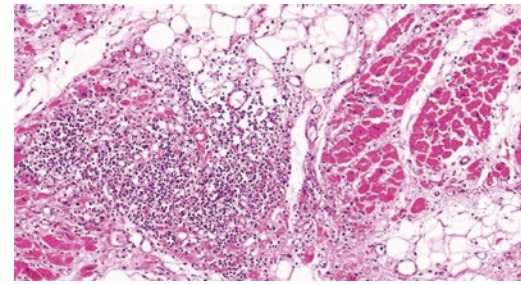

Fig. 6.3 Subacute viral myocarditis (female, 26 years old, sudden death). It shows a necrotic myocardium replaced by granulation tissue and infiltrates of monocytes and lymphocytes (HE 200×)

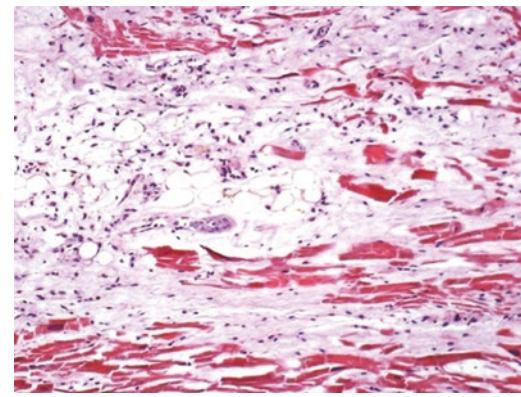

Fig. 6.4 Chronic viral myocarditis (male, 28 years old, sudden death). It shows interstitial fibrosis with infiltrates of monocytes and lymphocytes (HE 40×)

We conducted immunohistochemical examinations of heart specimens from cases of deaths caused by viral myocarditis. The results show that almost all cases have CD68-positive macrophage infiltration, and CD3 and CD4/CD8-positive T cells are present in most cases. Different numbers of CD56-positive natural killer cells and myeloperoxidase (MPO)-positive neutrophils can be found, while CD19-positive B cells are rare or absent (Fig. 6.5).

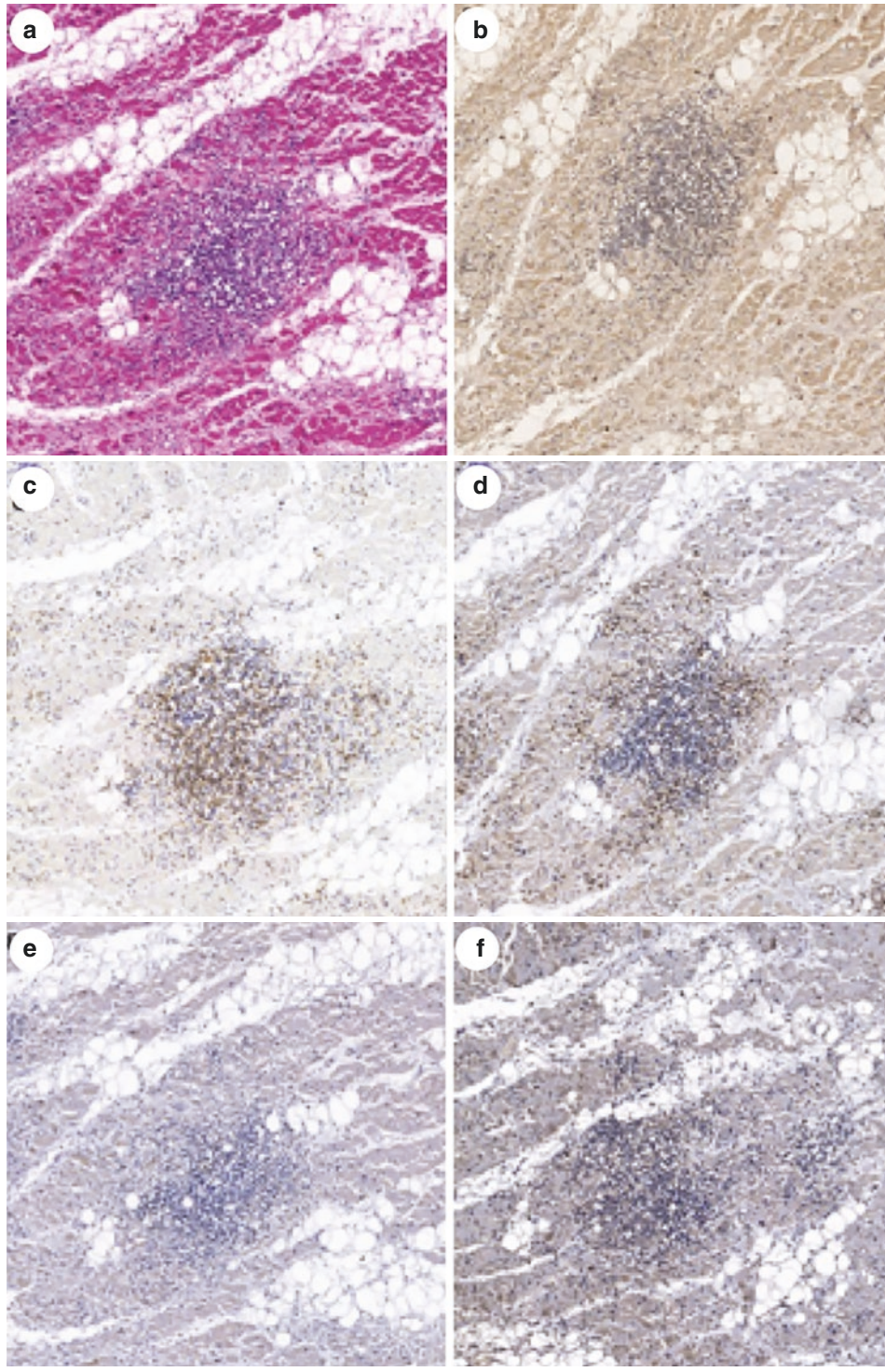

Fig. 6.5 Cell types of inflammatory infiltrates in viral myocarditis. It shows the necrotic cardiomyocytes with infiltrates of massive CD3/CD4/CD8-positive T cells and CD68-positive macrophages, and a few CD19/CD56-positive lymphocytes and MPO-positive neutrophils. (**a**) HE staining; (**b**) CD3; (**c**) CD4; (**d**) CD8; (**e**) CD19; (**f**) CD56; (**g**) CD68; (**h**) MPO

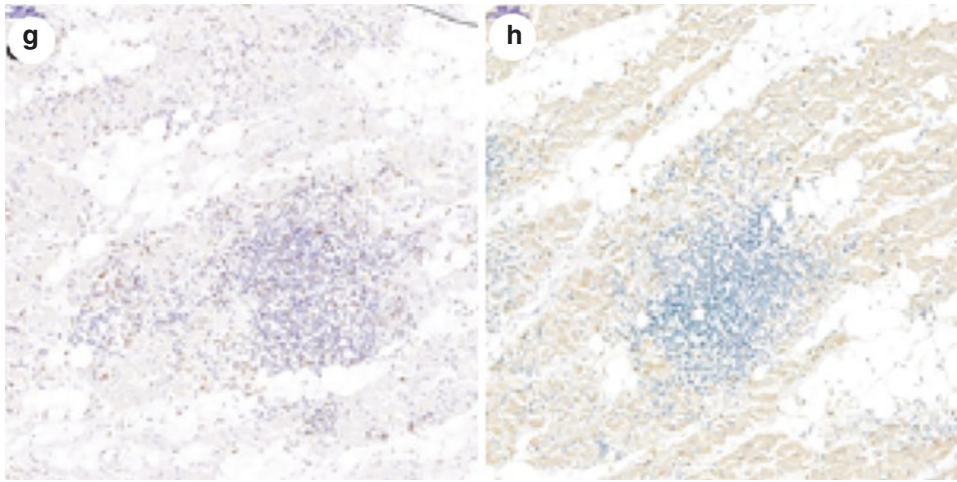

Fig. 6.5 (continued)

The posterior wall of the atrium, ventricular septum, and apical area are usually involved in adult viral myocarditis, and occasionally the cardiac conduction system is affected. When the atrioventricular node and the subendocardial myocardium are affected, inflammatory infiltrations can be found within the cardiac conduction system, such as in the atrioventricular node, atrioventricular bundle (His bundle), and its branches. The cardiac conduction cells may also undergo edema and coagulative necrosis. In some cases of sudden death from myocarditis, the inflammation in the sinus node, atrioventricular bundle, and left and right bundle branches is more serious than that of myocardial inflammation (Figs. 6.6 and 6.7). Even focal myocarditis in the conduction system or adjacent areas (Fig. 6.8) may lead to severe arrhythmia or sudden death. In samples from deaths caused by viral myocarditis, the immunohistochemical examinations of the cardiac conduction system also showed multiple mononuclear cells and lymphocyte infiltrations (Fig. 6.9).

The invasion of a virus into the human body will cause viremia (virusemia), which will then involve multiple organs or the target organs of the virus. Some patients with viral myocarditis may also have pathological damage to the brain, liver, lungs, and other organs, causing changes in relative tissues and cells including inflammation, edema, and necrosis, and leading to viral encephalitis (Fig. 6.10), viral hepatitis [8] (Fig. 6.11), viral pneumonia, and so forth [9].

Borderline myocarditis refers to a small amount of lymphocyte-based inflammatory infiltration without myocardial cell damage in endocardial biopsy examination. If repeated biopsies show persistent lymphocytic infiltration, it is called persistent myocarditis; sparse infiltration of lymphocytes indicate a recovery period of myocarditis, and a lack of inflammatory infiltration indicates that the myocarditis has been cured.

Note that false positives or other lesions should be excluded in endocardial biopsies. Common situations include: a few lymphocytes observed in normal myocardial interstitium but less than 5/mm^2 [10]; normal cells in the interstitium are mistaken for lymphocytes, such as endothelial cells, smooth muscle cells, mast cells, and so forth; extramedullary hematopoietic cells that appear in the necrotic area of ischemic heart disease are mistaken for lymphocytes in myocarditis [11]; the focal infiltration of monocytes and lymphocytes in the interstitium and fibrotic area of dilated cardiomyopathy, which can be distinguished from myocarditis by the absence of cardiomyocyte damage; the excessive secretion of vasopressin/catecholamines by

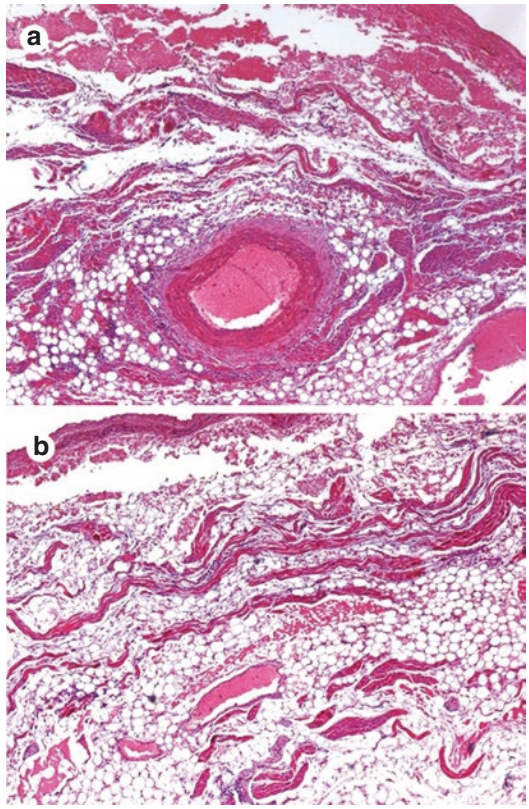

Fig. 6.6 Myocarditis with the cardiac conduction system affected (male, 52 years old, sudden death during antipsychotic treatment). (**a**) Infiltration of monocytes and lymphocytes around the sinus node artery, with hemorrhage (HE 40×); (**b**) Edema within the sinus node, with infiltration of monocytes, lymphocytes, and hemorrhage (HE 40×)

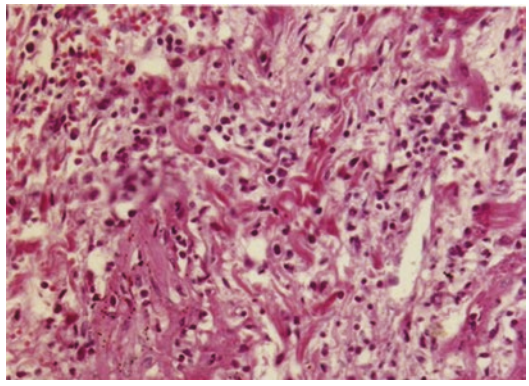

Fig. 6.7 Viral myocarditis (male, 25 years old, sudden death after fainting). Degeneration/necrosis of conduction cells in the atrioventricular node, with the infiltrate of monocytes and lymphocytes (HE 250×)

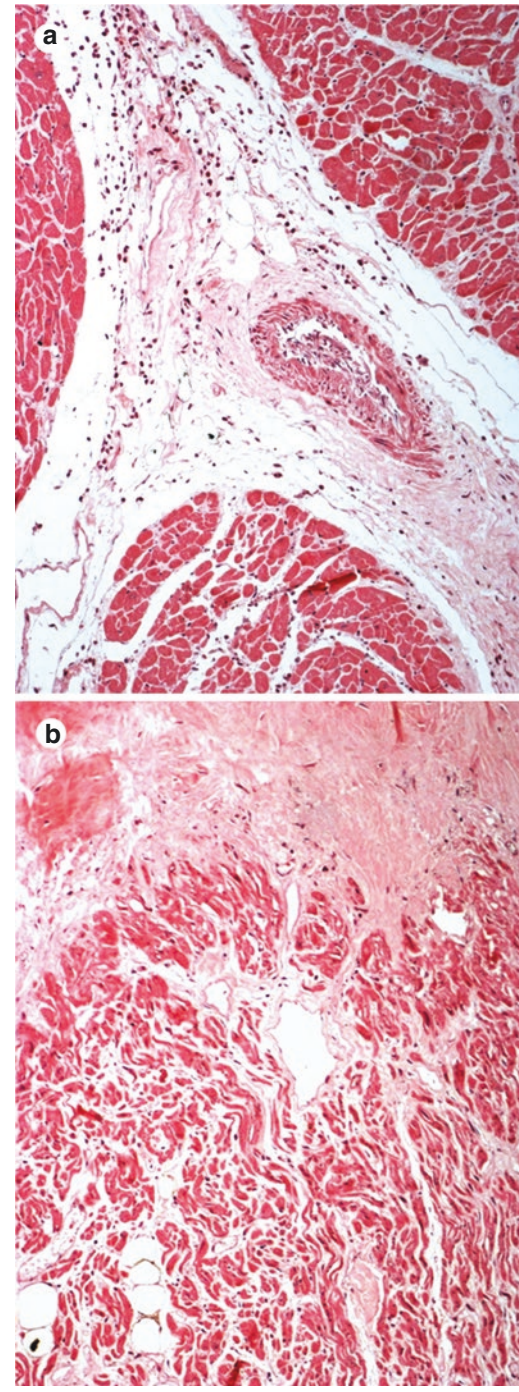

Fig. 6.8 Focal viral myocarditis (male, 40 years old, sudden death). (**a**) Focal infiltration of monocytes and lymphocytes under the His bundle on the top of the ventricular septum; (**b**) No inflammatory infiltration in the His bundle near the cardiac conduction system (HE 100×)

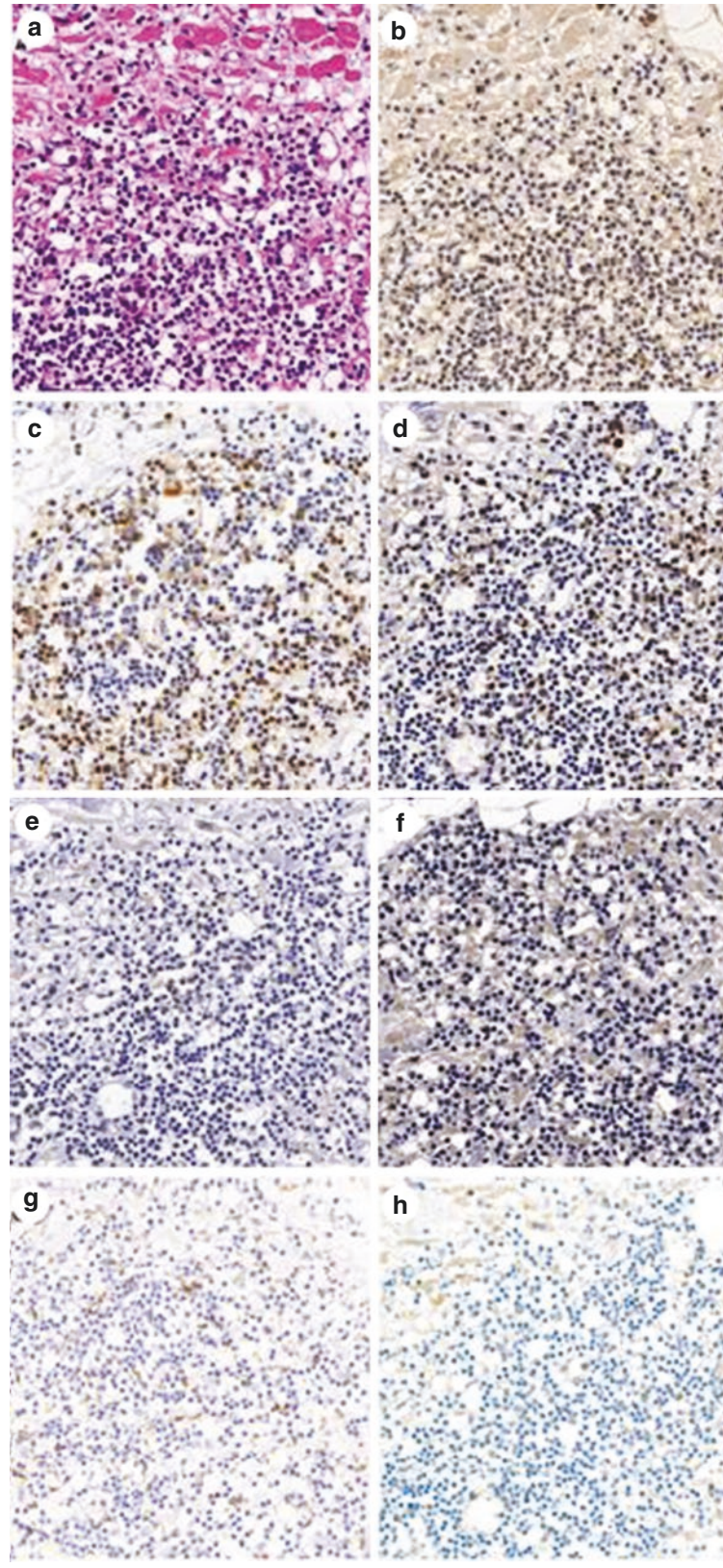

Fig. 6.9 Cell type of infiltration in the His bundle in viral myocarditis. Necrotic myocardium with infiltrates of massive CD3/CD4/CD8-positive T cells and CD68-positive macrophages, as well as a few CD19/CD56-positive lymphocytes and MPO-positive neutrophils. (**a**) HE staining; (**b**) CD3; (**c**) CD4, (**d**) CD8; (**e**) CD19; (**f**) CD56; (**g**) CD68; (**h**) MPO

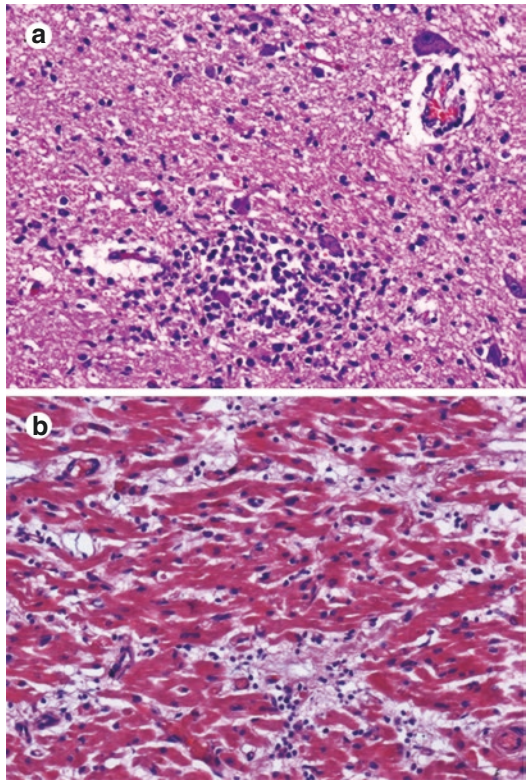

Fig. 6.10 Viral encephalitis combined with myocarditis (male, 2 years old, died after 3 days of fever). (**a**) Viral encephalitis (medulla oblongata); (**b**) Viral myocarditis (HE 200×)

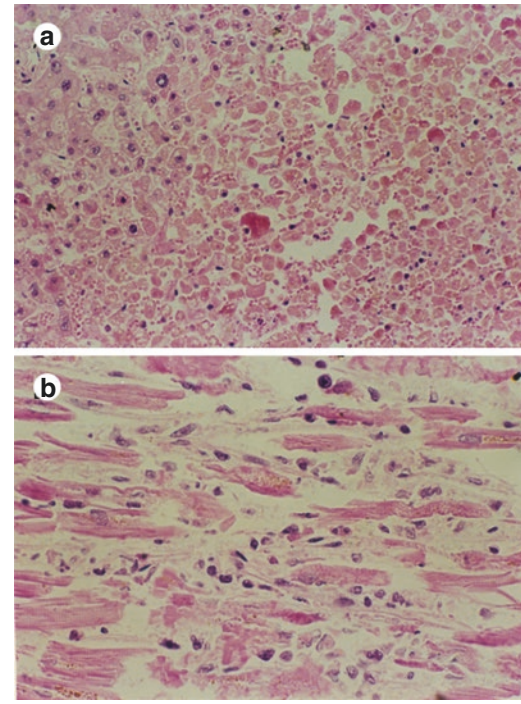

Fig. 6.11 Acute severe hepatitis B combined with myocarditis (female, 53 years old, death after 2 days of right upper abdominal pain). (**a**) Severe viral hepatitis, massive necrotic hepatocytes (HE 200×); (**b**) Viral myocarditis, necrotic cardiomyocytes with infiltrates of monocytes and lymphocytes (HE 400×)

pheochromocytoma cells may cause a rupture of cardiomyocytes and a few infiltrates of monocytes and lymphocytes in the interstitium, showing pathological changes similar to myocarditis [12], which can be distinguished by the distribution of the damaged area and the types of inflammatory cells. For identification, the characteristic of vasopressin/catecholamine-induced lesions is that myocardial injury is mainly manifested around interstitial arterioles with mixed inflammatory infiltration of neutrophils and lymphocytes; Masson's trichrome staining can be used to distinguish punctuated pathological calcification of cardiomyocytes and toxoplasma myocarditis. Typically, an endocardial myocardial biopsy will not locate tumor metastasis, but lymphocytic and hematopoietic malignant tumors such as leukemia and lymphoma can cause atypical changes in the subendocardial cardiomyocytes, but myocardial damage is rare. Immunohistochemical staining and genetic testing can help to differentiate from myocarditis and determine whether it is benign or malignant.

Clinically, it is difficult to definitely diagnose viral myocarditis. The increased viral titer in serum will provide a certain amount of help. An endocardial biopsy is crucial to confirm the diagnosis, but it is still difficult due to the limitations of specimen collection. The positive rate of virus detection is low in endocardial biopsy specimens, and the in situ nucleic acid hybridization, polymerase chain reaction-single strand conformation polymorphism analysis (PCR-SSCP), nested PCR, and other technologies can be helpful in improving the success rate of virus detection.

6.2.2 Bacterial Myocarditis

Bacterial myocarditis refers to myocardial inflammatory lesions caused by direct bacterial infection of the myocardium, the effects of toxins produced by bacteria, or due to allergic reactions induced by products from bacteria. Most bacterial myocarditis is purulent. Myocarditis induced by tubercle bacilli, *Corynebacterium diphtheria*, and *Bacillus typhia* can also be seen. Bacterial myocarditis is less common than viral myocarditis, and the underlying mechanisms of bacterial myocarditis include direct bacterial invasion, bacterial toxins, immune response, and so forth [13].

In recent years, the number of patients with bacterial myocarditis has continued to increase due to the increased incidence of immune system impairments [14]. Usually, cases of suspected bacterial myocarditis based on clinical tests are rarely diagnosed [15]. Although endocardial myocardial biopsies show high specificity, their sensitivity is low; thus, the diagnosis of bacterial myocarditis is rarely confirmed before the patient dies [16].

According to the size of the lesions, bacterial myocarditis can be divided into diffuse and localized myocarditis. According to pathological characteristics, it can be classified into substantial myocarditis with myocardial degeneration and interstitial myocarditis with interstitial damage; according to the course of disease, it can be divided into acute and chronic bacterial myocarditis. The healing of bacterial myocarditis generally occurs through the repair of granulation tissues and the formation of scars.

The pathological changes of suppurative and tuberculous myocarditis are described in the following sections.

1. Suppurative myocarditis (pyogenic myocarditis), also called myocardial abscess, refers to myocarditis characterized by a large number of neutrophils in the myocardium and the formation of pus. It is often a complication of purulent bacterial infection in other parts. The pathogens of suppurative myocarditis primarily contains *Staphylococcus aureus, Streptococcus, Pneumococcus,* and *Meningococcus*. Most cases of suppurative myocarditis are the consequences of sepsis, including acute angina, tonsillitis, pneumonia, epidemic cerebrospinal meningitis, urinary tract infection, metritis, mastitis, and even postoperative bacterial infections [17]. Bacterial endocarditis can also lead to suppurative myocarditis. Bacteria can be seen in suppurative myocarditis using bacterial culture and (or) microscopic examination.

   Pathological changes: Generally, multiple abscesses of different sizes can be found on the surface and cross sections of the heart. Usually, myocardial abscesses are numerous and small in size, within 1 cm in diameter, and most are round or pin-shaped yellow-green lesions, and are difficult to notice unless examined by microscope; on a few occasions, cord-like purulent bands can be seen, and dark red hemorrhagic reaction zones exist around the abscess. Pus exists in large abscesses and invades the entire layer of the ventricular wall, and can even cause heart rupture. A thin layer of fibrous tissue occasionally forms after the healing of an abscess, and the layer gradually bulges under the pressure of the ventricle, finally forming an aneurysm. Death may result due to cardiac tamponade when the acute rupture of the ventricular wall or an aneurysm occurs. In addition, abscesses in the myocardial wall can invade the epicardium, where fibrin is locally attached. Abscesses can also break into the pericardial cavity, resulting in purulent pericarditis.

   Histopathological examination of the heart: There is interstitial neutrophil infiltration or multiple small abscesses. Sometimes bacterial colonies will be found in the center of abscesses. These colonies are metastatic bacterial colonies from sepsis or suppurative embolus from bacterial endocarditis (Fig. 6.12). Myocardial interstitial edema is obvious. Thrombosis or various emboli can be observed in small blood vessels, such as bacterial emboli, pus emboli, hyaline thrombus, and so forth. The affected cardiomyocytes often undergo degeneration and necrosis (Fig. 6.12d). In some cases, bacterial endocarditis or valvulitis can be seen, and serious

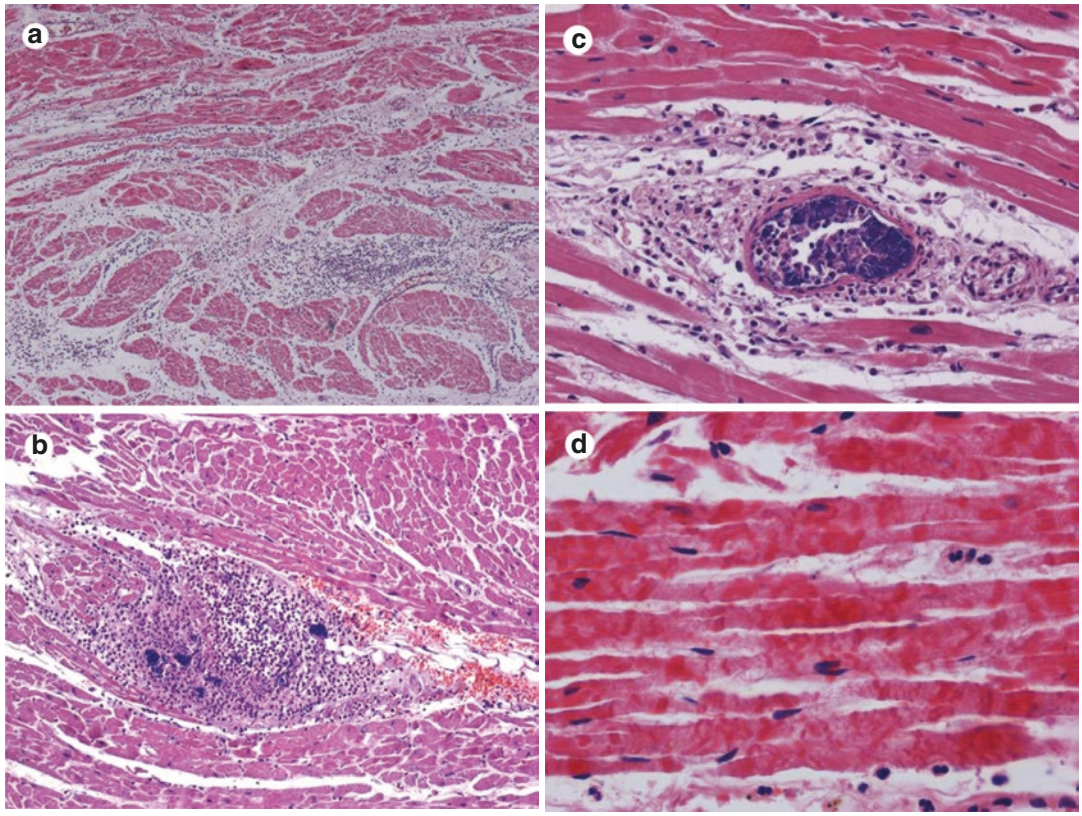

Fig. 6.12 Suppurative myocarditis. (**a**) Diffuse infiltrates of massive neutrophils in interstitium (HE 40×); (**b**) Formation of small abscess with necrosis of cardiomyocytes. The bacterial colonies and hemorrhagic zones are shown (HE 200×); (**c**) Pus embolus and bacterial embolus within a small vessel, with inflammatory infiltrates and tissue edema (HE 400×); (**d**) Necrosis in the contraction zone of the papillary muscle with scattered infiltrates of neutrophils (HE 200×)

consequences or sudden death may result if the cardiac conduction system is invaded or small abscesses have formed (Fig. 6.13). If the course of disease is prolonged, fibrosis and the organization of myocardial tissue will occur, leading to granulation tissues and scars.

2. Tubercular myocarditis, also known as myocardial *Tuberculosis*, is a special type of myocarditis caused by mycobacterium *Tuberculosis*. It is rare in clinical practice, and mostly stems from the blood transmission of primary *Tuberculosis* or the direct spread of tuberculous pericarditis and epicarditis. Characteristic tubercles can be seen in lesions, which mainly affect the pericardium, while heart valves and cardiomyocytes are rarely involved. It is very difficult to diagnose tuberculous myocarditis before death, and it is usually found in autopsies. Myocardial *Tuberculosis* was found to account for 0.25–0.28% of tubercular cases by autopsy.

Pathological changes: Tuberculous myocarditis is classified into nodular, miliary, and diffuse types; the nodular type is the most common.

- Nodular type: This is also known as tuberculoma. It is mostly located in the right atrium, and the nodules are round or oval, grayish-yellow, and solid, with a diameter of 1–7 cm. Nodules may be surrounded by fibers of different amounts, with yellow-white caseous necrotic material filled in the center. The nod-

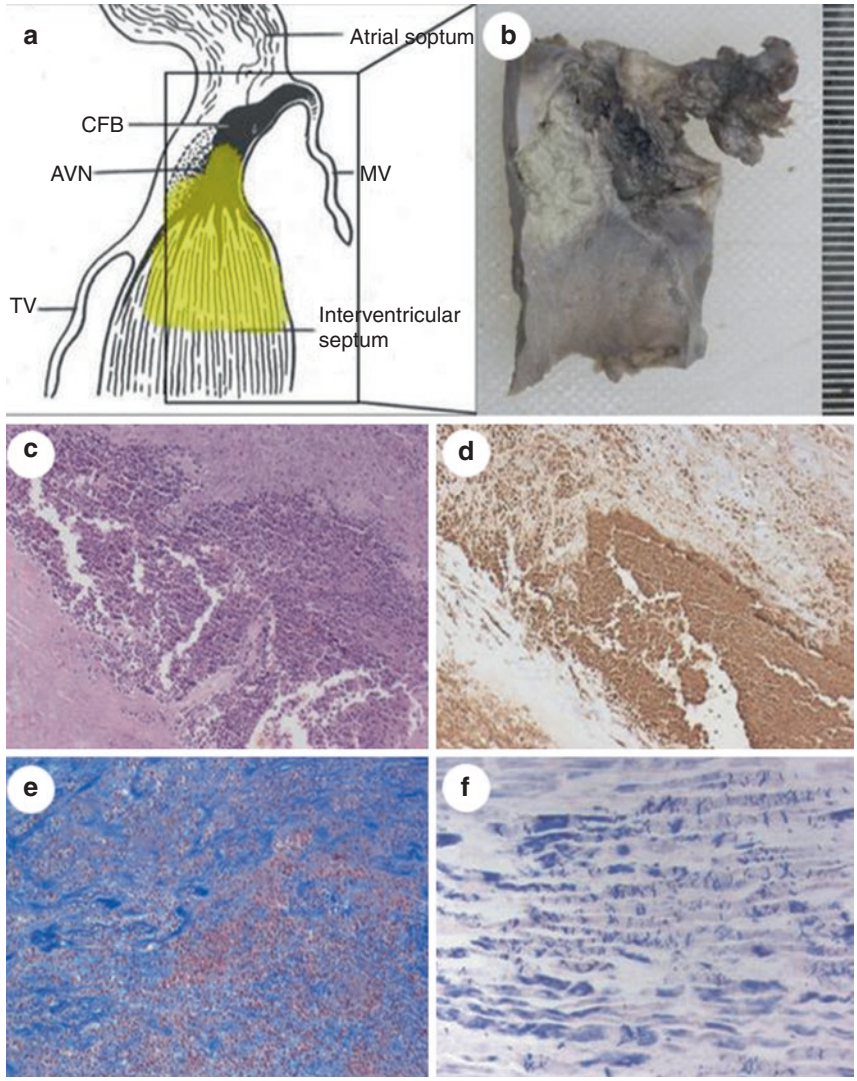

Fig. 6.13 Bacterial endocarditis with invasion of the atrioventricular node and abscesses in the interventricular septum. (**a**) A diagram of the atrioventricular septum and the location of an abscess (the area in yellow); (**b**) The top part of the interventricular septum; bacterial endocarditis of the mitral valve (MV) and a small pale abscess are shown; (**c**) An abscesses in the interventricular septum with massive infiltrates of neutrophils (HE 100×); (**d**) Immunohistochemical staining of MPO-positive neutrophils in a continuous slide (SABC 100×); (**e**) Necrosis of conduction cells in the atrioventricular node (AVN) with massive infiltrates of neutrophils (Masson 100×); (**f**) Multiple necroses in contraction bands of the left ventricle (PTAH 100×). PTAH, Mallory Phosphotungstate Hematoxylin

ules are either single or multiple. Ulcers or thrombosis may form when the endocardium is involved. The centers of nodules under microscopic views are mainly composed of caseous necrotic materials with a few Langhans giant cells on the edge of necrotic foci and fibrous tissues around the outer layer. There is lymphocyte infiltration in the fibrous tissues and the adjacent myocardium.

- Miliary type: Commonly found in patients with miliary *Tuberculosis*. The number of nodules varies, and they are mostly located in

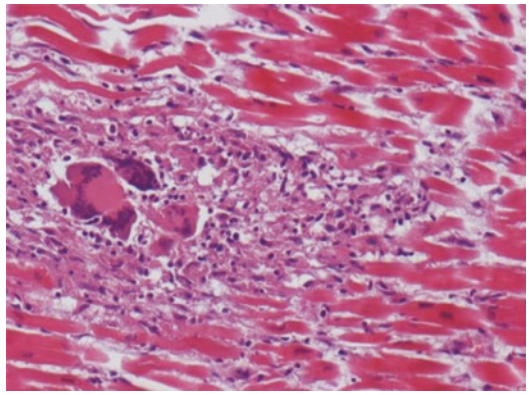

Fig. 6.14 Tubercular myocarditis (male, 40 years old, died from systemic miliary *Tuberculosis*). A myocardial *Tuberculosis* nodule with caseous necrosis and Langhans giant cells in the center, and necrosis in ambient cardiomyocytes (HE 400×)

the epicardium and endocardium. The nodules have a grayish-yellow, translucent appearance with diameters of 1–3 mm. The nodules can only be found under microscopic examinations, located in the connective tissues between muscle bundles, and are mostly distributed along the blood vessels, with caseous necrosis or several Langhans multinucleated giant cells in the center of nodules surrounded by many proliferated epithelioid cell and lymphocytes. Necrosis may appear in ambient cardiomyocytes (Fig. 6.14).

- Diffuse type: This type is rare and is usually caused by the expansion of pericardial *Tuberculosis*. The myocardium with lesions is grayish-yellow and distributed in stripes. Under the microscope, the myocardial tuberculous granulation tissues show diffuse hyperplasia, mainly composed of epithelial cells, lymphocytes, and multinucleated giant cells, with varying degrees of caseous necrosis. Mycobacterium *Tuberculosis* can often be detected here.

6.2.3 Fungal Myocarditis

Fungal myocarditis generally refers to an inflammatory lesion of the myocardium caused by a fungal infection. It is commonly seen in patients with prolonged use of antibiotics, adrenocortical hormones, and immunosuppressants. Therefore, fungal myocarditis is often part of systemic fungal infections. The pathogens mainly consist of *Candida* and *Mucor*. Primary fungal myocarditis is extremely rare. Fungal toxins may induce necrosis of cardiomyocytes, leading to inflammation of the myocardium.

Pathological changes: Generally, myocardial lesions of fungal myocarditis show no difference from fungal infections of other organs. In most cases, purulent or hemorrhagic necrotic foci of varying sizes are present in the heart.

Histopathological examinations: In the early stage, inflammatory lesions scatter in the interstitium, then spread and merge. The appearance of lesions varies according to different pathogens. Some have prominent hemorrhaging and necrosis but mild inflammation, while others are dominated by neutrophil infiltration accompanied by tissue necrosis and abscess formation. In the center of the necrosis foci, liquefaction emerges rapidly to form pus cavities with massive neutrophil infiltration and remaining blood vessels. The foci contain many fungal filaments and spores, such as *Aspergillus, Candida*, and *Mucor*. It is easier to find fungal hyphae in the acute phase. In the chronic phase, there are obvious macrophage infiltration, granulomatous transformation, and even multinucleated giant cells. Even *Tuberculosis*-like nodules may exist in the chronic phase, but the necrosis is not as severe as that in *Tuberculosis*, and mycobacterium *Tuberculosis* is absent. These are the main points for the identification and differentiation between fungal and tuberculous myocarditis. (Fig. 6.15).

Common fungi show certain microscopic characteristics. For example, aspergillus hyphae are mainly mycelium, and HE staining exhibits blue-purple with uniform diameters of 7–10 μm. The mycelial branches are radially arranged at an acute angle of 45°. Spores and hyphae can be seen in *Candida*. The spores are round or ovoid, and the hyphae are straight and slender with a separated appearance. It is clearer to display *Candida* with Gram or silver stain. *Mucor* is more likely to invade blood vessels. Its hyphae are mostly distributed in the blood vessel wall

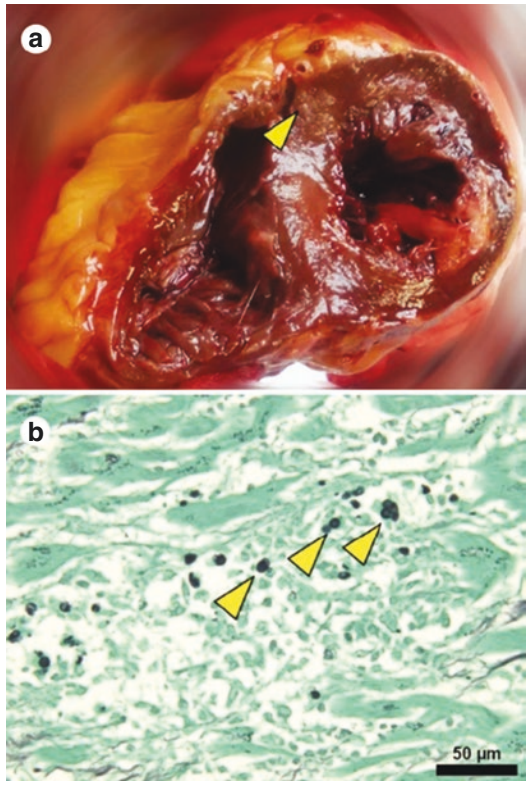

Fig. 6.15 Fungal myocarditis (male, 79 years old, died after 21 days of antibiotic therapy; *Candida albicans* was found in blood and urine cultures) [18]. (**a**) A small nodule in the cross section of the heart (yellow arrow); (**b**) The accumulation of fungi in the nodule (yellow arrow; Grocott methenamine silver stain)

or vascular cavity. The hyphae are thick and not separated, with a diameter of 6–40 μm. The width of hyphae is uneven with many wrinkles, and the few but blunt branches distribute in right angles, without spores.

6.2.4 Systemic Disease-Associated Myocarditis

Myocarditis can also occur in some systemic autoimmune diseases and perinatal women. In the former situation, it is common in connective tissue diseases such as SLE, rheumatoid arthritis, polymyositis/dermatomyositis, thrombotic thrombocytopenic purpura, Wegener's granulomatosis, ankylosing spondylitis, and mixed connective tissue disease. Among these diseases, SLE, rheumatoid arthritis, and polymyositis/dermatomuscular account for most of the related myocarditis. As for myocarditis in perinatal women, it is so-called perinatal myocarditis, also known as perinatal cardiomyopathy.

In immune-mediated myocarditis, it shows pathological characteristics of a large number of monocyte and lymphocyte infiltration. Lupus myocarditis, rheumatic myocarditis, and perinatal myocarditis will be described here.

1. Lupus myocarditis indicates a severe condition in SLE. It may be the first manifestation of SLE, and may also occur during the follow-up period, especially in untreated patients with SLE. The heart lesions in SLE includes pericarditis, myocarditis, endocarditis, and vascular diseases, of which lupus pericarditis is the most common (Fig. 6.16). Although the incidence of heart lesions is lower than that of skin and kidney damage, it still constitutes up to 50% of lesions.

   The pathogenesis of SLE contains systemic disorders characterized by cell damage caused by immune complexes among which anti-nuclear antibodies play a vital role. Anti-nuclear antibodies attack degenerated or damaged cell membranes. Once these antibodies gain access to the nucleus, the swelling, fragmentation, and dissolution of the nucleus will be induced. After this process, it will form a kind of uniform, structureless, round-shaped small body.

   These bodies will be eliminated from the cells. These bodies are purple-red in HE staining; thus, they are called lupus or hematoxylin bodies, which are characteristic evidence for the diagnosis of SLE. Lupus bodies have a chemotactic activity to neutrophils and macrophages; thus, it can promote phagocytosis in the presence of complements. Once a cell undergoes endocytosis of lupus bodies, it will be called a lupus erythematosus cell or lupus cell (Fig. 6.16a). The pathological changes of SLE vary, but there is no specific changes of SLE, except for lupus cells. Acute necrotic arteritis and arteriositis are the main lesions of

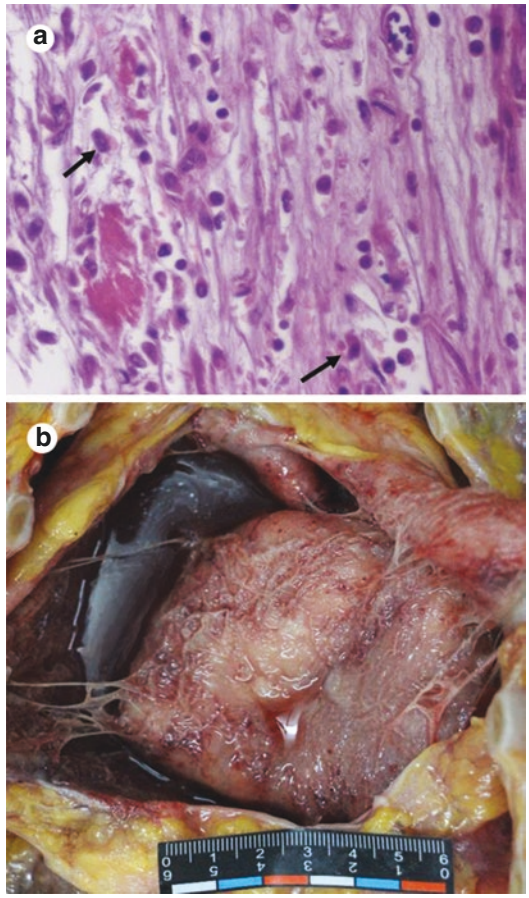

Fig. 6.16 SLE (female, 64 years old; she had SLE for more than 10 years, and died during infusion when the disease worsened). (**a**) Lupus cells are occasionally seen (black arrow) (HE 400×); (**b**) Villous heart and pericardial effusion

this disease. In the active stage, it is mainly fibrinoid necrosis; in the chronic stage, the blood vessel wall becomes fibrotic, with narrowed lumens and lymphocytes, edema, and an increased matrix around the vessels.

Pathological changes: The heart is generally enlarged in lupus myocarditis, and may be accompanied by pericardial effusion and villous heart (Fig. 6.16b). The endocardium is focally thickened, and the heart valve may become involved in non-bacterial verrucous endocarditis (Libman–Sacks endocarditis). The neoplasms often invade the mitral or tricuspid valve [19].

Histopathological examinations: Fibrinous pericarditis is characterized by fibrinous necrosis under the microscope, accompanied by mixed inflammatory infiltrates and granulation tissues (Fig. 6.17); lymphocytic myocarditis (similar to viral or idiopathic myocarditis) is present in the myocardium, and manifests with the extensive degeneration of cardiomyocytes, intermittent edema, lymphocyte infiltration, and so forth. (Fig. 6.18) [19].

Fibrinous vasculitis is another histological feature of SLE. The lesion mainly involves

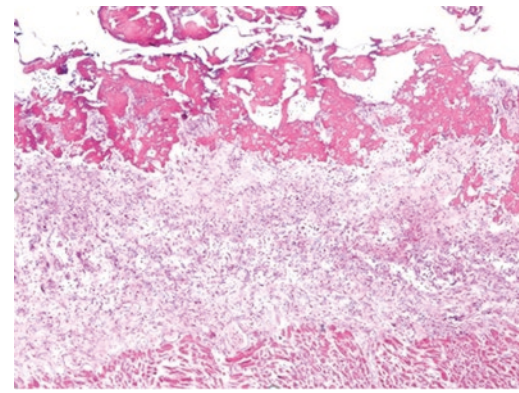

Fig. 6.17 Lupus pericarditis and lupus myocarditis. The fibrinoid necrosis of the pericardium and formation of granuloma (HE 40×)

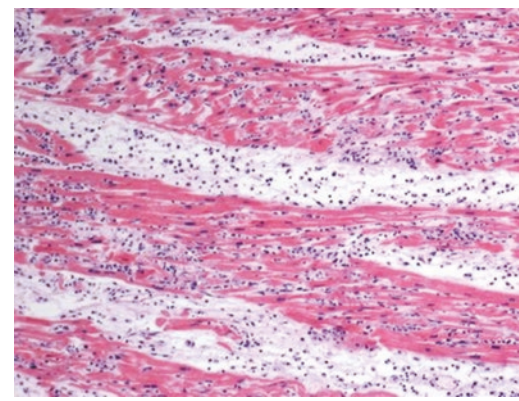

Fig. 6.18 Lupus myocarditis (male, 24 years old, diagnosed with SLE for 7 months, died after a severe fever). Focal necrosis of the ventricular cardiomyocytes with edema and massive infiltrates of monocytes and lymphocytes (HE 40×)

the small and middle arteries, where the blood vessel walls are replaced by amorphous fibrinoid substances. In lupus myocarditis, fibrinous vasculitis can be observed in the small arteries within the myocardial interstitium, which means fibrinous necrosis of the blood vessel walls with lymphocytes infiltration and perivascular edema. This illness is characterized by permanently existing antigens and uncleared immune complexes. Immunofluorescence will show the depositions of immunoglobulin, complement, and fibrinogen, which indicate that the disease is caused by immune complexes, which is how to differentiate it from viral myocarditis. In advanced stages of fibrinous vasculitis, the myocardial intermural arteriole may develop into "onion-skin" arteriopathy; even the arteries of the cardiac conduction system will be involved, which may cause severe arrhythmia or sudden death (Fig. 6.19).

For the endocardium, microscopic examination will find focal fibrosis with infiltrated monocytes and lymphocytes (Fig. 6.20). If non-bacterial valvular verrucous endocarditis is accompanied, the vegetations of valves are composed of fibrin, necrotic debris, and inflammatory cells.

Lupus myocarditis is often associated with coronary arteritis which leads to thickening of the arterial intima and narrowing of the lumen,

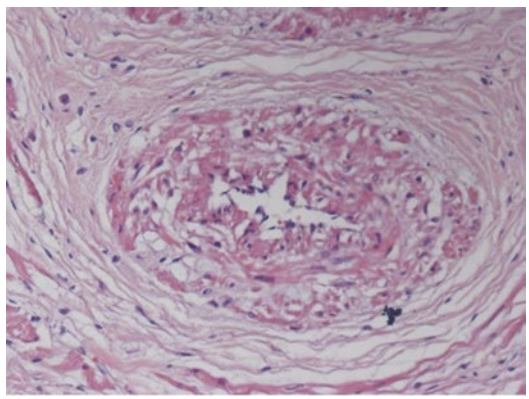

Fig. 6.19 Lupus myocarditis (male, 16 years old, died during wrestling). Obstruction of the sinus node artery which show edema and "onion-skin" arteriopathy (HE 400×)

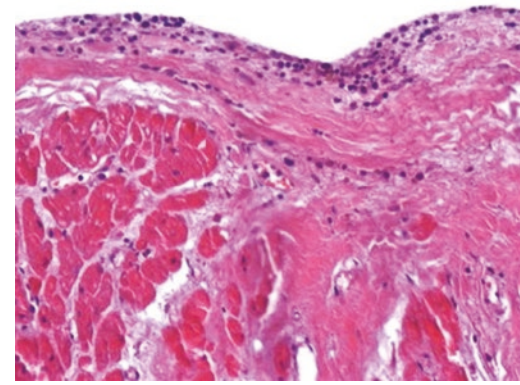

Fig. 6.20 Lupus endocarditis (male, 24 years old, diagnosed with SLE for 7 months, died after a severe fever). The focal thickening of the endocardium and a few infiltrates of monocytes and lymphocytes (HE 100×)

even causing diffuse small myocardial infarction foci and other lesions.

Attention should be paid to the differences between lupus myocarditis and drug-related myocarditis, especially in patients with SLE who are treated with quinidine. However, if no lupus body or lupus cells are found, it is difficult to distinguish lupus myocarditis from rheumatoid myocarditis. Cellulose vasculitis is not a unique characteristic of SLE, as it is also seen in rheumatoid disease, polyarteritis nodosa, and so forth; thus, it requires differential diagnosis between all the abovementioned diseases.

2. Rheumatic myocarditis is the main pathological manifestation of rheumatic carditis in the acute phase of rheumatic heart disease, which also includes rheumatic endocarditis, rheumatic pericarditis, and so forth. Rheumatic heart disease is the most common acquired heart disease in the world, and it is an important cause of disability and mortality in children in developing countries [20]. Rheumatic heart disease is caused by group A streptococcus hemolyticus-induced upper respiratory tract infections (acute pharyngitis, tonsillitis) and rheumatic fever. When the carbohydrates in the bacterial cell wall cross-react with the valvular tissue, acute rheumatic heart disease may occur, such as rheumatic myocarditis [21]. Up to 55% of patients with rheumatic

fever have antigen-antibody complexes in their endocardial tissues, and deposited complements in the perivascular connective tissues and sarcomeres; 65–80% of children with rheumatic fever have clinical manifestations of rheumatic carditis.

Pathological changes: In the early stage, the changes in the cardium are not obvious. If rheumatic endocarditis is combined, there will be swelling of the valves and decreased transparency. Miliary-sized (approximately 1–3 mm), off-white, translucent, verrucous vegetations can be seen on the surface of valves (white thrombus), which often arrange like beads on a string at the atresia edge of the valve. If repeated onsets eventually lead to chronic rheumatic valvular disease, the mitral valve is the most susceptible, followed by the aortic valve. There is diffuse fibrous hyperplasia of the valve leaflets and chordae, which may fuse and cause valvular stenosis and/or insufficiency. In the late stage, focal thickening of the left ventricular and atrial endocardium, fibrosis, mural thrombosis, flattened papillary muscles and fleshy columns, hypertrophy, and dilatation of cavities are also commonly present.

Histopathological examinations: The most important feature of rheumatic myocarditis is rheumatic granuloma (Aschoff body) in the myocardial interstitium, followed by diffuse interstitial myocarditis (Fig. 6.21a, b).

The formation of Aschoff bodies contains a series of pathological processes, namely, the fibrinous necrosis of collagen fibers, followed by the development of granulomas and finally fibrosis. Thus, myocarditis also manifests corresponding characteristics of sequential pathological changes according to the course of disease, such as fibrinoid necrosis of collagen fibers, perivascular Aschoff bodies, and thin, spotted myocardial fibrosis with perivascular scars.

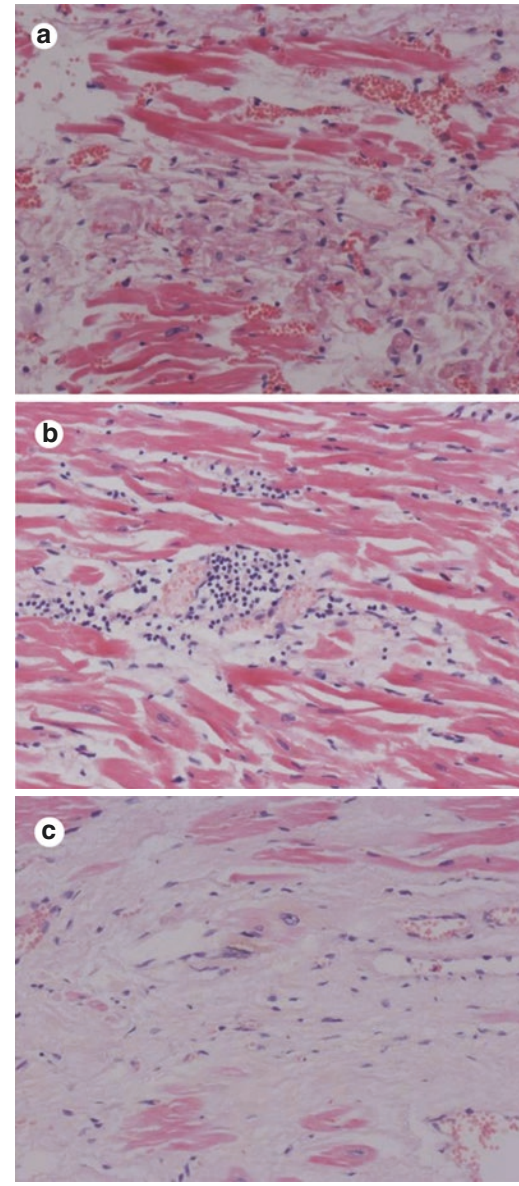

Fig. 6.21 Rheumatic myocarditis (male, 48 years old, sudden death). (**a**) Fibrous necrosis and rheumatic body in the interstitium (HE 200×); (**b**) Infiltrates of lymphocytes in the interstitium (HE 200×); (**c**) Gradual fibrosis in the interstitium, and several rheumatic cells can be found (HE 200×)

In the early phase of rheumatic myocarditis, namely, the degeneration and necrosis phase, the swelling of cardiomyocytes, interstitial edema, fibrinous necrosis, and myxoid degeneration can be found. One to two months after the onset of clinical symptoms, it enters the granuloma stage when Aschoff bodies appear inside and around the fibrous necrosis foci, and especially around small blood vessels. Aschoff bodies are characteristic for diagnosis under microscopic examination, which manifest with oval macrophages, lym-

phocytes, plasma cells, and so forth that gather near the small vessels in the interstitium. If the macrophages engulf cellulose-like necrotic material, they will transform into rheumatic cells (Aschoff cells). Rheumatic cells are large, round, or polygonal, with rich and homogeneous cytoplasm. They have large, round, or oval nuclei with clear nuclear membranes, and chromatin concentrates in the center with filiform radiations to the nuclear membrane, so that the cross section of the nucleus looks like an owl-eye, often called an awl-eye cell; for the longitudinal section of a long nucleus, it looks like a caterpillar, hence it is called a caterpillar cell. Besides the above-mentioned mononuclear cells, rheumatic cells can also be dual or multinuclear, and these are called Aschoff giant cells. Immunohistochemistry confirmed that rheumatoid cells are of monocyte-macrophage origin, but not cardiomyocyte origin. The granuloma stage lasts for 2–3 months and then enters to the fibrosis stage. At this time, the cellulose-like necrosis is dissolved and absorbed, and the nuclei of rheumatic cells may become densely stained with an unclear structure. The rheumatic cells will transform into fibroblasts and the granulomas gradually become fibrotic and form small spindle-shaped scars that will eventually be replaced by collagen scar tissue (Fig. 6.21c). Most patients will finally develop chronic rheumatic heart disease (especially valvular heart disease).

In children, it shows cardiomyocyte edema and steatosis, fasciculate fibrous necrosis of the left atrial cardiomyocytes, and significant interstitial edema. It may present diffuse interstitial myocarditis with infiltrations of many lymphocytes, eosinophils, and even neutrophils.

Aschoff bodies are specific in the pathological diagnosis of rheumatic myocarditis. They may appear in the myocardium, endocardium, and epicardium, especially in the left ventricular wall, mitral valve attachments, the connective tissue triangle in the root of the aorta, and papillary muscles. It can also affect the cardiac conduction system (Fig. 6.22). It could be the cause of ectopic excitatory foci with tachycardia or atrial fibrillation in rheumatic myocarditis.

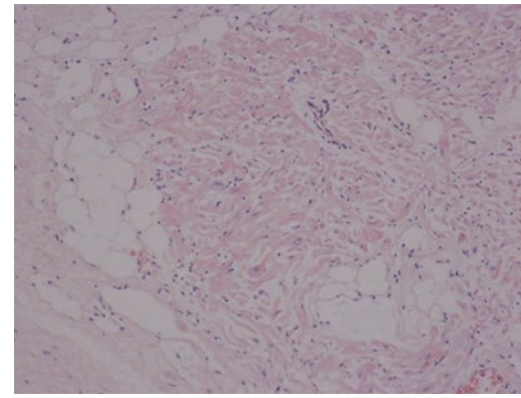

Fig. 6.22 Rheumatic myocarditis with the cardiac conduction system involved (male, 48 years old, sudden death). Infiltrations of macrophages and lymphocytes in the His bundle (HE 40×)

3. Perinatal myocarditis, or peripartum cardiomyopathy (PPCM), is a rare disease that usually occurs in the final month of pregnancy or 5 months after delivery. These patients show myocardial dysfunction and dilation secondary to left ventricular systolic insufficiency, while other causes of heart failure are excluded. Its incidence is between 1:4000 and 1:300, and is more common in women over the age of 30. The risk factors include obesity, a history of myocarditis, smoking, alcoholism, multifetal pregnancy, an elderly mother, malnutrition, pregnancy-induced hypertension (gestational hypertension) or eclampsia, metabolic disorders (such as gestational diabetes), and so on. Possible causes include viral infections, nutritional deficiencies, coronary artery disease of small vessels, and immune responses to myometrial or fetal antigens. Recent studies believe that the pathogenesis is related to the imbalanced myocardial microvascular angiogenesis during pregnancy that results in myocardial ischemic damage. Between 5% and 30% of patients with perinatal cardiomyopathy are accompanied by lymphocytic myocarditis, and occasionally with dilated cardiomyopathy complicated with myocarditis. It is as yet unclear whether perinatal myocarditis/cardiomyopathy is a unique

type of heart disease independent of idiopathic dilated cardiomyopathy or idiopathic lymphocytic myocarditis.

Pathological changes: No specific pathological changes. Usually the heart enlarges with dilation of the cavities. The lesions are focal and irregular, and may involve only the left ventricle or both ventricles. The cut surface of the myocardium may be pale or with a few gray stripes. If the right ventricle is involved in PPCM, it is associated with ventricular tachyarrhythmia [22].

Histopathological examination: Hypertrophy, edema, and focal necrosis of cardiomyocytes can be observed, with circular vacuoles in the cytoplasm. There are also interstitial edemas, focal hemorrhages, and focal fibrosis, with several scattered infiltrations of neutrophils, lymphocytes, and plasma cells, as well as perivascular inflammation. (Fig. 6.23).

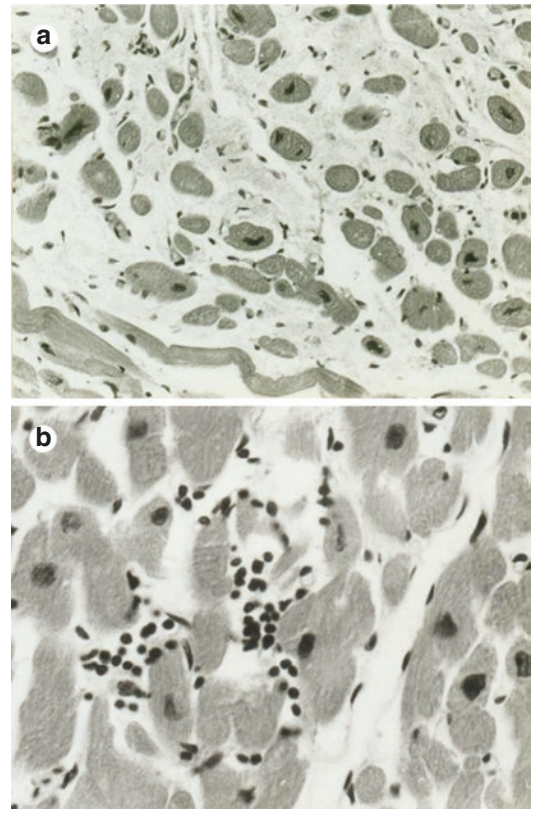

Fig. 6.23 Perinatal myocarditis (female, 21 years old, sudden death in the eighth month of pregnancy) [23]. (**a**) Hypertrophy of cardiomyocytes, interstitial edema, and fibrosis with scattered infiltrates of monocytes and lymphocytes (HE 200×); (**b**) Hypertrophy of cardiomyocytes and interstitial infiltrates of monocytes and lymphocytes (HE 400×)

6.2.5 Granulomatous Myocarditis

Granulomatous myocarditis is characterized by the appearance of giant cells in the inflammatory foci and the formation of granulomas, including two types: cardiac sarcoidosis and giant cell myocarditis.

1. Cardiac sarcoidosis is a type of granulomatous disease of unknown cause with multi-organ or multi-system involvement, which is characterized by the formation of non-caseous granulomas. The clinical symptoms are non-specific and easy to misdiagnose. Some research suggests that there is an immune dysfunction in the local environment of sarcoid granulomas, which is related to the cell-mediated immune responses to a certain unrecognized antigen. It is also related to systemic immune abnormalities and genetic factors. Although 90% of sarcoidosis primarily affects the lungs, 20–30% of sarcoidosis will affect the heart and is known as cardiac sarcoidosis (sarcoidosis of heart). Most patients with cardiac sarcoidosis have subclinical manifestations, less than 5% of patients show clinical symptoms, and a few patients only have heart disease without systemic disease. Since this disease involves the myocardium, it may lead to conduction block or arrhythmia. Atrioventricular block and tachycardia accounts for 75% of patients with arrhythmia, and sudden death will occur in approximately 2% of patients.

   Pathological changes: General examination: The myocardial section shows tough, small, gray-white nodular granulomas, mainly distributed in the ventricular septum, left ventricular wall, and papillary muscles, which needs to be distinguished from metastatic and fibrous tumors of the heart. The positive rate of EMBs of the right ventricle is usually less than 50%. When the myocardium is completely affected, the heart is enlarged and

becomes fibrotic, similar to dilated cardiomyopathy, with a few manifestations similar to restrictive cardiomyopathy.

Histopathological examination: There are several subtypes of pathological manifestations according to the results of EMBs, namely, typical non-caseating granuloma, lymphocytic myocarditis, dilated cardiomyopathy, or normal myocardium. The microscopic characteristics are similar to those of extracardiac sarcoidosis. The cardiac nodules can exist in isolation, or merge with each other to form a large lesion area, forming epithelial-like cellular granulomas that mainly contain non-caseating necrosis (Fig. 6.24). The granulomas are small and regular in shape without obvious necrosis in the center. They contain dense epithelioid cells and multinuclear giant cells arranged in the structure of a circular or oval granuloma. There are vacuoles in the cytoplasm of multinuclear giant cells, and red stellate bodies can be found (asteroid body). Asteroid bodies are eosinophilic, with a small, dark, radially arranged prickle-like body in the center. However, the asteroid body is not a specific lesion of sarcoidosis. There are obvious fibrosis around the granuloma with scattered monocytes and lymphocytes and rare eosinophils. Multiple isolated granulomas may fuse, and the surrounding fibrotic tissue will proliferate and envelop the granulomas. The granulomas wrapped in fibrous tissue will eventually become a hyalinized fibrous scar. Immunochemistry examination confirms that the granuloma is mainly composed of CD68-positive epithelioid cells, and the infiltrating lymphocytes are mainly CD4-positive T cells, while B cells are rarely seen. The endocardium and pericardium may also be involved. In most cases, myocardial hypertrophy and interstitial fibrosis emerge while endocardial thickening is present in only a few cases.

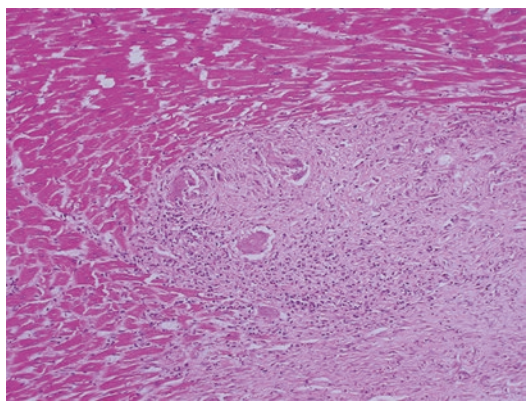

Fig. 6.24 Sarcoidosis in a heart. The formation of an epithelial-like cellular granuloma that mainly contains non-caseating necrosis, with multinuclear giant cells and lymphocytes (HE 100×)

Differential diagnoses of sarcoidosis usually involve infectious granulomatous heart disease, giant cell myocarditis, allergic myocarditis, and acute rheumatic fever. Infectious granulomas are rare in immune-healthy people; it requires routine staining of fungi and mycobacterium *Tuberculosis* for differentiation. In these infectious diseases, it usually manifests as a necrotic granuloma, such as *Tuberculosis* of the heart. For idiopathic giant cell myocarditis, it is characterized by multinuclear giant cells in the interstitium, usually without granuloma. For allergic myocarditis, there are collagen fibers in the center with infiltrations of many eosinophils, but multinuclear giant cells and fibrosis are rare. In acute rheumatic fever, the granulomatous lesions are often insignificant, and the giant cells are usually smaller than the multinuclear giant cells of sarcoidosis. In patients who received repeated biopsies, foreign body giant cells may be seen in the area around the catheter sheath. Myogenic giant cells will be observed in the marginal repair area of ischemic infarction, and lymphocytes and hemosiderin can be seen in the scar tissue. Granulomas can occur in metabolic diseases such as lipogranulomatosis, oxalosis, and gout, as well as in connective tissue diseases such as rheumatic heart disease, Wegener's granulomatosis, and Churg-Strauss syndrome. However, granulomas in cardiac sarcoidosis are usually focally distributed; thus, the possibility of cardiac sarcoidosis cannot be ruled out completely even if a biopsy is negative.

2. Idiopathic giant cell myocarditis, also known as isolated or Fiedler myocarditis, is a rare type of myocarditis. There are giant cells and

granulomas in the interstitial inflammatory focus. The cause is unknown and more common in young and middle-aged people between 20 and 50 years of age who are previously healthy. The clinical onset is rapid, with an acute and progressive course, and is usually fatal. For the fulminant type, the patients often die from heart dilation-induced acute heart failure and/or arrhythmia.

Idiopathic giant cell myocarditis has a poor prognosis, especially when accompanied by focal or even extensive myocardial necrosis; 20% of these patients have autoimmune diseases, such as ulcerative colitis, rheumatoid arthritis, myasthenia gravis, hyperthyroidism or hypothyroidism, and other concomitant diseases including drug allergies, thymoma, sarcoidosis, and so forth.

Pathological changes: The heart enlarges and the weight increases, with the main lesions concentrated in the myocardium. The endocardium and pericardium can also be affected. In the cutting surface of the heart, especially in the left ventricular wall and interventricular septum, there are fused or multifocal necrotic areas that are grayish-yellow or dark red and approximately ≥2 mm in diameter. Most of the four heart cavities are affected, and mural thrombus may emerge in some cases. In the late/repair phase, the ventricular wall decreases in thickness due to diffuse scarring. Due to the existence of visible island-like cardiomyocytes inside the fibrous scar tissue, it is not a true ventricular aneurysm.

Histopathological examination: The characteristic pathological change is the appearance of multinuclear giant cells (by fusion of macrophages) and necrosis of cardiomyocytes within the extensive inflammatory infiltration foci (Fig. 6.25). In the interstitium, there are multifocal or diffuse inflammatory infiltrations mainly consisting of lymphocytes, plasma cells, eosinophils, and macrophages, mixed with multinuclear giant cells. The size of multinuclear giant cells can reach 90 μm × 20 μm, with up to 20 nuclei in each cell, and they usually lie on the adjacent sarcolemma of necrotic cardiomyocytes. Extensive necrosis occurs in cardiomyocytes, which can be focal, map-like, or diffuse, accompanied by varying degrees of fibrosis. The necrotic myocardium is replaced by granulation tissue, and the boundary between necrotic and viable myocardial tissues is unclear.

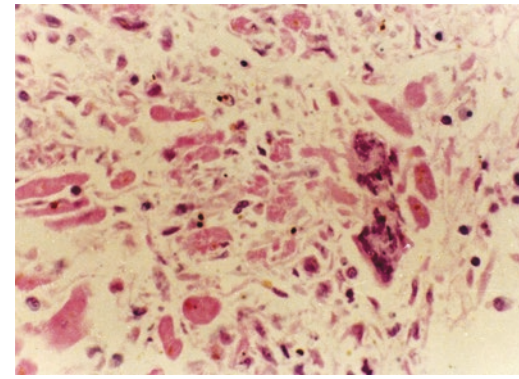

Fig. 6.25 Idiopathic giant cell myocarditis. Necrosis of the myocardium with interstitial infiltrates of lymphocytes and multinuclear giant cells (HE 400×)

Immunohistochemical stainings show that the multinuclear giant cells are CD68-positive macrophages, while they are actin-, desmin- and myosin-negative. Lymphocytes are mainly $CD3^+$ T cells, with rare B cells. $CD8^+$ T cells are much more numerous than $CD4^+$ T cells in the acute phase. During the repair phase, actin-positive macrophages are occasionally seen at the edge of inflammatory foci, indicating inflammatory damage to the cardiomyocytes.

If pathological examinations find myocardial necrosis and multinuclear giant cells in young patients, the diagnosis of idiopathic giant cell myocarditis should be considered when infectious diseases are eliminated.

The clinical diagnosis of idiopathic giant cell myocarditis requires a differential diagnosis from cardiac sarcoidosis. These two diseases share similar clinical features and general morphological appearances; thus, that they are often classified together. However, they are different diseases with significant differences in microscopic histopathological

characteristics and prognoses. First, the presence or absence of granulomas is the key distinguishing point of the histopathology. Second, there is more pronounced fibrosis in cardiac sarcoidosis than in idiopathic giant cell myocarditis, while few eosinophils are seen in cardiac sarcoidosis. The myocardial necrosis also differs: it is mass-shaped in cardiac sarcoidosis but band-shaped in idiopathic giant cell myocarditis.

6.2.6 Allergic Myocarditis

Allergic myocarditis, also known as hypersensitive myocarditis (hypersensitive myocarditis), refers to drug-induced hypersensitive myocardial inflammation with damage to the myocardium. It occurs rapidly after medication, and is a common adverse drug reaction. More than 40 kinds of drugs may cause allergic reactions, containing antibiotics, diuretics, and anti-allergic drugs [24]. The antibiotics include ampicillin, chloramphenicol, sulfonamides, and so forth. The anti-inflammatory drugs include phenylbutazone, indomethacin, and so forth. The rest are comprised of antidepressants such as amitriptyline, antiepileptic drugs such as phenytoin, and diuretics such as spironolactone. Seven percent of patients who have undergone heart transplantations will have allergic myocarditis, which may be related to the long-term use of dobutamine [24–28]. The clinical symptoms of allergic myocarditis include a skin rash, fever, increased eosinophils in peripheral blood, and occasional arrhythmia. It is usually not dose-dependent, and may occur at any period of medication use. This adverse reaction is usually benign, but in severe cases it may result in chronic heart failure or even sudden death.

Pathological changes: General examination shows that lesions are common in the left ventricular wall and the ventricular septum, resulting in dough-like myocardial softness with yellow-red spots.

Microscopic pathological changes: The lesion is transient interstitial myocarditis, and the main manifestations are inflammatory infiltrations around the small endocardial vessels and in the interstitium which mainly consist of eosinophils, as well as lymphocytes, plasma cells, and mast cells that may have degranulation (Fig. 6.26). The degeneration and necrosis of cardiomyocytes are mild. Occasional focal necrosis can resolve spontaneously after

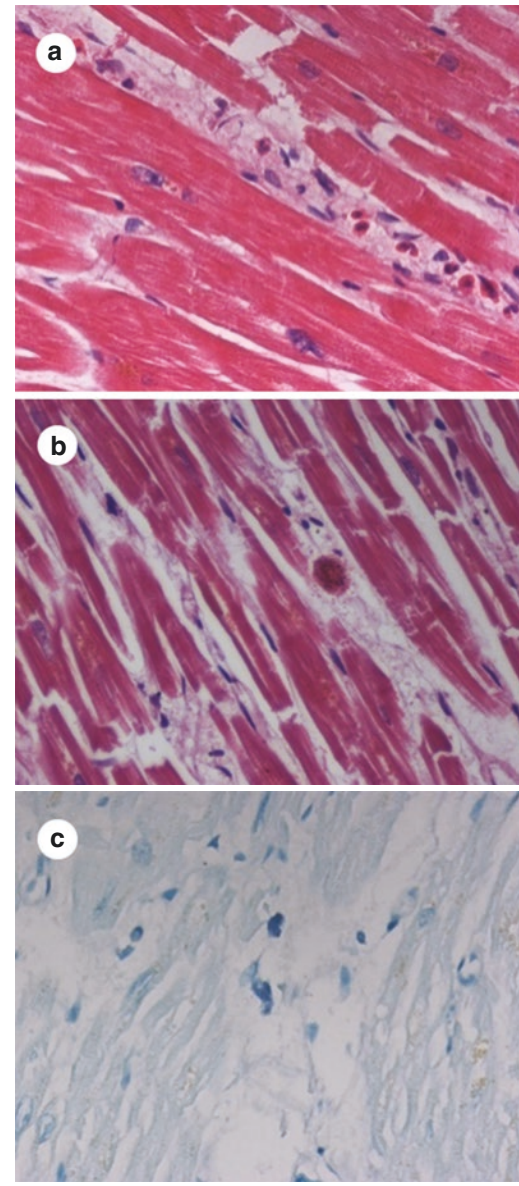

Fig. 6.26 Allergic myocarditis. (**a**) Infiltrates of eosinophils in the interstitium; (**b**) Infiltrates of mast cells and degranulation; (**c**) Infiltrates of mast cells and degranulation (Wright's staining)

ceasing the medication, leaving no fibrosis or fibrinous necrosis. Vasculitis or perivascular inflammation often occur within allergic myocarditis, but necrotic vasculitis is rare. The infiltrating lymphocytes are mainly T cells, with few B cells.

Allergic myocarditis lacks giant cell infiltration, which is the key point to distinguish it from drug-induced giant cell myocarditis. For the differentiation between allergic myocarditis and eosinophilic myocarditis, there is extensive myocardial necrosis, infiltrations of many eosinophils and inflammatory cells, and a lack of symptoms of systemic allergy in the latter [29, 30].

Eosinophilic myocarditis (Fig. 6.27) is sometimes called idiopathic eosinophilic endocarditis [31]. However, for some cases of eosinophilic myocarditis, when more eosinophils are detected in the myocardium, it should also be considered as allergic myocarditis, especially for myocarditis that responds to drugs. In some cases, immunohistochemical staining may provide evidence of IgE and allergic reactions, such as an increase of mast cells in the lung tissue. The evidence of contact with allergens should be investigated, if available. Eosinophilic myocarditis may be part of "drug-induced hypersensitivity syndrome" (DIHS), also known as a "drug rash with eosinophilia and systemic symptoms" (DRESS). This is a serious reaction that usually occurs one to eight weeks after medication, and is characterized by a fever, rash, and multiple organ failures. It is a type of immune response involving the activation of macrophages and T cells and the release of cytokines. No consensus has as yet been reached for the etiology of this disease.

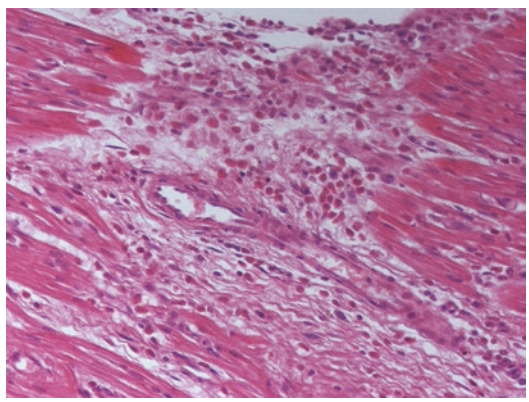

Fig. 6.27 Eosinophilic myocarditis. Necrosis of cardiomyocytes, infiltrations of massive eosinophils, and fibrosis (HE 200×)

6.2.7 Toxic Myocarditis from Snake Venom

Snake venom toxins can cause toxic myocarditis and damage to other organs after various venomous snake bites. Among them, a bite from a pallas pit viper, especially Ancistrodon acutus, may cause serious toxic myocarditis. The injured patient may die from heart failure, arrhythmia, and multiple organ failure [32]. The mechanism of toxic myocarditis from snake venom is related to the agkistrodotoxin which contains a variety of toxic components, such as anticoagulation and procoagulant toxins, hemorrhagic toxins, proteolytic enzymes, lecithinase A, and other toxic enzymes. These toxins can cause local bleeding and swelling, as well as myocardial damage. Therefore, in addition to local bleeding and blisters, the patient's clinical symptoms also include shortness of breath, chest tightness, progressive heart palpitations, and other manifestations of myocardial damage. A myocardial zymogram and a biochemical test will show an increase, and an ECG will show ST-T and/or rhythmic changes, and so forth.

Pathological changes: General examination shows myocardial congestion, edema, and multiple spotting hemorrhages in the epicardium and cut surface.

Histopathological examination: Infiltration of a small amount of monocytes and lymphocytes in the epicardium, with sarcolysis of some cardiomyocytes, eosinophilic enhancement of some myocardial sarcoplasm, contractile band or coagulative necrosis, interstitial edemas, spotting hemorrhages, and inflammatory infiltration dominated by neutrophils (Fig. 6.28),

as well as significant congestion in vessels. There is degeneration and necrosis in the heart conduction system including the sinoatrial node, atrioventricular node, and atrioventricular bundle cells, and is accompanied by interstitial hemorrhage and a small amount of inflammatory infiltration (Fig. 6.29).

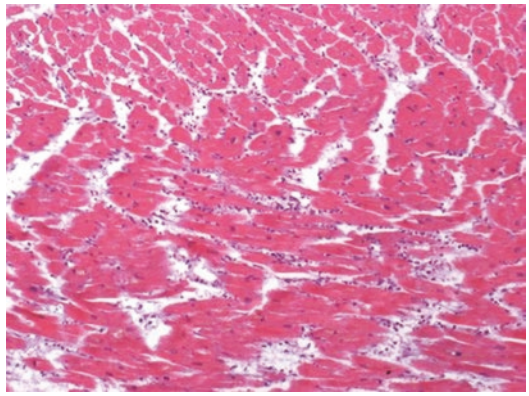

Fig. 6.28 Toxic myocarditis (female, 67 years old, died after a bite by Gloydius brevicaudus). Diffuse necrosis of the myocardium and interstitial infiltrations of neutrophils (HE 100×)

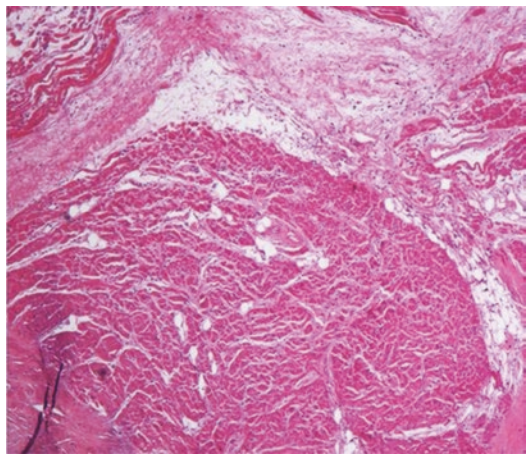

Fig. 6.29 Toxic myocarditis (male, 20 years old, died 1 day after a bite by Ancistrodon acutus). Interstitial hemorrhage, edema and inflammatory infiltrates in the His bundle (HE 40×)

6.3 Typical Cases

6.3.1 Case 1

Case Presentation

An 8-year-old girl had stomach discomfort in the morning and received treatments in a local clinic (no details for the medication), then she felt sort of relief. The patient complained of chill and nausea at 6 p.m. in the evening, and then received treatments in another clinic (injection with gentamicin plus metoclopramide, and one Huoxiang Zhengqi capsule taken orally). Repeated vomiting occurred since 9 p.m., and the patient had additional treatments in the second clinic in the next morning. The medication contained intravenous injection of gentamicin plus metronidazole, and half a pill of cimetidine for orally use. Then the patient went back home, feeling excessive fatigue. She did not eat anything since then, but drank water for 6 or 7 times. At approximate 7 p.m., the patient was found unconscious with decreased skin temperature. She was sent to a hospital immediately, but the ECG showed no electrophysiological signal already, with both corectasis. The declaration of clinical death was made.

Pathological Diagnosis

lymphocytic myocarditis (Fig. 6.30).

6.3.2 Case 2

Case Presentation

A 52-year old man was admitted to hospital because of fever (38.3 °C), chill, fatigue and poor appetite for 5 days. This patient was treated in a local clinic for 5 days (no details for the medication), but there was no improvement for symptoms. The body temperature increased up to 40 °C with listlessness and diarrhea (watery stool). The patient was sent to the hospital in early morning, and the temperature decreased to 36.7 °C after

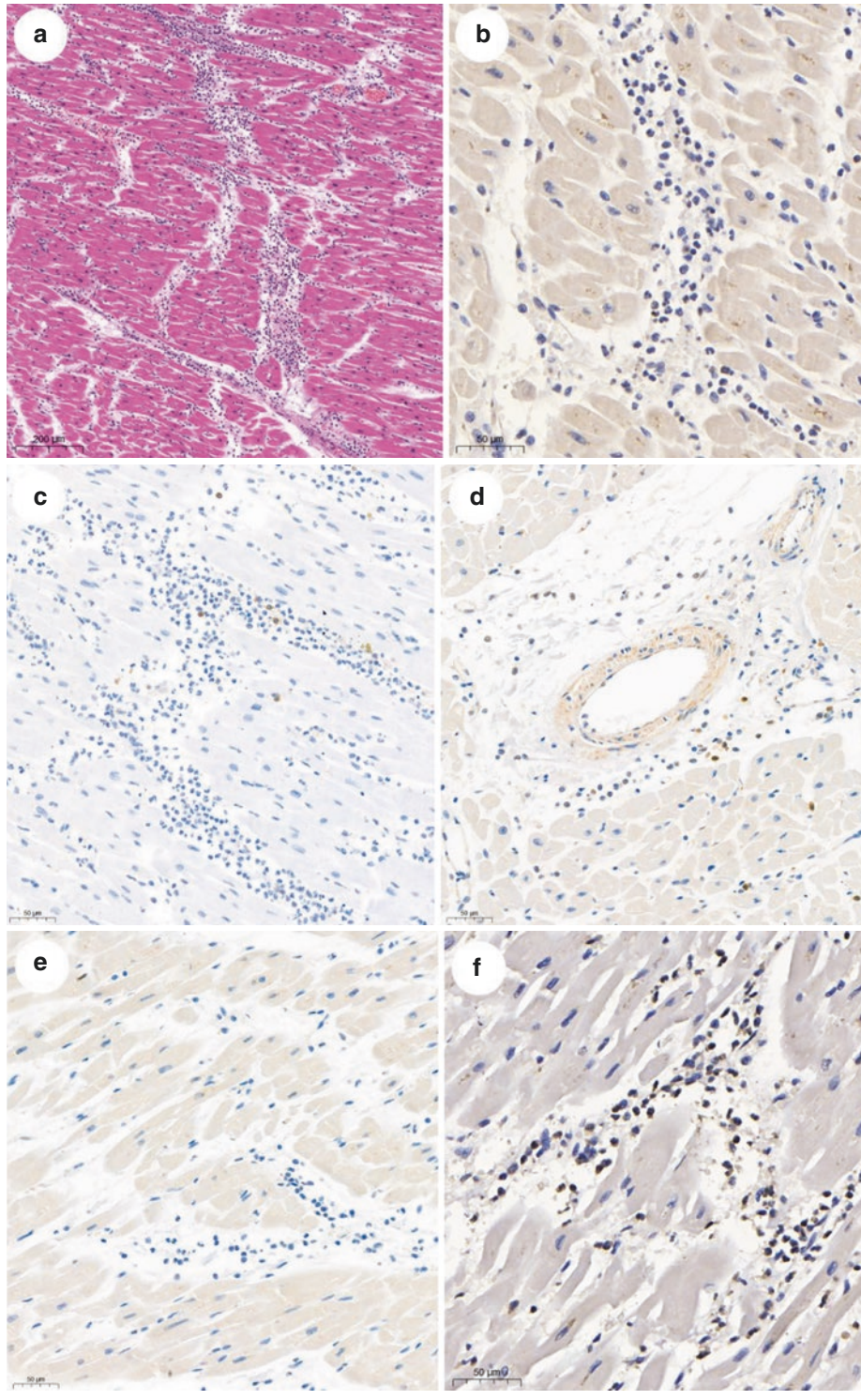

Fig. 6.30 Lymphocytic fulminant myocarditis. Cord-like necrosis of myocytes, with interstitial and perivascular infiltrates of massive inflammatory cells. Immunohistochemistry staining shows that the infiltrates consist of CD3 and CD4/CD8-positive T cells and MPO-positive neutrophils, while CD19-positive B cells are absent. (**a**) HE staining (50×); (**b**) CD3 (200×); (**c**) CD4 (200×); (**d**) CD8 (200×); (**e**) CD19 (200×); (**f**) MPO (200×)

treated with antibiotics, antipyretic and supportive care. In the morning, the patient had watery stool for 4 times with nausea and vomiting, and he was immediately given montmorillonite powder, berberine, potassium supplement, and infusion of piperacillin/ tazobactam plus inosine, vitamins C and B6. In the afternoon, the patient became sweated profusely, fidgety and cold in limbs. The blood pressure dropped to 70/30 mmHg with heart rate 152–172 bpm. Fluid infusion was conducted in two vessels with anti-shock therapies (dopamine and norepinephrine), and then the patient was transferred to a higher-level hospital. The blood pressure decreased to 47/33 mmHg in the transferal, followed by cardiac arrest. Tracheal intubation and cardiopulmonary resuscitation were immediately done. The heart rate was recovered, but the blood pressure was still undetectable. When arriving hospital, the patient was unconscious with both corectasis and cold body. CPR was conducted again with deep venous puncture, infusion of dopamine, dobutamine and norepinephrine, plus assisting breathing with ventilator. Despite all the treatments, cardiac arrest still occurred repeatedly, and it ended up with clinical death.

Supplementary Examination

Routine blood test: WBC 20.7 × 10^9/L, lymphocytes 10.2%, neutrophils 74.8%, platelets 9 × 10^9/L;

Blood biochemistry: AST 135 U/L, potassium 2.42 mmol/L, LDH 411 U/L;

Coagulation markers: D-D 23 mg/L, PT 17.1 s, PT-INR 1.39, APTT 89.6 s, TT 21.6 s;

Blood gas analysis: pH 6.661, pCO_2 140 mmHg, Lac 18 mmol/L, BE −42.9 mmol/L.

Pathological Diagnosis

Lymphocytic myocarditis (Fig. 6.31).

6.3.3 Case 3

Case Presentation

A 20-year-old man was admitted to hospital because of cardiac and respiratory arrest. He was treated in a local clinic for discomfort several days ago (no detail). At 5 pm in the day, a roommate found the patient appeared unconscious. After arriving in the school hospital, CPR was done for cardiac and respiratory arrest, and the patient was transferred to a higher-level hospital as soon as possible. The patient was in a coma with dilated pupils, undetectable blood pressure and pulse, and no electrophysiological signal in ECG. The diagnosis of sudden death was made.

Supplementary Examination

Routine blood test: WBC 22.26 × 10^9/L, neutrophils 73.4%, lymphocytes 23.4%, monocytes 2.9%;

Blood biochemistry: ALT 1583 U/L, AST 1604 U/L, BUN 12.7 mmol/L, Cr 327 μmol/L, potassium 10.6 mmol/L, blood glucose 14.3 mmol/L;

Myocardial injury markers: CKMB 12.23 ng/mL, myoglobin >1000 ng/mL.

Pathological Diagnosis

Lymphocytic myocarditis (Fig. 6.32).

6.3.4 Case 4

Case Presentation

A 29-year-old man got intravenous infusion because of “common cold” in a local clinic (no detail) in the morning. At about 11 a.m., dyspnea suddenly occurred, followed by unconsciousness. Cardiac and respiratory arrest and undetectable blood pressure was found when the patient was sent to a local out-patient department. CPR and oxygen inhalation were immediately done while the patient was transferred to a higher-level hospital. His heart rate was 139 bpm, and blood pressure was 97/50 mmHg (maintained by high dose of blood pressure elevating drugs) with both corectasis. The patient was also treated with tracheal intubation and ventilator -assisted breathing, blood transfusion, fluid infusion and supportive therapies. On the next day, cardiac arrests happen for 4 times from morning to dusk, and at every onset, he was rescued with CPR, injection of adrenaline calcium gluconate and pituitrin, infusion of sodium

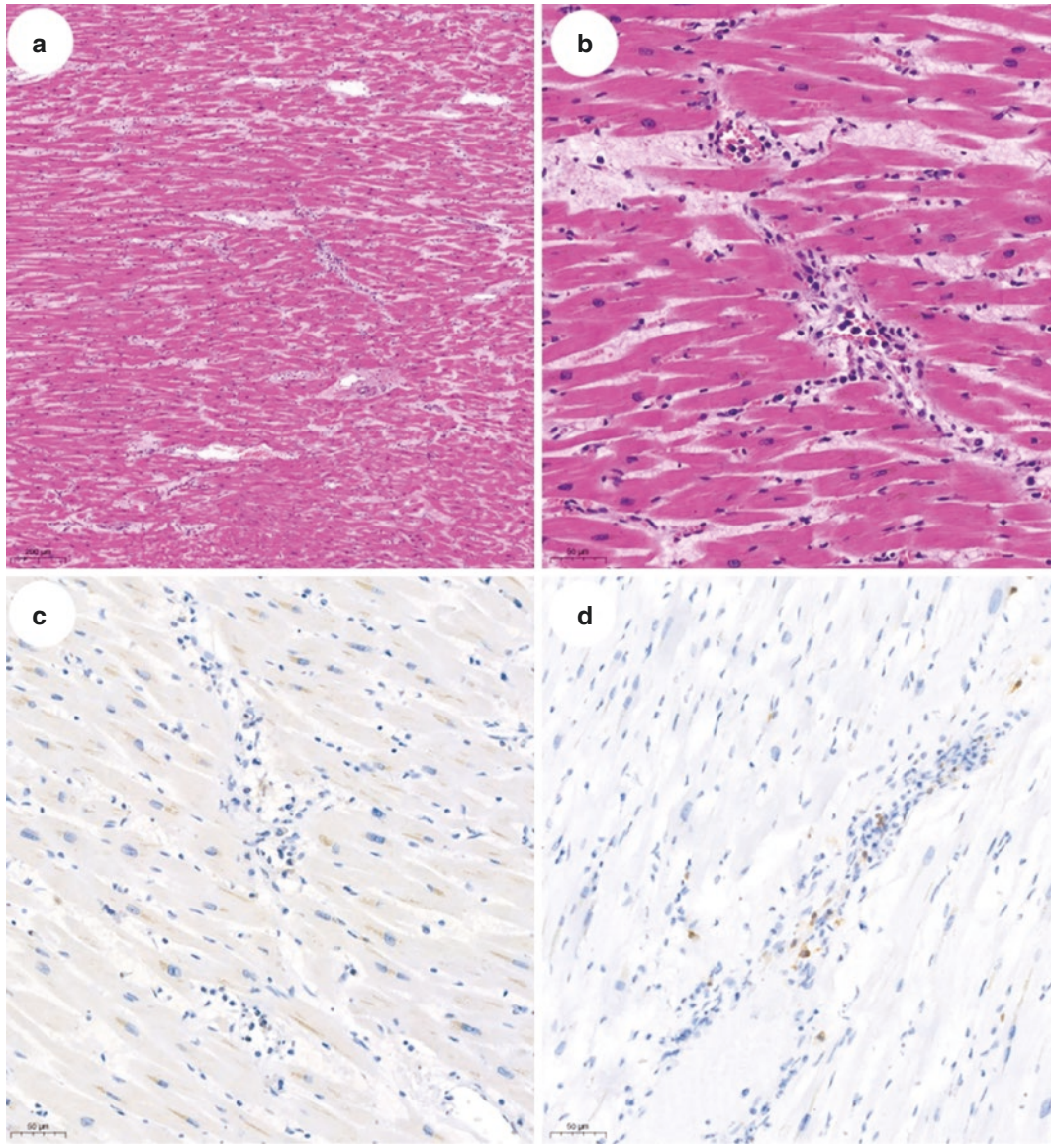

Fig. 6.31 Lymphocytic fulminant myocarditis. It shows multiple patches of necrosis of cardiomyocytes, especially predominant in the areas around small vessels, with interstitial and perivascular infiltrates of inflammatory cells. Immunohistochemistry staining shows infiltrates of mainly CD3 and CD4/CD8-positive T cells, CD19-positive B cells and CD68-positive macrophages. CD56-positive NK cells are rare. (**a**) HE staining (50×); (**b**) HE staining (200×); (**c**) CD3 (200×); (**d**) CD4 (200×); (**e**) CD8 (200×); (**f**) CD19 (200×); (**g**) CD56 (200×); (**h**) CD68 (200×)

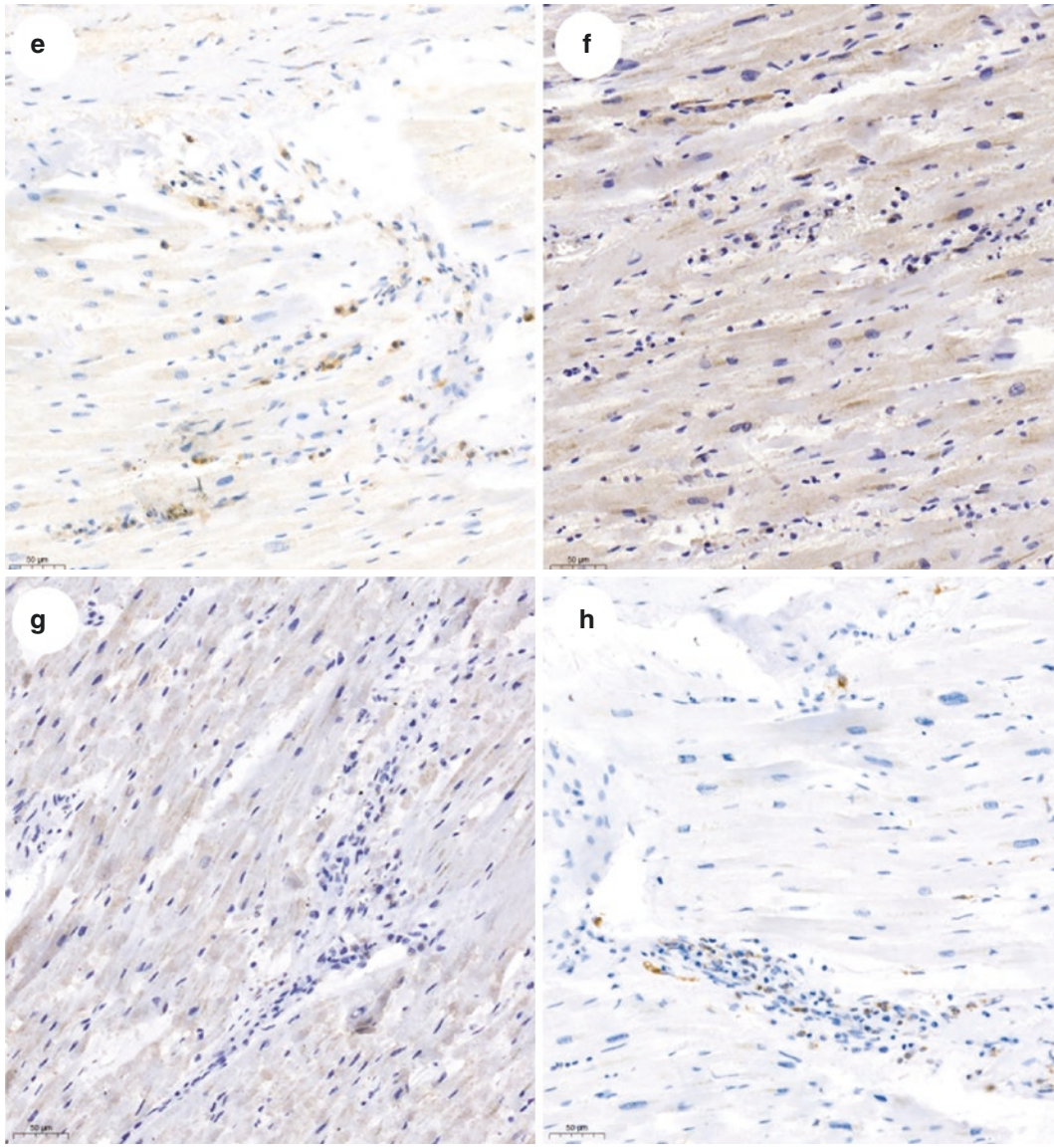

Fig. 6.31 (continued)

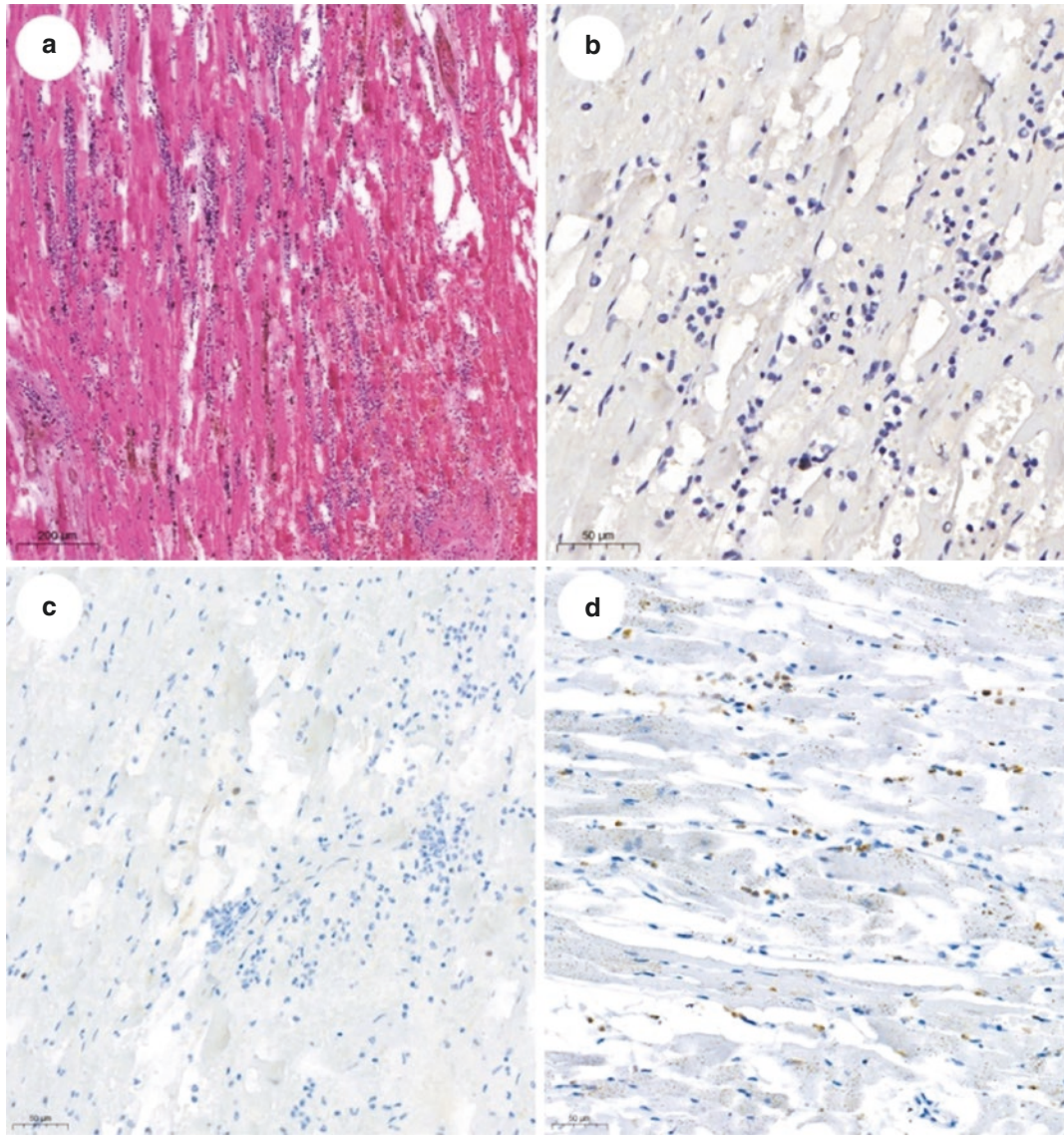

Fig. 6.32 Lymphocytic fulminant myocarditis. Necrosis of cardiomyocytes, with extensive infiltrates of inflammatory cells in interstitial areas. Immunohistochemistry staining shows infiltrates of CD3 and CD8-positive T cells, CD68-positive macrophages and MPO-positive neutrophils. CD19-positive B cells and CD4 -positive T cells are rare to see. (**a**) HE staining (50X), (**b**) CD3 (200X), (**c**) CD4 (200X); (**d**) CD8 (200X); (**e**) CD19 (200X); (**f**) CD68 (200X); (**g**) MPO (200X)

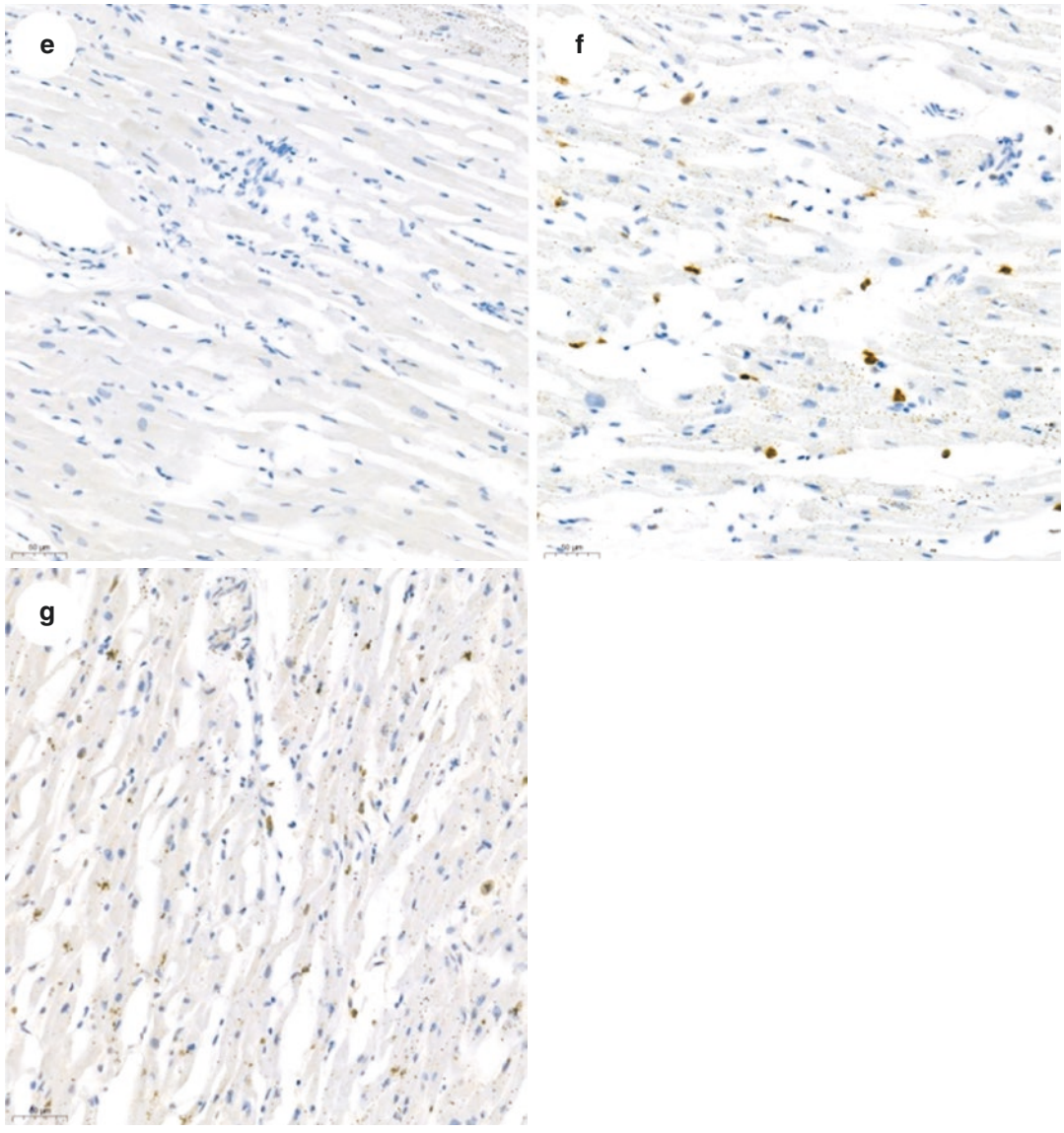

Fig. 6.32 (continued)

bicarbonate, pumping in with dopamine and electrical cardioversion. The heartbeat recovered for 3 times, but failed for the last time. Then the declaration of clinical death was made.

Supplementary Examination

Routine blood test: WBC 23.6 × 10^9/L, neutrophils 85%, lymphocytes 9.1%, monocytes 5.7%, platelets 61 × 10^9/L;

Blood biochemistry: ALT 955 U/L, AST 1005 U/L, LDH >1867 U/L, blood glucose 17.22 mmol/L;

Coagulation markers: PT >180 s, FIB <0.5 g/L, APTT >180 s, TT >180 s, D-D > 80 μg/mL, FDP >150 μg/mL, AT 30%;

Myocardial injury markers: cTnI >50,000 ng/mL, CKMB 126.6 ng/mL, myoglobin >1200 ng/mL;

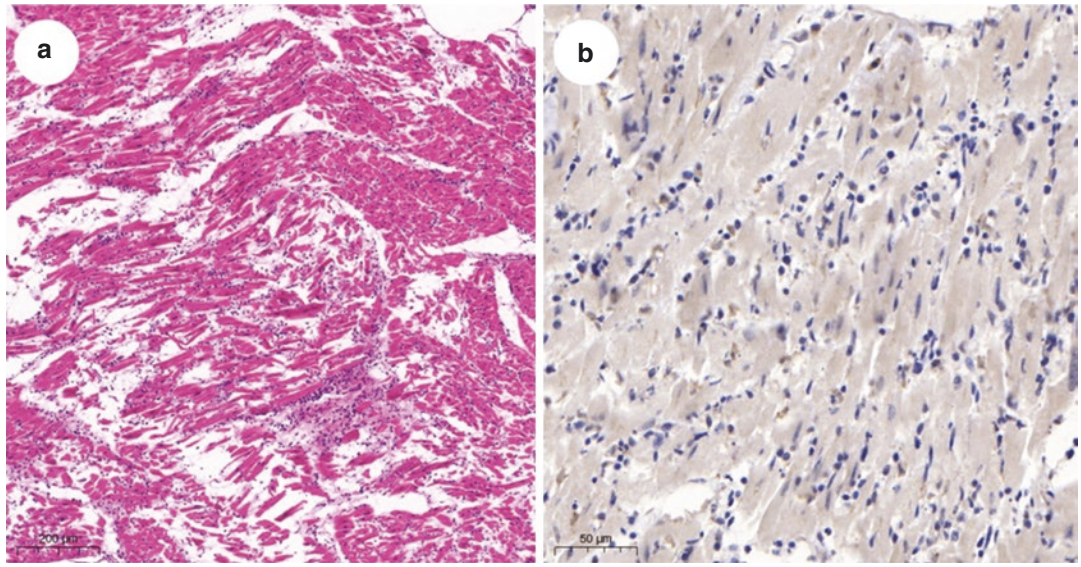

Fig. 6.33 Lymphocytic fulminant myocarditis. Multiple patches of necrotic and dissolved myocytes, with massive infiltrates of inflammatory cells. Immunohistochemistry staining shows infiltrates of MPO-positive neutrophils. (**a**) HE staining (50X); (**b**) MPO (200X)

Cytokines: IL-6 > 5000 pg/mL.

Pathological Diagnosis
Lymphocytic myocarditis (Fig. 6.33).

6.3.5 Case 5

Case Presentation
An adult male visited a local clinic in the morning for discomfort, and was diagnosed with "common cold with mild bronchitis". He was injected with one shot of andrographis paniculata nees, and givenorally-taken drugs including cefixime, Ganmao cough granules and others. Two additional shots of andrographis paniculata nees were injected at 6 p.m. in the evening and 8 a.m. the next day. At about 12 a.m., the patient retched severely and became critically ill (no detailed description), and the vital signs were undetectable when he was sent to hospital. Then the declaration of clinical death was made.

Pathological Diagnosis
Lymphocytic myocarditis (subacute phase) (Fig. 6.34).

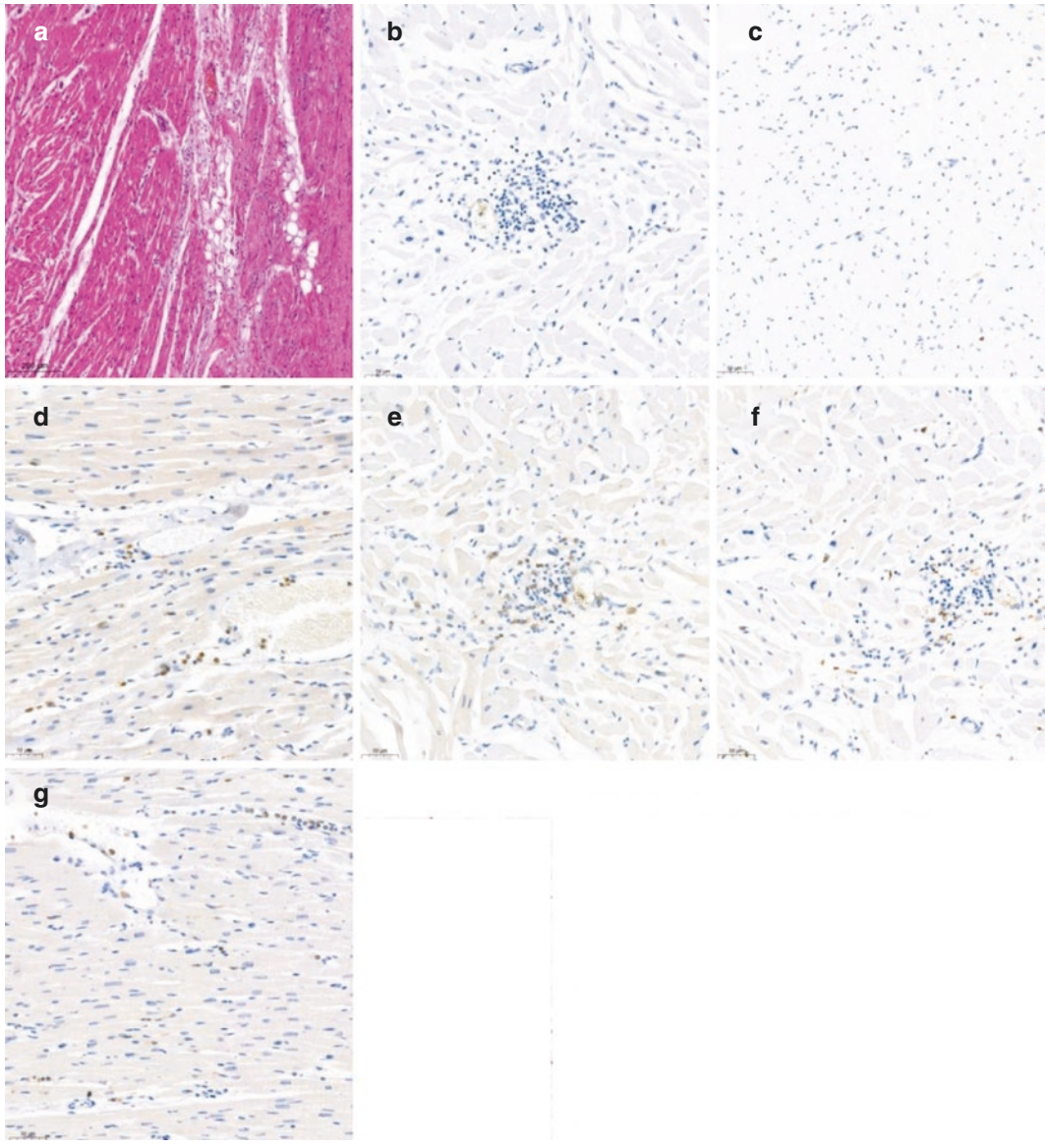

Fig. 6.34 Lymphocytic fulminant myocarditis (subacute phases). It shows necrotic and dissolved myocytes with infiltrates of inflammatory cells, formation of granulation tissue and fibrosis. Immunohistochemistry staining shows infiltrates of CD8-positive T cells and CD19-positive B cells, but CD4 -positive T cells are rare. CD68-positive macrophages and MPO-positive neutrophils are also present. (**a**) HE staining (50X); (**b**) CD3 (200X); (**c**) CD4 (200X); (**d**) CD8 (200X); (**e**) CD19 (200X); (**f**) CD68 (200X); (**g**) MPO (200X)

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7 Clinical Manifestations of and Laboratory Tests for Myocarditis and Fulminant Myocarditis

Dao Wen Wang

Myocarditis refers to inflammatory injury of the myocardium caused by various factors. Its clinical manifestations are related to the severity of myocardial damage. Mild cases only manifest as increased heart rate and mild reduction of cardiac systolic or diastolic function, while severe cases present with cardiogenic shock, heart failure, malignant arrhythmia, and even sudden death [1].

Myocarditis can be categorized as infectious or non-infectious myocarditis according to etiology. Viral infections are the most common cause of infectious myocarditis. Other causes of infectious myocarditis include bacterial, fungal, spirochetal, rickettsial, protozoal, or helminthic infections, but which are relatively uncommon. Meanwhile, non-infectious myocarditis can be induced by drugs, toxicants, radiation, connective tissue diseases, systemic vasculitis, giant cell myocarditis, and sarcoidosis.

According to the clinical course, myocarditis can be divided into fulminant myocarditis, acute myocarditis, chronic active myocarditis, and chronic persistent myocarditis.

Fulminant myocarditis is the most severe and special type of myocarditis; its occurrence results from the combined action of direct viral cytopathogenic effects and the overexuberant antivirus immune response. Viral infections can induce cardiac damage either by direct virus replication/killing of infected cells or by immune-mediated tissue damage, which is mainly mediated by T cells. Besides, various inflammatory cytokines also participate in myocardial damage and microvascular injury, thus contributing to cardiac tissue damage and cardiac dysfunction. Fulminant myocarditis is characterized by an acute onset and a rapid progression. Patients soon develop hemodynamic instability (pump failure and circulatory failure) and severe arrhythmia after the onset of the illness, which can be accompanied by respiratory, liver, or kidney failure. The early mortality rate of fulminant myocarditis is extremely high. However, after active treatment, most patients have a good long-term prognosis once they have passed the acute risk period.

Fulminant myocarditis occurs throughout the year but most frequently during winter and spring. It affects people of all ages, and most cases occur in young adults who are generally in good health and without basic organic diseases. There is no reported obvious sex difference in the occurrence of fulminant myocarditis.

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7.1 Clinical Manifestations

The clinical manifestations of fulminant myocarditis vary greatly. It begins with prodromal symptoms of respiratory infections, followed by mild chest pain, palpitations, and transient electrocardiogram (ECG) changes and then progresses to life-threatening cardiogenic shock, malignant arrhythmias, and multiple organ dysfunction. Fulminant myocarditis is characterized by a sudden onset and a rapid progression.

7.1.1 Predisposing Factors

Factors that lead to the reduction of the systemic or local respiratory immune defense function, such as cold, sudden climate change, and excessive fatigue, can decrease patients' immunity and facilitate invasion of pathogens, which consequently leads to fulminant myocarditis. Predisposing factors exist at different stages of the disease. The first stage is the period before the onset of illness. Persistent or intense stress, such as fatigue and long-term overwork, is the most common cause of fulminant myocarditis. The second stage is when patients have already developed symptoms but are still at an early stage or in a mild state. Continuing to engage in high-intensity work can exacerbate the disease, and severe arrhythmia, shock, and sudden death may occur. Acute exacerbations are frequently present in various situations, such as physical education, military training, marathons, and other strenuous exercises.

7.1.2 Early Symptoms

Accurate knowledge and understanding of the early symptoms of fulminant myocarditis are extremely important for timely diagnosis. Different patients may have different early manifestations [2].

7.1.2.1 Respiratory Symptoms

Respiratory symptoms of fulminant myocarditis are uncommon and are generally mild, which is different from a "cold." Fulminant myocarditis can mimic a cold, manifesting as nasal congestion, runny nose, fever, headache, and other discomfort, followed by a mild, short-term cough, usually without sputum [3]. Different degrees of fever can occur, ranging from a temperature of 37–39 °C. However, some patients report short-term chills but deny fever, and they generally present with discomfort, such as chest tightness, chest pain, and shortness of breath. Notably, only approximately <50% of patients have respiratory infection, and this infection is generally mild and transient [4].

7.1.2.2 Gastrointestinal Symptoms

A small number of patients have mild diarrhea, often presenting as loose stools, which can last for 2–3 days. Most patients have poor appetite and anorexia and even develop nausea, vomiting, abdominal distension, and mild abdominal pain [5, 6].

7.1.2.3 Systemic Symptoms

Systemic symptoms mainly manifest as fever, fatigue, and dizziness. Over time, patients show an obvious lack of speech, obvious fatigue, and anorexia. Some patients prefer to lie supine because of low blood pressure and obvious dizziness when sitting or standing [7].

7.1.2.4 Symptoms of Myocardial Damage

Similar to the symptoms of myocardial infarction, a small number of patients present with chest pain at first, followed by persistent chest tightness. Chest pain occurs when inflammation involves the pericardium and/or pleura and can also be caused by inflammation-induced coronary artery spasm. Chest tightness and shortness of breath may be caused by myocardial damage. Some patients present with palpitations and blackouts, which are usually caused by arrhythmias, such as tachycardia or bradycardia. In severe cases, the symptoms may manifest as syncope or sudden death, and some patients have palpitations and syncope as their first symptoms [7].

7.1.3 Progressive Symptoms

After the occurrence of prodromes over a short period, patients' condition usually worsens, and patients soon show extreme fatigue, anorexia, dizziness, chest tightness, and palpitations. They usually prefer to stay in bed to save energy and even feel tired to open their eyes. Some patients develop syncope and arrhythmia repeatedly.

7.1.3.1 Symptoms of Myocardial Damage

A few days or 1–3 weeks after the onset of prodromal symptoms, patients develop dyspnea, chest tightness, chest pain, palpitations, dizziness, extreme fatigue, and anorexia, which are primary reasons for medical visits. One European study suggested that 72% of patients with fulminant myocarditis had dyspnea; 32% had chest pain; and 18% had arrhythmias. Statistics from the author's hospital show that approximately 90% of patients with fulminant myocarditis presented to or were referred to the hospital because of dyspnea or chest tightness accompanied by extreme fatigue, anorexia, and dizziness; meanwhile, 10% of patients presented to or were referred to the hospital because of syncope or after cardiopulmonary resuscitation.

Chest Pain and Tightness

The chest pain is intense and unbearable for most patients, with a sense of being on the verge of dying. It generally appears in the precordial area, behind the breastbone, and on both sides of the front chest. Numbness or tingling in the left wrist and fingers can also occur. The pain is persistent and cannot be relieved by medicine or rest. Some patients, especially elderly patients, show chest tightness and acute left heart failure.

Painless Myocarditis

Painless myocarditis occurs in a minority of patients who are commonly old, is accompanied by diabetes or severe infection, or develops in the perioperative period. In most patients, painless myocarditis is accompanied with cardiogenic shock, severe arrhythmia, or heart failure, which can cause sudden death. In some patients, the pain can be masked by symptoms, such as congestive heart failure, extreme fatigue, fear and nervousness, acute indigestion, and syncope.

Arrhythmia

Arrhythmia is very common and occurs in almost every patient with fulminant myocarditis. Various arrhythmias can be seen in patients with fulminant myocarditis, with sinus tachycardia as the most common type. Tachyarrhythmias include atrial flutter, atrial fibrillation, atrial tachycardia, ventricular tachycardia, and ventricular fibrillation. Inflammation and edema of the myocardium can affect the cardiac conduction system, causing sinus arrest, intraventricular block, and atrioventricular block. Patients can present with palpitation, dizziness, cold sweats, syncope, and even Adams–Stokes syndrome. In a very small number of patients, the symptoms exacerbate rapidly after the onset of the disease, with hemodynamic disorders and even cardiac arrest.

7.1.3.2 Hemodynamic Disorder

Hemodynamic disorder is an important feature that distinguishes fulminant myocarditis from acute myocarditis. Some patients rapidly develop acute left heart failure and cardiogenic shock and show signs of pulmonary congestion and shock.

Acute Heart Failure

Patients may present with severe dyspnea, orthopnea, cough with pink foamy sputum, shortness of breath, anxiety, profuse sweating, oliguria, or anuria. However, edema, liver enlargement, and jugular vein filling are rare because of reduced systemic blood vessel tone. Clinically, severe acute left heart failure is uncommon, and most patients can lie supine, which is related to total heart failure and peripheral vasodilatation.

Cardiogenic Shock

Patients may show clammy, pale, cyanotic, and cold limbs and weak pulse. When the blood pressure is extremely low, the peripheral blood pressure cannot be measured. Patients' peripheral circulation is also poor, and they may be unresponsive, confused, or even in coma [8, 9].

Adams–Stokes Syndrome

A few cases present with syncope or sudden death and are generally accompanied by severe arrhythmias, such as ventricular tachycardia, ventricular fibrillation, sick sinus syndrome, and third-degree atrioventricular block.

Notably, an abnormal cardiac pump function is the main cause of hypotension in fulminant myocarditis among the three basic determinants of cardiac output (myocardial contractility, cardiac preload, and cardiac afterload), while blood volume and vascular resistance also have contributions. Since most patients with fulminant myocarditis have no basic organic heart disease, the abnormal cardiac pump function is only manifested by diffuse reduction in myocardial contraction and decreased ejection fraction. However, because patients have no basic cardiac disease, the myocardial compensation mechanism is too late to establish; the disease progresses very rapidly; and cardiogenic shock is very easy to ignore.

7.1.3.3 Manifestations of Multiple Organ Involvement

Fulminant myocarditis can cause multiple organ dysfunction or failure, including abnormal liver function, abnormal kidney function, abnormal blood coagulation, and respiratory system dysfunction. Multiple organ dysfunction is most secondary to cardiac damage and cardiogenic shock at later stage, while virus erosion and immune response also play a very important role.

1. **In the presence of acute respiratory distress syndrome (ARDS)**, patients with fulminant myocarditis develop pump failure and cardiogenic shock. Under multiple conditions, such as ischemia, pulmonary congestion, and inflammatory storms, lung exudation occurs; tissue fluid increases; pressure increases; and exudation even penetrates the alveoli, leading to ARDS. Patients present with hypoxia and dyspnea, and the blood lactic acid level is increased. However, owing to extreme fatigue, patients have no strength to breathe, making breathing superficial or shallow. Doctors should pay great attention to this scenario and provide timely respiratory assistance. Prolonged severe shock and long-term use of norepinephrine and other vasoconstrictors can cause irreversible damage to multiple organs, including disseminated intravascular coagulation (DIC), ARDS, and severe leakage syndrome. In addition, a small number of patients may have a pulmonary infection, that is, pneumonia. Different types of pneumonia have different symptoms. Bacterial pneumonia accounts for 80% of adult infectious pneumonia cases and has a very high mortality rate among children, elderly patients, and patients with immunosuppression. Most patients have chills, fever, cough, sputum, and chest pain, while a few patients have hemoptysis and dyspnea. Other symptoms include nausea, vomiting, general discomfort, and muscle aches. Viral pneumonia is caused by a variety of viral infections, which mostly occur during winter and spring. The clinical manifestations are mainly cough, fever, dyspnea, cyanosis, and anorexia. Approximately 10% of patients with fulminant myocarditis also have pleural effusion. Pleural effusion is mostly bilateral and is caused by inflammation and leakage. If it does not form compression, no special treatment is needed, and it will disappear as the systemic inflammatory storm and myocardial inflammation attenuate.
2. **In the presence of an abnormal liver function**, only a very small number of patients have obvious liver damage in the early stage, which is related to the virus and inflammatory storm. However, inappropriate treatment regimens, such as the application of high-dose vasoconstrictors (e.g., noradrenaline) or prolonged shock, can result in liver damage and jaundice. The transaminase level can reach 8000 U/L, and in severe cases, bile/enzyme separation may occur. Hypoproteinemia due to decreased protein synthesis leads to systemic edema and even polyserous effusions. Decreased synthesis of coagulation factors leads to coagulation dysfunction, namely DIC. If it reaches this stage, the situation is difficult to reverse.
3. **In the presence of an abnormal renal function**, patients with fulminant myocarditis may

develop acute kidney injury, which is mainly caused by insufficient renal perfusion resulting in a low cardiac output. Some patients may have severe renal function injury; however, when the systemic symptoms are attenuated with mechanical support treatment, such as IABP, renal function gradually returns to normal after going through the oliguria and polyuria phases.

4. **In the presence of DIC**, the clinical manifestations of patients with fulminant myocarditis are complex and diverse, with the main manifestations including bleeding, shock, organ dysfunction, and anemia. The occurrence of DIC is directly related to prolonged shock, delayed diagnosis, and inappropriate treatment, such as long-term use of vasoconstrictors (e.g., norepinephrine or pituitrin). Therefore, they should be actively avoided.
5. **Thyroiditis, it** only occurs in a very small number of patients with fulminant myocarditis and is part of the inflammation. Various types of thyroiditis may occur, and the onset is insidious and often undetected. Sometimes, they are found accidentally during physical examination or when relevant clinical symptoms appear. Hashimoto's thyroiditis is the most common type, which may be characterized by diffuse thyroid enlargement with a hard texture and smooth surface, sometimes with nodules. It is generally painless or has mild tenderness. Local compression and systemic symptoms are not usually observed, while pharyngeal discomfort occurs occasionally. Thyroid function can be either normal or abnormal. Patients with hyperthyroidism can show hypermetabolic symptoms, such as fever, sweating, hand tremors, and weight loss. The goiter may enlarge, and vascular murmurs may occur.

In summary, the clinical manifestations of fulminant myocarditis vary greatly from individual to individual. Many patients have only low-grade fever, significant fatigue, anorexia, or mild diarrhea in the early stages. Objectively, patients are usually quiet, without pain or groaning. The symptoms can last for 3–5 days. Most primary diseases are ignored because the symptoms are mild and are generally not the main reason for the patients' visit. However, these are important clues for the diagnosis of myocarditis. Therefore, it is important to obtain a detailed medical history. If patients have the abovementioned symptoms and recover after taking medicine or receiving no special treatment for 2–3 days, the condition should be considered as a common cold. If patients do not recover, especially if the symptoms are aggravated, and symptoms, such as extreme fatigue, chest tightness, palpitations, and dizziness, occur, the possibility of fulminant myocarditis and investigation through related examinations or transfer to a higher-level hospital for diagnosis and treatment should be considered.

7.2 Physical Signs

7.2.1 Vital Signs

Patients usually exhibit severe changes in their vital signs. Abnormal blood pressure, respiration (fast or slow), and heart rate indicate hemodynamic instability, which is the most significant manifestation of fulminant myocarditis and an indication of the severity of the disease.

7.2.1.1 Fever

Some patients may have an increased body temperature, while other patients may not develop fever. The increase in body temperature caused by primary viral infection is generally not too high. However, when it is complicated by pulmonary (or other organic) bacterial infections, the body temperature can reach 39 °C or even higher. A very small number of patients may also experience a situation where the body temperature does not increase (below 36 °C), which indicates that the disease is extremely severe.

7.2.1.2 Hypotension

Patients with fulminant myocarditis can develop hypotension as a consequence of abnormal vasomotor systole resulting from severe cardiac dysfunction and systemic inflammatory storm. The blood pressure can be lower than 90/60 mmHg in most patients and can decrease to <70% of the

basal value in patients with previous hypertension. In severe cases, the blood pressure cannot be measured. Patients with hypotension or shock usually have an increased heart rate. However, there are also patients with hypotension presenting with no obvious increase in heart rate, while some patients even show bradycardia or conduction block resulting from myocardial inflammation. However, in these patients, the blood pressure will decrease markedly as the disease progresses, and shock may occur. Patients with severe hypotension may present with repeated ventricular tachycardia or ventricular fibrillation, which can easily lead to death.

7.2.1.3 Breathing Changes

Patients may show tachypnea (respiratory rate of up to 20–30 beats/min) or hypopnea (respiratory rate of <10 beats/min) in severe cases. Blood oxygen saturation is generally lower than 90%. Some patients manifest dyspnea and require mechanical ventilation.

7.2.1.4 Heart Rate and Heart Rhythm Changes

Sinus tachycardia (heart rate of >120 beats/min) is relatively common in patients with fulminant myocarditis. Bradycardia (heart rate of <50 beats/min) may also occur in some patients. Sinus tachycardia is a remarkable characteristic of fulminant myocarditis, and it is a normal response to shock. Half of patients have a markedly increased heart rate. In a resting state, the heart rate is above 80–100 beats/min, usually 100–150 beats/min, and even higher than 150 beats/min in a few patients. Although tachycardia (heart rate of >10 beats/min) that is not commensurate with increases in body temperature is not a specific sign of myocarditis, it is an important clinical clue for the diagnosis of myocarditis, which needs to be taken seriously. In addition to sinus tachycardia, other types of arrhythmias can also occur, including ventricular or supraventricular premature contractions, ventricular and supraventricular tachycardias, and ventricular fibrillation. Some patients present with bradycardia and conduction block as a consequence of conduction system damage caused by myocardial inflammation and myocyte edema. Among these, ventricular tachycardia and ventricular fibrillation are the most serious types of arrhythmias [10, 11].

7.2.2 Heart-Related Signs

7.2.2.1 Cardiac Size

The heart border does not usually enlarge (that is, the heart is not large); however, in a very small number of patients, the heart is enlarged at the early stage of the disease [12]. Patients with an enlarged heart can present with mitral or tricuspid valve insufficiency. Even so, since the contractility of the myocardium is extremely low, systolic murmurs at the apex of the heart or the left lower edge of the sternum are rarely heard. However, it has been reported that such murmurs were heard in a patient with fulminant myocarditis who developed papillary muscle and valve leaflet rupture during Impella treatment [13].

7.2.2.2 Heart Sounds and Murmurs

The apex beats are dispersed as a consequence of cardiac damage and decreased myocardial contractility. Muffled and dull heart sounds can be present in the early stage, and a third heart sound and gallop rhythm can often be heard. The first heart sound in the apical area is diminished or split. The heart can sound like a fetal heart. Pericardial friction sounds may be indicative of pericarditis. A well-trained physician, especially a cardiovascular physician, should be able to identify these abnormalities regardless of the chest wall thickness and patient sex and age. A slightly louder P_2 at the pulmonary valve can occur, but is usually not obvious. P_2 is not markedly enhanced even if heart failure is severe because the left and right sides of the heart fail simultaneously, and the pulmonary artery pressure may not increase considerably.

7.2.2.3 Cardiac Insufficiency

Lung rales may occur when left ventricular dysfunction is present. Rare patients can have distention of the jugular vein, hepatomegaly, a positive

hepatojugular reflux, and lower limb edema although right ventricular dysfunction occurs. However, all manifestations are uncommon because of systemic dilation and vascular leakage of the arteries and veins.

7.2.3 Lung Signs

Most patients can lie down or require bed rest, while a small number of patients prefer to be in a semi-recumbent position as a consequence of the presence of left heart failure. Patents may have dry/moist rales due to left heart failure or pneumonia (mainly viral in the early stage). However, most patients have no rales due to heart failure.

7.3 Laboratory Examination

Laboratory tests are essential for making a timely diagnosis of fulminant myocarditis.

7.3.1 Myocardial Injury Marker Cardiac Troponin I or T (cTnI or cTnT) Assessment

Both cTnI and cTnT are small molecule proteins that are specifically expressed in cardiomyocytes (molecular masses of 23.88 and 37 kDa, respectively). They can exist in both bound and free forms. When the myocardium is damaged, cTnI and cTnT are released into the circulation. The current detection methods can be performed rapidly and are sensitive, aiding timely detection and diagnosis. The cTnI or cTnT levels in patients with fulminant myocarditis are usually very high, and the level change is rapid. If it is not particularly high at the beginning, it will increase rapidly within a few hours. Protein levels beyond the detection threshold (e.g., >50,000 pg/mL) are common in patients with fulminant myocarditis [14]. Although an increase in the cTnI or cTnT level can also be seen in patients with acute myocardial infarction, the increase in patients with fulminant myocarditis is more obvious and is not commensurate with the damage site and area shown in the ECG. Another distinguishing factor between cardiac infarction and fulminant myocarditis is that the levels of creatine kinase isoenzymes increase along with the levels of cTnI or cTnT during myocardial infarction, while the increase in the levels of creatine kinase isoenzymes is usually not so significant during fulminant myocarditis [15].

Notably, unlike in acute myocardial infarction, the marked increase in the levels of cTnI or cTnT in fulminant myocarditis does not indicate a large area of myocardial necrosis. In fulminant myocarditis, immune cells and inflammatory storms affect the function and metabolism of cardiomyocytes, thus leading to the leakage of cTnI or cTnT from the cells. Because the damage is severe and affects the entire heart, the levels of cTnI or cTnT are high.

7.3.2 Brain Natriuretic Peptide (BNP) Assessment

BNP or NT-proBNP is a biomarker of cardiac dysfunction. It is released by cardiomyocytes when injured and is an indicator of decreased cardiac function and increased myocardial tension. Similar to the troponin levels, the plasma BNP or NT-proBNP levels of patients with fulminant myocarditis are also very high (usually reaching 1000 pg/mL and can reach >10,000 pg/mL); the levels are markedly higher in patients with fulminant myocarditis than in those with general myocardial infarction. Troponin and BNP are sensitive and reliable markers of myocardial damage and cardiac dysfunction, respectively. Their levels increase considerably in patients with fulminant myocarditis and change rapidly. The levels can also reflect the severity of the clinical condition of patients. When patients receive reasonable treatment and recover, the levels of troponin and BNP can rapidly decrease and restore to normal levels within 1–2 weeks. However, if the treatment is improper or not timely, their levels will remain relatively high. Persistently high levels of troponin and BNP are signs of poor prognosis [15].

7.3.3 Blood Routine Examination

Blood routine examination may be normal at the early stage. In some cases, the total white blood cell count and neutrophil count may increase, but which does not mean that the patient has a bacterial infection. Our observations show that the total white blood cell count increases in varying degrees in approximately 60% of patients; the neutrophil count increases in 70% of patients; and the white blood cell and neutrophil counts decrease in remaining patients. Attention should be paid to the possibility of a combined bacterial infection at a later stage. A small number of patients (25%) have a decreased platelet count, which may be related to thrombosis and platelet consumption caused by inflammation and shock [16].

7.3.4 General Biochemical Tests

General biochemical tests, including liver function tests, kidney function tests, and blood electrolyte tests, are necessary and need to be performed every day in the early stages of the disease. Some patients with fulminant myocarditis have varying degrees of liver damage and kidney damage at the onset of the disease. This may be because the disease (viral infection) also involves these organs. In rare cases, the serum levels of liver enzymes (alanine aminotransferase and aspartate aminotransferase) can be as high as 10,000 U/L, among which the level of aspartate aminotransferase seems to show a slightly more marked increase than do the levels of other enzymes [17]. Similarly, after reasonable treatment, the liver enzyme levels can rapidly decrease and return to normal levels earlier than the troponin levels. In general, the transaminase levels are normal or slightly elevated. However, prolonged shock and long-term use of high-dose norepinephrine can lead to liver ischemic necrosis. In these situations, the liver enzyme levels increase considerably; the liver enzyme/bilirubin levels are separated; and DIC occurs. In addition, the serum albumin level can be reduced, which is related to liver damage, reduced hepatocyte synthesis capacity, and vascular leakage. The blood lactic acid level should also be checked, as it reflects the tissue anaerobic metabolism level, that is, hypoxia, which is very helpful for selecting treatment programs and judging treatment efficacy.

7.3.5 Coagulation Function Tests

Coagulation function tests include assessment of the prothrombin time, activated partial thromboplastin time, D-dimer level, activated clotting time, thrombin time, fibrinogen content, and other indicators. Patients with fulminant myocarditis are prone to developing DIC, and heparinization is required during circulatory support treatment. Thus, close monitoring of coagulation function is necessary. Decreases in the fibrinogen level and platelet count; prolongation of the prothrombin time, activated partial thromboplastin time, and thrombin time; and increases in the D-dimer level are signs of DIC [18]. Ninety percent of patients with fulminant myocarditis have varying degrees of D-dimer level increase when they are admitted to the hospital, indicating that the coagulation process has already started. Therefore, measuring coagulation function is very important for timely detection and diagnosis of DIC.

7.3.6 Inflammatory Indicator Assessment

The detection of inflammatory indicators is particularly important because the core pathophysiological mechanism of fulminant myocarditis is excessive immune activation and inflammatory storm formation.

1. The high-sensitivity C-reactive protein level and erythrocyte sedimentation rate are important indicators that can reflect the severity of inflammation. Approximately 27% of patients with fulminant myocarditis have different degrees of erythrocyte sedimentation rate increase, and 90% of patients have elevated C-reactive protein levels, among a few patients with extremely high C-reactive protein levels. A follow-up study has shown that among patients with obvious elevated inflammatory indicators, the inflammatory indica-

tors generally decrease soon after the disease is controlled. Of note, levels of high C-reactive protein and erythorocyte sedimentation rate are not specific and therefore, they have no value for diagnosis.

2. The most importantly, levels of multiple cytokines and inflammatory mediators include interleukin-1 (IL-1), interleukin-6 (IL-6), and other interleukins, tumor necrosis factor alpha (TNF-α), and interleukin-33 receptor soluble ST2 (sST2) [19, 20]. Our research has shown that the levels of these cytokines and inflammatory mediators are markedly increased in patients with fulminant myocarditis, which plays an important role in the inflammatory storm, and have diagnosis value, especially sST2. When acute myocardial injury occurs (plasma cTnI and BNP levels significantly elevate),elevated cytokine levels, especially sST2, can help diagnosis of fulminant myocarditis. Also see Chap. 13.
3. Procalcitonin (PCT) is rapidly cleaved to calcitonin in healthy individuals. Thus, the serum PCT level is very low and cannot be detected. However, in an inflammatory state, especially during bacterial infection, various tissues and cells can produce PCT and even a large amount of undegradable PCT, thus increasing the level of PCT. If patients with fulminant myocarditis show elevated PCT levels, attention should be paid to the possibility of bacterial infection. However, our observation in 69 patients with fulminant myocarditis without bacterail infection found that PCT level is 2.917±1.544 ng/mL (reference level is < 0.05 ng/mL) at admission day, increases to 21.679±7.564ng/ml at next day and it is still 3.017±1.446 ng/ml at discharge, which suggests that elevated PCT level does not represent bacterial infection during fulminant myocarditis.

7.3.7 Pathogen Detection

Pathogen detection includes pathogenic nucleic acid detection, antigen detection, and antibody detection, which were discussed in the special chapter (see Chap. 4 Etiology and Detection Methods of Fulminant Myocarditis).

7.3.8 ECG

In patients with fulminant myocarditis, the manifestations on ECG vary greatly. Among them, QRS complex widening, voltage reduction, and ST segment elevation are the most common manifestations that mimic acute myocardial infarction (with or without lead selectivity) [21]. Manifestations similar to non-ST-segment elevation myocardial infarction are also present. Arrhythmias are very common, including sinus tachycardia and bradycardia, conduction block, various premature beats, atrial or ventricular tachycardia, and ventricular fibrillation (see Chap. 10 ECG manifestations in myocarditis).

7.4 Case Reports

Case 1 A 52-year-old man was admitted to the hospital because of syncope. He was in general good health and engaged in paperwork. Recently, one of his relatives has passed away. He helped organize the funeral and did not sleep for 3 days. After the funeral, he felt extremely tired and slept continuously for nearly 24 h. On the next day, he fainted suddenly when he got up to go to the toilet. The patient was brought to the hospital by his family. At admission, the patient was confused and felt fatigued with a heart rate of 100 beats/min and blood pressure of 70/50 mmHg. His heart sounds were considerably reduced, and a third heart sound and galloping rhythm could be heard. ECG showed V_1–V_5 ST segment elevation, which might indicate extensive anterior wall myocardial infarction. However, the emergency coronary angiography yielded normal findings. Echocardiography showed diffuse reduction in myocardial contraction, thickened ventricular septum (13 mm), and decreased ventricular ejection fraction (35%). The cTnI level was markedly increased. The patient was then diagnosed with fulminant myocarditis. The "life support-based comprehensive treatment plan" introduced in Chap. 15 was immediately conducted. The patient was treated with IABP, adequate doses of glucocorticoids, adequate doses of immunoglobulin, and oseltamivir p.o. After 12 days of treatment, his condition improved greatly, and the

ventricular ejection fraction recovered to 62%. Thereafter, he was discharged.

Case 2 A 33-year-old woman was admitted to the hospital because of syncope. She was a manager and worked continuously lately because it was at the end of the year. After the overwork, she felt fatigued and went home to sleep. She was awakened by the alarm clock at 8 o'clock the next day and fell down after sitting up. Thereafter, she fell asleep. Two hours later, she contacted a colleague and then lost consciousness. Her colleague brought her to the hospital immediately. ECG at admission showed a third-degree atrioventricular block. Her blood pressure was 50/40 mmHg, with very muffled heart sounds, decreased left ventricular diffuse movement, and decreased left ventricular ejection fraction (30%). The levels of cTnI and NT-proBNP were considerably increased, and the levels of inflammatory factors IL-1 and IL-6 were also remarkably increased. She was then diagnosed with fulminant myocarditis. After active treatment, including temporary cardiac pacing, IABP+ECMO, and immune regulation, she recovered and was discharged after 2 weeks.

Case 3 A 14-year-old girl was admitted to the CCU owing to cardiac arrest. She was a student who felt tired for several days during their final examination but still insisted on attending class. After an 800-meter running test, she suddenly felt chest tightness and discomfort, accompanied by dizziness and fatigue. The patient was immediately sent to the medical room. Her pulse was weak, and the pulse rate reached 150 beats/min, with a blood pressure of 40/20 mmHg. The patient was treated with vasoconstrictors and transferred to the CCU. However, she experienced cardiac arrest during transfer. CPR was performed, and 8 min later, the stroller arrived at the CCU. Persistent cardiopulmonary resuscitation was performed. Meanwhile, tracheal intubation, mechanical ventilation, and emergency bedside venous-arterial extracorporeal membrane oxygenation were urgently needed. Her heart beated again. Her cTnI level was 4434.6 pg/mL, while her NT-proBNP level was 452 pg/mL on admission. Cardiac ultrasonography showed a normal heart size and normal ventricular wall thickness. Left ventricular systolic function was markedly reduced (ejection fraction, 8%). Her cTnI level increased to >50,000 pg/mL 6 h later; other biomarkers, such as the sST2, IL-1, IL-6, and TNF-α levels, also increased markedly. A diagnosis of fulminant myocarditis was made.

Key Points

1. The clinical manifestations of fulminant myocarditis are variable. Fulminant myocarditis begins with prodromal symptoms of respiratory infections, followed by mild chest pain, palpitations, and transient ECG changes and then progresses to life-threatening cardiogenic shock, malignant arrhythmias, and multiple organ dysfunction. It is characterized by a sudden onset and a rapid progression.
2. Hemodynamic disorder is an important feature that distinguishes fulminant myocarditis from acute myocarditis. Since most patients with fulminant myocarditis have no basic organic heart disease, the myocardial compensation mechanism has not been established, and patients soon develop cardiogenic shock.
3. Laboratory tests, such as assessment of the cardiac troponin, brain natriuretic peptide, and inflammatory factor levels; ECG; and cardiac color Doppler ultrasonography, combined with evaluation of clinical manifestations, are essential for a timely diagnosis of fulminant myocarditis.

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8 Diagnostic Values and Clinical Application of Endomyocardial Biopsy in Fulmiant Myocarditis

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Myocarditis is an inflammatory disease of the myocardium with various clinical manifestations, including asymptomatic, severe arrhythmia, and cardiac insufficiency. Later in the course of myocarditis, decreased cardiac function and severe heart failure may occur and may even require active circulatory support [1]. Myocarditis may progress to dilated cardiomyopathy, which is a common indication for heart transplantation and is also one of the leading causes of sudden death in young patients. Therefore, it is essential to quickly and accurately diagnose myocarditis.

In the early 1960s, Sekiguchi and Konno first introduced endocardial myocardial biopsy (EMB) in clinical practice [2]. The Dallas criteria, proposed in 1986, were used in endocardial biopsy as the gold standard for the diagnosis of myocarditis. However, EMB is not widely performed in China due to the skilled operation technique, possibility of serious complications, and high examination cost. Studies have also reported that EMB results have errors in sampling and film reading [3, 4], especially viral myocarditis and autoimmune myocarditis. The positive rate of diagnosis of EMB is low [5]. In recent years, with the advancement of EMB technology, the safety of muscle biopsy has improved. With the help of new technologies, such as immunohistochemical detection and viral nucleic acid amplification, the sensitivity and specificity of the diagnosis of myocarditis have improved. The value of EMB in the diagnosis of myocarditis has gained increasing attention and promotion. This chapter describes the diagnosis of fulminant myocarditis by endocardial biopsy, and we hope to further promote the clinical application of myocardial biopsy.

8.1 EMB

Endocardial biopsies were first performed in 1956 using special needles to collect samples from the chest. Endocardial tissue was first collected intravenously in 1962. In 2007, according to a joint agreement published by the American Heart Association, the Society of Physicians, and the European Heart Association, endocardial biopsy can be used in the diagnosis of many heart diseases, including unexplained onset heart failure with hemodynamic disturbance, heart failure with ventricular arrhythmia, heart failure that does not respond to conventional treatment, and myocarditis [6].

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8.1.1 Preoperative Preparation

The EMB was performed under local anesthesia. Patients must undergo an electrocardiogram, noninvasive blood pressure monitoring, and oxygen satiation during the procedure. Before EMB, the patient's international standardized ratio of coagulation function (INR) should be less than 1.5, and anticoagulant therapy should be discontinued at 16 h preoperatively and 12 h postoperatively. Color Doppler echocardiography should be performed before and immediately after EMB operation to monitor pericardial effusion. If conditions permit, electrocardiogram (ECG) monitoring should be performed 12–24 h after surgery. In addition, before biopsy, transthoracic cardiac ultrasound should be performed to check for cardiomyopathy, evaluate left ventricular ejection fraction and left ventricular hypertrophy, detect changes in myocardial structure, and screen for all cases in which left ventricular EMB is appropriate (e.g., left ventricular wall thickness less than 8 mm, myocardial insufficiency, left ventricular thrombosis, congenital aortic valve stenosis) [7].

8.1.2 Approach Selection and Equipment Preparation

In the early years, endocardial tissue was usually obtained from the right ventricle through the central vein to facilitate endocardial biopsy. However, many clinical heart diseases, such as cardiomyopathy and myocarditis, involve the left ventricle. In a study of 755 patients with suspected myocarditis, the detection rate of myocardial biopsies from the left ventricle was more than twice that of biopsies from the right ventricle [8]. Another study reported that in 2396 patients who underwent myocardial biopsies of the left and right ventricles, evidence was found in the left ventricle (96.3%) and the right ventricle (71.4%) ($P < 0.01$) [9]. Therefore, a myocardial biopsy of the left ventricle is recommended.

It is important to note that although it is traditionally believed that the left ventricular free wall is associated with a higher risk than the right ventricular site, no studies have shown that left ventricular myocardial biopsy is associated with a higher risk of complications than right ventricular biopsy.

Recent studies have shown that the radial approach has become the preferred approach for the diagnosis and interventional treatment of coronary artery disease. On this basis, it can also be applied to myocardial biopsies. Modern techniques and materials such as sheathed 6F catheters have been used for the radial artery approach, and left ventricular biopsy is a very safe method with a high success rate [10]. Currently, there are many types of cardiac biopsy forceps available in the clinic (Fig. 8.1) [11].

To further enhance sensitivity during sampling, noninvasive imaging or anatomical electrical imaging techniques can be used to locate the area of the myocardium (Fig. 8.2). Cardiac magnetic resonance imaging can provide advice on the location of myocardial biopsy based on the distribution of inflammatory areas in the ventricles, thus improving the detection sensitivity [12]. Echocardiography can also be used to locate and avoid damage to other parts of the heart during sampling.

In addition to the site of myocardial biopsy, the detection rate was also related to the number of myocardial biopsy samples. Generally, at least three to five pieces should be taken for further analysis, such as pathological, immunohistochemical, and molecular biological analysis (viral PCR, etc.). Electronic microscopes can be used to distinguish myocardial mitochondrial disease from storage diseases.

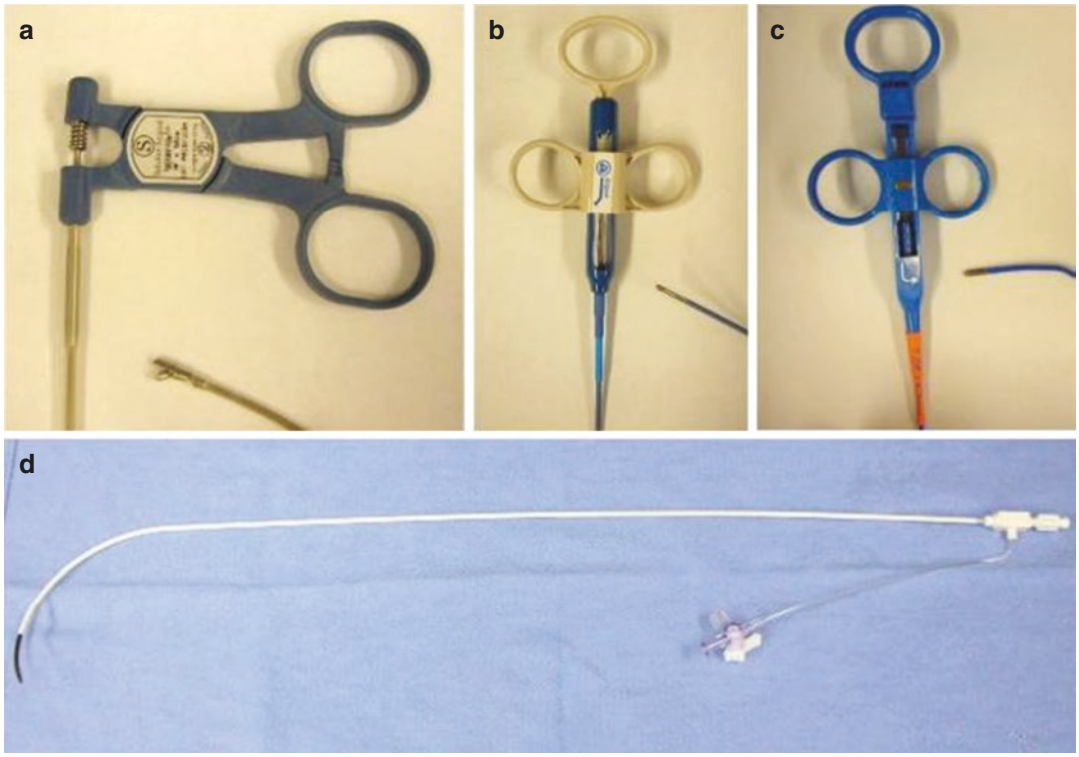

Fig. 8.1 Common endocardial forceps for myocardial biopsy. (**a**) Sholten Surgical Instruments, Inc., Lodi, CA; (**b**) Argon Medical Devices, Inc., Athens, TX; (**c**) Cordis Corp, Miami Lakes, FL; (**d**) Medtronic, Inc., Minneapolis, MN

8.1.3 Several Common EMB Operation Processes

8.1.3.1 Transradial Left Ventricular EMB

After local anesthesia, a 6F sheathing tube (Radifocus Introducer II,10 cm, Terumo, Japan) was punctured into the right radial artery. Before puncture, the patient received 3000 IU of ordinary heparin and 5 mg of villa. Pami artery injection to prevent radial occlusion or spasm. A 5F pigtail catheter (Boston Scientific, USA) was extended to the left ventricle, and the J-guide wire (260 cm, 0.03500) was used to determine the position of the ventricle through the pigtail catheter, and then the 6F sheath catheter and the pigtail catheter were removed. A 7.5F sheathless multipurpose guide catheter (MP1.0, Asahi Intecc, Japan) was introduced along the guidewire, and the expander was removed when the guide catheter reached the ascending aorta. The catheter was then carefully guided into the left ventricular lumen along the guidewire. The J-guide wire was removed and a Y-connector (Copilot, Abbott Vascular, USA) was connected. The position of the tip of the guiding catheter was checked under 20° left anterior oblique (LAO) fluoroscopy to determine if the tip refers to the lateral wall of the left ventricle

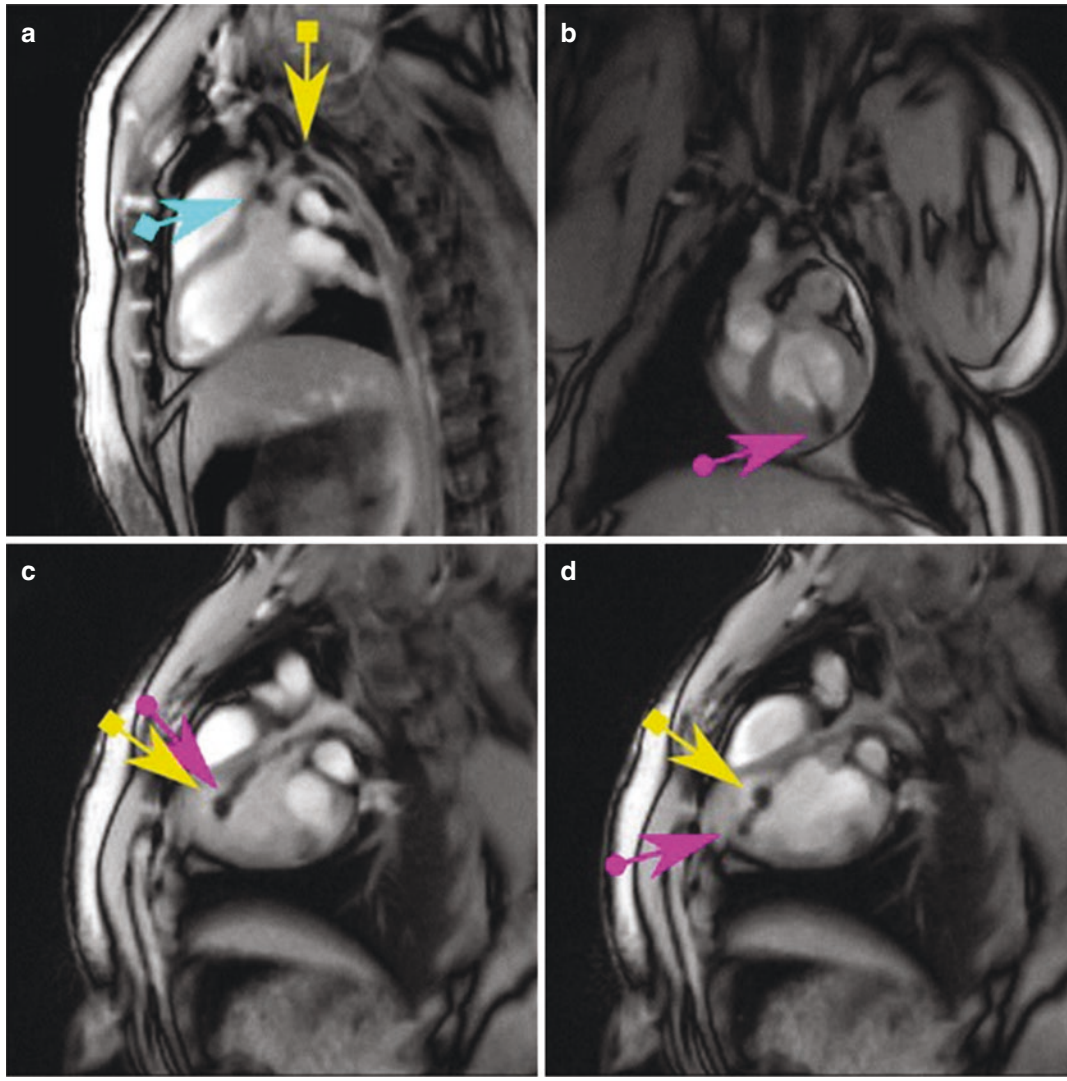

Fig. 8.2 Myocardial biopsy was performed under the guidance of cardiac magnetic resonance [12]. (**a**). The blue arrow shows the guidewire, and the yellow arrow shows the catheter; (**b**) The purple arrow shows biopsy forceps; (**c**) Yellow arrow shows the sampling site; the purple arrow shows the catheter; (**d**) Yellow arrow shows the sampling site; the purple arrow shows the catheter

(Fig. 8.3a). Once the position was determined, 6 ml of contrast was injected to determine the distance between the tip of the guide catheter and the lateral wall of the left ventricle. Before EMB, thrombus formation during the procedure should be prevented by testing the active coagulation time (ACT) range of 200–250 s. The biopsy forceps were rinsed in water to prevent air embolism and then gradually entered through the Y-connector of the MP1.0 guide catheter. Under fluoroscopy, the biopsy forceps gradually extended forward toward the guidance, and the anterior end of the catheter was gradually and carefully extended toward the lateral wall of the left ventricle. As soon as resistance is felt or the biopsy forceps are seen to reach the chamber wall under fluoroscopy, the forceps should be clipped, sampled, and immediately withdrawn from the guide catheter to place the specimen. At the end of the procedure, the sheathless guide catheter was withdrawn, and a vessel closure device was used to stop bleeding. After surgery, each patient received a small dose

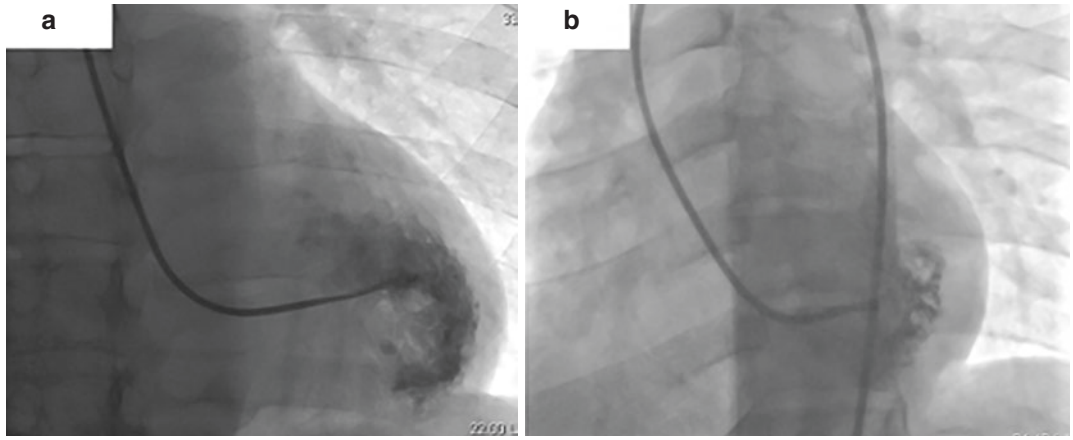

Fig. 8.3 Left ventricular (LV) angiography fluoroscopy in the left anterior oblique (LAO) 20° view with an injection of 6 ml of contrast agent to visualize the position of the 7.5 F MP-1 guiding catheter inside the left ventricle (tip pointing to the lateral LV wall). This image shows transradial approach

of aspirin for 4 weeks to prevent clots at the biopsy site [7].

8.1.3.2 Transfemoral Left Ventricular EMB

A 7F sheath catheter (Radifocus II, 10 cm, Terumo, Japan) was inserted through the right or left femoral artery under local anesthesia while the patient received 3000–4000 IU of common heparin (ACT: 200–250 s). The 5F pigtail catheter (Boston Scientific, USA) was then extended to the left heart. A long J-guide wire (260 cm, 0.035 00) was passed through the porcine tail catheter to determine the ventricular position. The porcine tail catheter was removed, and an 8F multipurpose guide catheter with an edge hole (MP1.0SH, Medtronic, USA) was introduced into the femoral artery, followed by a careful and gradual extension of the guidewire to the left heart cavity. The J-guide wire was removed, and the Y-connector (Copilot, Abbott Vascular, USA) was used to guide the position of the catheter in the heart cavity under fluoroscopy (Fig. 8.3b). The next steps are the same as the left ventricular EMB via the radial artery [7].

8.1.3.3 Transfemoral Right Ventricular EMB

Heparinization or aspirin prophylaxis is not recommended. A 7F sheath tube (Arrow Flex, 30 cm, Tereflex, USA) was inserted through the right or left femoral vein under local anesthesia. We used flexible biopsy forceps that could be adjusted in the right direction according to the anatomy of the individual patient. Unlike any other path, we did not use a guiding catheter during the procedure because it might affect flexibility and increase the risk of cardiac perforation. In principle, the use of any rigid or inflexible biopsy device for right ventricular biopsy is not recommended. Under 0° Right anterior oblique (RAO) fluoroscopy, the biopsy forceps were gradually extended to the right atrium. Carefully reach the right ventricle through the posterior tricuspid forceps. The optimal biopsy site can be determined at 90° LAO fluoroscopy, while right ventricular biopsy at RAO fluoroscopy is not recommended because it is not possible to determine whether the biopsy forceps are still in the right atrium or touch the coronary sinus. When opening the forceps, it is necessary to ensure that the forceps have touched the ventricular wall to avoid uncontrolled tissue damage. After the biopsy, the forceps contact the ventricular wall, they are slightly retracted slightly so that the forceps open in the right ventricle and then advance to the lower ventricular septum to clamp a few samples (Fig. 8.4). After completing all biopsy sampling, the 7F sheath tube was withdrawn, and the puncture points were manually pressed for minutes to stop bleeding [7].

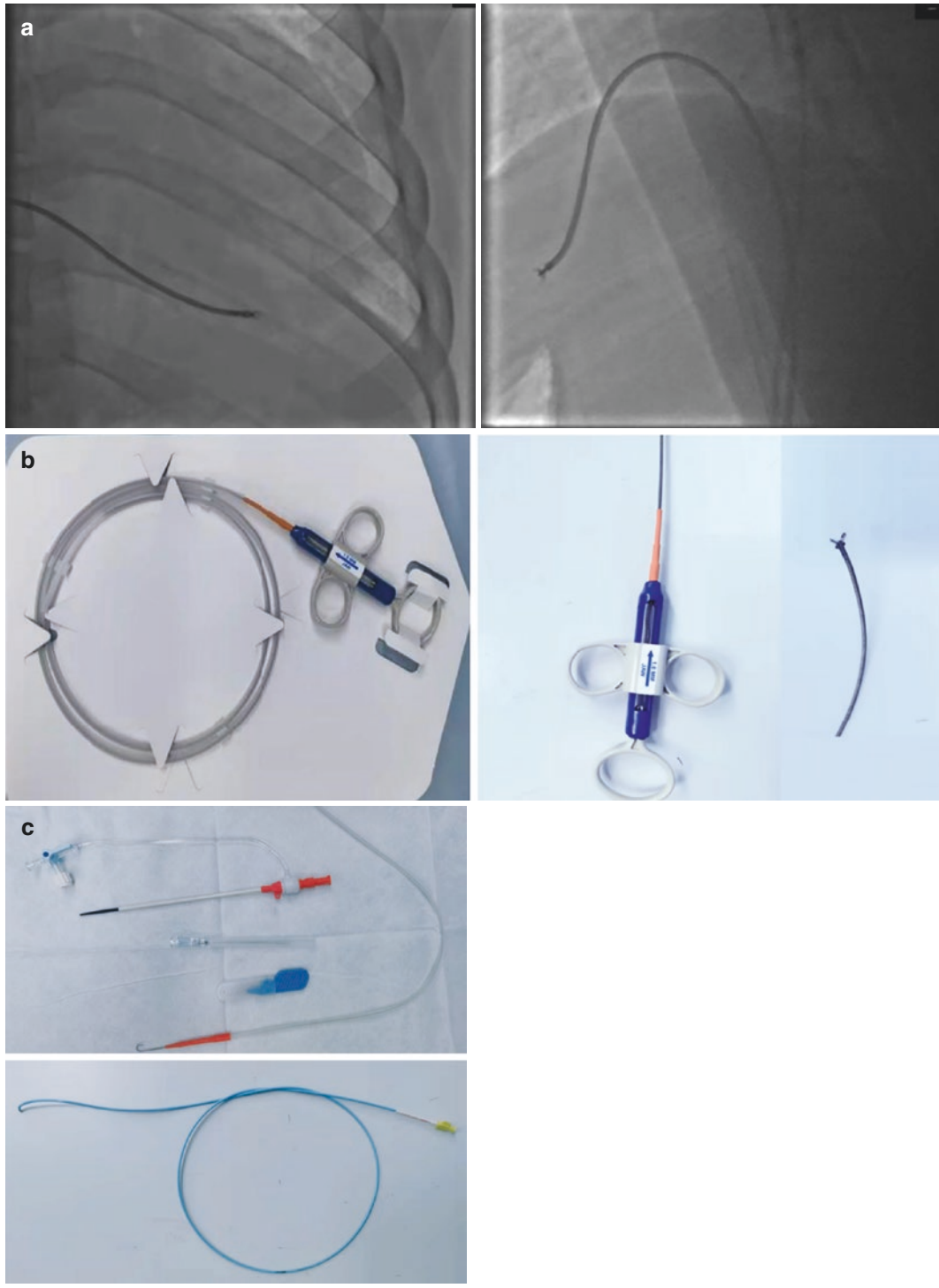

Fig. 8.4 (**a**) Right ventricular (RV) angiography fluoroscopy in RAO 0° and LAO 90° view visualization of the position of the biotome within the right ventricle. (**b**) Biopsy forceps used in our center. (**c**) The puncture sheath and guiding catheter used for biopsy

8.2 Management and Analysis of Myocardial Intimal Tissue

Generally speaking, more than two sites of myocardial tissue should be selected and at least 3–5 samples with a size of 1–2 mm^3 should be taken. Based on the different purposes of analysis used after sampling [13]. The specimen fixative (10% formalin) was fixed at room temperature (25 °C) or frozen in liquid nitrogen at −80 °C [13]. Special attention should be paid to the operation of the forceps and slicing machines when taking samples to avoid artifacts generated after tissue crushing and affecting pathological diagnosis (Fig. 8.5). Normally, samples can be examined with a light microscope first, and if there are special needs (e.g., identification of amyloidosis, glycogen storage disease, lysosomal storage disease), transmission electron microscopy can be used for analysis. For myocarditis, tumor typing, amyloid protein classification, etc., frozen sections can be made after sampling for corresponding molecular biological analysis, immunofluorescence, and immunohistochemical analysis [14].

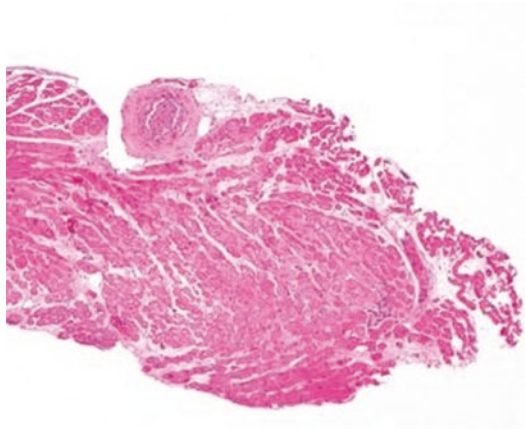

Fig. 8.5 Hematoxylin-eosin (HE) staining of crushed myocardial tissue

8.2.1 Light Microscopic Examination and Staining of Myocardial Intimal Tissues

In general, tissue obtained from myocardial biopsy is embedded in paraffin and sectioned for examination under a light microscope [13]. Hematoxylin-eosin (HE) staining may be used for inflammatory cells, elastin staining for collagen and elastin tissue, and iron staining for the intimal myocardium, if necessary, in males and postmenopausal females.

8.2.2 Molecular Study of Myocardial Intimal Tissue

In the past, research on targeted therapies for heart failure and cardiomyopathy has been greatly hampered by the lack of myocardial tissue. With improved detection technology, it has been gradually recognized that transcription and epigenetic regulation exist in these diseases. Studies have shown that some genes, such as cardiac stress signals (atrial natriuretic peptide and brain natriuretic peptide) and developmentally related genes (*TBX5* and *HAND2*), are methylated, and their mRNA transcription levels are altered during heart failure [15]. The widespread use of myocardial biopsy techniques, particularly in the left ventricle, can advance transcriptome, metabolome, and proteome studies of cardiac diseases and ultimately identify new therapeutic targets for these diseases.

8.2.3 Molecular Biological Detection of the Virus Genome in Myocardium Tissue

In recent years, with the application of quantitative (real-time fluorescence quantitative polymerase chain reaction, qPCR) and qualitative

(nested PCR) PCR techniques, it has been possible to detect viruses with less than 10 copy numbers in myocardial tissue. These highly sensitive techniques have significantly improved the diagnostic and application value of myocardial biopsies.

In the past 20 years, evidence of cardiotropic viruses in patients with secondary heart disease has been found by nested PCR. Studies in patients with myocarditis or dilated cardiomyopathy have found the presence of a variety of viruses in the myocardium, including enterovirus, adenovirus, parvovirus B19, cytomegalovirus, influenza virus, respiratory syncytial virus, herpes simplex virus, Epstein-Barr virus, human herpesvirus 6, and HIV, etc. [16–25] Among them, nested PCR was used to amplify myocardial tissue samples from 773 patients (624 cases of myocarditis and 149 cases of dilated cardiomyopathy), and relevant viruses were found in more than 40% of the samples, mainly enterovirus and adenovirus [20]. Other studies have detected enterovirus, parvovirus B19, and human herpesvirus 6 in adults with dilated cardiomyopathy or unexplained left ventricular dysfunction [23]. Currently, real-time quantitative PCR has been applied for the quantitative detection of cardiophilic viruses. The viral load of patients with parvovirus B19-positive myocarditis has been reported to be between 50,000 and 500,000 copies/μg [26].

Various inducements can cause myocarditis, including bacterial and viral infections, drugs, radiation, metabolic disorders, and immune disorders. Viral infection is the main cause of acute myocarditis [27]. Enteroviruses, especially Coxsackievirus B (CVB), are considered a common cause of myocarditis. Adenovirus, parvovirus B19 (PVB19), and human herpesvirus 6 have also been found to be common causes of cardiac disease [26, 27]. Studies have shown that the most common virus in the myocardium of patients with adult idiopathic dilated cardiomyopathy in Germany is parvovirus B19 [22], and adenoviruses and enteroviruses were detected most frequently in patients with myocarditis in the United States [26]. In addition, some scholars believe that influenza viruses, especially pandemic strains, may cause fulminant myocarditis [28], but there is no clear evidence to support this.

Owing to technological limitations, there is still a high false negative rate for virus detection in myocardial tissue. Therefore, it is still controversial whether it is necessary to detect the virus genome in myocardial biopsy tissue.

8.2.4 Immunohistochemistry of the Myocardium

Making frozen sections of myocardial tissue and using immunohistochemistry to detect subsets of inflammatory cells can improve the diagnosis of myocarditis. The detection of some cytokines can indicate the type of inflammatory cells, such as CD3, CD4, and CD8, which are lymphocytes, CD19 is a symbol of B cells, CD56 is a symbol of NK cells, and CD68 is a symbol of macrophages; MPO is a symbol of neutrophils. Other cytokines, including CD11a (lymphocyte function-associated antigen-1), CD11b (MAC-1), CD45R0 (memory or active lymphocytes), CD54 (intercellular cell adhesion molecule), CD106 (vascular cell adhesion molecule-1), and HLA-1, have been detected at high levels in the myocardium [30]. Several studies have shown that the presence of more than 7 CD3+ or CD2+ lymphocytes or 14 CD45+ or LCA+ leukocytes per mm^2 of cardiomyocytes can be a diagnostic basis for myocarditis [31–36]. Some studies have also suggested that the elevation of some adhesion molecules (CD56, CD106, etc.) may also indicate myocarditis [37–40]. In the clinic, it may be helpful to improve the accuracy of diagnosis by adding relevant immunohistochemistry to myocardial biopsy tissue.

8.3 Clinical Application of EMB in Fulminant Myocarditis

Myocarditis is a disease characterized by localized or diffuse myocardial inflammatory lesions.

According to the 1984 Dallas criteria, infiltration of inflammatory cardiomyocytes with degeneration and necrosis of adjacent cardiomyocytes is the major histological evidence of myocarditis [41, 42].

This criterion classifies myocarditis into two types: (1) active myocarditis, in which light microscopy reveals inflammatory cell infiltration and nearby myocardial cell damage, including clear cell necrosis, vacuoles, irregular cell shape, and cell disintegration. (2) Critical myocarditis, inflammatory infiltration, sparse myocardial tissue, and no obvious cell damage under light microscopy. The results were considered negative if there was no lymphocytic infiltration or cardiomyocyte lysis. This standard considers that myocardial tissue biopsy is the "gold standard" for the diagnosis of myocarditis.

Histopathologically, myocarditis can be divided into lymphocytic myocarditis, eosinophilic myocarditis, giant cell, or granulomatous myocarditis according to the main type of infiltrating cells. Lymphocytic myocarditis, the most common pathological type of myocarditis, is characterized by extensive infiltration of CD4+ and CD8+T lymphocytes, macrophage infiltration with CD68+, and rare occurrence of B lymphocytes (Fig. 8.6) [43]. Eosinophilic myocarditis is characterized by significant infiltration and degranulation of eosinophils in the myocardium (Fig. 8.7) [44]. Giant cell myocarditis is characterized by a typical infiltration of giant cells in the myocardium (Fig. 8.8), but

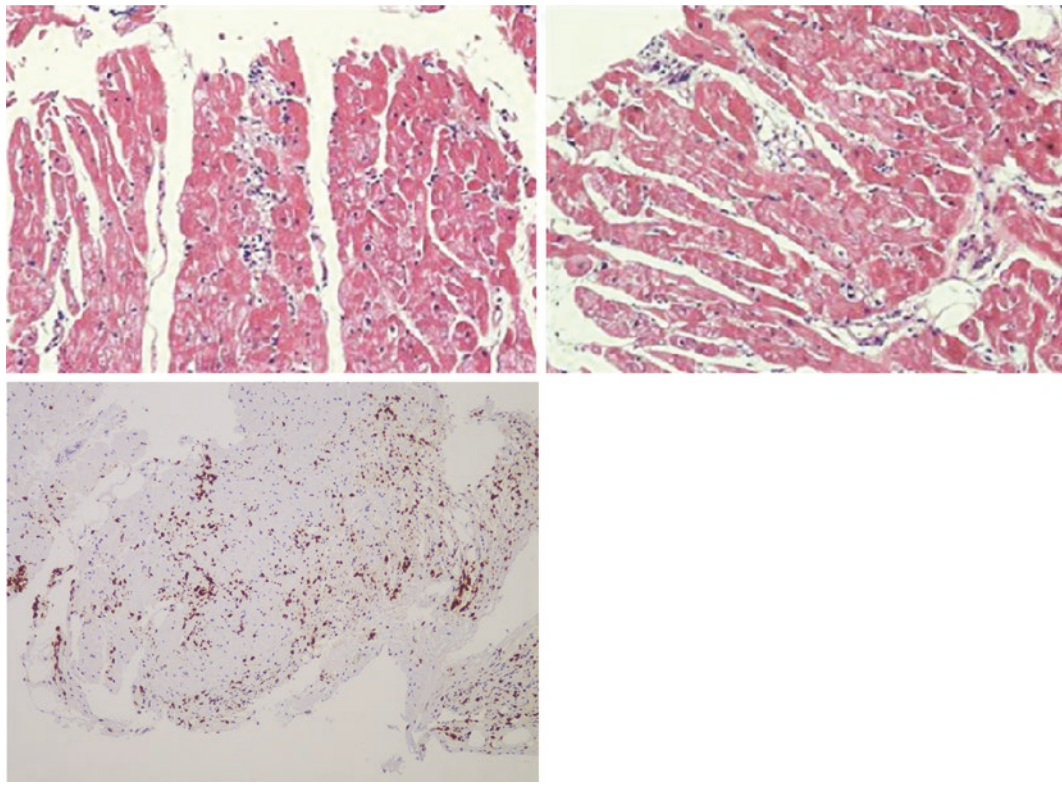

Fig. 8.6 HE staining of the myocardium in lymphocytic myocarditis [45]. A 31-year-old male patient was clinically diagnosed with fulminant myocarditis. Mild edema, cardiomyocytes degeneration, and the infiltration of chronic inflammatory cell (lymphocyte) in the myocardial interstitium can be seen under the light microscope. Immunohistochemistry: CD3 (+), CD20 (−), positive control (+), 100X

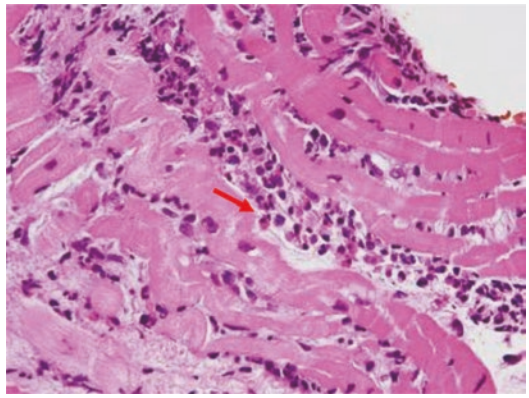

Fig. 8.7 Histological findings of right-ventricular endomyocardial biopsy specimen on admission. Hematoxylin-eosin staining (formalin-fixed; paraffin-embedded) shows damaged myocardium and infiltration of degranulated eosinophils (arrow) [46]

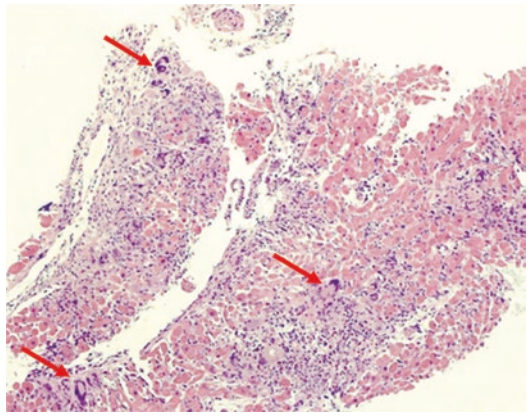

Fig. 8.8 Endomyocardial biopsy demonstrating inflammatory infiltration of cardiac myocardium with a hematoxylin and eosin stain. Numerous giant cells (arrow) within inflammatory infiltrate consisting of lymphocytes, histiocytes, and eosinophils [47]

special attention should be paid to distinguish it from sarcoidosis (sarcoidosis is characterized by a non-necrotizing epithelioid granuloma). Histological classification of myocarditis helps guide specific clinical management, such as eosinophilic myocarditis and giant cells. Myocarditis can be treated with corticosteroids, while giant cell myocarditis may require a stronger immunosuppressant.

Histological classification of myocarditis can help guide specific clinical treatments, such as eosinophilic and giant cell myocarditis, which may be treated with corticosteroids, while giant cell myocarditis may require the use of stronger immunosuppressive agents.

Histopathological examination of myocardial biopsy specimens can not only diagnose and classify myocarditis but also indicate the progression of the disease. Generally speaking, specimens obtained within a few days after the onset of myocarditis show mainly inflammatory infiltration of tissues and myocardial cell damage of varying degrees, such as myocardial cell necrosis, vacuolation, irregular cell contour, or cell fragmentation [42]. Damage to heart muscle cells triggers an innate immune response, followed by tissue repair. During the development of myocarditis, damaged cardiomyocytes are gradually swallowed by macrophages, and a stroma is produced in this area, which subsequently forms a granulation tissue rich in capillaries and myofibroblasts. Later, as the inflammation ends, the area is filled with mature collagen fibers because heart muscle cells themselves have limited ability to regenerate. This healing process is similar to the tissue repair process after an aseptic injury, such as myocardial infarction [48, 49].

Although different guidelines have different diagnostic criteria for myocarditis, endocardial biopsy has always been the "gold standard" for the diagnosis of myocarditis [50]. With the progress of technical means, myocardial biopsy tissue can only be performed with a simple post-staining pathological examination in the past, and now it has developed into a variety of detection methods (virology, immunohistochemistry, etc..) [51]. Cardiac biopsies are becoming less false-negative and more useful. An endocardial biopsy is a relatively safe examination, which plays an important role in the diagnosis of fulminant myocarditis and is of significant significance for clinical treatment.

Key Points

1. Endocardial biopsy is a relatively safe examination that plays an important role in the diagnosis of fulminant myocarditis and has significant significance for clinical treatment.

2. Left ventricular biopsy via the radial artery via a sheathless 6F catheter is a very safe and successful method.
3. Histopathological examination of myocardial biopsy specimens can not only diagnose and classify myocarditis but also indicate the progress of the disease.

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9 Association between Histological Changes and Clinical Manifestations of Fulminant Myocarditis

Chen Chen and Dao Wen Wang

Myocarditis is an inflammatory disorder of the myocardium, usually involving mononuclear cells infiltrating the myocardium. The lesions can be focal or diffuse. The core mechanism of myocarditis is the pathophysiological changes caused by an inflammatory response [1]. Fulminant myocarditis, an acute form of myocarditis, involves the rapid generation of numerous inflammatory cells that invade the heart [2] (Fig. 9.1).

Based on the type of infiltrating cells, myocarditis can be classified as lymphocytic, giant cell, eosinophilic, or cardiac sarcoidosis [2], while based on the clinical course of the disease, it can be classified as fulminant, acute, chronic active, or chronic persistent [3]. In general, the pathophysiological processes of the different types of myocarditis are similar. Viral infections are the main cause of myocarditis, and enterovirus infections are the most thoroughly studied ones, especially the Coxsackievirus B3 (CVB3) infection [4]. At the cytological level, the pathophysiological process of myocarditis is divided into three stages, acute: viral colonization and replication, subacute: inflammatory cell infiltration, and chronic: ventricular remodeling (Fig. 9.2) [5]. Most viruses that cause myocarditis are localized in cardiomyocytes, but some viruses can also infect the non-cardiomyocyte cells of the heart such as endothelial cells and lymphocytes (Table 9.1). Cardiac damage during viral myocarditis occurs mainly through two aspects: direct damage caused by virus infection and indirect damage caused by the immune response of the host [1].

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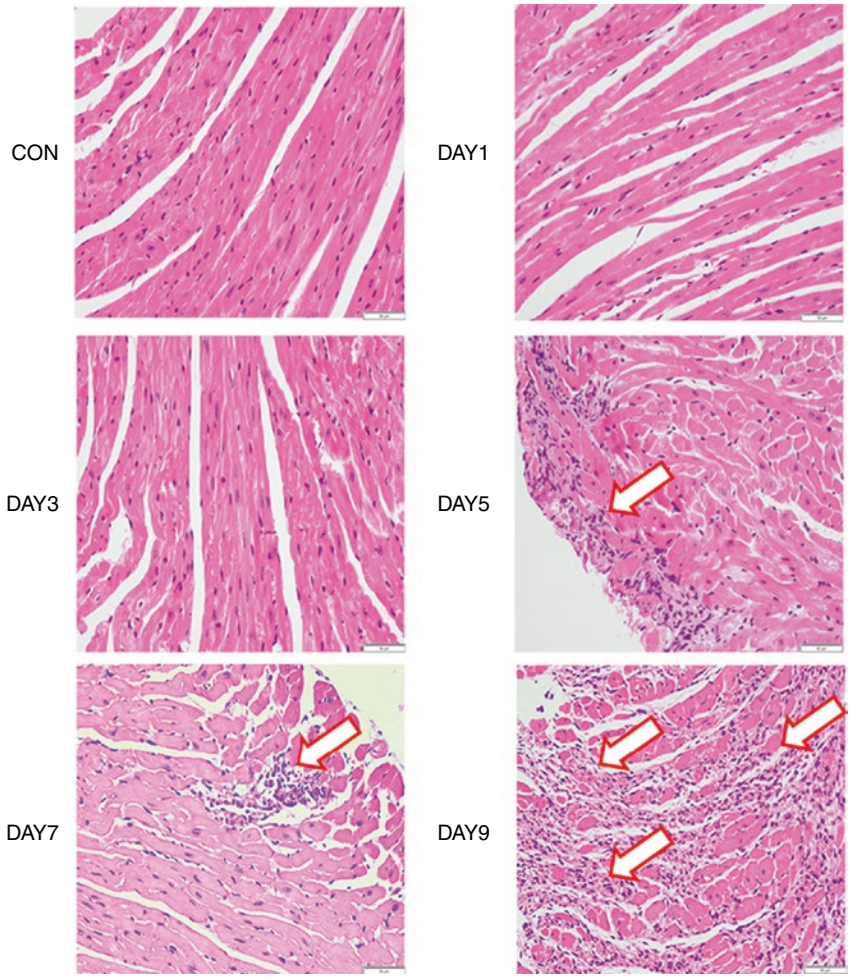

Fig. 9.1 Disordered myocardial cells infiltrated by numerous inflammatory cells (blue blobs indicated by arrows), as detected by hematoxylin and eosin staining of myocardium of mice with fulminant myocarditis

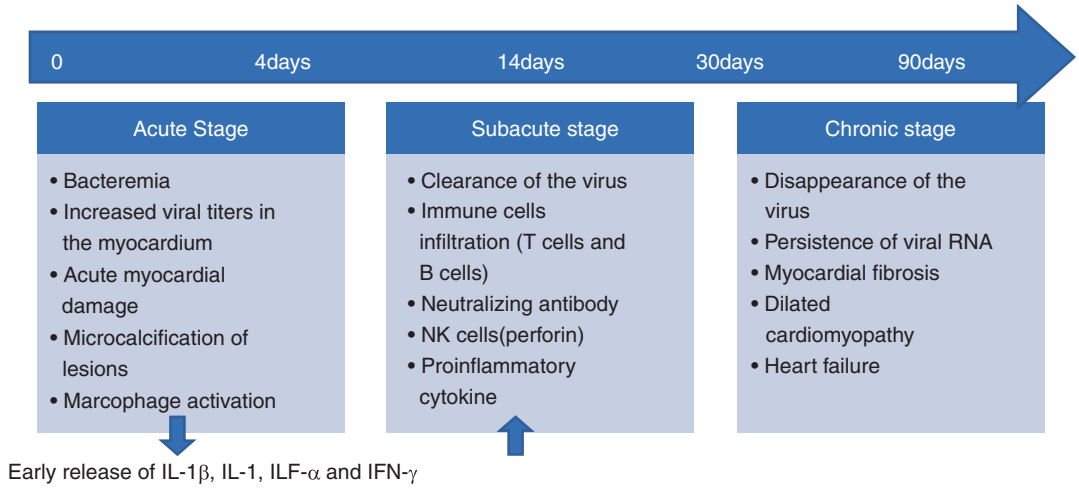

Fig. 9.2 Three stages of viral myocarditis in mice

Table 9.1 Target cells of different pathogenic viruses in myocarditis

Virus	Main target cells
Adenovirus	Myocardial cell, fibroblast, endothelial cell
Enterovirus/ Coxsackie virus	Myocardial cell
Parvovirus	Myocardial cell, endothelial cell
Human herpes virus	Endothelial cell?
Cytomegalovirus	Myocardial cell
EB virus	Lymphocyte
Influenza virus	Macrophage, lymphocyte
Hepatitis C virus	Myocardial cell
HIV	Myocardial cell

9.1 Lymphocytic Myocarditis

Lymphocytic myocarditis is the most common type of myocarditis, and viral myocarditis mostly manifests as lymphocytic myocarditis. The pathology of lymphocytic fulminant myocarditis is characterized by a huge infiltration of lymphocytes in the myocardial and perivascular interstitium, along with the presence of edema (fluid trapped in gaps between cardiomyocytes) and plasma cells (Fig. 9.3). Immunohistochemical studies followed by classification of the infiltrating lymphocytes identified $CD3^+$, $CD4^+$, and $CD8^+$ cells as well as $CD20^+$ B lymphocytes. Furthermore, an equivalent number of $CD56^+$ macrophages as well as MPO^+ monocytes are also presented (Fig. 9.3).

The classification of the inflammatory cells provides important clues regarding the mechanism of action of the pathogenic molecules; the molecules act on the pattern recognition receptors of cardiomyocytes, resulting in the production of cytokines and chemokines and the infiltration of monocytes or macrophages. This is followed by the initiation of the adaptive immune response via a series of mechanisms that include production of lymphocytes and plasma cells, which leads to an immoderate immune activation and inflammatory storm [6].

In clinical practice, 32 patients of lymphocytic fulminant myocarditis, as confirmed by endomyocardial biopsy, who initially appeared healthy, experienced a sudden onset of symptoms after prolonged stress and arrived at the hospital within 3–5 days in a state of hypotension, shock, and with recurrent syncope.

It has long been recognized that myocarditis is primarily caused by viruses; studies have identified CVB3 receptors in cardiomyocytes and established mouse models of myocarditis accordingly [7]. Although viruses were not detected in most patients, the role of viral infections as initiators of the immune response cannot be excluded. The results of the study in the CVB3 mouse model are briefly introduced below.

Myocarditis caused by CVB3 infection is divided into a pre-infection period (stage 0) followed by three post-infection periods (stages 1, 2, and 3) [7]. The pre-infection period (stage 0) is very important for the prevention of fulminant myocarditis, which can be effectively prevented if susceptibility to viral infection is rapidly identified and appropriate measures are taken. Stage 1 comprises the acute phase during which the virus actively replicates in myocardial cells; most patients with fulminant myocarditis present in this phase. Stage 2 is the subacute phase during which viral replication ceases. However, the viral genome continues to be expressed in the myocardial cells and can effectively recruit inflammatory cells to infiltrate and induce an immune response that damages the myocardium. Stage 3 is the chronic phase, during which the viral genes have been cleared, but the immune response persists, and the heart remodels. There is a high probability that the virus will not be detected in a Stage 3 myocarditis patient.

9.1.1 Stage 0 (Pre-Infection Stage)

In terms of clinical value, prevention of myocarditis reduces its morbidity and mortality radically, and should therefore be prioritized. Advances in immunization against enteroviruses have proven to be effective in preventing myocarditis [8–10]. However, since the morbidity and mortality rates of various types of viral myocarditis, especially fulminant myocarditis, are currently unclear, the risk-benefit ratio of using viral vaccines to prevent myocarditis is unknown.

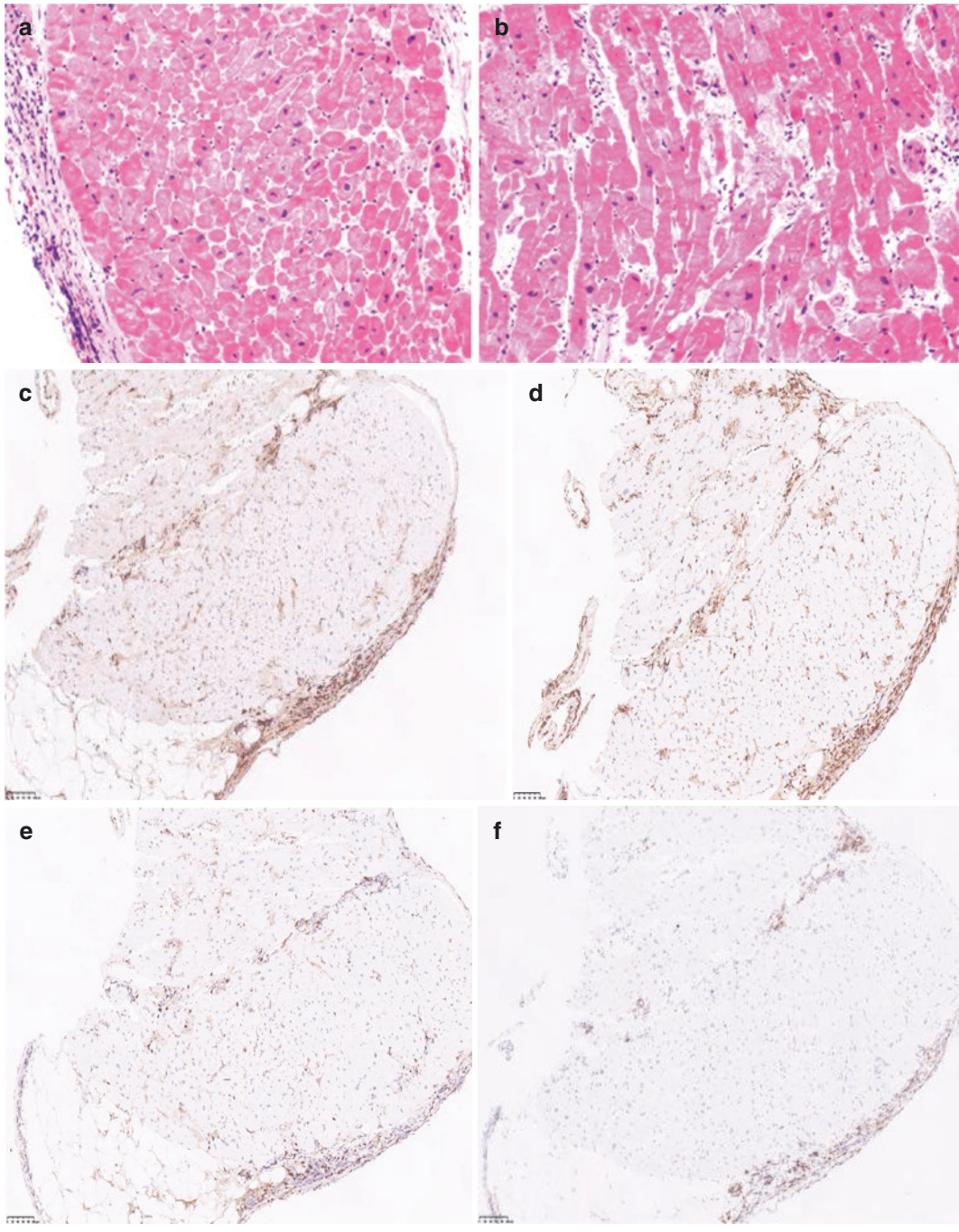

Fig. 9.3 The pathology of endocardial biopsy sample of a patient with lymphocytic fulminant myocarditis. Hematoxylin and eosin staining (**a**, **b**) showing infiltration of neutrophils and lymphocytes in endocardium and myocardial interstitium, degeneration and partial lytic necrosis cardiomyocytes, and interstitial edema; as well as immunohistochemical staining of CD3 (**c**), CD4 (**d**), CD8 (**e**), CD20 (**f**), CD56 (**g**) and MPO (**h**) showing the infiltration of various classes of lymphocytes and neutrophils

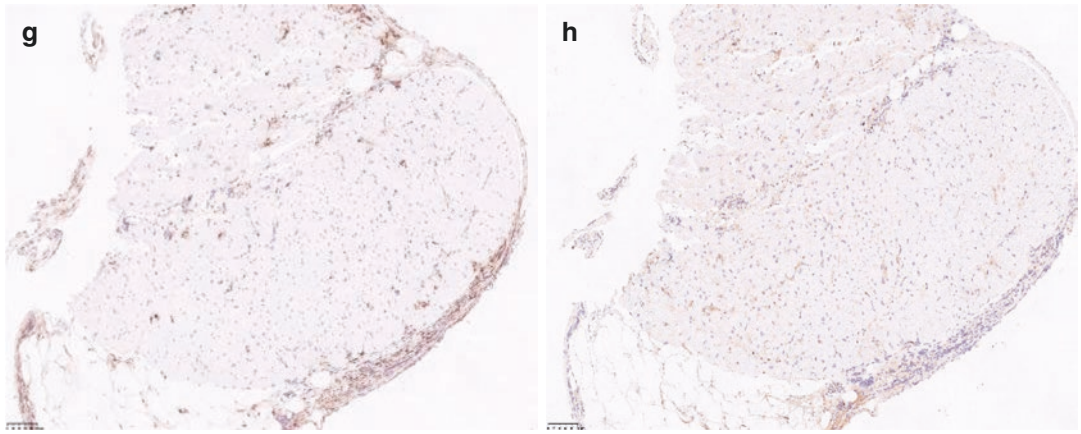

Fig. 9.3 (continued)

Hence, they are not yet suitable for promotion in the general population.

Factors that influence the susceptibility of the heart to viral infections are not completely understood yet. Why do some people contract viral infections after exposure while others do not, despite living in the same closed environment? Why do individual symptoms of infection vary from mild discomfort to acute myocarditis or even to fulminant myocarditis? The influence of genetic as well as environmental factors on the development of myocarditis, especially fulminant myocarditis, deserves further investigation.

Normally, the non-pathogenic strain of coxsackievirus, CVB3/0, does not attack the heart, but the occurrence of genetic mutations in six nucleobases renders its genome (CVB3/0Se-) identical to that of pathogenic strains (CVB3/M1 or CVB3/20), causing it to develop pathogenicity and increasing the incidence of viral myocarditis in selenium-deficient mice [11].

Susceptibility to viral myocarditis is affected not only by the genetic variation of viruses but also by the genetic polymorphism of the host. In 2010, genes of 57 patients who had positive endomyocardial biopsies for enterovirus infection were sequenced, which led to the identification of genetic variants of the *TLR3* (Toll-like receptor 3) gene that increased host susceptibility to viral cardiomyopathy [12]. Mutations in the *TLR3* gene (P554S or L412F) inhibits the NF-κB and type I interferon signaling pathways, attenuates cardiac autophagy and repair functions, enhances viral replication in the heart, and activates abnormal immune responses, ultimately resulting in impaired cardiac function [12].

There are limited genetic studies on myocarditis, most of which have been disseminated as small sample reports. Although polymorphisms in genes, such as *HLA-DQ* and *CD45*, have been reported to be associated with the risk of developing myocarditis, validation of the sites of these genetic variances using large multicenter samples and biological studies to determine the specific mechanisms by which these polymorphisms lead to myocarditis, especially fulminant myocarditis, are required [13, 14].

9.1.2 Stage 1 (Acute Stage)

This stage comprises the period from the beginning of the viral infection in the heart to the cessation of viral replication, which is usually within 2 weeks of infection; fulminant myocarditis is typically presented at this stage. The pathophysiological processes include: (i) entry of the virus

into cardiomyocytes, (ii) virus replication within the cardiomyocytes, (iii) direct viral damage to cardiomyocytes, and (iv) transcellular viral infection of adjacent cardiomyocytes. The treatment of viral myocarditis could target these key processes.

9.1.2.1 Entry of Virus into Cardiomyocytes

It has been previously demonstrated that coxsackieviruses and adenoviruses are mediated into host cells by the Coxsackievirus and adenovirus receptor (CAR) [15]. Additionally, these viruses can infect host cells via decay-accelerating factor (DAF, CD55) or integrin (αvβ3 and αvβ5) that act as receptors [16].

The CAR is a transmembrane protein belonging to the intercellular adhesion molecule family that mediates rhinovirus and enterovirus infection in host cells. It has a region comprising two extracellular immunoglobulin structural domains that forms an inverse parallel dimer by binding to another CAR on an adjacent cell (Fig. 9.4). In the physiological state, CARs are localized in the AV node and mediate electrical conduction; therefore, their impairment by the virus leads to the development of different forms of arrhythmia in patients of myocarditis.

9.1.2.2 Replication of Virus

Once the virus enters the host cell, it utilizes various host cell molecules for replication, including proteins and non-coding RNAs, thus further aggravating the damage to cardiac function that could even progress to dilated cardiomyopathy. Various signaling pathways in the host cell have been identified to play important roles in the different stages of the viral life cycle, such as viral entry, replication, release into other cells, and evasion of the host's immune response (Fig. 9.5) [17].

Entry of viruses into epithelial cells via tight junctions is mediated by Fyn and Abl kinases [18]. Coxsackievirus infection activates the tyrosine protein kinase p56lck, MAPK1/2 kinase, and protein kinase C (PKC) signaling pathways, which in turn activate the host cell immune response while promoting viral replication [19]. In addition, the virus-induced p38 MAPK as well as glycogen synthase kinase (GSK-3β) pathways promote apoptosis and necrosis, which then pro-

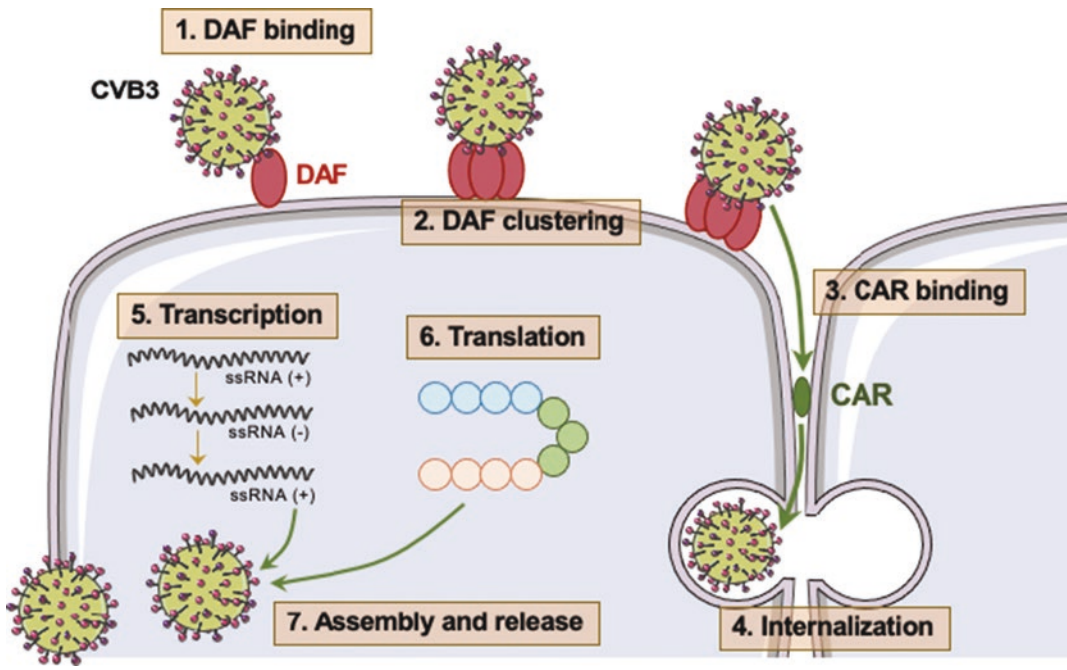

Fig. 9.4 Entry of CVB3 into cardiomyocytes via CAR

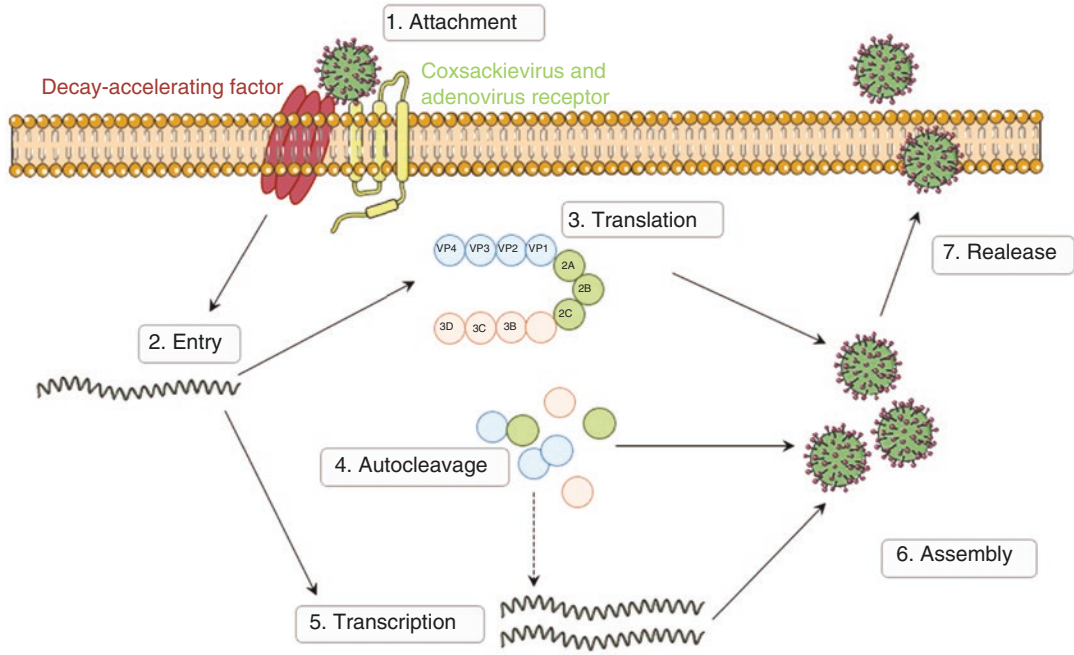

Fig. 9.5 Life cycle of CVB3

mote the release of the virus from the cell, facilitating subsequent cell invasion and infection [20]. Administration of p38 MAPK inhibitors to mice with coxsackievirus infection-induced myocarditis reduced viral replication in cardiomyocytes, attenuated myocardial injury, and improved cardiac function [21]. Notably, these pathways are unable to mediate the injurious effects of viruses on the heart independently and require interaction with each other. Furthermore, viruses utilize different signaling pathways of host cells at various life cycle stages to ensure their continued survival.

Viruses are able to exploit non-coding RNAs, especially microRNAs (miRNAs), present in host cells to promote their own replication and inflict damage on the host cells. Infection with coxsackieviruses promotes the expression of miR-141, which was the first miRNA identified to be associated with coxsackievirus replication. MiR-141 blocks the expression of various proteins in host cells by inhibiting eIF4E [22]. Host-derived miRNAs can also interact with viral genomes; host miR-10a-3p promotes viral synthesis by interacting with a sequence of coxsackievirus RNA [23].

Although most virus-induced host miRNAs promote viral replication and host cell destruction, some of them, such as miR-221 and miR-222, protect the host from viral invasion. These miRNAs, whose expression is significantly elevated in coxsackievirus-induced myocarditis, inhibit viral replication as well as host cell inflammatory responses, and reduce host cell apoptosis, mainly by suppressing host genes such as interferon regulatory factor 2 (*IRF2*), C-X-C Motif Chemokine Ligand 12 (*CXCL12*), and B-cell lymphoma 2 (*bcl-2*) [24].

9.1.2.3 Direct Viral Damage to Cardiomyocytes

After a successful evasion from the host's innate immune response, the virus begins to replicate in host cells and produces viral proteins that directly attack the cardiomyocytes (Fig. 9.6). Therefore, viral infection of immunodeficient mice led to severe symptoms that manifested as fulminant myocarditis [25].

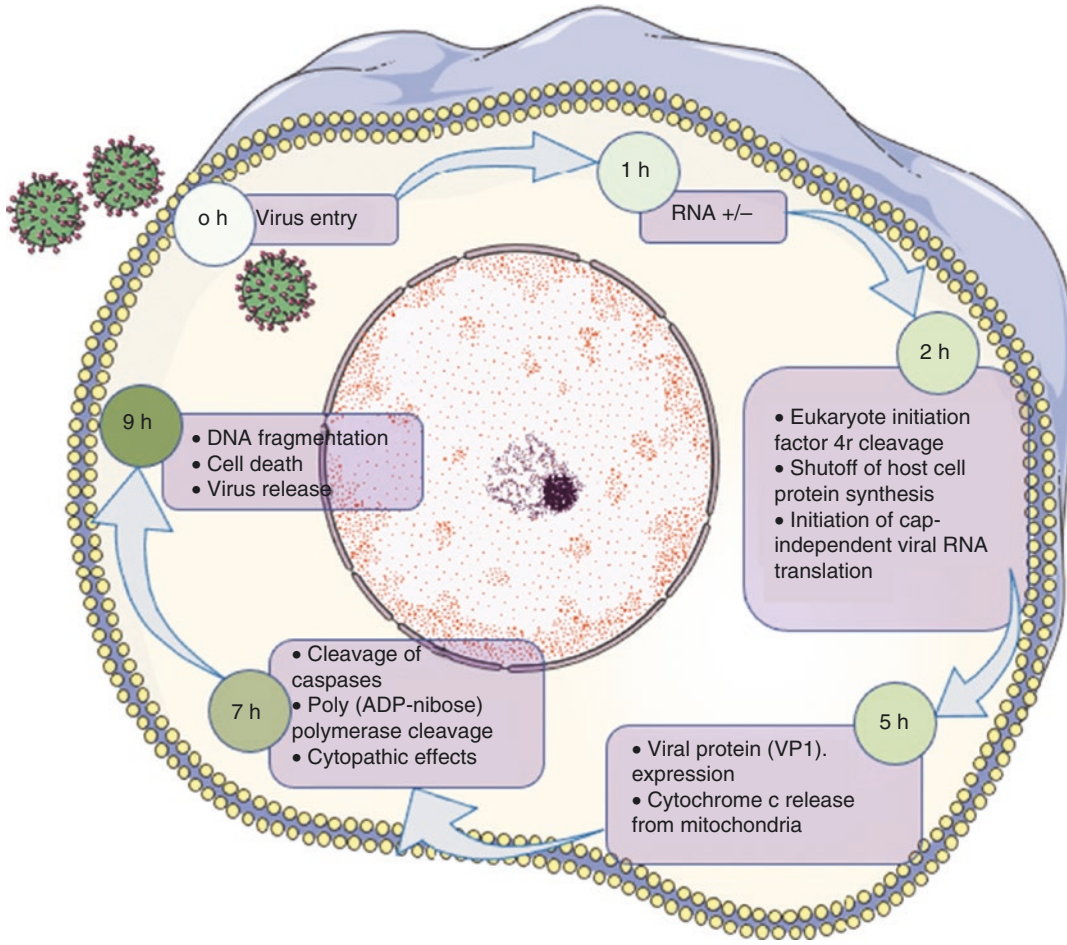

Fig. 9.6 Direct cell damage by CVB3 after cell entry

The enterovirus genome encodes protease 2A and protease 3C, which process the viral polyproteins into separate structural or nonstructural proteins that are essential to complete the entire viral life cycle. These proteases inhibit the formation of translation initiation complexes and prevent the production of cell membrane repair proteins [26]. In addition, protease 2A specifically affects many host proteins related to cardiomyocyte structure, signal transduction, and contractile function. It is capable of shearing the host eukaryotic initiation factor-4G (eIF4G), a key initiation factor required for translation, and inhibiting the synthesis of contractile proteins in cardiomyocytes [27]. It also shears the hinge 3 region of the cell repair-related protein dystrophin. This disrupts the integrity of the myocardial membrane, increases cell permeability, promotes virus spread to neighboring cells, and increases the susceptibility of the heart to the virus [28, 29].

Autophagy is an important mechanism by which cells repair themselves. During CVB3 infection, cell function is damaged due to shearing of glycine at position 241 in Sequestosome 1 (SQSTM1), an important protein in the autophagic response, which leads to the impair of autophagic response, reduction in the clearance of damaged proteins and subsequent accumulation of misfolded proteins [30].

To investigate the role of proteinase 2A, transgenic mice with high expression of proteinase 2A in cardiac myocytes were developed. These mice

displayed rapid enlargement of heart chambers, decreased cardiac function, cardiac fibrosis, disturbed cardiomyocyte arrangement, and impaired cardiac cytoskeletal structure, suggesting that proteinase 2A causes direct damage to the structure and function of cardiac myocytes [31].

During viral infection, proteinase 2A also shears the melanoma differentiation-associated protein 5 (MDA5) of the host, inhibits the production of type I interferon, and weakens the host's virus-clearance mechanism [32]. In addition to shearing proteins, proteinase 2A and proteinase 3C activate the exogenous (caspase-8-mediated) and the endogenous (mitochondrial) apoptotic pathways, directly causing cardiomyocyte apoptosis or necrosis.

These studies demonstrated that virus-encoded proteases can directly attack cardiomyocytes in several ways (Table 9.2), suggesting that effective inhibition of viral protease function is necessary for the treatment of viral myocarditis [33].

Table 9.2 Targets of enterovirus proteases

Type	Protease	Virus	Target genes
Cytophylaxis	2A	PV, EV71	MDA5
	2A, 3C	CVB3, HRV, EV71, PV	MAVS
	3C	CVB3, PV, EV71	RIG-I
	2A, 3C	EV71	NLRP3
	3C	EV71, CVB3	TRIF
RNA/protein synthesis	2A	PV	DCP1a
	3C	PV	La/SSB
	2A	CVB3	p62/SQSTM1
	2A, 3C	CVB3	NBR1
	3C	CVB3	RIP3
Cell integrity	2A	CVB3	Dysferlin
	2A	CVB3	Dystrophin
	2A	HRV	Cytokeratin 8
	3C	PV	MAP-4
Gene transcription	3C	PV	Oct-1
	2A	PV	TBP
	3C	PV	TFIIIC
	3C	PV	CREB
	2A	CVB3	SRF
	3C	CVB3	AUF1
	3C	PV	PTB
	3C	PV	hnRNP M
	2A	PV	Gemin3
	3C	CVB3	TDP-43
Protein translation	2A	CVB3, PV, EV71, RV	eIF4GI, eIF4GII
	2A, 3C	CVB3, PV	PABP
	2A	CVB3	DAP5
	3C	CVB3, PV, HRV	eIF5B
	3C	PV	PCBP
	3C	PV, HRV	p65-RelA
Others	3C	CVB3	IKBa
	2A, 3C	CVB3	GAB1
	2A	HRV	Nup
	3C	PV, CVB3, EMCV	G3BP1

CVB3 Coxsackie virus, *EMCV* encephalomyocarditis virus, *EV* enterovirus, *HRV* human rhinovirus, *PV* poliovirus

9.1.2.4 Host Defense—Innate Immune Response

Once a virus is successfully bound to a receptor, it confronts the host's immune response; this is inevitable and crucial for the clinical regression of myocarditis, especially for fulminant myocarditis. The immune system of higher vertebrates is divided into two main categories: innate and acquired immunity. Innate immune responses are not antigen-specific and can occur rapidly after pathogen stimulation of the immune system, whereas acquired immune responses are antigen-specific. In addition to pathogens such as viruses, other non-infectious etiologies can activate innate and acquired immunities in the host via various mechanisms.

The innate immune response is highly conserved in interspecies evolution and is the host's first defense against invading pathogens. Upon activation by TLRs, the innate immune response induces macrophages and natural killer (NK) cells, which constitute the main inflammatory cells that infiltrate the heart in lymphocytic myocarditis (Fig. 9.7). During the first 4–5 days of viral infection in the myocardium, acquired immune response is not activated, and the innate immune response induces the release of a variety of cytokines, including interleukin-1 (IL-1), IL-6, and tumor necrosis factor α (TNF-α), to limit viral replication and dissemination. Previous studies have suggested that activation of endoplasmic reticulum stress inhibits macrophage infiltration in the hearts of mice with viral myocarditis, thereby reducing inflammatory factors released by macrophages and improving cardiac function [34, 35]. Recently, it has been reported

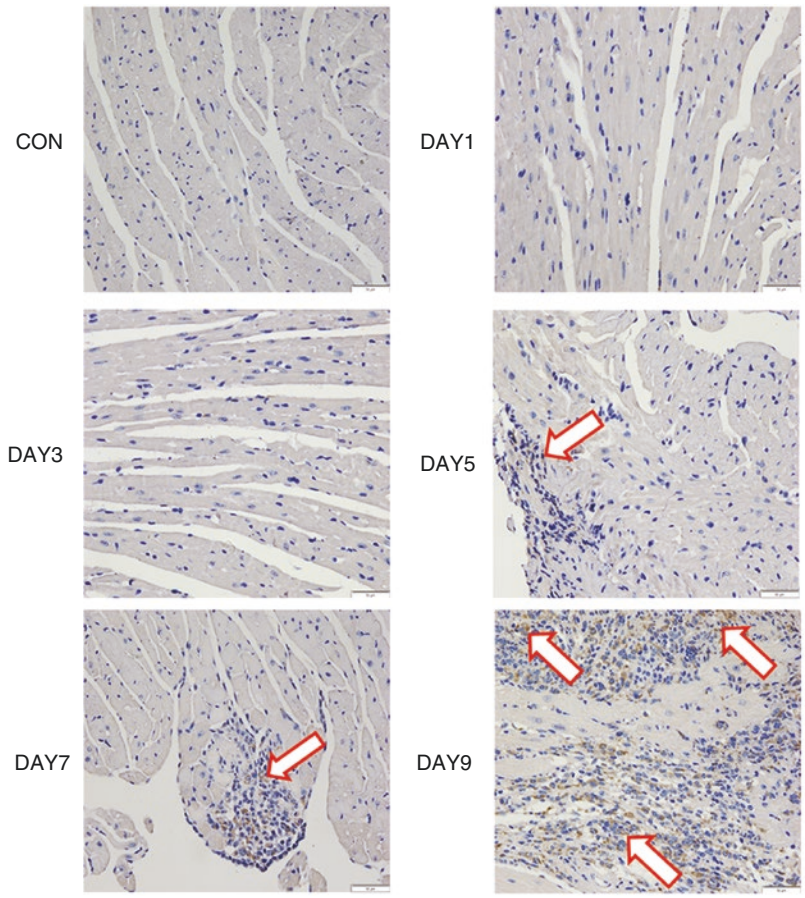

Fig. 9.7 Immunohistochemical staining showing infiltration of macrophages (brownish areas marked by arrows) and NK cells in the heart of mice with fulminant myocarditis

that the inflammatory response induces neutrophils to migrate to the heart, promote cardiomyocytes to undergo pyroptosis, and impairs cardiac function [36].

However, by the time the innate immune response manages to remove the virus in fulminant myocarditis, the immune system becomes over-activated and recruits a high number of inflammatory cells to the heart, all of which release large amounts of inflammatory factors. The resultant "inflammatory storm" magnifies the damage to the patient's heart, leading to a dramatic decrease in cardiac function. Simultaneously, the "inflammatory storm" also induces the release of large amounts of vasoactive substances that dilate blood vessels and result in shock (see Chap. 3, Pathogenesis of fulminant myocarditis: The role of cytokine storm in the development of fulminant myocarditis). Therefore, proper control of the "inflammatory storm" to limit the damaging effects of the immune response is one of the priorities in the early stages of fulminant myocarditis treatment. In case the immune response fails to clear the virus completely, the disease becomes chronic and may develop into dilated cardiomyopathy.

Interferons

This is a class of powerful antiviral cytokines and important effector molecules of the innate immune response. Type I interferons include interferons α and β, while type II includes interferon γ. In vitro cellular assays have demonstrated that exogenous type I and type II interferons inhibit coxsackievirus replication in cells, while exogenous type I interferons improve the impaired cardiac function in mice with coxsackievirus-induced myocarditis [37]. To investigate the role of endogenous interferon molecules in the pathophysiology of viral myocarditis, mice with type I or type II interferon receptor deficiency were infected with coxsackievirus. Mice with type I interferon receptor deficiency displayed a significant increase in viral replication in the liver and in mortality. However, there was no increase in viral RNA titers in the heart, suggesting that the increase in mortality was not secondary to heart infection. Similar results were observed after coxsackievirus infection in mice with interferon β deficiency. This suggests that the endogenous type I interferon receptor signaling pathway plays a critical role in organ damage due to viral infection, such as liver damage, but not in viral replication in the heart during the early stages of infection. The absence of the endogenous type II interferon signaling pathway resulted in a slight increase in viral titers in the heart and liver but did not have any effect on mortality. These suggest that there may be other molecules that mediate the role of interferon-related signaling pathways in myocarditis, thus necessitating further investigation.

TLRs

TLRs are important molecules in the innate immune response that can recognize pathogen-associated molecular patterns (PAMPs) and initiate innate immune defense mechanisms. Various pathogens can activate TLR signaling pathways via different ligands. Ten and thirteen TLR isoforms have been identified in humans and mice, respectively. It has been reported that mutation of the human *TLR3* gene at P554S or L412F decreases its function, inhibits host NF-κB and type I interferon signaling pathways, attenuates cardiac autophagy repair, enhances viral replication in the heart, and activates abnormal immune responses, ultimately impairing cardiac function [12]. In addition, polymorphisms in *TLR2* and *TLR4* genes have been reported to be associated with bacterium-induced septic shock. TLR2, TLR3, TLR4, TLR7, TLR8, and TLR9 are capable of mediating the antiviral effects of type I interferons (Table 9.3). Compared with other tissues, TLR3 and TLR4 expression is relatively low and TLR7, TLR8, and TLR9 are barely expressed in the human heart. Therefore, there is a high

Table 9.3 TLRs and viral infections

TLRs	Virus ligands
2	Envelope proteins of measles virus, cytomegalovirus, and herpes simplex virus type I
3	Viral double stranded RNA
4	Respiratory syncytial virus F protein, mouse mammary tumor virus envelope protein
7/8	Viral single-stranded RNA
9	CpG DNA

probability of other signaling pathways in the heart that mediate the antiviral effects of interferon in addition to the TLR signaling pathway.

The TLR3 and TLR7/8 signaling pathways are activated by double-stranded RNA (dsRNA) and single-stranded RNA (ssRNA), respectively. However, the genome of the enterovirus is an ortho-stranded ssRNA. Following entry into the host cell, viral RNA is released from the capsid protein and used as a template to form dsRNA. Infection of TLR3-deficient mice with ssRNA viruses leads to the development of severe myocarditis with significantly higher levels of viral replication in the heart, greater myocardial damage, and ultimately, a significant increase in early mortality [38]. Morphological examination of the heart on days 3 and 5 post viral infection revealed that viral titers as well as inflammatory responses were significantly higher in the hearts of TLR3-knockout mice than in the hearts of wild-type mice. This suggests that by inhibiting viral replication in the heart, TLR3 plays an important role in the host's antiviral response. Interestingly, interferon expression was significantly higher in the hearts of TLR3-deficient mice, suggesting that TLR3 may activate the innate immune response via an interferon non-dependent pathway.

TLR4 mainly recognizes lipopolysaccharides of gram-negative bacilli. Coxsackieviruses, among others, activate TLR4 in macrophages, promoting the secretion of inflammatory factors and increasing viral replication in cardiomyocytes [39]. However, the specific mechanism by which viruses activate the TLR4 signaling pathway remains poorly understood. TLR9 primarily recognizes CpG DNA regions of bacteria and viruses. The role of other TLRs in early viral replication in the heart has not been clarified. Myeloid differentiation factor-88 (MyD88) is an important molecule that mediates TLR2, TLR4, TLR5, TLR7, and TLR9 signaling pathways. MyD88-deficient mice revealed significantly lower viral titers in the hearts on days 4, 7, and 10, along with higher survival rates, after coxsackievirus infection as compared to wild-type mice [40]. These results demonstrate the importance and complexity of TLR signaling pathways in cardiac regulation and suggest that viruses could mediate their actions in the heart via non-classical TLR signaling pathways. The potential roles of different TLRs are inconsistent and require further investigation.

RNA Helicases

Although the majority of TLRs are localized on the surface of the cell membrane, TLR3, TLR7/8, and TLR9 are localized in the cellular endosome wherein they recognize viral nucleic acids following viral entry into the host cell [41]. Since viral nucleic acid replication products may also be present in the cytoplasm outside the endosome, the TLR signaling pathway in the endosome may not interact with all viral nucleic acid molecules in the host cell. It has been demonstrated that intracellular viral dsRNA can be recognized by two RNA helicases, retinoic acid-induced protein I (RIG-I) and MDA-5 [42, 43]. Further, intracellular viral DNA can be recognized by the DNA-dependent activator of interferon regulatory factor (DAI, also known as DLM-1/ZBP1) [44]. By constructing RIG-I- or MDA-5-deficient mice, the anti-RNA virus properties of RNA helicases have been confirmed, but the anti-DNA viral role of DAI *in vivo* remains to be confirmed. RIG-I recognizes paramyxoviruses, influenza viruses, and epidemic B encephalitis viruses, while MDA-5 recognizes encephalomyocarditis viruses and dsRNA viruses. Both RIG-I and MDA-5 contain two important structural domains: the caspase activation and recruitment domain (CARD) and the RNA helicase domain. The RNA helicase domain recognizes and binds to dsRNA, enabling RIG-I and MDA-5 to form a dimer having an altered structure, thus facilitating the binding of CARD to downstream signaling molecules and activating a series of signaling pathways. In recent years, mitochondrial antiviral signaling (MAVS) has been found to mediate the activation of downstream signaling pathways of RIG-I and MDA-5 [45]. The N-terminal region of MAVS is the CARD, and the C-terminal is the mitochondrial transmembrane structural domain. The complex formed by binding of dsRNA with RIG-I or MDA-5 attaches to the N-terminal CARD of MAVS and subsequently activates a series of transcription factors, such as NF-κB and

interferon regulatory factors 3 and 7, ultimately producing a series of innate immune responses, including type I interferon release. Compared to wild-type mice, the viral titer in the hearts of MDA-5- or MAVS-deficient mice at 48 h after infection with encephalomyocarditis virus was more than 1000-fold higher than that in wild-type mice, suggesting that RNA helicase plays an important role in the removal of intracellular viral nucleic acids [46, 47].

9.1.2.5 Host Defense–Acquired Immune Response

After 6–7 days of viral infection, the acquired immune response is activated and T-lymphocytes begin to infiltrate the heart, which indicates the terminal phase of Stage 1. The peak of T lymphocyte infiltration usually occurs between the seventh and the 14th day post viral infection [48]. However, in fulminant myocarditis, the acquired immune response is activated rapidly, within 2–3 days after infection, or even on the day of infection, recruiting T-lymphocytes to the heart and triggering an "inflammatory storm," which forms the core pathophysiological mechanism underlying the rapid onset and critical nature of fulminant myocarditis (Fig. 9.8).

Infiltration of T-lymphocytes leads to two distinct effects: the advantageous removal of virally infected cardiomyocytes, and the disadvantageous effect of damage or necrosis of cardiomyocytes. In a severely and acutely injured heart, upon significant infiltration of terminally differentiated and non-dividing T-lymphocytes, the cellular damage caused by the removal of virally infected cells by T-lymphocytes, cannot be compensated for by the proliferation of normal non-infected cells, which ultimately leads to impaired cardiac function. A previous study had reported that following infection with coxsackievirus, the morbidity and mortality of myocarditis were significantly reduced in CD4+ (helper T-lymphocytes) and CD8+ T-lymphocytes (cytotoxic T-lymphocytes) double-knockout mice as compared to those in wild-type mice [49]. Interestingly, despite complete knockdown of both CD4+ and CD8+ T-lymphocytes, the titer of coxsackievirus in the hearts of double-knockout mice did not change significantly as compared to that in wild-type mice, suggesting the existence of a T lymphocyte-independent viral clearance mechanism in the heart.

9.1.2.6 Damage to Host Cells by Host Immune Response

In the absence of proper control of the host immune response, the damaging effects of the "inflammatory storm" caused by the overactivation of the immune response are stronger

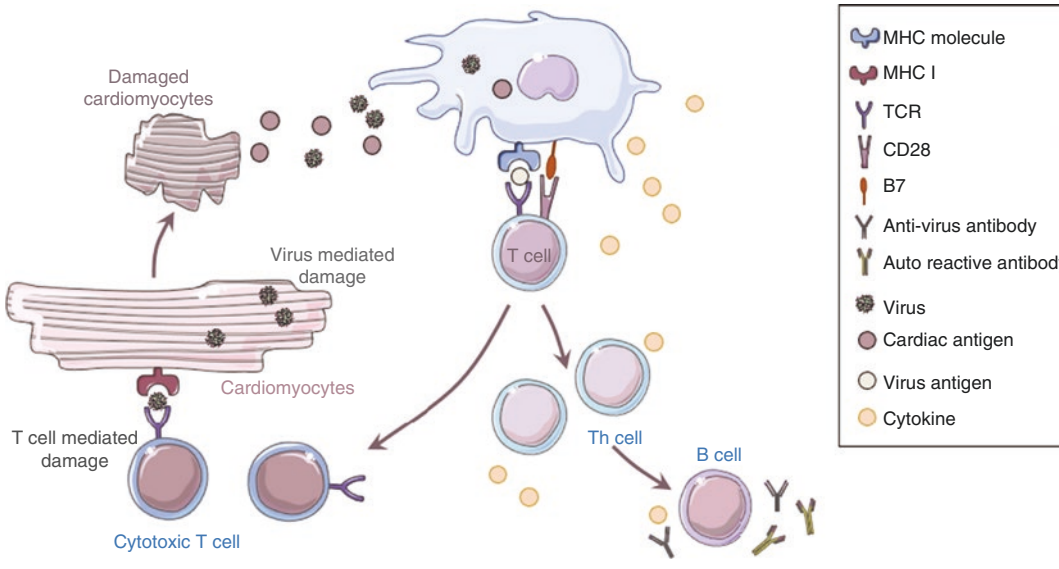

Fig. 9.8 Immune activation-mediated cellular injury during the course of viral myocarditis

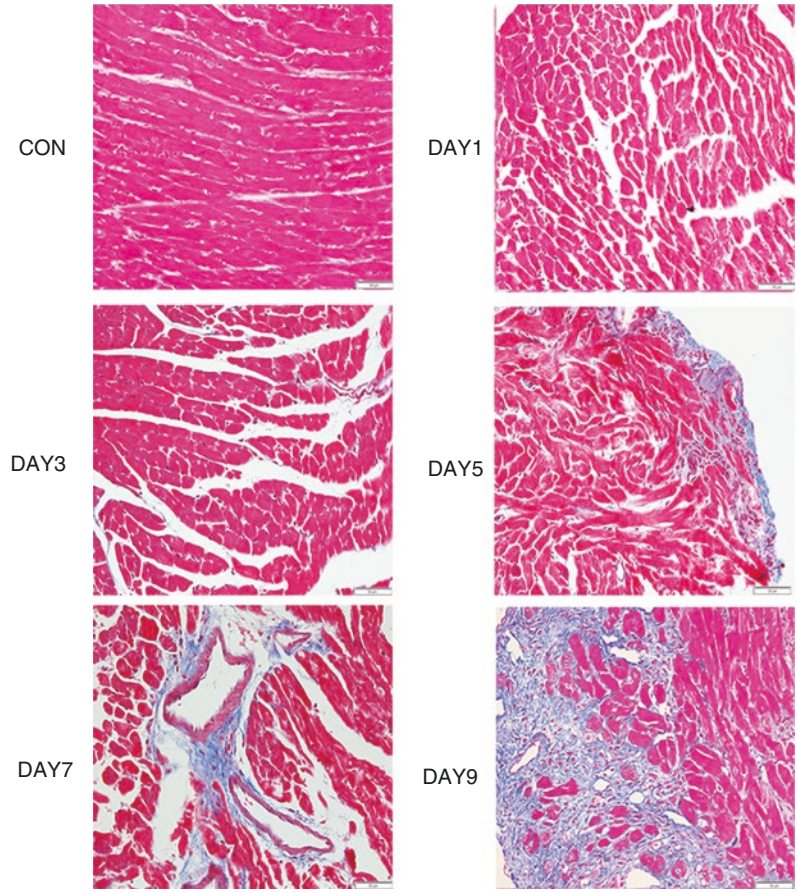

Fig. 9.9 Masson staining confirms the presence of severe fibrosis (blue stains) in the hearts of mice with fulminant myocarditis

than its beneficial effects of virus clearance, ultimately leading to myocardial fibrosis, ventricular remodeling, and even heart failure (Fig. 9.9).

Regulatory T cells (Tregs) suppress the inflammatory response and reduce host cell immune damage, whereas T helper 17 (Th17) cells enhance the immune inflammatory response and promote host cell damage; together they maintain a delicate yet dynamic balance in the development and regression of myocarditis [50]. Although Tregs promote the release of anti-inflammatory factors, such as transforming growth factor-beta (TGF-β) and IL-10, these factors are unable to inhibit the massive amount of pro-inflammatory factors (such as TNF-α and IL-1) consistently released by host cells during infection, thus leading to irreversible myocardial injury and even acute heart failure [51, 52].

The conversion between M1 pro-inflammatory macrophages and M2 anti-inflammatory macrophages can also influence the regression of myocarditis [53]. Comparison of inflammatory responses to coxsackievirus infection in mice of different sexes showed a higher expression of M1 macrophages in the hearts of males and higher expression of M2 macrophages in the hearts of females [54]. More importantly, the myocardial inflammatory response in male as well as female mice was boosted by exogenous M1 macrophages, whereas M2 macrophages altered the inflammatory factor profile of the heart, increased anti-inflammatory factors, promoted Treg differentiation, and significantly reduced the cardiac inflammatory response in male mice [54].

After the activation of the acquired immune response, the massive infiltrating lymphocytes not only removes the infected myocardial cells, but also causes damage to normal myocardial cells. In the 1970s, researchers have observed a significant decrease in the cardiac inflammatory response in T lymphocyte-deficient mice infected with coxsackievirus, as well as in the extent of

myocardial injury and mortality as compared to those in wild-type mice [55].

Further, it is not just the virus that induces an immune response in the host; the host itself produces antigens that induce an autoimmune response. Viral infection in cardiac myocytes damages intracellular autoantigens (such as cardiac myosin), which cross-react with coxsackievirus antigens and induce autoimmune responses, which further activates B lymphocytes, produces large amounts of cardiac autoantibodies and inflammatory factors, and ultimately causes damage to the cardiac myocytes [56].

Since current pathological diagnostic criteria define only the type and number of infiltrating inflammatory cells without a distinction of subtypes or functional types, they are relatively less suitable for prognostic assessment. Further analysis of various cell subtypes and functions is required in the future.

9.1.3 Stage 2 (Subacute Stage)

This stage ranges from a few weeks to a few months after viral infection. Studies on animal models have shown that coxsackieviruses persist in cardiomyocytes for an extended period following infection, even without replication. In order to investigate whether the persistence of the non-replicating genome of coxsackievirus in cardiomyocytes promotes the development of dilated cardiomyopathy, cardiac-specific coxsackievirus-mutant transgenic mice were constructed, in which low levels of intact coxsackievirus were expressed in the heart. However, these were incapable of forming intact viral particles and were therefore unable to replicate. The lack of intact viral particles also prevented the production of corresponding antibodies in the host. Histomorphological examination depicted a series of typical dilated cardiomyopathy phenotypes such as interstitial fibrosis of cardiomyocytes, myocardial hypertrophy, and cardiomyocyte degeneration in the hearts of these transgenic mice [57]. In clinical practice, viral genome expression is detected in myocardial biopsy specimens of patients of myocarditis or dilated cardiomyopathy; however, replicative state viruses are rarely detected in the specimens from patients of myocarditis. These results suggest that the mere presence of the viral genome is sufficient for the development and progression of cardiomyopathy.

9.1.4 Stage 3 (Chronic Stage)

This stage mostly ranges from several months to years after viral infection. Since the majority of the patients at this stage fail to detect the presence of the virus or viral genome in the myocardium, they are often diagnosed and treated for other types of heart disease. Even in cases where dilated cardiomyopathy is diagnosed, the cause remains undetermined since the previous infection is unconfirmed. Therefore, the importance of diagnosis early in the infection is even more emphasized along with an urgent need to design tests that are more specific, as well as sensitive, to the detection of viral infection.

9.2 Giant Cell Myocarditis

Giant cell myocarditis (GCM) is a rare and extremely critical myocarditis that was first reported in 1905 [58]. The onset of the disease is acute, with rapid deterioration of cardiac function. Prior to the introduction of heart transplantation or immunomodulatory drugs, almost all patients of GCM perished within a few days of onset, relying solely on autopsy findings for diagnosis. The onset age of GCM patients is about 40 years old, and 20% of patients have a history of autoimmune diseases [59]. Most patients of GCM present with acute heart failure, with approximately 50% of them developing ventricular tachycardia, different degrees of atrioventricular block, and having a median survival time of 3 months without resorting to heart transplantation or treatment with immunomodulatory drugs [60].

GCM is a T lymphocyte-mediated autoimmune disease; gene expression profiling of myocardial tissue from patients of GCM showed an abnormally enhanced immune response in their hearts, particularly a marked increase in the expression of chemokines associated with Th1 activation in T

helper (Th) cells [61]. In contrast to viral myocarditis, cardiac autoantibodies are uncommon in patients of GCM, suggesting that the pathogenesis of GCM is dominated by T-lymphocytes, rather than B lymphocyte-mediated autoimmune responses. The main pathological feature of GCM is the formation of multinucleated giant cells following massive lymphocyte infiltration is the main pathological feature of GCM, with highly activated T cells, leading to an inflammatory storm.

Monotherapy with glucocorticoid-based immunosuppressants does not improve the prognosis of GCM. However, the combination of concurrent T cell-targeted immunosuppressants effectively mitigates GCM progression. Nevertheless, drug therapy is less effective than heart transplantation and is associated with multiple cardiovascular complications. Moreover, even after heart transplantation, GCM recurs in approximately 25% of post-transplant patients [60].

9.3 Eosinophilic Myocarditis

Eosinophilic myocarditis is caused by a variety of etiologies and comprises eosinophil infiltration into the heart followed by myocardial endocardial fibrosis. Eosinophils comprise cytoplasmic granules which release cytotoxic proteins in response to immunogenic stimulation, thereby inducing oxidative stress and leading to apoptosis or necrosis. Furthermore, eosinophils can directly damage cardiomyocytes.

One of the etiologies of eosinophilic myocarditis is drug allergy, associated with the use of drugs (antibiotics, such as penicillin, diuretics, or dopamine) or vaccines (such as smallpox vaccine), with a very rare onset. Usually, the onset occurs at the time of administering the drug; however, in rare cases, the onset occurs after several years of drug administration [62].

9.4 Sarcoidosis Myocarditis

Sarcoidosis is an inflammatory disease involving multiple organs and systems (such as the eyes, skin, lungs, or heart). The pathogenesis of sarcoidosis has not yet been elucidated; histomorphologically, it manifests as an accumulation of T-lymphocytes, mononuclear phagocytes, and non-neoplastic granulomas. The main pathological feature that differentiates sarcoidosis from GCM is the presence of granulomas which appear as follicular structures composed of tightly packed lymphocytes (especially $CD4^+$ T cells), giant cells, and epithelial cells, and surrounded by fibroblasts and more lymphocytes (including B cells, $CD4^+$ T cells, and $CD8^+$ T cells) [63]. In the early stages of the nodal disease, Th1 cells are stimulated to mediate the activation of the inflammatory response in the heart, as well as to interact with antigen-presenting cells (APCs) to form granulomas. Subsequently, Th2 cells are activated, leading to fibrosis. Sarcoidosis patients have increased levels of Th1 cell-associated cytokine expression in the heart [64]. Myocardial tissue biopsies of sarcoidosis myocarditis patients had revealed a high number of $CD209^+$ dendritic cells as well as $CD68^+$ macrophages, whereas the number of $CD163^+$ M2 macrophages was low [65], suggesting a higher number of injurious macrophages. Although the pathogenesis of sarcoidosis myocarditis is clearly different from that of lymphocytic myocarditis or GCM, there are no specific biomarkers available yet for the clinical diagnosis of sarcoidosis myocarditis [66].

9.5 Connective Tissue Disease-Induced Autoimmune Myocarditis

Multiple connective tissue disorders (CTDs), such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, or dermatomyositis are complicated by myocarditis [67]. Approximately 10% of SLE patients show clinical manifestations of myocarditis, mostly lymphocytic; RA patients have a comparatively lower incidence of myocarditis, which is mostly interstitial or sarcoid [68].

SLE causes monocyte infiltration, formation of immune complexes, as well as complement deposition in the heart tissues of patients of myocarditis. In RA patients, anti-citrullinated protein antibodies are produced following the conversion

of arginase to citrulline. A study using cardiac magnetic resonance technique found that RA patients showing high levels of anti-citrullinated protein antibodies had a higher left ventricular weight index than those with low levels, suggesting that RA may induce myocardial injury [69]. The formation of these anti-autoantibodies in massive numbers followed by their deposition in the heart activates autoimmune responses and impairs cardiac function.

Notably, CTDs also indirectly damage cardiac function by impairing blood vessels.

9.6 Immune Checkpoint Inhibitor-Induced Myocarditis

Myocarditis induced by immune checkpoint inhibitors (ICIs) is the most common side effect of ICIs in the cardiovascular system. Infiltration of T-lymphocytes in massive numbers has been observed in the hearts of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) knockout mice, leading to autoimmune dilated cardiomyopathy [70]. Several studies have shown that PD-1 knockout mice are more susceptible to autoimmune myocarditis and suffer greater cardiac damage than the wild type [71–73].

The mechanisms by which ICIs cause myocarditis have not been completely elucidated yet; multiple impairment effects (as follows) may synergize to affect cardiac function: (i) ICIs act as monoclonal antibodies that bind directly to antigens (such as CTLA-4) on the surface of normal cells, leading to T lymphocyte infiltration and complement activation, thus causing myocardial tissue damage. (ii) ICI treatment enhances the off-target effect by promoting the function of T-lymphocytes, which then recognizes the tumor antigen or healthy tissue expressing the antigen through the circulatory system. (iii) ICIs increase the circulating as well as tissue levels of cytokines and promote the infiltration of inflammatory molecules in non-targeted tissues. (iv) ICIs promote autoimmune-associated antibody production, leading to autoimmune responses (Fig. 9.10) [74].

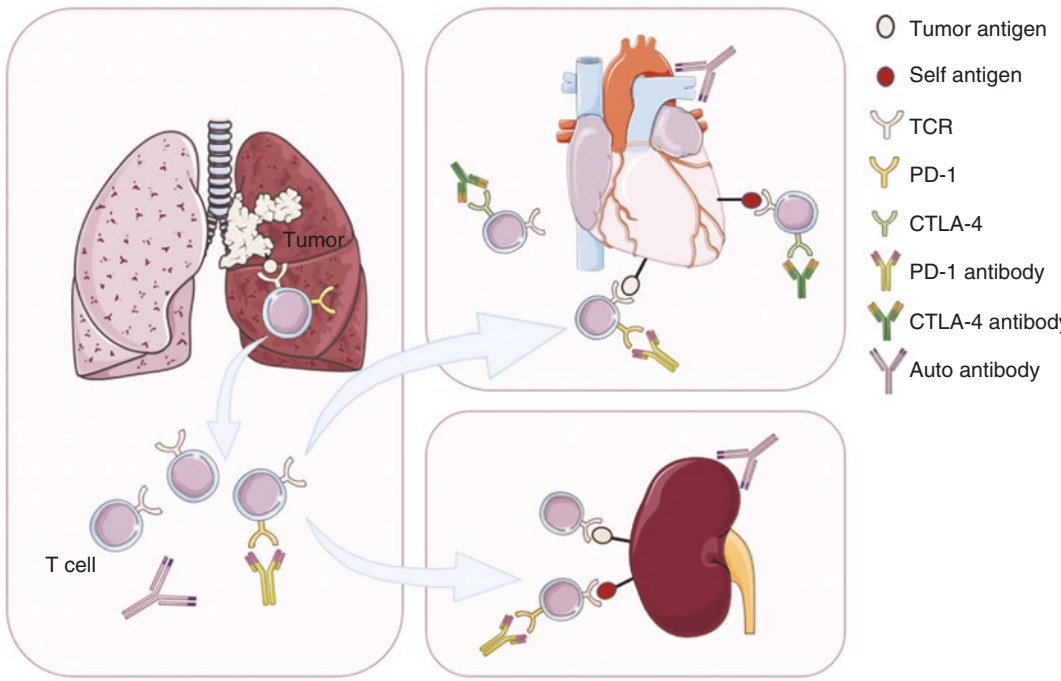

Fig. 9.10 Mechanisms by which immune checkpoint inhibitors damage the heart and kidney

The CTLA-4 monoclonal antibody affects the binding of CTLA-4 (present on the surface of T cells) to B7 (present on the surface of APCs), thus reducing the threshold of cardiac T cell activation. CTLA-4 monoclonal antibody interacts with CTLA-4-expressing Treg cells, thereby affecting the inhibitory function of Tregs *in vivo* and leading to enhanced T cell activity in the heart. PD-1 antibodies damage the heart by blocking the binding of PD-1 and its ligands to APCs and cardiomyocytes, thus inducing T cell activation (Fig. 9.11).

In addition, T cells attack common antigens of tumors and the heart. In patients of ICI-induced myocarditis, some of the T cells infiltrating the myocardial tissue were identical to those present in tumor cells or skeletal muscle, suggesting that these T cells respond to a common antigen. Furthermore, an abnormal increase in the expression of muscle-specific antigens (troponin and junctional proteins) was observed in the tumor tissues of these patients. This suggests that T cells target antigens common to the tumor and heart; ICIs damage the heart by enhancing the action of such T cells, leading to fulminant myocarditis (Fig. 9.12).

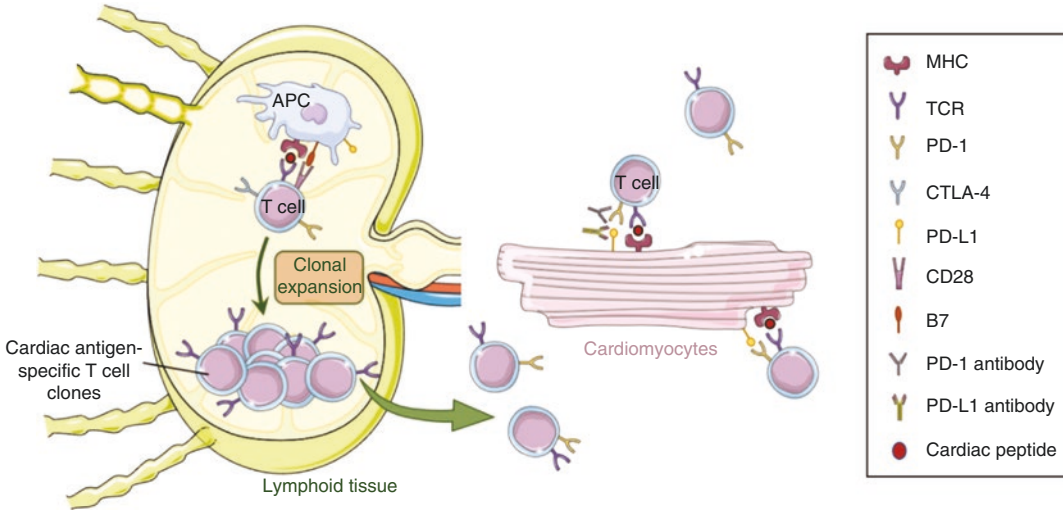

Fig. 9.11 Immune checkpoint inhibitors disrupt the body's immune tolerance to the heart

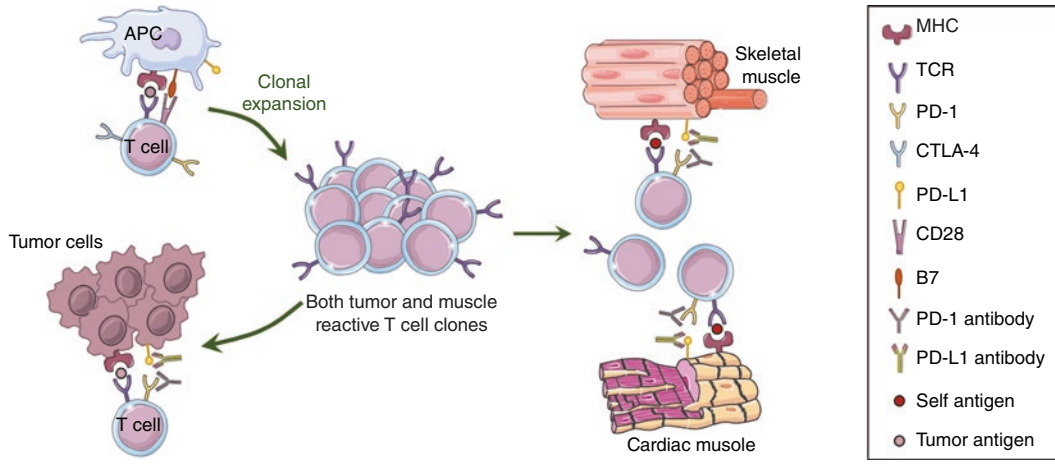

Fig. 9.12 Tumors, skeletal muscle, and myocardium share antigenic epitopes. Immune checkpoint inhibitors induce a massive expansion of T cells targeting shared antigenic epitopes, leading to T cell attack on skeletal and cardiac muscle

All pathological types of fulminant myocarditis present with rapid cardiac dysfunction and lethal arrhythmias. In general, lymphocytic myocarditis is more common. However, giant cell as well as eosinophilic myocarditis have a comparatively rapid onset and are often more severe. Therefore, a pathologic diagnosis is essential for deciding the treatment strategy.

Key Points

1. Myocarditis is an inflammatory disorder of myocardial cells in which mononuclear cells infiltrate the myocardium.
2. The pathophysiological process of myocarditis is divided into three stages at the cellular level: acute stage of viral colonization and replication, subacute stage of inflammatory cell infiltration, and chronic stage of ventricular remodeling.
3. In fulminant myocarditis patients, by the time the virus is removed via the immune response, the immune system is over-activated and inflammatory cells will be infiltrated. Meanwhile, massive inflammatory factors are stimulated and released, causing an "inflammatory storm" that amplifies the damage to the patient's heart caused by pathogenic erosion, resulting in a decrease in myocardial contractility and a sharp decline in cardiac function, ultimately leading to cardiogenic shock and arrhythmia. Inflammatory storms also induce the release of numerous vasoactive substances, which dilate blood vessels and aggravate the state of shock.

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10 Changes of Electrpcardiography in Patients with Fulminant Myocarditis

Guanglin Cui and Dao Wen Wang

The diagnostic specificity of the simple electrocardiogram (ECG) examination for fulminant myocarditis is low; therefore, it should be repeated several times to compare dynamic changes. Sinus tachycardia is the most common; frequent atrial presystolic (premature atrial) or ventricular presystolic (premature ventricular) is one of the reasons for hospitalization of patients with myocarditis, and short ventricular tachycardia may be detected during monitoring; bundle branch block or atrioventricular block suggests a poor prognosis. Low voltage in the limb leads, especially the anterior lead, suggests extensive and severe myocardial damage.

ST-T changes were more common, representing abnormal myocardial repolarization. The ECG of some patients can even show a pattern similar to acute myocardial infarction, showing selective lead elevation of the ST segment arched upward. It is difficult to distinguish between the two from the ECG alone. Ventricular fibrillation is rare and causes sudden death/syncope. It is important to note that the patient's ECG changes can be very rapid and should be monitored continuously with 12 or 18 lead ECG recorded when there is a change. All patients underwent a 24 h ambulatory ECG examination.

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There are three types of ECG changes in early myocarditis within 1 month of onset: (1) atrioventricular blocks, accounting for approximately 40%, mostly first-degree blocks; (2) pre-phase contraction, accounting for approximately 30% (premature ventricular contractions are common); (3) ST-T anomalies, accounting for approximately 30% (a few visible anomalies Q and single curve). In addition, there can be bundle branch conduction block, paroxysmal tachycardia (ventricular tachycardia), atrial fibrillation, junction rhythm, left ventricular high voltage, atrial enlargement, etc. More than 60% patients on admission have low voltage in all leads, 30% patients have QTc prolongation and 23% have QRS wave broaden, which are important clues for diagnosis.

Part of fulminant myocarditis can transform into chronic myocarditis, and ECG changes are similar to acute myocarditis, which is characterized by atrioventricular hypertrophy, accounting for approximately 45% of cases. However, left ventricular hypertrophy is not observed in acute myocarditis, indicating that ventricular hypertrophy is an important manifestation of chronic myocarditis.

ECG changes in convalescent myocarditis were few, mild, and relatively stable. Commonly, only have 1–2 kinds of ECG change, basically the period before systolic, but neither symptom also does not have cardiac function to change, treatment often does not have a particularity. There may also be a first-degree atrioventricular block or an incomplete bundle branch block.

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Changes in ECG in acute and chronic viral myocarditis are often diverse, varied, and changeable, while the changes in recovery and sequelae are small and mild. The clinical outcome was characterized by the disappearance of approximately 1/2–4/5 of pre-phase contractions, the disappearance of approximately 1/2–2/3 of atrial premature beats, and 90–100% recovery of ST-T changes; if the ECG is not recovered for a long time, this may be the form of chronic myocarditis.

10.1 Mechanism of Arrhythmias in Viral Myocarditis

Viral myocarditis is a common disease caused by direct invasion of the myocardium by the virus and damage to the myocardium by virus-mediated autoimmune reactions, with myocardial necrosis and interstitial monocyte infiltration as the main pathological changes. Microelectrodes were used to detect electrophysiological abnormalities in the myocardium of virus-infected rats, such as decreased negative resting potential, maximum rate of 0 phase, action potential amplitude and overshoot value, and shortening of action potential duration. These electrophysiological abnormalities can increase the self-discipline and excitability of myocardium cells and reduce their conductivity, resulting in tachyarrhythmias or conduction blocks.

After the acute period of 3 months, although myocardial inflammation had gradually reduced and the myocardial injury index had recovered, the above myocardial electrophysiological abnormalities still had significant changes and even lasted for 9 months before basic recovery. However, arrhythmias may last longer, suggesting that the integrity of the cell membrane is destroyed and fluidity and permeability increase after cardiomyopathy, which is the main cause of arrhythmias in viral myocarditis. Furthermore, viral myocarditis can produce autoantibodies against ADP/ATP carriers on the mitochondrial inner membrane through autoimmunity, which affects the energy transport of the mitochondrial membrane and binds to calcium channels on the cell membrane. It increases calcium influx, leading to intracellular calcium overload and prolonged action potential duration, which is also one of the causes of arrhythmia.

Myocarditis is common in the clinic, but clinicians should pay more attention to patients with fulminant myocarditis. These patients have a high abnormal rate of ECG, usually without specific manifestations. Clinical diagnosis must be combined with the patient's history, symptoms, cardiac enzymes, troponin, and other data, and the diagnosis and misdiagnosis rate are high with ECG alone. The abnormal ECG of myocarditis is a combination of manifestations; its type and degree vary from person to person.

10.2 Common ECG Findings of Fulminant Myocarditis

10.2.1 Sinus Arrhythmia

In the acute stage of fulminant myocarditis, 10–30% of patients have sinus tachycardia, while sinus bradycardia, sinus atrial block, and sinus arrest are rare (approximately 2%), but their severity cannot be ignored, and it is often the main cause of sudden death from myocarditis. Studies have shown that the average sinus heart rate of patients who died of fulminant myocarditis was significantly higher than that of patients who survived (113.80 ± 35.22 vs. 76.95 ± 30.39) [1].

Sinus tachycardia is a common ECG finding (Fig. 10.1), and most patients can develop disproportionate sinus tachycardia with increasing temperature, which may be caused by the inflammatory response of sympathetic excitement of the myocarditis itself, vagal tone reduction, and cardiac dysfunction caused by compensatory tachycardia; in the case of sinus tachycardia in patients with fulminant myocarditis, active intervention is not recommended. The

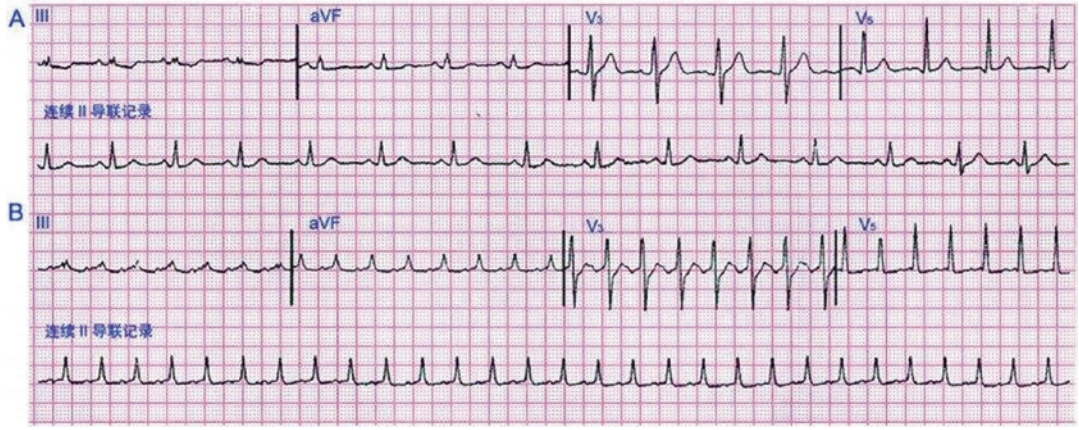


Fig. 10.1 Sinus tachycardia (1) P wave: P wave in sinus tachycardia is emitted from the sinoatrial node, P II is upright, and pavr is inverted. The amplitude of the P wave in sinus tachycardia is slightly higher than that of the normal sinus rhythm and is more obvious in leads II–III. This is because, in sinus tachycardia, excitement often occurs at the head of the sinoatrial node, which is the starting part of the anterior internodal bundle of the atrium, and the sinus excitement often passes down the anterior internodal bundle; (2) PR interval: 0.12–0.20 s; (3) PP interval: slightly irregular under the influence of the autonomic nerve; (4) QRS wave: shape and time limit are normal, and atrial rate is equal to the ventricular rate; (5) Frequency: adult P wave frequency is 100–160 times/min, mostly about 130 times/min, and some can reach 160–180 times/min

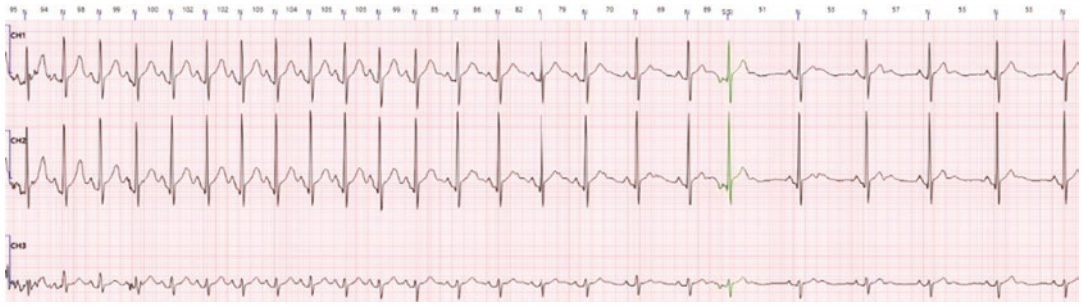


Fig. 10.2 Sinus rhythm disorder

primary disease should be treated unless the patient presents with intolerable clinical symptoms; if the patient's primary disease tends to be stable, sinus tachycardia persists for a long time. Based on the specific clinical situation of the patient, the use of a small dose of β-blockers alleviates sinus tachycardia.

It is worth noting that in the acute stage of myocarditis, lesions in the sinoatrial node and surrounding tissues can cause significant sinoatrial node dysfunction and ECG changes in sinus arrhythmias (Fig. 10.2), which can present intermittent and recurrent sinus rhythm disturbances: heart rate slows rapidly from the fastest (105 beats/min) to 53 beats/min.

Sick sinus syndrome (SSS) is one of the causes of sick sinus syndrome. Fulminant myocarditis, when cardiomyopathy is involved in the sinoatrial node and its surrounding tissues, can lead to chronic sinus arrhythmias, such as severe sinus bradycardia, transient sinus arrest, and sinus block.

1. Sinus bradycardia: Sinus bradycardia is also a common sinus arrhythmia in fulminant myocarditis. In patients with fulminant myocardi-

tis, sinoatrial node function is impaired due to myocardial cell inflammation, pericarditis, endocarditis, myocardial cell ischemia, and myocardial damage. The impaired function of the sinoatrial node can be transient or permanent, depending on the patient's condition. Sinus bradycardia often indicates that the patient is in a critical condition and the condition changes rapidly, which may be caused by invasion of the sinoatrial node of the heart and the conduction system by myocardial inflammation. These patients have a high possibility of a high atrioventricular block or even sinus arrest. If sinus bradycardia continues without remission, patients have a high risk of sudden cardiac death. Permanent pacemaker installation should be considered for these patients, which should be closely monitored clinically (Fig. 10.3).

2. Sinus cardiac arrest: The occurrence of sinus arrest in patients with fulminant myocarditis is mainly caused by the inflammatory response or even damage to myocardial cells in the sinoatrial node. ECG findings (Fig. 10.4): If sinus arrest is transient, it may be asymptomatic for a short period of time. When the duration of sinus arrest is longer than 3 s, patients may develop amaurosis, temporary loss of

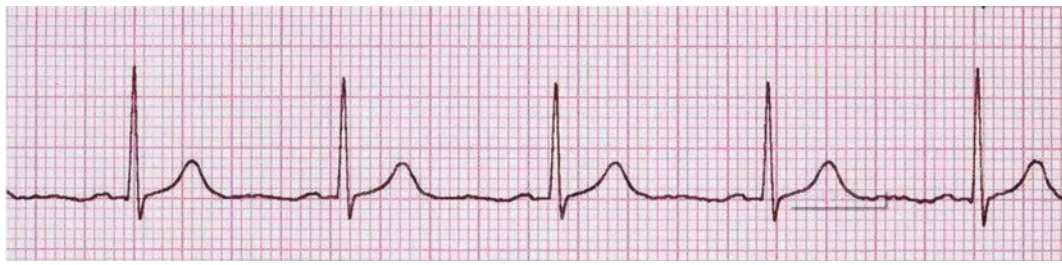


Fig. 10.3 Sinus bradycardia. (1) Sinus P wave: frequency <60 times/min, generally not less than 40 times/min, 24 h dynamic electrocardiogram sinus beats <80,000 times. (2) The PR interval was 0.12–0.25 s. (3) QRS was normal

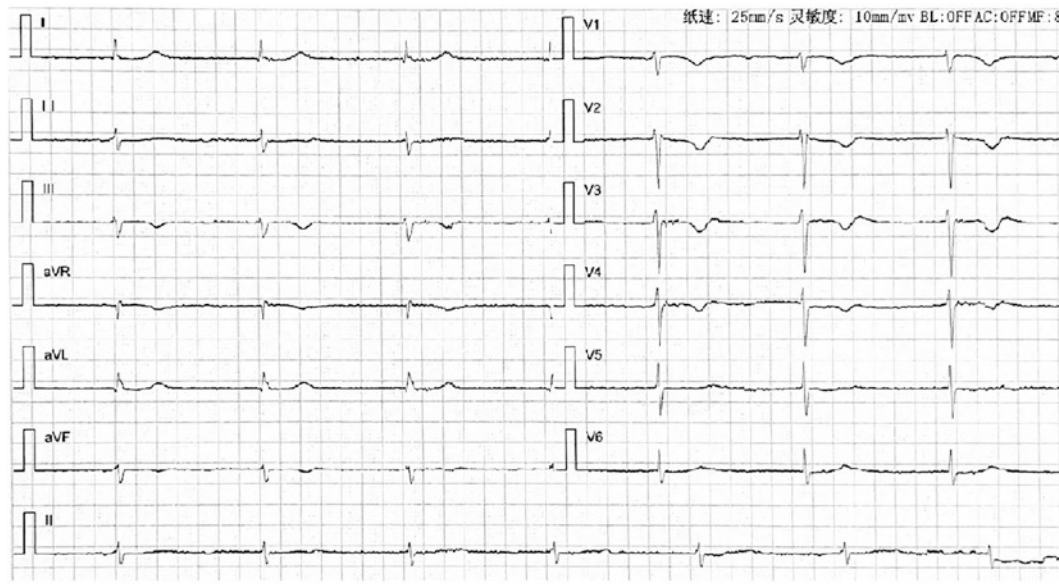


Fig. 10.4 Sinus cardiac arrest

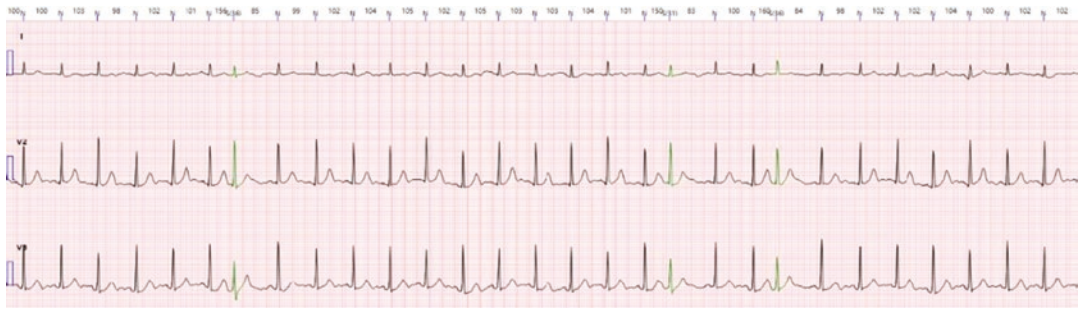


Fig. 10.5 Atrial premature beats occur in a rapid sinus rhythm, the ectopic p′ wave is unclear, and the T wave of the anterior cardiac beat has no obvious notch or deformation. In this case, incomplete compensation is an important basis for determining the attribute of atrial premature beats. Atrial premature beats originated from the atrial septum, the ectopic P wave of the ECG is small or hidden, which is easy confused with high near Hippo ventricular premature beats

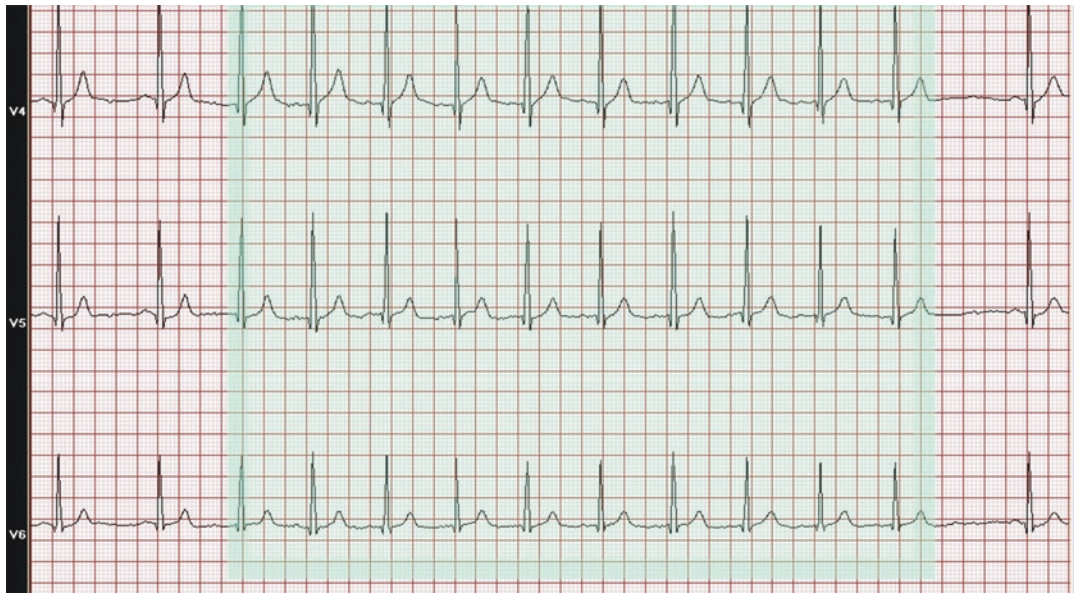


Fig. 10.6 Sinus rhythm; accelerated atrial autonomic rhythm; reverse clock transposition. The part marked in blue is the p′-qrs-t complex, the p′ wave is retrograde (leads II, III, and AVF are inverted; the lead aVR is upright), the p′ R interval is 120 ms, and the frequency is 84–88 bpm, which is consistent with accelerated atrial tachycardia

consciousness, or syncope, and in severe cases, Adams-Stokes syndrome may result in death. Prolonged sinus arrest without escape may result in death. Treatment of sinus arrest primarily focuses on etiology treatment and actively treats the primary disease that causes sinus arrest. Episodic transient sinus arrest without symptoms does not require symptomatic treatment. Patients with frequent and prolonged sinus arrest accompanied by obvious clinical symptoms should be actively treated with heart rate enhancement or early placement of an artificial cardiac pacemaker.

10.2.2 Atrial Arrhythmia

Atrial premature beat Fulminant myocarditis is rare (Fig. 10.5). Severe impairment of cardiac function and poor blood pumping function lead to high atrial pressure, leading to atrial premature beats, which can show frequent atrial premature beats, accelerated atrial autonomic rhythm (Fig. 10.6), etc. When the sinus heart rate exceeds the frequency of the atrial rhythm, the rhythm of the latter is reorganized or inhibited. The frequency of the sinus rhythm decreases, leading to an accelerated atrial rhythm. When the atrial fre-

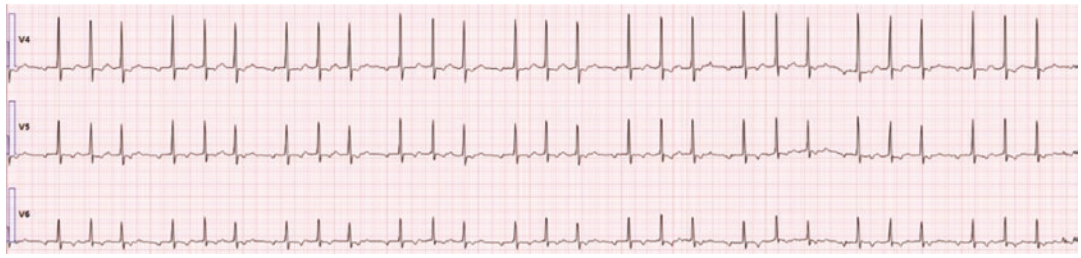


Fig. 10.7 The inverted ectopic P wave rhythm is regular; the heart rate is 147 beats/min, showing a left eccentric type (negative direction of the left chest lead), suggesting that the ectopic excitation originates from the lower left atrium

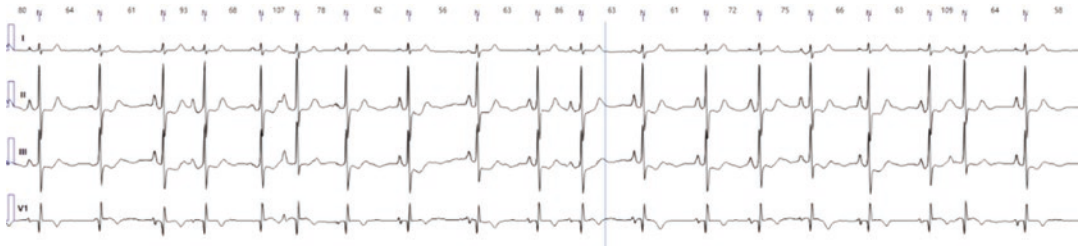


Fig. 10.8 Disordered atrial arrhythmia

quency is similar to the sinus frequency, sinus atrial competition occurs due to self-discipline competition between them.

Atrial flutter, atrial fibrillation, and atrioventricular ectopic tachyarrhythmia, ventricular tachycardia (VT) in fulminant myocarditis are often reported, but the causal relationship between atrial flutter, atrial fibrillation, and myocarditis is unclear. The following is the ECG of a 23-year-old female diagnosed with fulminant viral myocarditis, low left atrial spontaneous tachycardia, and Weng's (second-degree I) atrioventricular block (Fig. 10.7).

There are three or more forms of P waves in the same lead, with irregular rhythm, multisource atrial premature beats, and disordered atrial rhythm; if the frequency exceeds 100 times/min, it is disordered atrial tachycardia. It should be noted that there are less than three forms of P waves, but the premature beat-like rhythm between P waves with the same or similar forms is also a manifestation of disordered atrial rhythm (Fig. 10.8).

10.2.3 Changes in the Cardiac Conduction System

The main lesions of fulminant myocarditis directly involve the cardiac conduction system, such as the atrioventricular ganglion, atrioventricular junction area, or atrioventricular bundle branch. At the same time, it is also related to an increase in vagus nerve tension. Most of them are primary atrioventricular blocks and single-bundle branch blocks. In severe cases, a second-degree or third-degree atrioventricular block or even double bundle branch block can occur. These ECG changes often improve with recovery from myocarditis and can completely return to normal after the lesion is cured. Only a few cases have permanent conduction disorder due to serious damage or fibrosis of the conduction system, which requires permanent pacemaker implantation.

Although arrhythmia caused by viral myocarditis has diversity and variability that are closely related to its pathological changes, which are

caused by inflammatory invasion or spread to the cardiac conduction system caused by the virus or invasion of specialized cardiomyocytes by the virus itself. The main function of the cardiac conduction system is to produce electrical stimulation and transmit electrical stimulation to the ventricular muscles in a certain direction, sequence, and path to maintain normal cardiac rhythm. The cardiac electrical conduction of the normal body is as follows: sinoatrial node → internodal bundle → atrioventricular node → His bundle → left and right bundle branches → Purkinje fibers → working cardiomyocytes. Due to the long path and wide distribution of the conduction system, it is easily infringed in myocarditis.

The pathological characteristics of the conduction system caused by viral myocarditis are similar to those of the myocardium, and some are even heavier than those of the myocardium. The main pathological manifestations were interstitial inflammatory changes, parenchymal degeneration, necrosis, and fibrosis, and some had adipocyte infiltration. Usually, the acute phase can be characterized by cell swelling, unclear cell transverse lines, enhanced eosinophilic cytoplasmic staining, nuclear pyknosis and nuclear fragmentation in the nucleus, cell necrosis and disintegration, disappearance of the nucleus and cell contour, and inflammatory cell infiltration around, mainly monocytes and lymphocytes. In the chronic stage, inflammatory cells decreased, fibroblasts increased, collagen fibers increased, fibrous scar foci and a large number of calcification foci appeared, and some lesions were completely absorbed and dissipated. Under an electron microscope, in the acute stage, it can be seen that the shape of the nucleus is distorted or chromatin pyknosis in the nucleus; the cell membrane and myofibrils are basically complete, but the outer membrane of mitochondria can be broken; the gap inside the cristae increases; the structure of some cristae is fuzzy; the myofibrils in severe cases are incomplete; the transverse myocardial system expands, some cell nuclear membranes disappear, chromatin pyknosis is more obvious, and mitochondria dissolve. In the chronic stage, myofilament dissolution, local swelling of mitochondria, fusion, unclear structure, expansion of the endoplasmic reticulum, and formation of many vacuoles in the sarcoplasmic reticulum can be observed [2].

Usually, the degree of damage to each part of the cardiac conduction system in patients with myocarditis is inconsistent. The lesions of the bundle are very light, the lesions of the sinoatrial and atrioventricular nodes are more serious, and the lesions of the two bundle branches are the most serious [2–4]. This may be related to anatomical characteristics. The dense connective tissue separates the bundle from the myocardium. In myocarditis, the bundle is lightly or unaffected, while the left and right bundle branches are adjacent to the myocardium, which is easily affected by inflammation and produces the corresponding pathological changes. Similarly, the atrioventricular and sinoatrial nodes are adjacent to the endocardium and epicardium, making it easy for inflammation to spread after the virus infects the myocardium. The branches of the right bundle branch are shallow and slender and vulnerable to inflammatory injury. Inflammatory lesions in the right ventricle and ventricular septum can affect the conduction function of the right bundle branch.

The nature of the cardiac conduction system determines its conduction disorder and prognosis. Electrophysiological changes in third-degree atrioventricular block caused by special cardiomyocyte necrosis or a large number of interstitial fibrosis are often long-term, while conduction barriers caused by the degeneration of myocardial specialized cells, inflammatory cell infiltration, fat infiltration, interstitial hemorrhage, and edema are gradually improved and finally cured with the regression of inflammation and tissue repair. Furthermore, multifocal or diffuse inflammatory injury of the atrial muscle can cause multiple excitatory foci, form multiple micro-reentry, leading to atrial fibrillation or tachyarrhythmia, while focal or extensive cardiomyocyte necrosis

and fibrosis can lead to the formation of an injury zone between the diseased myocardium and normal cells, produce a potential difference, and cause the instability of cardiomyocyte electrical activity, inducing ventricular arrhythmia. Arrhythmia caused by viral myocarditis is inseparable from changes in the cardiac conduction system, which is affected by inflammation.

1. Atrioventricular block and various heart conduction blocks are also a common manifestation on the ECG in patients with myocarditis and have high diagnostic value. Atrioventricular block can occur in the early stages of acute rheumatism and viral myocarditis. The difference between atrioventricular blocks caused by other causes is that due to the invasion of the cardiac conduction system, the electrophysiological characteristics are unstable and the ECG shows a great change in the length of the PR interval (Figs. 10.9, 10.10, 10.11, and 10.12).

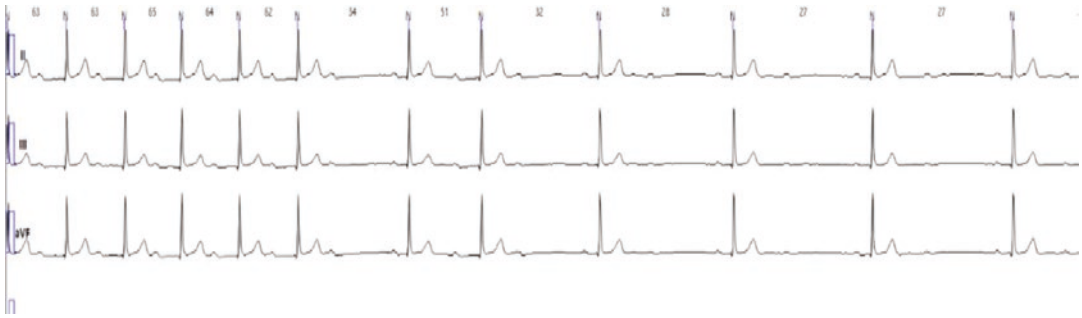


Fig. 10.9 Second-degree atrioventricular block. In this case, the ECG showed a P wave shedding, and there was no doubt of a second-degree atrioventricular block. There are short and long PR intervals; the short and long PR intervals are transformed by jumping, which is similar to the dual atrioventricular node pathway. However, the clinical background of P wave abscission and myocarditis supports the lesions of the cardiac conduction system, which are aggravated in a fast frequency-dependent manner

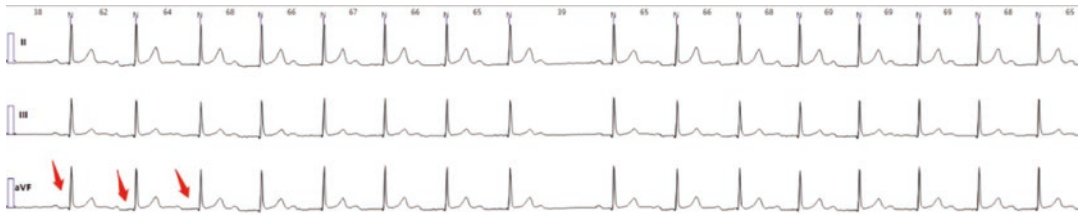


Fig. 10.10 Second-degree atrioventricular block (Wen's type). This case of atrioventricular block was confirmed by Venn's atrioventricular conduction in another ECG segment (the arrow indicates that the PR interval is non-jumping). The course of the disease was mild and was not a lesion at the distal end of the Xipu system. The ECG shows blocking atrioventricular separation and borderline escape rhythm (Fig. 10.11); the course of the disease is severe, and lesions in the distal Xipu system. Most of the ECG manifestations are high atrioventricular block and borderline escape rhythm with bundle branch block (Fig. 10.12)

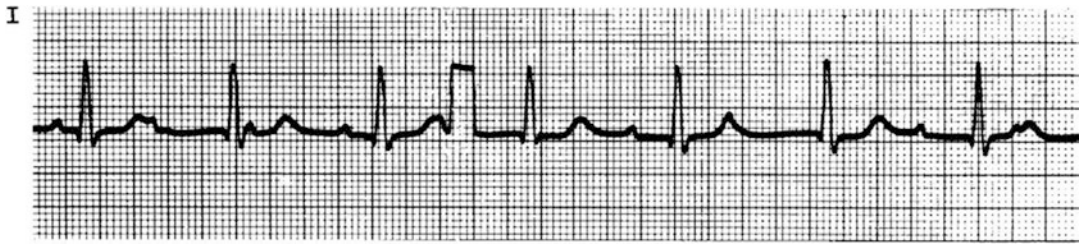


Fig. 10.11 Atrioventricular separation and borderline escape rhythm

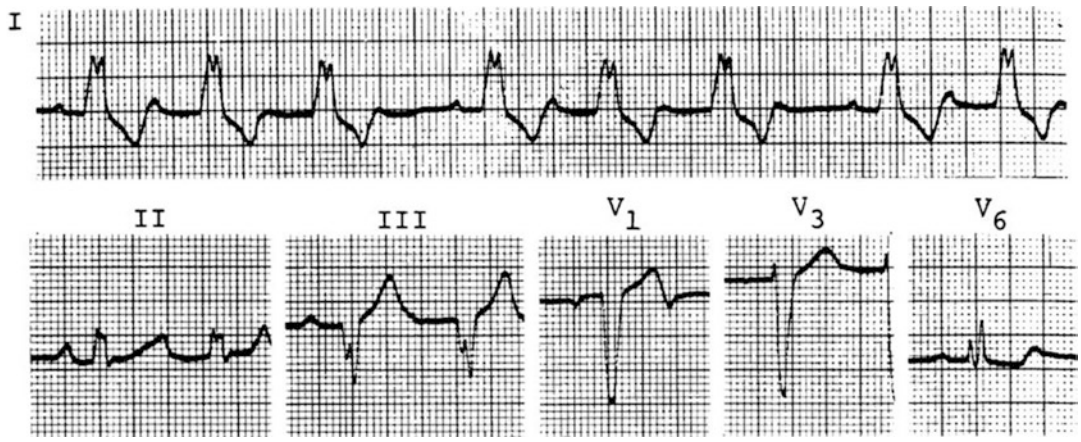


Fig. 10.12 Third-degree AVB

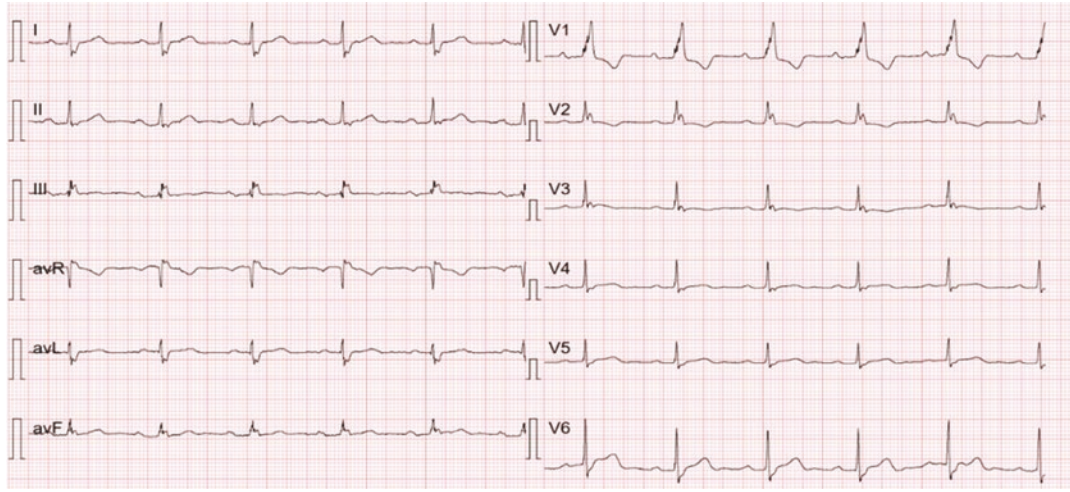


Fig. 10.13 Sinus rhythm, first-degree atrioventricular block, combined with complete right bundle branch block

2. Bundle branch block
   (a) Simple complete right bundle branch block can be seen in normal people (Fig. 10.13). However, the clinical background of myocarditis, emergence of the right bundle branch block system, and primary atrioventricular block suggest progressive cardiac conduction system lesions, and the possibility of a poor prognosis is not ruled out. A Japanese study showed that in-hospital mortality of patients with fulminant myocarditis was significantly higher than in patients with sinus heart rate after high atrioventricular block during hospitalization [5]. Complete left bundle branch block (Fig. 10.14) is also common in fulminant myocarditis, but it is rarely seen in healthy people, and most of them suffer from organic heart disease.
   (b) Double bundle branch block: Patients with fulminant myocarditis may develop double bundle branch block (Fig. 10.15). Once a double bundle branch block occurs, it indicates that the patient has a serious myocardial injury and may have high atrioventricular block, VT, ventricular fibrillation, or even cardiac arrest at any time, which should be closely observed. This is mainly related to focal or extensive cardiomyocyte necrosis and

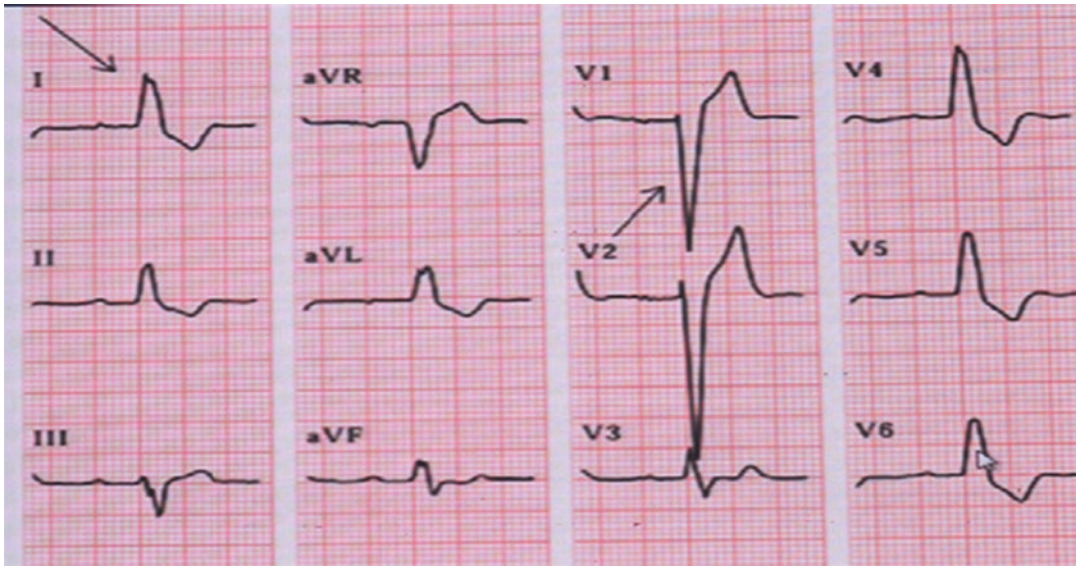


Fig. 10.14 Sinus rhythm with complete left bundle branch block

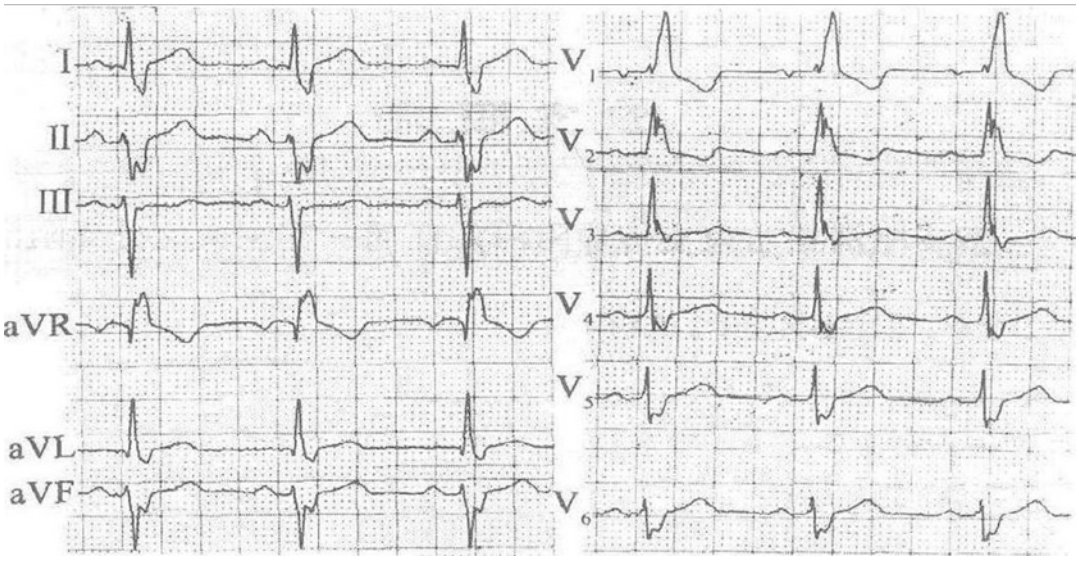


Fig. 10.15 Sinus rhythm, right bundle branch block, and left anterior branch block

fibrosis, and some patients may leave a permanent bundle branch block. The right bundle branch block plus the left anterior branch block is the most common type of double branch block.

(c) Alternating bundle branch block: The left (or right) bundle branch block changes to the other bundle branch block, or the left and right bundle branch blocks occur alternately. When this alternating bundle branch block occurs, it is vigilant that the patient will have (or exist) third-degree atrioventricular block or even sudden death (Fig. 10.16).

3. A ventricular premature beat (or ventricular premature contraction) is referred to as a ventricular premature beat. Premature ventricular pulsation is also one of the characteristics of

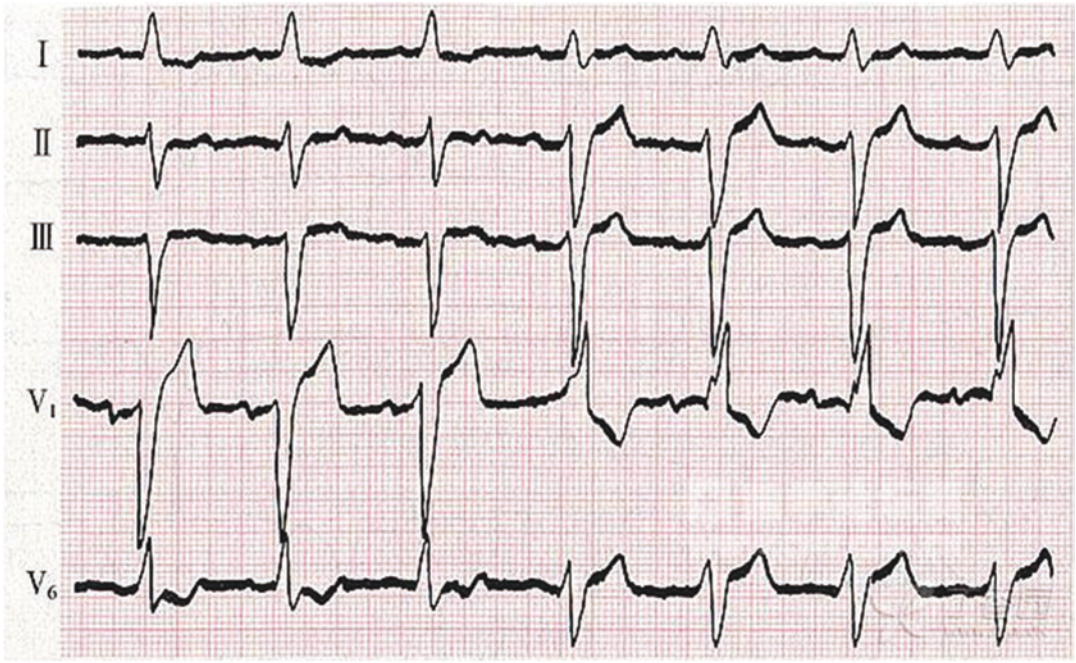


Fig. 10.16 Alternating bundle branch block

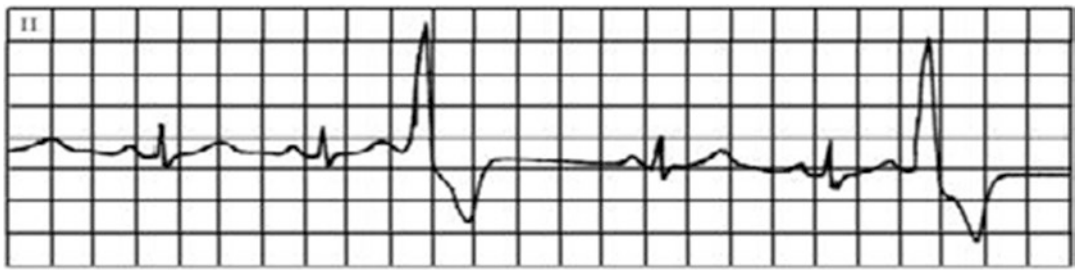


Fig. 10.17 Ventricular premature beat

myocarditis involving cardiac conduction system lesions (Fig. 10.17). Ventricular premature beats often induce malignant arrhythmias in the clinic: (1) multiple ventricular premature beats (6 times/min); (2) pleomorphic ventricular premature beats, multisource ventricular premature beats; (3) R on T phenomenon; (4) paired ventricular premature beats. A study from China showed that frequent ventricular premature beats were one of the high-risk factors for the high mortality of fulminant myocarditis, while another study from Japan showed that the mortality of patients with fulminant myocarditis with VT and ventricular fibrillation in hospitalized patients was significantly higher than that of patients with sinus heart disease [5].

(a) Ventricular premature beat (or ventricular premature contraction): This is a common arrhythmia in the clinic. It occurs in a wide range of people, including healthy people and patients with various heart diseases. Ventricular premature beats are commonly observed in ECG in the early stage of fulminant myocarditis. Clinical symptoms vary greatly, ranging from asymptomatic and slight palpitations to syncope or amaurosis caused by premature beats that trigger malignant ventricular arrhythmia (Fig. 10.17).

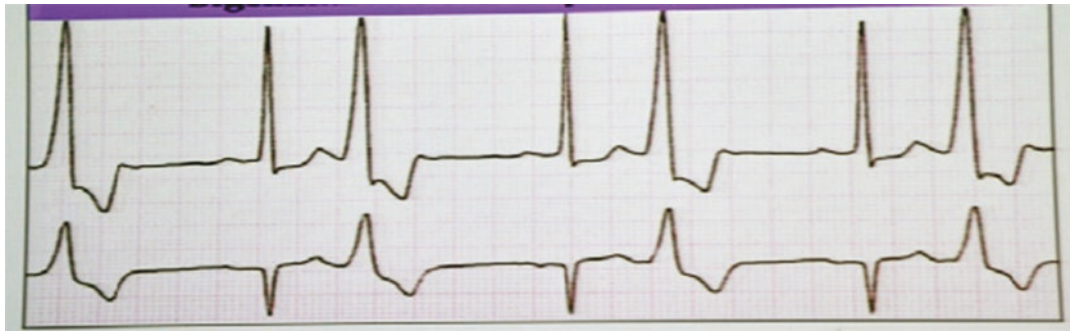


Fig. 10.18 Ventricular premature dyadic rhythm

(b) Ventricular premature dyadic rhythm: Once patients with fulminant myocarditis have a frequent ventricular premature and ventricular premature dyadic rhythm, it indicates that the myocardium is seriously damaged and cardiac function is very poor. If the patient's condition is not controlled in a timely and effective way, it is likely to have serious malignant arrhythmias, such as VT and ventricular fibrillation. At the same time, we should attach great importance to the patient's internal environment, correct the internal environment disorder in time, and avoid the occurrence of malignant arrhythmias. For the insertion of premature ventricular beats, experienced doctors routinely measure their premature beat index. If the ventricular premature dyadic interval is shorter than the QT interval of the anterior sinus beats, the premature beat index of <1, suggesting a poor prognosis (Fig. 10.18).

(c) Multiple ventricular premature beats: Fulminant myocarditis has frequent multisource ventricular premature beats or pleomorphic ventricular premature beats (Fig. 10.19), suggesting the risk of progression to malignant ventricular arrhythmia. This type of VT is very harmful to the heart and requires high attention and emergency treatment.

(d) R on T phenomenon: Fulminant myocarditis occurs frequently, ventricular premature beats are common, and the R on T phenomenon is not uncommon, and once the R on T phenomenon is found in patients with fulminant myocarditis, it indicates that the potential risk is very high (Fig. 10.20). The peak of the T wave in the ECG is the boundary between the two types of ventricular refractory periods. The former is the effective refractory period, and the latter is the relative refractory period. In the relative refractory period, the excitability of the ventricular muscle gradually recovers from 0 to 100%, and 20–30 ms before the peak of the T wave is called the ventricular fibrillation prone period. The ventricle falling into this period is like a fuse, which can cause ventricular fibrillation. Whether R on ventricular premature can cause VT and fibrillation is related to many factors, especially the basic state of the heart, the activity of sympathetic nerves, and the threshold of ventricular fibrillation.

(e) VT and ventricular fibrillation

Arrhythmia is the first symptom in 90% of patients with viral myocarditis, while ventricular arrhythmia accounts for 70% of patients with fulminant myocarditis. In severe cases, high atrioventricular block, VT (Fig. 10.21), and ventricular fibrillation (Fig. 10.22) can occur. Once VT and ventricular fibrillation occur in patients with fulminant myocarditis, it

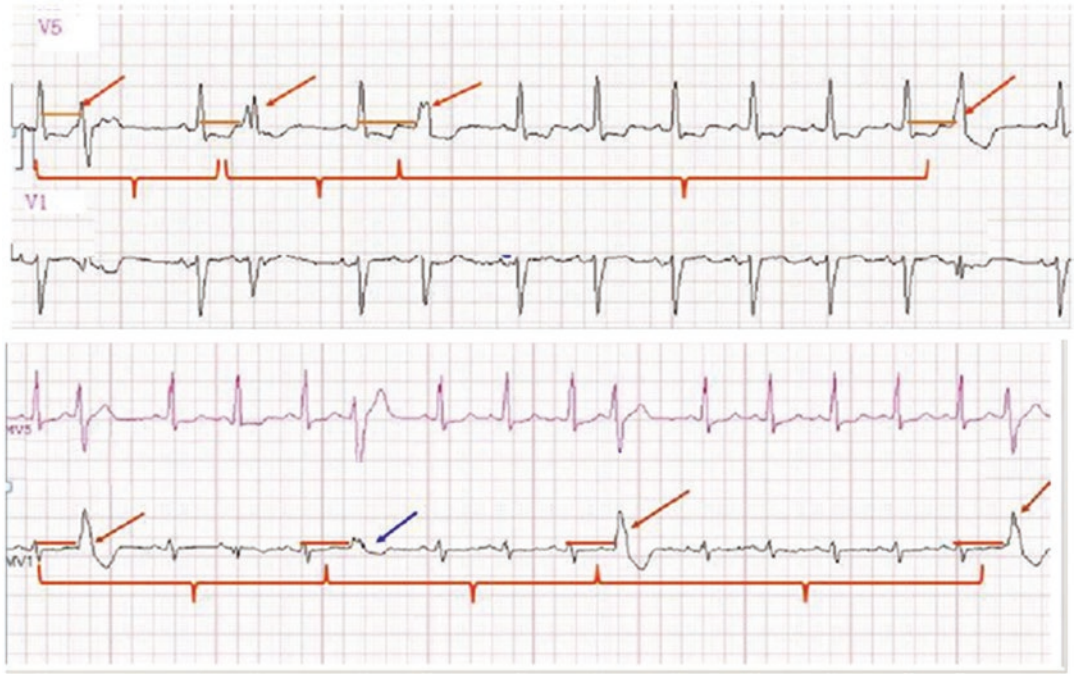


Fig. 10.19 Polygenetic ventricular tachycardia and pleomorphic ventricular tachycardia

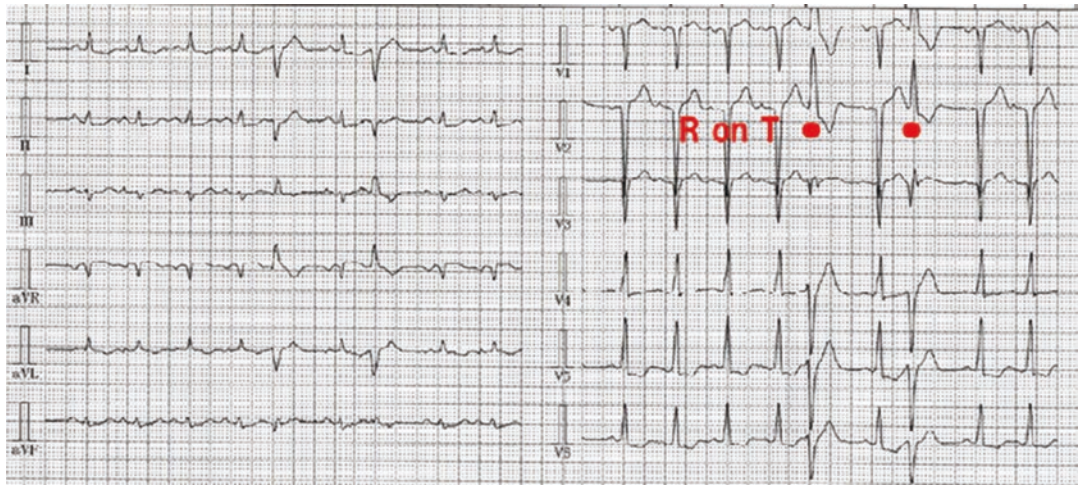
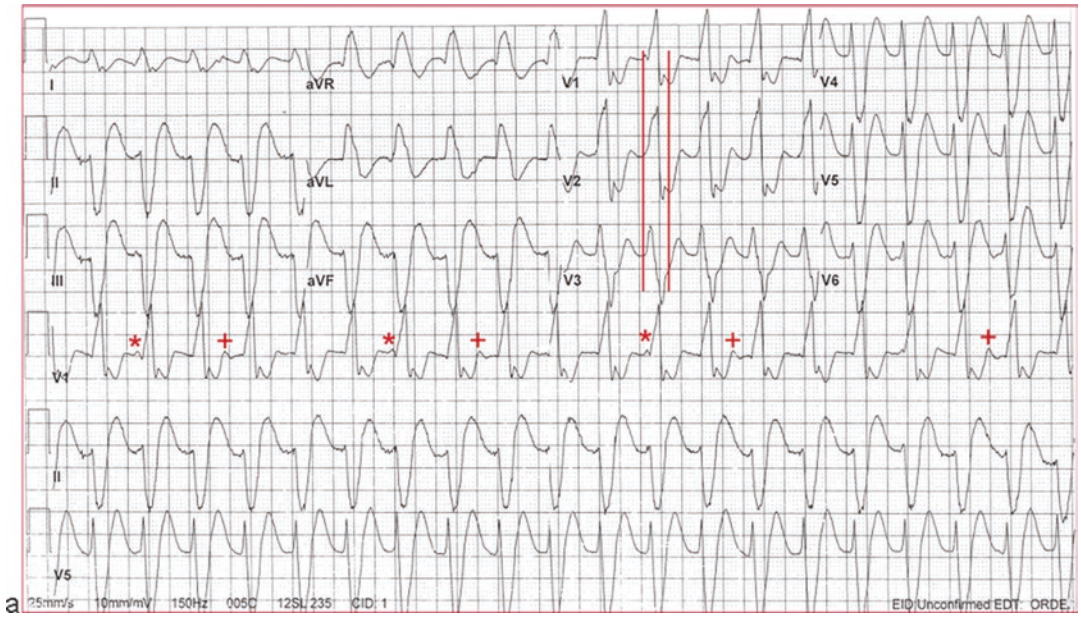


Fig. 10.20 R on T

often indicates that the condition is critical. Some patients showed malignant VT and ventricular fibrillation that did not alleviate continuously.

This ECG is a monomorphic VT, which is defined as a ventricular rhythm higher than 100 beats/min and lasting more than 30 s, or a ventricular rhythm terminated due to hemodynamic instability within 30 s. Its occurrence is not an arrhythmia caused by ischemia but often occurs in inflammation (myocarditis) with the formation of a reentry loop caused by scar formation near normal



a

Fig. 10.21 Wide QRS tachycardia with a heart rate of 130 beats/min (QRS, 0.18 s). There is no obvious P wave (*) before and after the QRS complex, but it seems that the P wave can be seen before R2, R7, and R12 on lead V1. Furthermore, the T wave (+) after R3, R8, R13, and R18 of lead V1 is different from other T waves, and its terminal has a positive deflection, suggesting that the P waves overlap (+). A notch (↓) can be seen on the T wave of lead I R3, but there are no other T waves. Therefore, it is considered that there is a trace of atrioventricular separation. Although only some P waves (not all P waves) of the whole ECG are related to QRS waves, it still suggests the existence of atrioventricular separation. Furthermore, the relationship between the P wave and the QRS wave is variable; small changes in the ST-T waveform also suggest the existence of atrioventricular separation. All wide QRS arrhythmias with evidence of atrioventricular separation were VT. It should be emphasized that the forward waveform after V1–V2 leads is not P wave, but the terminal part of the QRS waveform, which can be determined by comparison with other leads, such as AVF, II, V3 lead (II). The QRS complex has the same shape, similar to the right bundle branch block, but there is no atypical pattern of the right bundle branch block, and the electrical axis obviously deviates to the left

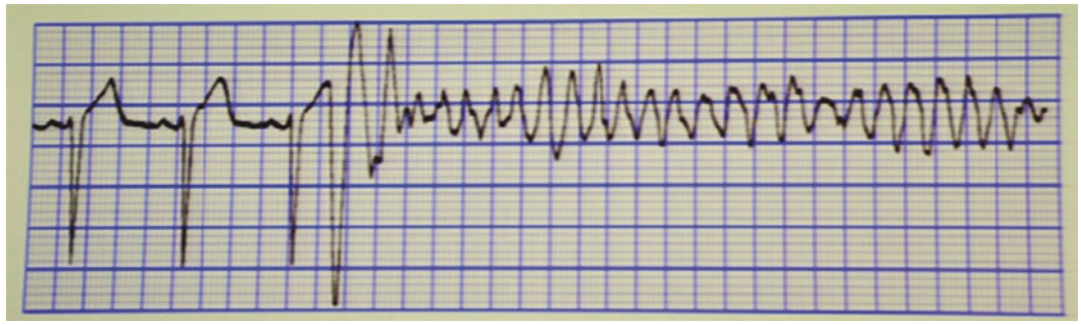


Fig. 10.22 Ventricular fibrillation

myocardial tissue; hence, patients with heart disease are related to scarring.

Ventricular fibrillation is caused by multifocal local excitation of the heart, resulting in complete loss of blood drainage function. This is a transient cardiac arrest phenomenon. ECG characteristics: The qrs-t wave disappears completely, and low wavelets of different sizes and extremely uneven appear, with a frequency of 200–500 times/min (Fig. 10.22).

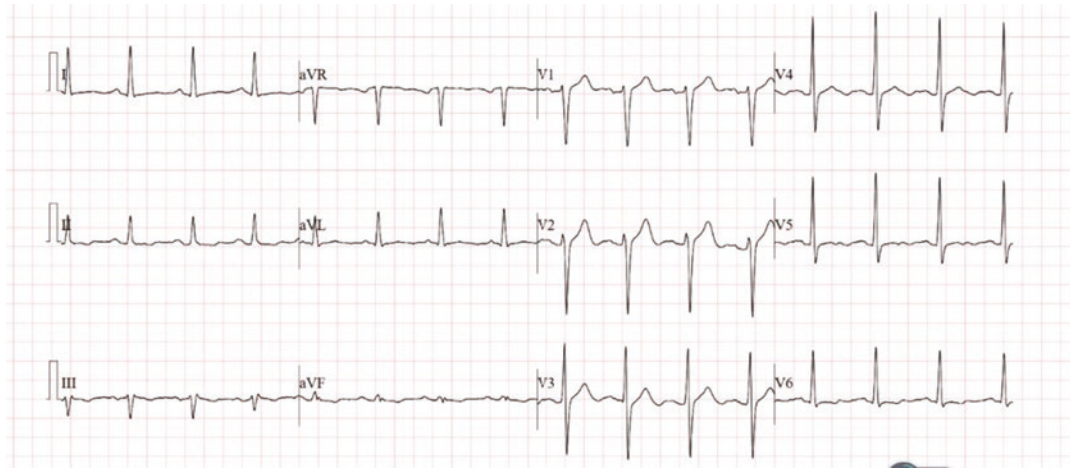


Fig. 10.23 ECG features: sinus rhythm, slightly faster rate (89 bpm); Multiple R waves are upward, ST segment is depressed, and T wave is low; QTc interval was prolonged (483 ms). The T wave of lead V1–V2 in the chest is upright, suggesting that the main body of the T wave vector is slightly right in the forward direction, and the azimuth is abnormal

4. ST-T change

ST-T changes can be seen in all leads, especially in the left precordial lead. Most of them had mild horizontal reduction in the ST segment and flat or inverted T waves, and the detection rate was approximately 75%. Some patients with severe myocarditis can show an elevation of the ST segment in multiple leads. ST-T changes evolve with the progression or reduction of lesions. When excluding the possibility of ST-T changes caused by other causes, combined with clinical manifestations, this change and evolution process is helpful for the diagnosis of myocarditis. However, it should be noted that many normal young female or menopausal women often have a T wave horizon or inversion on ECG, which is mostly seen in leads II, III, and AVF. This change is often caused by autonomic nerve dysfunction. Patients with myocarditis can also have ST segment depression, PR segment depression, and pathological Q wave. PR segment depression and concomitant ST segment elevation suggest that the lesion involves the epicardium and pericardium.

The most common are nonspecific ST-T abnormalities (Fig. 10.23)

An important feature of nonspecific ST-T changes in patients with myocarditis is the mild prolongation of the QTc interval. The QTc interval was normal or shortened in patients with functional ST-T changes, and whether the QTc interval is prolonged under the influence of non-drugs can be used as the distinguishing point between pathological and functional ST-T changes. A 24 h ambulatory ECG was performed in patients with myocarditis. It can be seen from the ST segment trend analysis that nonspecific ST-T abnormalities in patients with myocarditis (Fig. 10.24) are not fixed. When the active heart rate increases and the amplitude of ST segment depression increases, the R wave amplitude remains unchanged or slightly increases (Fig. 10.25); the characteristic of the functional ST-T change is that the amplitude of the R wave decreases with the acceleration of the heart rate and the depression of the ST segment.

When the active heart rate increases, the ST segment depression and the decrease in R wave amplitude characterize sympathetic (or functional) ST-T changes. However, in the clinical background related to myocarditis, increased R wave amplitude is another distinguishing point of pathological ST-T abnormalities.

The abnormal ST-T of the ECG in patients with severe myocarditis can be exaggerated

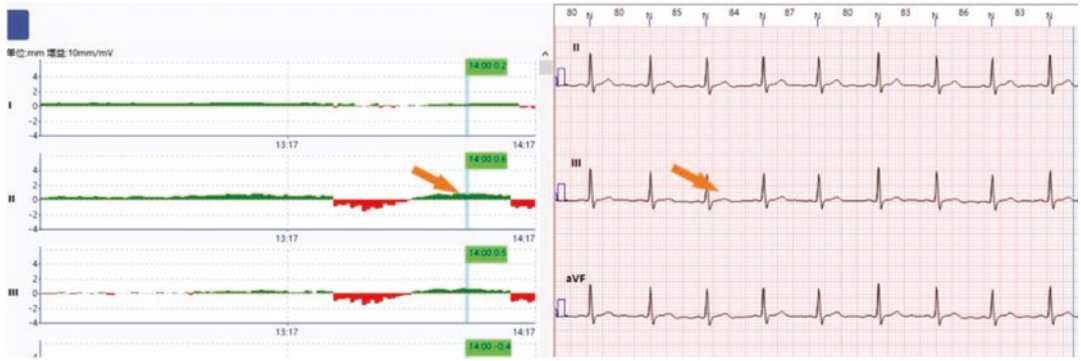


Fig. 10.24 Sinus rhythm, QTc interval normal (male, 16-year-old)

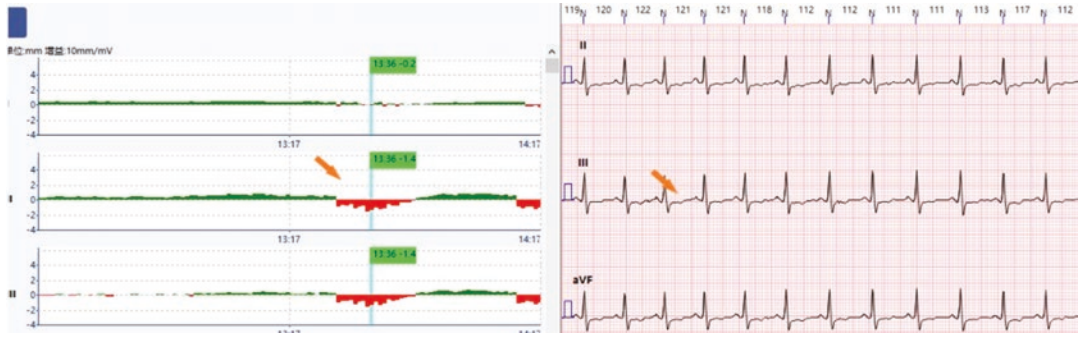


Fig. 10.25 Sinus rhythm, mild ST segment depression

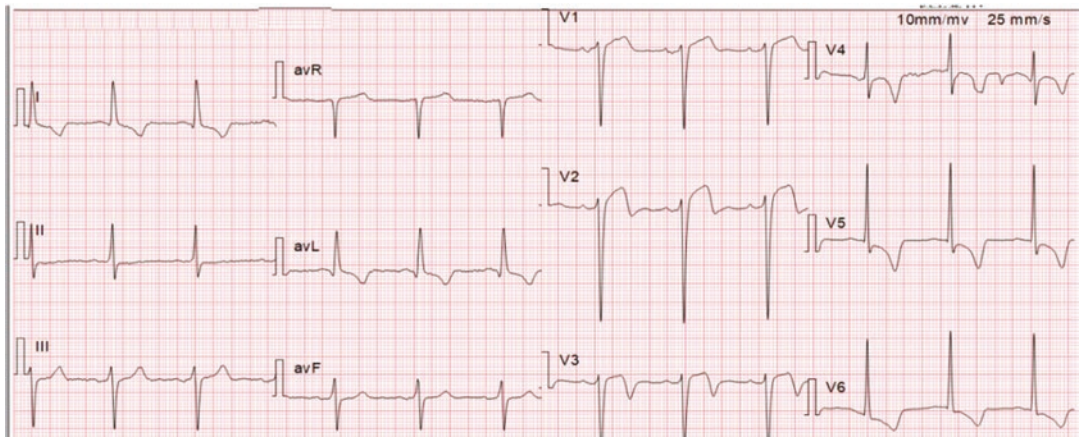


Fig. 10.26 Sinus rhythm, QTc interval was 468 ms, and the interval was prolonged (male, 14-year-old, fulminant myocarditis, heart failure, echocardiography showed ventricular enlargement)

(Fig. 10.26). ST-T is opposite to the main wave of the QRS complex, which is similar to the secondary ST-T change. In fact, this is a primary abnormality.

ST segment elevation of several reports have shown that some patients with fulminant myocarditis have ECG manifestations similar to acute ST segment elevation myocardial infarction [6] (Figs. 10.27 and 10.28), suggesting that the patients have serious myocardial damage, and ST segment elevation is mainly due to local or diffuse myocardial inflammation, myocar-

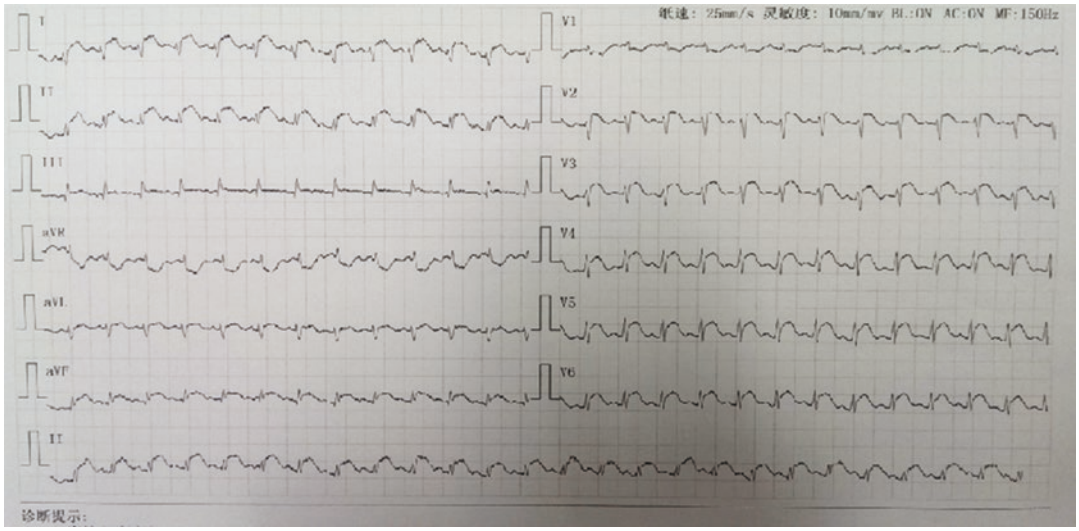


Fig. 10.27 Sinus tachycardia: extensive lead ST segment elevation

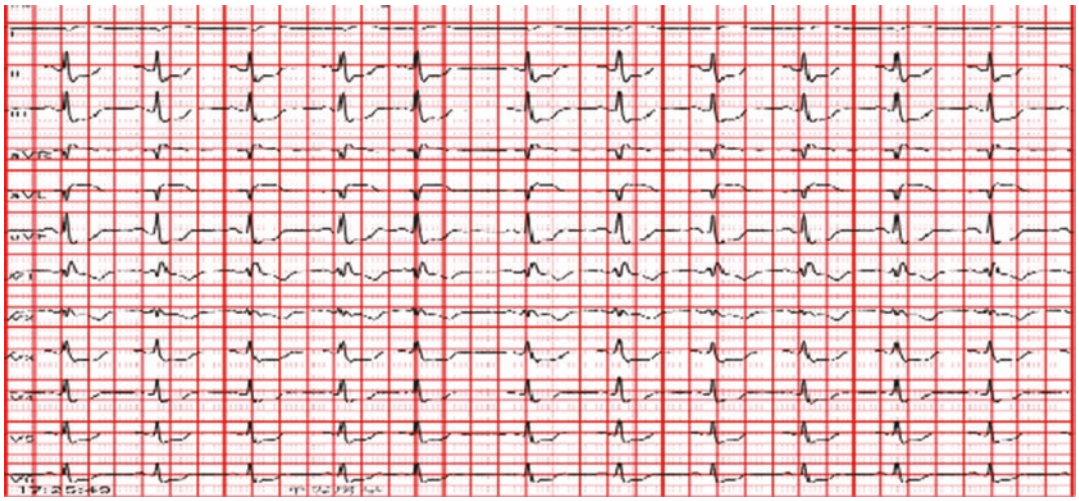


Fig. 10.28 Sinus rhythm, atrial premature beat, complete right bundle branch block. The ST segment of the lower and front walls moved down significantly, and the ST segment of the aVR lead was raised

dial toxin invasion, myocardial edema, and metabolic disorders caused by myocarditis reaction, myocardial necrosis or coronary artery spasm in severe cases, and ST segment elevation with or without abnormal Q wave. This situation often seriously affects myocardial systolic and diastolic function and can lead to serious arrhythmia and heart failure.

ECG features: (1) There are often multiple patterns of coronary artery damage, that is, ECG changes at more than two infarct sites; (2) ST elevation does not have a mirror image of the corresponding lead; (3) acute myocardial infarction (AMI)-like changes were transient and reversible, with rapid changes, the rapid disappearance of the Q wave, and no dynamic evolution of myocardial infarction; (4) It is often accompanied by various arrhythmias, even fatal arrhythmias, and low voltage [7].

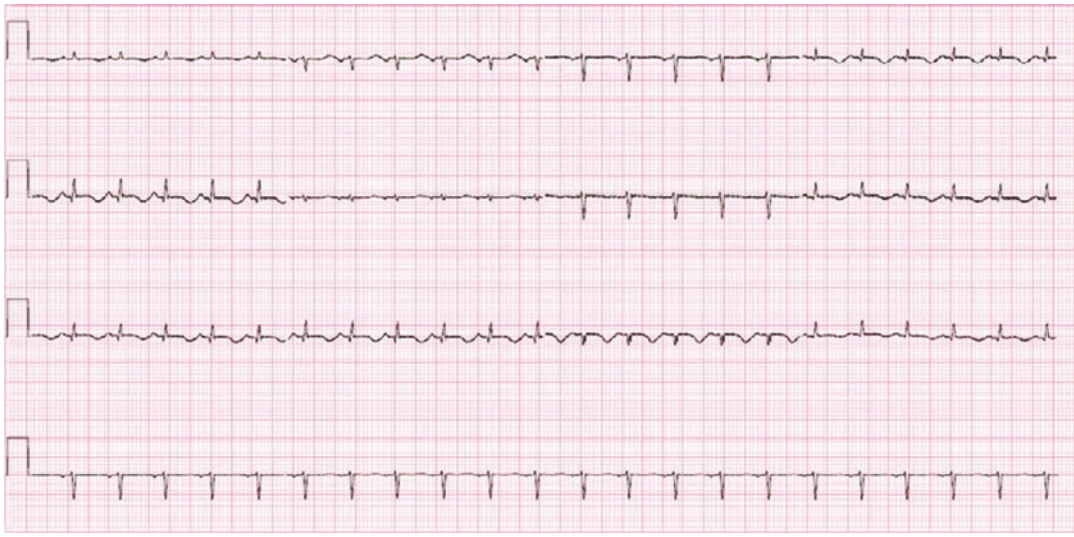


Fig. 10.29 The ECG showed sinus tachycardia, II, III, AVF, T wave inversion of V3–V6 leads, low QRS voltage and prolonged QT interval

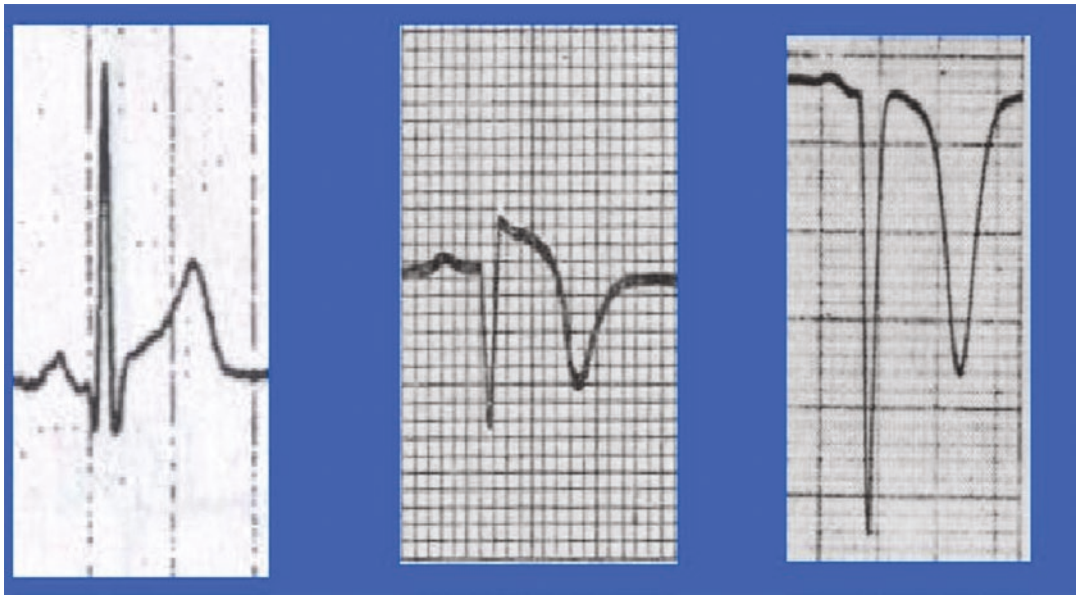


Fig. 10.30 Comparison of different types of Q wave patterns

5. Abnormal QRS complex and abnormal Q wave
   (a) QRS complex low voltage. Approximately 20% of patients with myocarditis have an abnormal QRS complex (Fig. 10.29). Abnormal Q waves can also appear on the ECG of patients with severe myocarditis. These changes may be due to inflammatory lesions in the myocardium that affect myocardial depolarization, delay depolarization, and reduce or even disappear ECG power. After remission, the QRS voltage gradually recovered, abnormal Q waves (Fig. 10.30) disappeared, and ECG returned to normal.

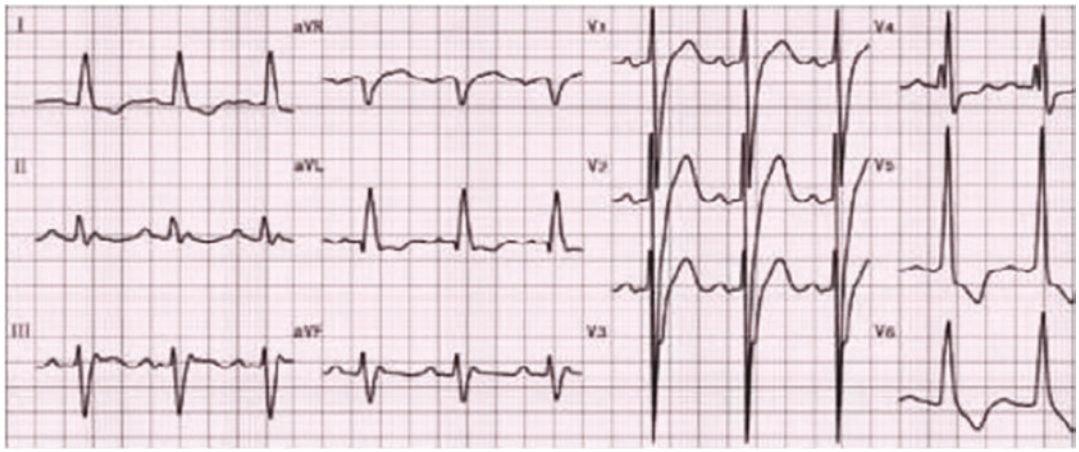


Fig. 10.31 Sinus tachycardia and widening of QRS wave suggest severe indoor conduction block

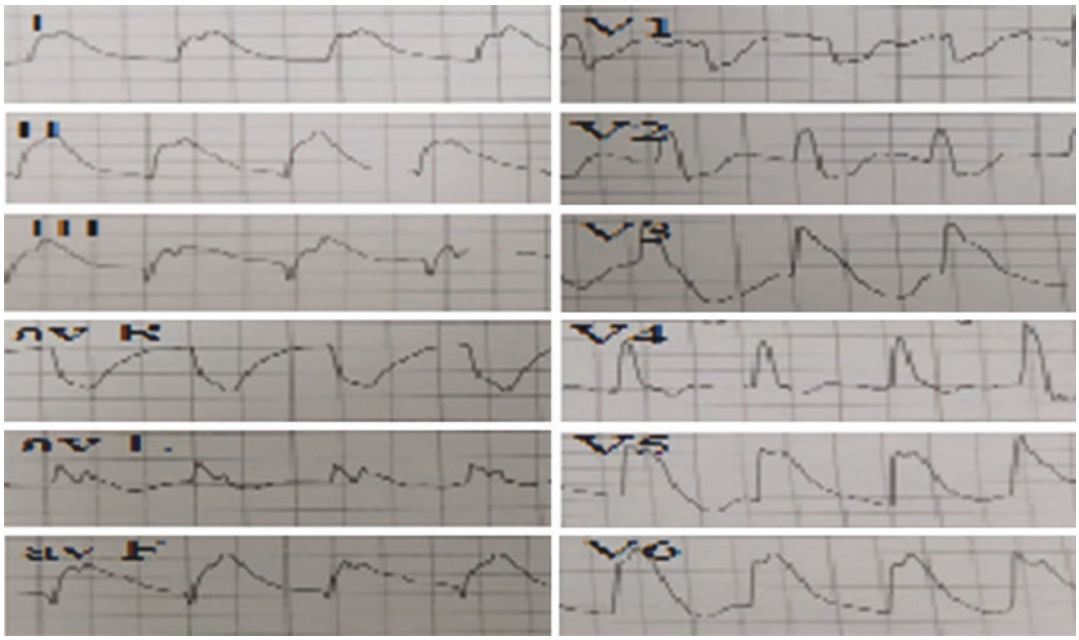


Fig. 10.32 Giant R wave ST segment change

(b) QRS wave duration broadening. The boardening of the QRS wavelength is related to myocardial interstitial edema (Fig. 10.31). The QRS time limit can be recovered by improving myocardial interstitial edema. It is rare that patients with myocarditis report to still have a wide QRS wave after recovery, which is considered related to myocardial fibrosis caused by myocarditis [8]. Low limb voltage on ECG manifests severe impairment of cardiomyocyte function, loss of myocardial tissue, or replacement by non-myocardial tissue [9]. It is worth noting that if patients have QRS wave broadening, which needs to be paid great attention, it often indicates that the condition is serious, and the risk of sudden death is very high. It is rare for fulminant myocarditis to cause the ECG to show giant changes in the R wave (Fig. 10.32). The ECG mainly showed that the QRS

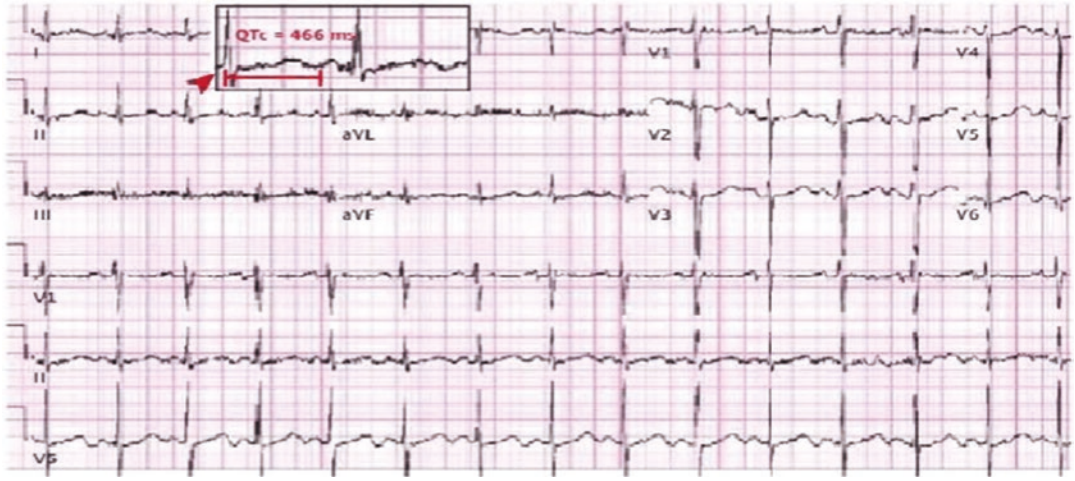


Fig. 10.33 Sinus tachycardia, QTc slightly prolonged (466 ms)

complex combined with the ST segment to form a single-phase QRS-ST complex. Furthermore, this ECG pattern can also be similar to the bundle branch block or VT, especially when the P wave becomes blurred due to the rapid ventricular rate. The electrophysiological mechanism of giant R wave syndrome (grws) is considered the focal indoor conduction block in the area of severe ischemia or myocardial infarction due to increased extracellular K+ concentration, membrane depolarization, intracellular ATP depletion, and shortening of the action potential caused by ischemia. Fulminant myocarditis causes extensive myocardial injury and necrosis due to a large number of viral invasions. The conduction of a viable myocardium around the necrotic myocardium was slow and activation was delayed; depolarization from the endocardium to the epicardium was slow, resulting in giant R wave ST segment changes. Fulminant myocarditis with a graft on the ECG remains challenging because it is similar to early AMI. Therefore, cardiac catheterization is essential for the differential diagnosis of fulminant myocarditis and AMI.

6. T interval prolongation

The QT interval represents the time of complete depolarization and repolarization of the myocardium. Theoretically, myocarditis must affect the depolarization and repolarization of the myocardium, thus prolonging the QT interval (Fig. 10.33).

However, in clinical practice, not all patients present with this manifestation. Only approximately 30% of ECGs in patients with acute rheumatic myocarditis have a prolonged QT interval. Previous studies have shown that the QTc interval changes significantly in different stages of myocarditis, and the prolonged QTc interval is significantly correlated with the in-hospital mortality of fulminant myocarditis (Fig. 10.34) [10].

Its potential molecular mechanism: in patients with fulminant myocarditis, the virus may directly invade cardiomyocytes and lead to inflammatory cell infiltration. Furthermore, the destruction of the relationship between the cytoskeleton and sarcomere structure of cardiomyocytes based on connective membrane binding dystrophin-associated glycoprotein and outer basement membrane actin, leading to a change in cardiomyocyte membrane potential and affects the myocardial conduction system [11].

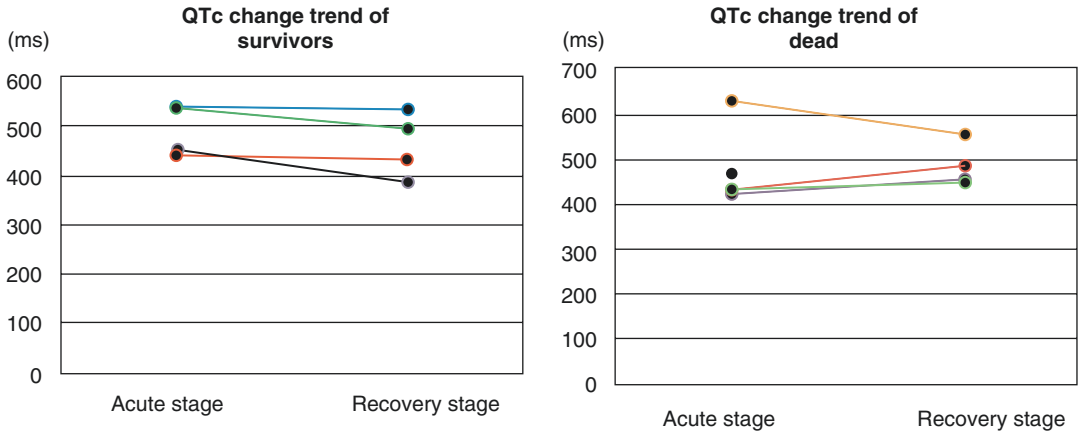


Fig. 10.34 QTc changes in patients with fulminant myocarditis and those who died of fulminant myocarditis in different periods

In addition to prolonging the QT interval, QTc dispersion is also the main index of malignant arrhythmia in patients with fulminant myocarditis. Patients with viral myocarditis have cardiomyocyte inflammation, myocardial fiber rupture, focal necrosis and fibrosis, and interstitial cell proliferation, which increases the difference in the action potential refractory period between the diseased myocardium and normal myocardium, i.e., the inconsistency of segmental myocardial repolarization and electrical instability, which is the pathophysiological basis of ventricular arrhythmia in such patients. This dispersion of myocardial repolarization is manifested in increased QTcd on the body surface ECG, which provides a theoretical basis for the application of increased QTcd to predict the occurrence of ventricular arrhythmia.

10.3 Arrhythmias and Prognosis of Myocarditis

The prognosis of acute viral myocarditis is related to the degree of myocardial damage, lesion size, and serious complications (arrhythmia, cardiogenic shock, and heart failure). Generally, patients with premature systole and mild atrioventricular block have mild clinical symptoms. Even if the residual ECG is abnormal, it does not affect the quality of life of patients, suggesting that these patients may have focal myocarditis with a small lesion range and good prognosis. Serious arrhythmias, such as paroxysmal VT and high atrioventricular block, can be controlled with drug treatment, and there is no significant cardiac enlargement or heart failure in the clinic, suggesting that the malignant degree of arrhythmia is not necessarily positively correlated with the degree of myocardial lesions. However, persistent malignant arrhythmias can directly endanger life and should be actively treated. Fulminant myocarditis often manifests itself as diffuse pericarditis, cardiac enlargement, and heart failure. Clinically, patients often die suddenly due to repeated heart failure or malignant arrhythmias, and some patients may develop dilated cardiomyopathy at a later stage.

In conclusion, viral myocarditis can cause a variety of arrhythmias, especially fulminant myocarditis. Some arrhythmias may also be the only clinical manifestation of a subclinical state of viral myocarditis. Generally, the risk of arrhythmia determines the nature of the arrhythmia and the severity of myocarditis symptoms. Great attention should be paid to the ECG performance of patients with myocarditis.

Key Points

1. Patients with fulminant myocarditis generally have obvious ECG changes, but their diagnostic specificity is low. Repeated examinations should be performed many times to compare their dynamic changes.
2. Various types of arrhythmias, low voltage, significant ST fragment, and T wave changes can occur in the acute stage of fulminant myocarditis, which is sometimes difficult to distinguish from acute myocardial infarction and is usually characterized by diversity, variability, and variability.
3. It can easily cause malignant arrhythmia and sudden death, which can directly endanger life, so it should be identified and actively handled in time, and its occurrence is related to acute inflammation, while hypoperfusion and sympathetic excitements (e.g., stress, exercise, and dopamine use) are easy to induce.
4. Long-term nonrecovery of the ECG may be an existing form of chronic myocarditis.
5. Arrhythmia may be the only clinical manifestation of a subclinical state in some patients with fulminant myocarditis.

Typical Case

Patient: A 32-year-old female patient was hospitalized for "fever with palpitations for 3 days". Three days prior, there was no obvious induction of fever, mostly fluctuating at 38–39 °C, accompanied by general fatigue, gradual palpitations, chest tightness, nausea, and no shortness of breath. Blood pressure was measured in a local hospital at 70/40 mmHg. On day one, the ECG showed an acceleration in ventricular autonomic rhythm, and the ventricular rate was 85 times/min; the ST segment elevation of the precordial lead (Fig. 10.35a, b) and the myocardial enzymes CK 286 u/l and CK-MB 56 u/l were checked. The patient previously denied "hypertension, diabetes, hyperlipidemia," and other medical history, smoking, drinking, and other bad habits.

Physical examination on admission: body temperature of 36.4 °C, pulse of 74 times/min, respiration of 19 times/min, and blood pressure of 83/52 mmHg. The heart-voiced boundary expanded to the left. The heart rate was 74 beats/min, the heart sound was low, the rhythm was neat, and no murmur or additional sound was heard in the auscultation area of each valve. Chest and abdominal examinations revealed no abnormalities. There was no edema in the lower limbs. The ECG examination was performed immediately after admission, and there was still an accelerated ventricular autonomic rhythm originating from the right ventricle (the QRS waveform was completely left bundle branch block-like) (Fig. 10.35c). Echocardiography showed that the whole heart was large (transverse diameter of each atrium and ventricle × the length: diameter of the right atrium was 50 mm × 57 mm; right ventricle was 47 mm × 86 mm; left atrium was 50 mm × 58 mm; left ventricle 49 mm × 88 mm; left ventricular end-diastolic anteroposterior diameter was 53 mm; right ventricular anteroposterior diameter 25 mm), diffuse movement of the right ventricular wall decreased, right ventricular overall systolic function decreased, left ventricular overall systolic function was normal (EF, 60%), and the estimated pulmonary artery pressure was 26 mm. The myocardial enzyme CK of 210.5 u/l and CK-MB of 39.8 u/l were rechecked after admission; troponin of T 2.78 ng/ml (normal value, 0–0.014 ng/ml); blood routine: WBC, 10.36 × 10^9/l; neutrophil percentage, 86%; Coxsackie virus negative; Pro-BNP, 7195 pg/ml; high sensitivity CRP, >11 mg/l.

After admission, the patient was instructed to stay in bed, eat a high-protein diet, administer with intra-aortic balloon pump (IABP) and dopamine intravenous drip to maintain blood pressure, take oral coenzyme Q10, slow intravenous injection of high-dose hormone, gamma globulin, and high concentration vitamin C to improve myocardial metabolism. Considering that bacterial infection is one of the important conditional factors of viral myocarditis, third-generation cephalosporin was administered based on ganciclovir antiviral to prevent bacterial infection. On day 2 of hospitalization, the ECG monitoring changed from an accelerated ventricular autonomic rhythm to a third-degree atrioventricular block (Fig. 10.35d), and the ventricular rate was 56 times/min. Therefore, a temporary pacemaker

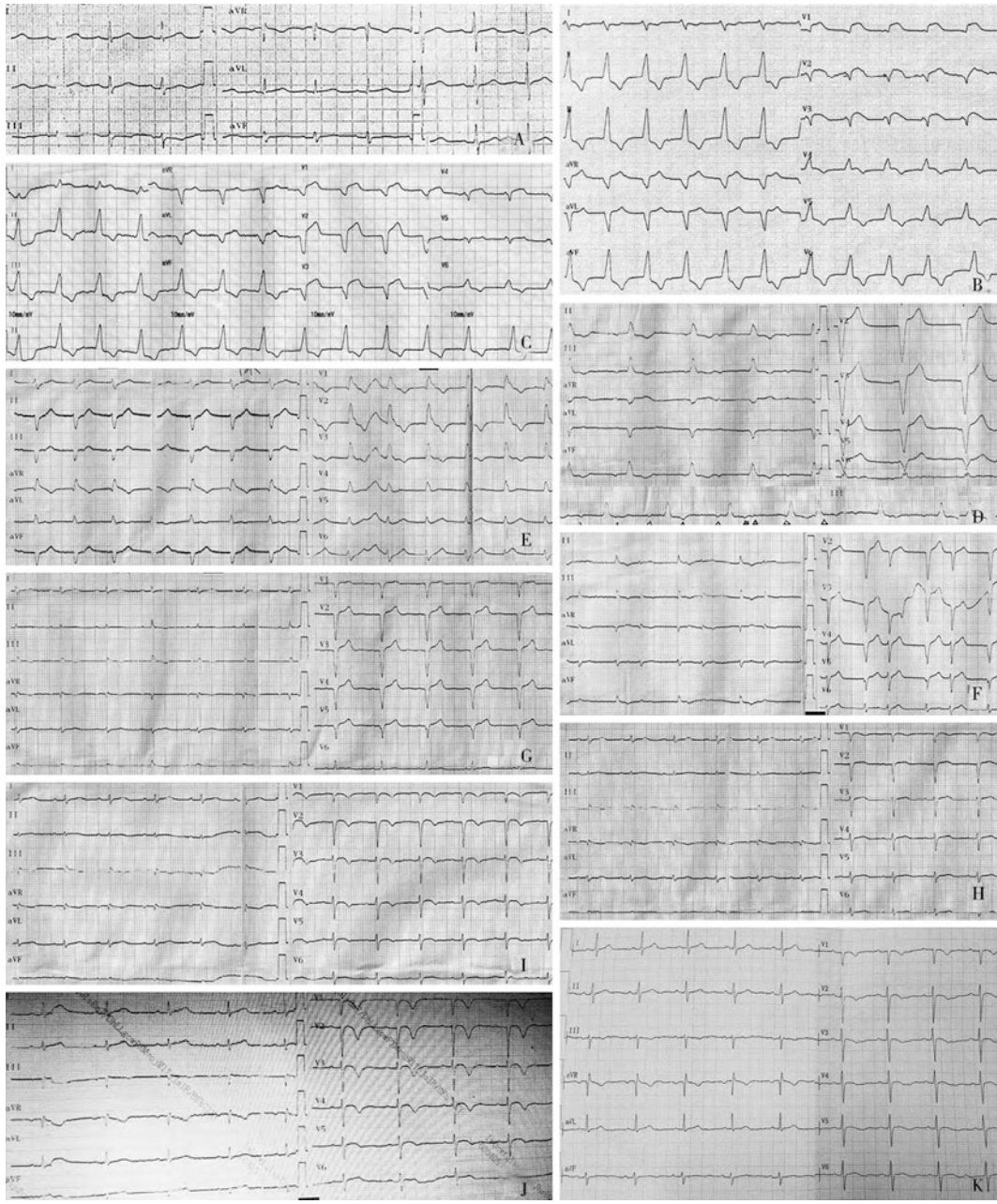


Fig. 10.35 ECG evolution of the same patient with acute fulminant myocarditis. (**a**) The normal ECG a year ago; (**b**) ECG the day before admission; (**c**) ECG immediately after admission; (**d**) ECG on the second day of admission; (**e**) ECG on the third day of admission; (**f**) ECG on the fourth day of admission; (**g**) ECG on the fifth day of admission; (**h**) ECG on the sixth day of admission; (**i**) ECG on the seventh day of admission; (**j**) ECG on the 13th day of admission (before discharge); (**k**) ECG 1 month after discharge

was implanted immediately, and glucocorticoid methylprednisolone 200 mg once a day and pulse therapy continued for 3 days, and human immunoglobulin 20 g/day was continuously injected intravenously. On day 3 of hospitalization, the ECG (Fig. 10.35e) showed an accelerated ventricular autonomic rhythm originating from the left ventricle (QRS waveform was complete right

bundle branch block), and the ventricular rate was 8 times/min. The patient's blood pressure was 100/66 mmHg; hence, dopamine was stopped. On day 4 of hospitalization, the ECG (Fig. 10.35f) showed a borderline escape capture duplex, the limb lead QRS wave was low voltage, and the ventricular rate was 78 beats/min. On day 5 of hospitalization, the ECG (Fig. 10.35g) showed recovery of sinus rhythm, but the QRS waveform of the precordial leads V1–V5 was QS type, and the T wave upright limb lead showed low voltage. On day 6 of hospitalization, the ECG (Fig. 10.35h) showed sinus rhythm. Precordial leads V1–V2 were still QS type, V3–V5 were RS waveforms, the T wave was low, flat, and bidirectional, and the limb leads were low voltage. On day 7 of hospitalization, the ECG (Fig. 10.35i) showed sinus rhythm, the chest lead was the same as the previous day, the T wave was significantly inverted, and the limb lead was low voltage.

The patient was discharged after 13 days in the hospital. Before discharge, there was no discomfort, such as chest tightness or shortness of breath. Her blood pressure was 118/75 mmHg, and her heart rate was 72 beats/min. The ECG showed sinus rhythm, and the inversion of the T wave in the precordial lead deepened (Fig. 10.35j). Echocardiography showed that the biventricles were slightly larger, which was significantly better than at admission (left ventricular end-diastolic diameter, 52 mm; right ventricular anterior posterior diameter, 21 mm), EF (59%), and left ventricular soothing function and right ventricular soothing function were reduced. After discharge, the patient was prescribed metoprolol, perindopril, CoQ10, vitamin C, and vitamin B1 orally. One month after discharge, the patient's follow-up ECG (Fig. 10.35k) showed sinus rhythm, the R wave of V1–V6 leads increased well, except V1, the T wave of other chest leads was upright, and the low voltage of the previous limb leads returned to normal voltage. There was little change in the ECG at 4 months and 1 month after discharge. Echocardiography showed decreased left ventricular relief function (left ventricular end-diastolic anterior posterior diameter, 50 mm; right ventricular anterior posterior diameter, 18 mm; EF, 63%). Myocardial magnetic resonance imaging showed little fibrosis in the resting left ventricular myocardium, and no obvious abnormalities were found in the rest.

Discussion: The patient was a middle-aged female who was not menopausal and had no risk factors for coronary heart disease, such as hypertension, diabetes, and hyperlipidemia. There was a history of precursor virus infection before the onset, characterized by fever, followed by palpitation, chest tightness, hypotension, elevated myocardial enzymes, and abnormal ECG. Based on the above cases, the primary diagnosis is still fulminant viral myocarditis. Ultrasound showed that the whole heart was involved, and the right heart was mainly involved; hence, the patient's blood pressure was low, and the ECG showed an accelerated ventricular autonomic rhythm, suggesting a wide range of myocarditis. Diseases that need to be differentiated: (1) AMI. Although there are few risk factors for coronary heart disease in this patient, the ST segment of the V1–V3 lead of the ECG in the first out of the hospital is elevated, and the myocardial enzyme is increased proportionally, which cannot completely rule out myocardial infarction. After admission, coronary angiography showed 7–8 segments of the myocardial bridge of the anterior descending artery, systolic stenosis was approximately 30%, distal TIMI blood flow was grade 3, and no abnormalities were found in other vessels. (2) Dilated cardiomyopathy. The admission ultrasound showed that the whole heart was large, but there were no previous manifestations of cardiac dysfunction, such as shortness of breath and edema after activity. The ECG was normal 1 year ago (Fig. 10.35), so the possibility of dilated cardiomyopathy was small. Static myocardial perfusion imaging after admission showed that the uptake function of the anterior wall near the apical segment was reduced and there was no radionuclide imaging of dilated cardiomyopathy with a thin lumen wall and reduced patchy uptake of the whole heart.

In acute fulminant myocarditis, direct cytotoxicity of the virus destroys cardiomyocytes, and the cell-mediated immune response kills sad myocytes and interferes with myocardial metabolism and function. Viral myocarditis leads to myocardial cell injury and electrical quiescence, which makes the local myocardium unable to depolarize normally and produces abnormal Q waves. This abnormal Q wave reflects the extensive myocardial damage caused by the virus. The virus can also release a large amount of vasoactive kinin and catecholamines to induce coronary artery spasm, or the virus directly invades the coronary artery to cause coronary arteritis, resulting in the aggravation of myocardial ischemia with inflammatory edema. The change in the gap junction and ion flow between the myocardium after ischemia can increase the cross-ventricular wall repolarization difference and cause abnormal myocardial repolarization, ST segment elevation, and T wave inversion in ECG; therefore, the ECG is similar to that of AMI, in which case, with the gradual recovery of cardiomyocyte function after the regression of inflammatory myocardial edema, the precordial lead V1–V5 changes from the QS waveform to RS, i.e., the disappeared R wave gradually recovers. This Q waveform is transient and reversible, while the QS waveform of the ECG in the AMI is often permanent.

When the patient was admitted, the ECG showed accelerated ventricular autonomic rhythm and third-degree atrioventricular block, suggesting serious inflammatory changes in the initial cardiac conduction system and possible cardiac arrest. The patient's inflammatory injury and conduction system tissue edema lasted for a short time. After active nutrition of the myocardium, glucocorticoid, and gamma globulin treatment, the ECG gradually changed to a borderline rhythm and then to a sinus rhythm, suggesting that the function of the cardiac conduction system gradually recovered from bottom to top (left and right bundle branches, atrioventricular node, sinoatrial node).

In conclusion, fulminant myocarditis has a rapid onset and rapid progression, and ECG performance often indicates the location or degree of myocardial damage. Therefore, correctly identifying and understanding the dynamic change process of ECG in fulminant myocarditis will help clinicians accurately diagnose and treat patients and improve their prognosis [12].

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Echocardiography in Fulminant Myocarditis

11

Rui Li and Hong Wang

11.1 Introduction

The diagnosis of acute myocarditis is a clinical challenge since its manifestation may mimic different cardiac abnormalities such as acute myocardial infarction. Therefore, conventional echocardiography is warranted as an initial imaging tool and is part of standard diagnostic work up in patients with suspected non-fulminant myocarditis (NFM) and fulminant myocarditis (FM). Its importance has been described in scientific statements on myocardial and pericardial diseases from the European Society of Cardiology (ESC) [1]. Echocardiography can provide a thorough evaluation of cardiac structural and functional abnormalities and is important in excluding other causes of chest pain or heart failure and differentiating FM from NFM. Moreover, echocardiography is not time-consuming and can be performed at bedside; thus, it is invaluable in monitoring disease course and guiding patient management, particularly in the case of FM. It can also provide prognostic information and is a useful modality during follow-up.

Conventional echocardiography may show a broad spectrum of features, however, it shows a lack of specific diagnostic value for both NFM and FM. In contrast, myocardial strain features using advanced echocardiography as speckle-tracking echocardiography (STE) and layer specific STE may be useful in the diagnosis of myocarditis as evidenced by recent studies, although more data is needed in the field. In this chapter, we will review the presentation of conventional echocardiography and myocardial strain features by STE in FM in comparison with NFM. We will also discuss the utility of echocardiography in diagnosis and prognosis and during follow up as well as protocols regarding the performance of echocardiography in FM.

11.2 Two-Dimensional Echocardiography

11.2.1 Left Ventricular (LV) Function

LV systolic dysfunction, either regional or global, could be present in acute NFM, however, normal LV function has been reported in some NFM patients [2]. In comparison, the reduction in LV systolic function is present in all patients with FM and is usually significantly greater in most patients with FM than in patients with NFM [3, 4]. The average initial left ventricular ejection

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fraction (LVEF) of FM in our study was approximately 30% [4], which is significantly lower than the normal healthy controls. In addition, the LV function in FM is with rapid dynamic changes during the course of FM, which is one of the most important characteristics of FM [4]. In some patients who presented initially with normal or relatively normal LVEF, cardiac function may decline sharply within hours. In contrast, the cardiac function in patients with FM who were treated appropriately and survived the acute phase may recover within days. At our center, the average hospitalization time was about 12 days, and the cardiac function in surviving FM patients often improved to approximately LVEF of 50% at around 6 days after admission [4]. The study by Ammirati et al. also indicated the greater improvement in LVEF during hospitalization period in FM than NFM [3]. Since echocardiography allows for serial scans, it is particularly useful in monitoring the dynamic changes of LV function during the course of FM.

LV systolic dysfunction in most patients with FM is usually global or diffusive, although regional LV dysfunction may be seen in some FM patients, which include even LV aneurysm [5]. In addition, global and regional dysfunction may affect each other during the course of FM. Regional dysfunction is caused by patchy distribution of inflammatory myocardial damages and is typically associated with non-coronary distribution [6]. However, wall motion abnormalities may follow coronary artery territories in some cases of FM, which need coronary angiography to differentiate from myocardial infarction in clinical practice, particularly in patients presenting with symptoms of acute chest pain suspicious of coronary ischemia.

11.2.2 Left Ventricular Dimension and Wall Thickness

In comparison to significantly reduced LVEF, the LV dimension is usually in normal range or increased slightly [3, 4]. In addition, the dimension remained unchanged during hospitalization period [4]. The average LV end diastolic dimension was approximately 4.5 cm in our study [4], which is within the normal range.

Increased LV wall thickness caused by myocardial interstitial edema may be detected by echocardiography. Although it was reported occasionally in NFM, it was more common with greater thickness in FM than NFM [2]. Asymmetrical hypertrophy with remarkably thickened LV septum had been reported in a patient with FM [2] and seen in our practice (Fig. 11.1), which may mimic hypertrophic cardiomyopathy (Fig. 11.2). Thickened LV wall is

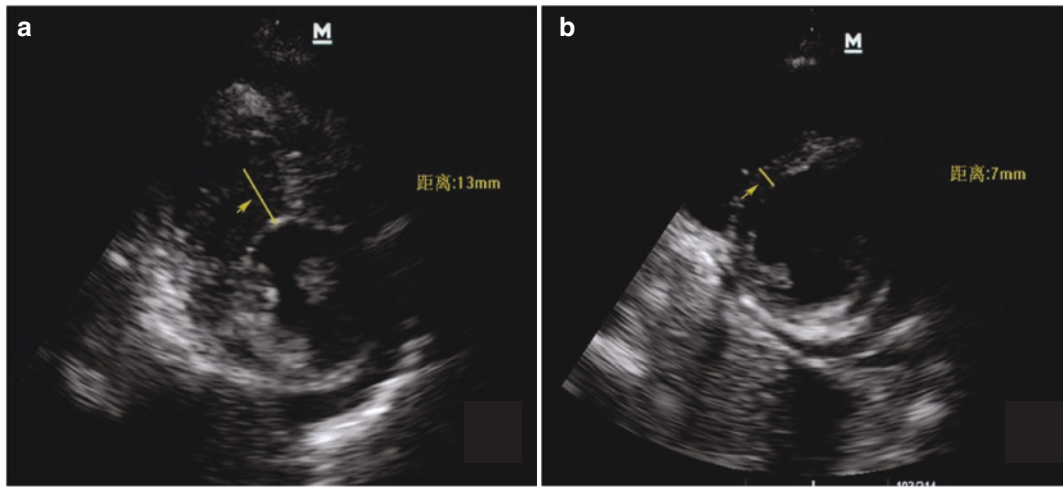

Fig. 11.1 Echocardiographic short axis views in a patient with FM. (**a**) Thickened interventricular septum during hospitalization (13 mm, yellow arrow); (**b**) Thickened septum normalized at 1 month follow-up (7 mm, yellow arrow)

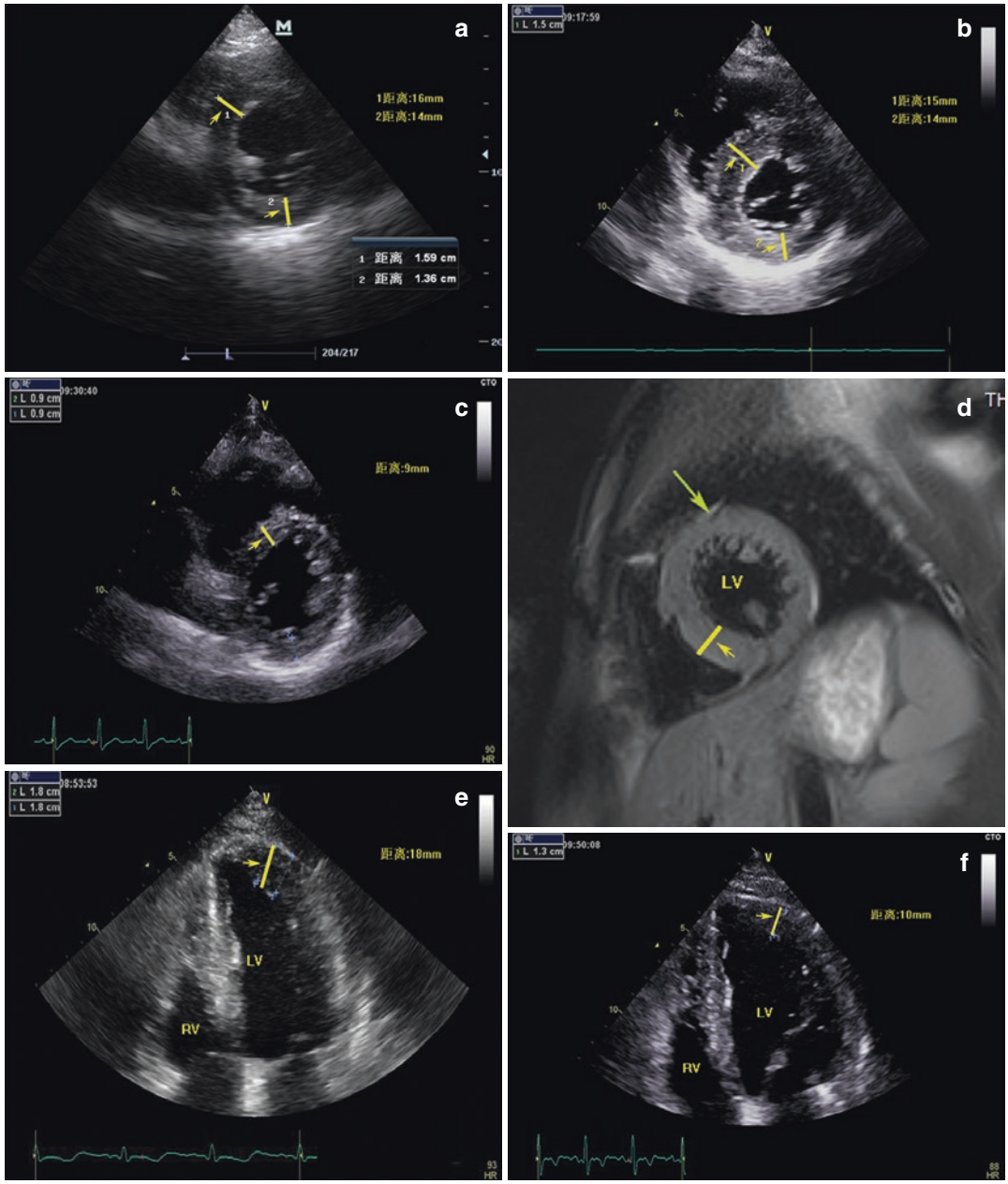

Fig. 11.2 Echocardiographic (**a**–**c**) and CMRI (**d**) short axis views in a patient with FM, and apical four chamber views in another patient with FM (**e** and **f**). (**a**) Thickened interventricular septum (16 mm) and posterior wall (14 mm) on admission; (**b**) Septal thickness was 15 mm and posterior wall thickness was 14 mm before discharge; (**c**) Septal and posterior wall thickness were 9 mm at 3 months follow-up; (**d**) CMRI short axis view showed thickened septum before discharge (15 mm); (**e**) significantly thickened LV apical wall (18 mm); (**f**) thickened LV apical wall decreased to 10 mm

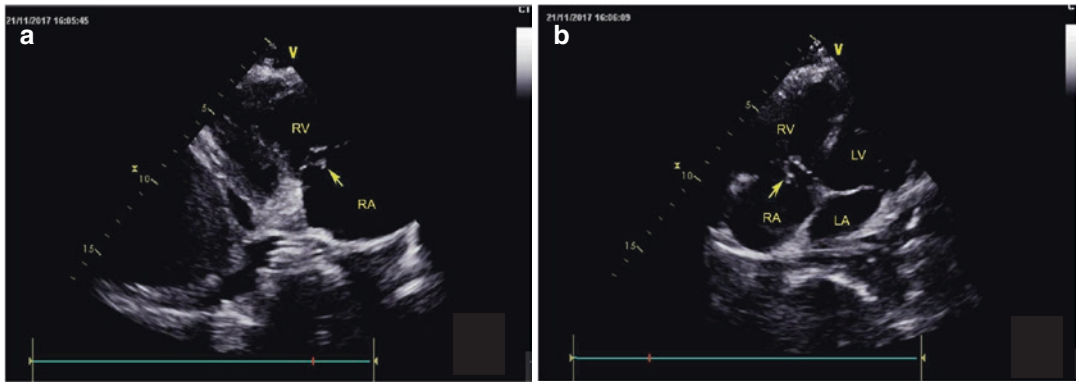

Fig. 11.3 Thrombus attached to tricuspid valve in a patient with FM. (**a**) echocardiographic right ventricular inlet view and (**b**) apical four chamber view show thrombus (yellow arrow) in RA and attached to tricuspid valve. *LV* left ventricle, *LA* left atrium, *RV* right ventricle, *RA* right atrium

transient and reversible during the course of FM and usually normalized before discharge in surviving patients [4]. The accuracy of echocardiography in detecting wall thickness is less than that of cardiac magnetic resonance image (CMRI) and echocardiography may not be able to detect a mildly thickened LV wall.

11.2.3 Right Ventricular (RV) Function

Assessment of right ventricular function is also recommended in myocarditis. An earlier study in biopsy-proven myocarditis reported that RV dysfunction was fairly common accounting for approximately 23% of their study patients [5]. RV dysfunction may be an independent predictor of poor outcome in myocarditis [7]. In a recent study in patients with COVID-19, parameters of RV dysfunction as RV fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE) and RV longitudinal strain (RVLS) were predictors of higher mortality in a median follow-up of 51 days [8]. However, RV dysfunction and its value in FM have not been well studied.

11.2.4 Pericardial Effusion and Intracardiac Thrombus

The presence of pericardial effusion may provide supportive evidence in diagnosing myocarditis. In comparison with NFM, patients with FM are more likely to have pericardial effusion, which usually disappear before discharge in surviving FM patients. Intra-cardiac thrombus in case of FM, particularly LV thrombus, has been reported occasionally, which may be associated with significantly reduced LV systolic function in FM [9–11]. RV thrombus is rarely seen. In our practice, we found a case with thrombus attached to tricuspid valve, which disappeared after anticoagulation treatment (Fig. 11.3). The presence of thrombus may be difficult to image by standard transthoracic echocardiography and contrast echocardiography should be performed in suspected cases as recommended by the guideline [12].

11.3 Speckle-Tracking Echocardiography (STE)

STE was introduced in the last decade for evaluating myocardial deformation changes. Myocardial strains by 2-dimensional STE (2-D STE) can determine LV global and regional function quantitatively and offer better sensitivity than conventional echocardiography in detecting subclinical cardiac dysfunction in coronary artery disease and diabetes [13, 14]. Accumulated evidences suggest that strain measurement has additive value to LVEF and aids risk prediction in case of different cardiovascular diseases [15]. Recent studies have proven that strains by 2-D STE were well correlated with edema detected

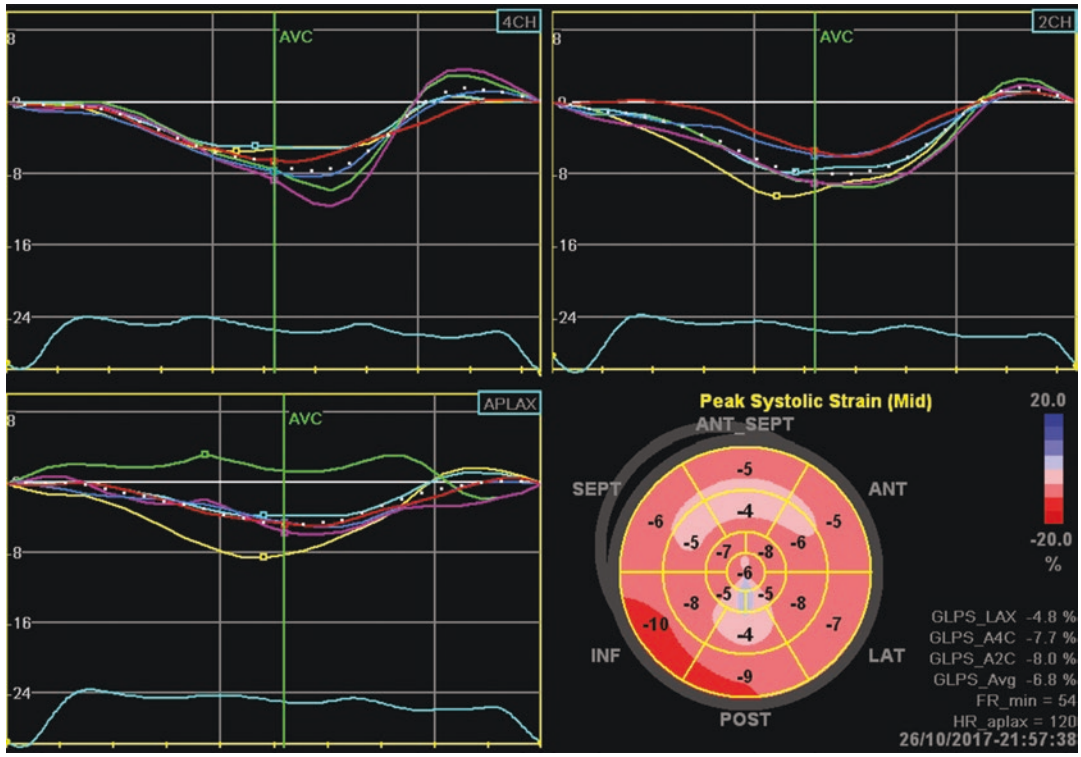

Fig. 11.4 Representative GLS images and a "bull's-eye" display in a patient with FM showed severely and diffusively reduced strains

by CMRI and cell infiltration in tissue specimens by EMB in acute NFM [16–18]. The strain imaging is able to provide incremental information about the degree of cardiac injury in myocarditis in comparison with LVEF [17, 19].

In FM, global longitudinal strain (GLS) is significantly lower than in NFM. The initial GLS at admission of FM patients in our study was approximately −8.45%, in comparison with −16.2% in acute myocarditis [4]. Significantly reduced GLS implies the severity of myocardial inflammatory injuries and supports the diagnosis of FM. Compared with visual wall motion abnormalities, diffused distribution of remarkably reduced strains was the typical presentation of myocardial deformation in FM (Fig. 11.4), reflecting the more severe and diffuse inflammatory injuries in FM [4]. Occasionally, regional distribution of reduced strains may be present, which is usually in non-coronary territories (Fig. 11.5a). In surviving patients, the GLS had rapid improvement at a median time of 6 days and increased to approximately -16.95% before discharge (Fig. 11.6) [4]. In our recent study, GLS by 2-D STE has been proven to be correlated with T1 relaxation time and extracellular volume (ECV) by CMRI in FM and is an emerging tool to monitor inflammatory injuries during the course of FM [20]. GLS analysis is also valuable in quantification of LV functional improvement at follow-up (Fig. 11.5b).

In addition, layer-specific strain analysis by STE may be of specific diagnostic value in NFM by proving the different strain patterns from myocardial infarction, predominantly reduction of strains in the sub-epicardium instead of subendocardium [21, 22]. However, more data is needed to confirm this. In comparison with NFM, the inflammatory injuries were usually transmural and the GLS reduction was equal through epicardium to endocardium in FM (Fig. 11.7) [4]. Severely and equally impaired GLS among different layers of myocardium is valuable in differentiating FM from NFM.

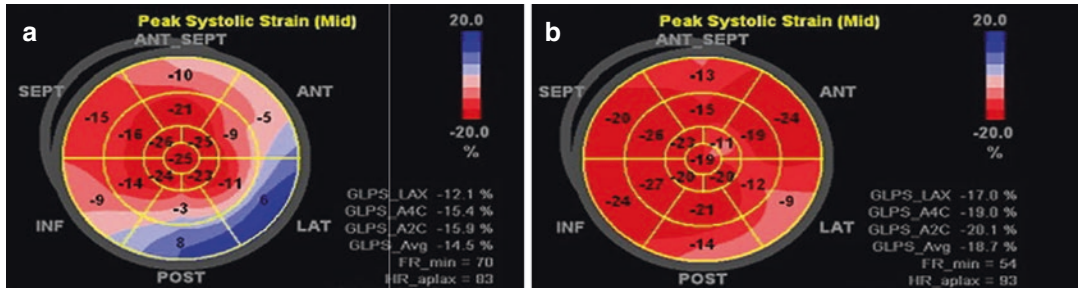

Fig. 11.5 Representative GLS images in "bull's-eye" displays in a patient with FM. (**a**) initial GLS image at admission showed reduction of strains preferentially involving anterior, lateral and posterior basal segments, which did not follow coronary distribution; (**b**) GLS image at 3 months follow-up in the same patient showed the great improvement of GLS

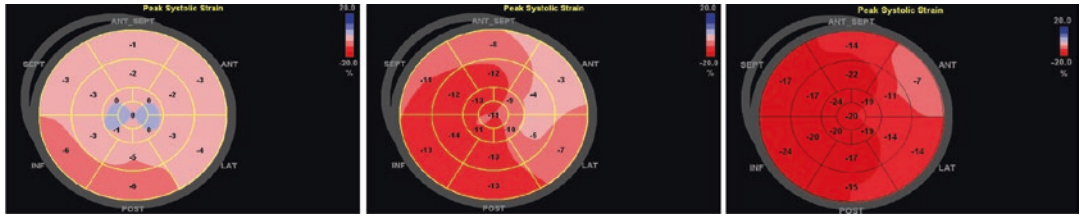

Fig. 11.6 Dynamic and rapid changes of GLS were shown in a patient with FM by serial 2-D STE analysis. The "bull's-eye" displays of GLS was extremely low at day 1 of admission (**a**), improved rapidly 5 days later after treatments (**b**) and recovered to near normal range at day 12, when was before discharge (**c**)

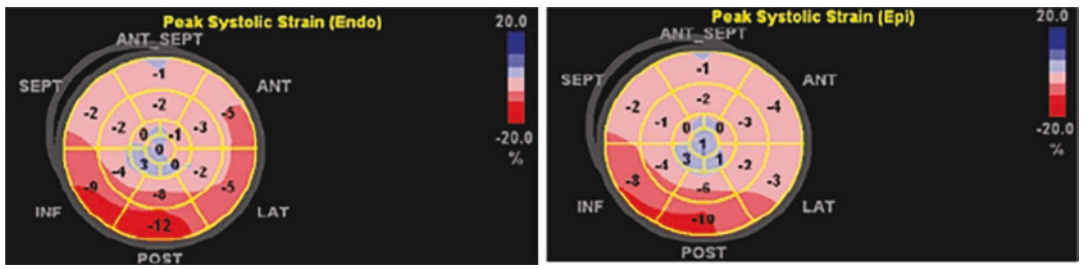

Fig. 11.7 The "bull's-eye" displays of layer-specific GLS in a patient with FM showed significantly reduced GLS in both sub-epicardium (**a**) and sub-endocardium (**b**)

11.4 Proposed Echocardiographic Scan Protocols

As discussed above, structural and functional assessment of both LV and RV are critical in FM. Strain analysis can provide additional information for evaluation of FM. At our center, in addition to conventional echocardiographic parameters, a complete protocol for echocardiographic scan and measurements in FM should focus on and include: (1) LV measurements as LVEF, LV end diastolic and systolic dimensions, wall thickness in septum and LV posterior wall; (2) RV measurements as RVFAC and TAPSE, and GLS of RV if possible; (3) Strain analysis, including mainly global and regional longitudinal strains of LV, and layer-specific strains of LV if possible; (4) in case of poor image windows or suspected intra-cardiac thrombus, contrast echocardiography is recommended. Moreover, due to

the rapid changes in cardiac function in FM, serial scans are warranted at our center at a frequency of at least one scan per day till the recovery of LV function to or near to normal range (50% of LVEF). In some case or in the super acute phase, two scans per day may be necessary. In addition, a scan before discharge is required in surviving patients.

11.5 Utility of Echocardiography in Treating FM with Extracorporeal Membrane Oxygenation (ECMO)

In patients with FM who present with cardiogenic shock and are refractory to medical therapy, temporary mechanical circulatory support (MCS) is fundamental in preventing multiple organ failure and allow a bridge to recovery. ECMO is one of the most commonly used MCS at many centers [23, 24]. In our center, approximately 25% of FM patients were treated using venous-arterial (V-A) ECMO. Echocardiographic scan is useful in aiding the treatment with ECMO.

Firstly, echocardiography is a useful tool at ECMO cannulation for precise placement of a venous cannula or verification of proper cannula position. At our center, we usually use bedside echocardiography for guiding cannula position (Fig. 11.8), particularly during difficult cannulations. Secondly, cardiac function monitored by echocardiography is helpful in deciding the time of weaning from V-A ECMO. Timing and strategy for weaning from ECMO is important for patients' survival but there is no clear guideline currently. Some patients die or have to reundergo ECMO after removal because of inadequate heart recovery. In an observational study in 129 V-A ECMO cases, the LVEF increased to 35% at weaning and a significant improvement in RV function was also observed in weaned patients [25]. Moreover, reduction of cardiac function at the beginning of ECMO treatment may be seen, mostly in the first 24 h after ECMO, due to hemodynamic influence or myocardial stunning caused by ECMO [23, 26]. This should be realized and distinguished from progression of disease itself. At our center, the FM patients with ECMO treatment were usually weaned from V-A ECMO when their LV function recovered to near 50%. However, more data is needed for proper timing and strategy for weaning from V-A ECMO in FM.

11.6 Prognostic Value of Echocardiographic Measurements in FM

Echocardiographic parameters may provide prognostic information in myocarditis. A study showed children with myocarditis who had reduced LVEF were at higher risk of mortality and thus more intensive therapies may be warranted [27]. In immune checkpoint inhibitor related myocarditis, lower GLS was strongly associated with major adverse cardiac events in patients with either a preserved or reduced EF [28]. In our unpublished data of 1 year follow-up study in FM patients, the GLS at discharge and the delta GLS (changes of GLS between discharge and admission) but not the GLS on

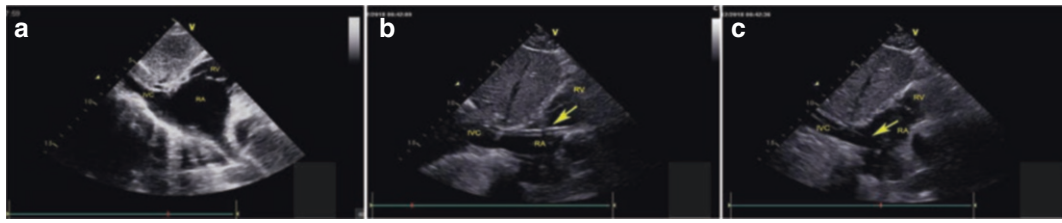

Fig. 11.8 Echocardiography aids for precise placement of a venous cannula at ECMO cannulation. (**a**) subxiphoid view showing inferior vena cava (IVC), right atrium (RA) and right ventricle (RV); (**b**) a venous cannula was placed through IVC to RA, but extended too far; (**c**) a venous cannula was positioned properly in RA

admission were associated with GLS improvement at 1 year. The data indicate that the initial lower GLS does not necessarily mean poor outcomes in FM patients. In contrast, the patients who have better recovery of LV function during hospitalization may have better long-term prognosis. RV function related parameters, including GLS of RV, RVFAC and TAPSE, may be valuable in predicting outcomes of myocarditis but are not well studied in FM.

11.7 Conclusions

FM is not an etiological diagnosis but rather a clinical syndrome with rapid disease progression and severe hemodynamic disorder. In the setting of FM, the value of echocardiography is not only in excluding other cardiovascular diseases and distinguishing it from NFM, but more importantly in monitoring the disease course and directing timely critical care. Echocardiography may also provide prognostic information and is an important tool in the follow-up of patients with FM.

Key Points

1. FM patients usually present with diffuse or global LV systolic dysfunction, with significantly lower LVEF than NFM patients. Regional wall motion abnormalities may be seen occasionally, where coronary angiography may be needed to exclude myocardial ischemia. Transiently thickened LV wall is more common in FM and LV dimension is often within normal range.
2. One of the most important characteristics of FM is the rapid and dynamic changes in LV systolic function. The cardiac function can decline steeply in the early phase and recover within a relatively short period with appropriate management.
3. 2-D STE may provide incremental information in diagnosis of FM and is of greater value in monitoring changes in myocardial injuries. Cardiac involvement is usually transmural in FM instead of predominant involvement of sub-epicardium in NFM.
4. Echocardiography is useful in guiding cannula position for V-A ECMO and helping in determining the timing of weaning from ECMO.
5. Due to the rapid changes in LV function, serial echocardiographic scans are recommended at a frequency of 1–2 scans per day during the acute stage of FM till recovery of LVEF to or near to 50%.
6. Echocardiography is an important initial imaging tool in FM but lacks specific diagnostic value. Combined with clinical presentation and elevated troponin level, it can aid in the diagnosis of FM in suspected patients. In addition, it also has great implications in guiding timely critical care, risk stratification, monitoring disease progression, and predicting prognosis.

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12 Cardiac Magnetic Resonance in Fulminant Myocarditis

Hong Wang

12.1 Introduction

The 1996 World Heart Federation/International Society and Federation of Cardiology (WHF/ISFC) task force defined myocarditis as an inflammatory disease of the myocardium that is diagnosed by established histological, immunological, and immunohistochemical criteria [1]. Given this definition, endomyocardial biopsy (EMB) is widely accepted as the gold standard for the diagnosis of myocarditis [1], and a definitive diagnosis of myocarditis can only be made by demonstration of inflammatory infiltrates in myocardial tissues via EMB. However, EMB has a relatively low diagnostic sensitivity [2, 3] and procedural risk, and is rarely performed in most medical centers. As a result, the diagnosis of myocarditis has been a clinical challenge for decades.

Over the past decades, the rapid advancement of cardiovascular magnetic resonance imaging (CMRI) has changed this paradigm. The hallmark is the introduction of the CMR Diagnostic Criteria (Lake Louise Criteria, LLC) for myocardial inflammation in 2009 [4]. Subsequently, scientific statements on myocarditis from the European Society of Cardiology and the American Heart Association clearly indicate the importance of CMRI in the diagnosis of myocarditis [5, 6]. In addition to evaluating the structural and functional abnormalities of the heart, the unique ability of multiparametric CMRI can also provide the pathophysiological characteristics of myocardial injury in myocarditis, including myocardial edema, hyperemia, capillary leak, and myocardial necrosis/fibrosis [7–9]. CMRI coupled with increased high-sensitivity troponin levels has provided a new noninvasive diagnostic work-up and has changed the management of suspected myocarditis. A CMRI-based diagnosis has been adopted more in the recently published series [10–12] than in the previous series, in which a biopsy-based diagnosis was usually used [13, 14].

Current studies and applications of CMRI are focused mainly on uncomplicated acute myocarditis (AM). Fulminant myocarditis (FM) can be considered AM, although with rapid onset, dramatic clinical course, and severe hemodynamic compromise, in which CMRI is usually not the initial diagnostic technique. Therefore, in this chapter, we will first describe the diagnostic and prognostic utility of CMR parameters in AM and then introduce the application of CMRI in FM, mainly based on our own studies and experiences.

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12.2 Utility of CMRI in Acute Myocarditis

The CMRI manifestations of myocardial inflammation and the diagnostic utility of the CMR parameters in myocarditis are described in detail as follows.

T2-Weighted Imaging (T2WI) T2WI has been proposed to detect myocardial edema, which appears as regional or global signal hyperintensity [15–17]. Edema is a typical marker of soft tissue inflammation, including myocardial inflammation. Damage to cardiomyocytes and the subsequent release of inflammatory factors lead to an increase in tissue-free water and protein content. The proton in free water has a long T2 effect in the magnetic field, and the increased free water content appears as an enhanced tissue signal on T2WI. Localized hyperintensity in T2WI represents focal myocardial edema and inflammatory lesions. An edema ratio, defined as the ratio of the signal intensity of the myocardial to adjacent skeletal muscle, is used to reflect the global T2 signal intensity and detect diffuse edema [4]. However, this ratio may yield false-negative results in the case of coexistence of myositis [18, 19]. The pooled weighted diagnostic sensitivity, specificity, and accuracy of T2WI for AM were 63%, 76%, and 68%, respectively [9]. Moreover, the T2WI scan performed within 2 weeks of symptom onset showed a higher incidence of abnormal signals [20, 21]. In addition to T2WI, novel CMRI techniques, such as quantitative T1 and T2 mapping, can also detect myocardial edema, which will be described below.

Early Gadolinium Enhancement (EGE) In addition to increased tissue-free water content, inflammation also leads to hyperemia and capillary leakage, which increases the retention of the contrast agent. T1-weighted CMR images acquired before and after the administration of an extracellular gadolinium-based contrast agent (GBCA) can be used to analyze the retention of the contrast agent. Retention can be quantified using the EGE ratio, defined as the ratio of the early myocardial signal intensity after GBCA injection to the signal intensity in a skeletal muscle reference region. A ratio of ≥4.0 is believed to be EGE positive and is consistent with inflammation. Alternatively, the retention of GBCA can be analyzed semi-quantitatively by calculating the increase in myocardial signal intensity after early injection of GBCA [4, 8, 9]. A value of more than 45% relative to that before injection is pathological and indicates the presence of inflammation. The pooled weighted diagnostic sensitivity, specificity, and accuracy of EGE for AM are 66%, 70%, and 67%, respectively [9].

Late Gadolinium Enhancement (LGE) If a myocardial injury caused by inflammation is severe enough, irreversible myocardial injury occurs, such as myocardial necrosis, fibrosis, and scarring, which can further increase GBCA accumulation and cause a hyperintense signal in the images acquired following a delay (usually 10 min) after contrast agent administration. Therefore, LGE has traditionally been considered to demonstrate irreversible injury and necrosis [4, 21–23]. However, studies have shown temporal changes in LGE content in AM and the histological correlation between LGE and active inflammation [24, 25]. LGE likely represents a reversible and irreversible injury in the acute phase of myocarditis but only an irreversible injury in the chronic phase. Overall, LGE is not specific for active or acute inflammation, and it alone cannot reliably differentiate acute from chronic myocardial injury [4, 8]. Of note, LGE had a higher signal-to-noise ratio, indicating myocardial necrosis and fibrosis. When the appropriate T1 time was selected, normal myocardial tissue showed a low signal, while the necrotic area had more contrast agent retention and showed a markedly enhanced signal. However, LGE imaging may not be sensitive to diffuse myocardial injury because it requires a normal myocardium as reference [26].

Additionally, the LGE distribution pattern is valuable in differentiating myocardial injury caused by inflammation from other etiologies, such as myocardial ischemia. In the case of myocarditis, the LGE pattern tends to be patchy and predominantly involves the sub-epicardium with a variable extension of the intramyocardial, in contrast to myocardial ischemic lesions that are mainly sub-endocardial and transmural, followed by coronary territories. The LGE "non-ischemic inflammatory injury" pattern shows high specificity and low sensitivity to diagnose

myocarditis [4, 27]. The distribution and content of LGE may also predict the outcomes of patients with AM, and patients with LGE in the interventricular septum have a poor prognosis [28].

12.3 Lake Louise Criteria (LCC)

The three CMRI techniques discussed above were combined to form the consensus criteria for CMR in myocardial inflammation, first published in 2009 as "Lake Lousie Criteria" [4]. The original criteria proposed three major diagnostic targets using three corresponding tissue characterization techniques: (1) myocardial edema detected by T2-weighted imaging (T2WI); (2) cardiac hyperemia and capillary leak evaluated by EGE; and (3) myocardial necrosis and fibrosis assessed by LGE. A high probability of AM was suggested if two of the three above criteria were positive by CMRI.

Earlier studies reported a diagnostic accuracy, sensitivity, and specificity of 78%, 67%, and 91%, respectively [4, 15], for the 2009 LCC. Since then, these criteria have been widely used both clinically and in studies of myocardial inflammatory diseases. A recently published review and meta-analysis showed a diagnostic accuracy, sensitivity, and specificity of 83%, 80%, and 87%, respectively [9], based on pooled data for the 2009 LCC. Overall, the original LCC has good diagnostic performance, and in the clinical setting of suspected myocardial inflammation, the diagnosis of AM can be considered if two out of the three criteria are positive.

12.4 Novel CMR Mapping Techniques

In recent years, advances in CMRI technology, especially the development of cardiac mapping techniques (T1 mapping, T2 mapping, and extracellular volume [ECV]), have allowed the direct quantification of the characteristics of myocardial tissue. A quantitative myocardial map can be produced pixel by pixel, providing regional and global T1 or T2 values of the tissue. ECV was calculated by T1 mapping changes before and after GBCA injection and then adjusted by the hematocrit value. Each tissue has a normal range of T1/T2 and ECV values for the specific methods and protocols used, and changes in these values can identify pathological conditions [29, 30]. CMR mapping techniques have the advantage of not relying on relative signal intensity changes, less observer variability, and less artifacts. Moreover, native T1 and T2 mappings have the advantage of not requiring contrast agent administration. Recently, cardiac mapping techniques have been increasingly applied in myocarditis, and multiple studies have described their excellent diagnostic accuracy in myocarditis [9, 29–31].

Cardiac mapping is affected not only by the internal characteristics of tissues but also by different MRI systems, mapping approaches, and methods. Standardized mapping methods and protocols, as well as normal ranges and diagnostic thresholds for specific pathological conditions, including myocarditis, remain being established [32, 33].

T2 Mapping T2 mapping allows direct measurement of water-induced myocardial relaxation time, and thus increased T2 relaxation time in the myocardium, reflecting increased tissue water content (edema) [34]. Recent data have shown that T2 mapping has higher diagnostic accuracy than traditional T2WI in detecting active inflammation. It may be particularly valuable for ruling out acute or active myocarditis and distinguishing active from healing inflammation [35, 36]. Therefore, in the absence of acute myocardial ischemia, an increase in T2 relaxation time is specific for and is an important marker of acute inflammation [36, 37].

Native T1 Mapping T1 relaxation time is highly sensitive to the increase in free water content in the myocardium caused by acute and chronic inflammation. Meanwhile, vascular dilation, congestion, and tissue space volume expansion caused by acute inflammation can also increase T1 relaxation time [38]. Compared with T2 mapping, T1 relaxation time is less specific for acute myocardial inflammation and edema and may not be useful to distinguish acute inflammation from chronic inflammation [18, 37, 38]. Overall, T1 is a sensitive index for diagnosing myocardial inflammation, and its negative predictive value for myocardial inflammation was

92% [9, 36]. It alone is not specific for the activity of the disease and may be best paired with T2-based imaging to detect AM.

Extracellular Volume (ECV) Mapping The quantification of ECV requires the administration of a contrast agent, and the percentage of ECV is then estimated using T1 maps acquired before and after GBCA administration. ECV expansion reflects increased extracellular tissue space in myocarditis compared with LGE; ECV can detect mild and diffuse edema and fibrosis, which may not be detected by LGE [29, 30]. Therefore, it can be used as an additional indicator to detect inflammatory lesions in myocarditis [30]. More data are needed to verify its diagnostic performance alone and in combination with other CMR mapping parameters.

12.5 Functional Abnormalities

Cardiac dysfunction results from myocardial inflammation and can occur as regional or global left ventricular dysfunction. In mild cases, the ejection fraction may be normal, even in the presence of elevated T2 or LGE. Wall motion abnormalities and ventricular systolic dysfunction may be caused by other conditions, such as ischemic heart disease. Therefore, functional abnormalities are neither sensitive nor specific to the diagnosis of myocarditis and can only be used as supporting evidence of myocarditis. However, in patients with suspected myocarditis, severe ventricular systolic dysfunction usually indicates more extensive myocardial involvement.

12.6 Pericardial Abnormalities

Myocarditis can involve the pericardium and vice versa. Of note, the presence of pericardial effusion alone cannot be used as a marker of active pericarditis, as it may only be a manifestation of heart failure coexisting with myocarditis. Active pericardial inflammation is likely in the presence of pericardial thickening in high-resolution fast spin-echo T1 images, pericardial high signal in T2WI and T1/T2 mapping, and abnormal pericardial LGE. Pericardial active inflammation can be used as supporting evidence of myocarditis [39].

12.7 Update to the LCC

With more data that prove the diagnostic performance of CMR mapping techniques, the original 2009 LLC was updated in 2018 by incorporating the novel cardiac mapping parameters discussed above (*Central Illustration* in Fig. 12.1) [8]. The

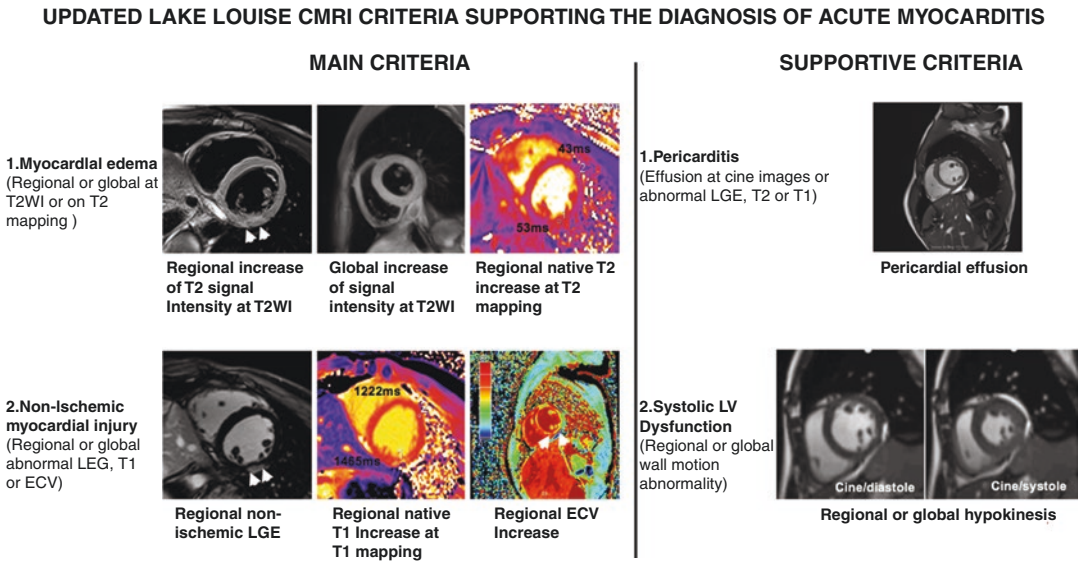

Fig. 12.1 Overview of the updated Lake Louise criteria

updated 2018 criteria proposed the following two categories of CMRI parameters to support myocardial inflammation: (1) T2-based markers of myocardial edema: T2 weighted imaging or T2 mapping; (2) T1-based markers of myocardial injury: delayed enhancement (LGE), T1 mapping, or ECV. In the revised criteria, EGE was removed and superseded by T1 quantification. The Consensus Group recommends that in patients with a high pretest clinical probability of AM, having both positive T1 and T2 markers will provide the strongest evidence of acute myocardial inflammation with high specificity; having only one of the two markers may still support a diagnosis of acute myocardial inflammation, albeit with less specificity [8]. The updated criteria also include functional and pericardial abnormalities as supporting evidence for the diagnosis of myocarditis.

The updated 2018 criteria represent a "two out of two" approach, and different combinations may have different diagnostic performances. The combination of T2 mapping and LGE produces very good diagnostic accuracy, according to two published studies [36, 37]. Combining T2-based CMR with native T1-mapping is attractive because it does not require contrast agent administration. Combining T2 mapping and ECV may increase sensitivity in cases of diffuse edema where LGE may be negative. A recent study compared the original LCC with the updated 2018 criteria in a cohort and demonstrated better diagnostic performance for the updated criteria, with a sensitivity of 87.5% and a specificity of 96.1% [40].

12.8 Utility of CMRI in FM

In contrast to acute non-FM, the utility of CMRI in FM has not been systematically studied, but individual reports and personal experiences of experts. A small study at our center has described the appearance of CMRI and the application of multiparametric CMR in detecting and monitoring myocardial inflammatory injury in FM [41]. Here, we describe the appearance of FM based on our experience and unpublished data. It is worth noting that CMRI is usually not the initial diagnostic modality for FM. In our center, the CMRI examination time in most patients was in the convalescence stage, usually a few days before discharge, and a very small percentage of patients were in the very early stage before deterioration of the disease. The median interval between patient admission and CMRI scan was 7 days, and the average hospitalization time at our center for FM was 12 days. Therefore, the characteristics of CMRI in FM summarized here may not represent the true characteristics of FM in the peak or mostly active stage of inflammatory myocardial injury, which may have the best diagnostic performance for FM.

Myocardial Edema Compared with acute non-FM, myocardial edema in FM is usually diffuse and presents as a diffusive or global enhanced signal on T2WI (Fig. 12.2a). Some patients with FM may also present with patchy areas of edema, which are typically in a non-coronary distribution as non-complicated AM. Due to the lack of

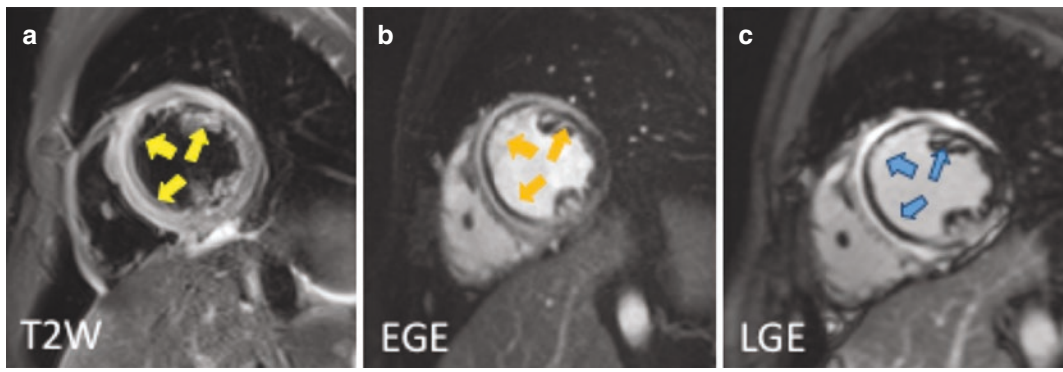

Fig. 12.2 CMRI in a 19-year-old male with a clinical diagnosis of FM. On T2WI, there was global enhanced signal in the left ventricular myocardium (**a**, yellow arrowheads), significant EGE (**b**, orange arrowheads) and LGE (**c**, blue arrowheads) signals in the corresponding segments, predominant involving the mid-wall and subepicardium myocardium, and involving the left ventricular septum

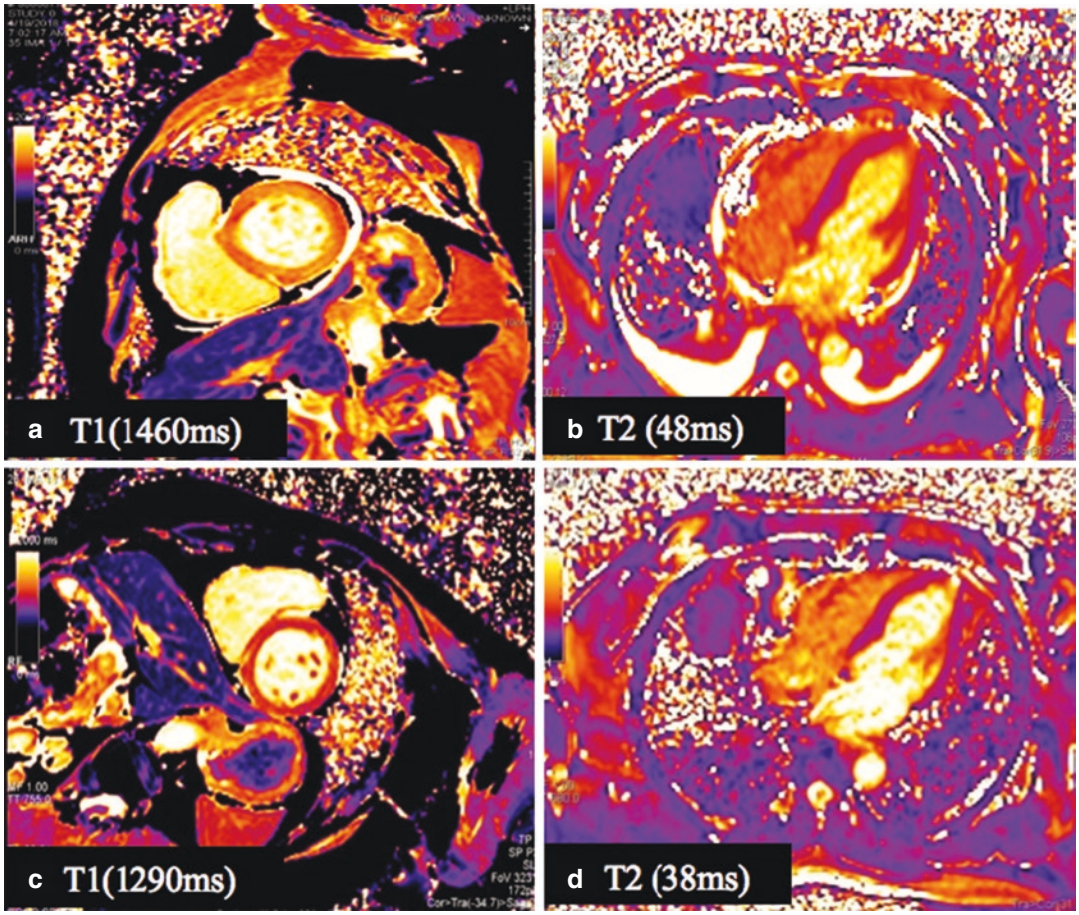

Fig. 12.3 T1 and T2 mapping in the same patient as in the Fig. 12.1. (**a**) and (**b**) showed significantly increased T1 (1460 ms) and T2 relaxation time (48 ms); (**c**) and (**d**) showed decreased T1 (1290 ms) and T2 relaxation time (38 ms) to the level of about normal range in the repeated CMRI at 3-month follow-up visit. Normal references of T1 and T2 relaxation time are about 1240 and 40 ms in our center

normal myocardium as a reference for diffusive edema, T2WI is likely negative and quantitative T1 and T2 mapping and ECV are superior to T2WI in the case of FM. Patients with FM had significantly higher T1 and T2 relaxation times than normal controls (Fig. 12.3a, b), indicating a wider involvement of the myocardium and more severe inflammatory injuries. In the healing stage of FM, T1 and T2 relaxation times decreased significantly but were still higher than normal controls (Fig. 12.3c, d). Therefore, T1 and T2 mappings are excellent tools to discriminate FM from healed myocarditis and are useful in monitoring changes in inflammatory myocardial injury [41].

Hyperemia and Capillary Leakage EGE, assessed in T1-weighted CMR images before and shortly after GBCA administration, also appear as diffusive or global hyperintensities (Fig. 12.2b).

Myocardial Necrosis and Fibrosis LGE are also diffusive in most patients with FM. The spatial extent of LGE is more extensive in patients with a regional LGE appearance. The subepicardium and mid-myocardium are predominantly involved, but some patients with FM had transmural involvement (Fig. 12.2c). It remains unclear whether patients with transmural LGE have a poor prognosis. Our unpublished data

showed that LGE in most patients with FM predominantly involved the sub-epicardium and mid-myocardium, while 34% of them had transmural LGE. Meanwhile, LGE in the interventricular septum was observed in 93% of cases, followed by the inferior wall of the left ventricle; 38% of cases presented with diffuse LGE, while others presented with linear or patchy LGE. The LGE appearance in FM demonstrated that patients with FM had more extensive and severe myocardial injury than those with non-fulminant AM, which is consistent with the more severe clinical manifestations of patients with FM. However, further studies are warranted to prove whether the extent and location of LGE can predict the outcomes of FM.

Cardiac Structural and Functional Abnormalities Compared with non-fulminant AM, all patients with FM had a variable reduction in left ventricular systolic function (Fig. 12.4a). Our unpublished data showed that the average left ventricular ejection fraction was 47.8% in patients with FM, and it is worth noting that the CMRI scans in most patients were performed in the convalescence stage at our center. In addition, patients with FM usually had a thicker interventricular septum than normal controls, with an average thickness of 10.6 mm (Fig. 12.4a, b). However, the thickened septum returned to the normal range during follow-up (Fig. 12.4c, d). A previous study using echocardiography also showed a thicker interventricular

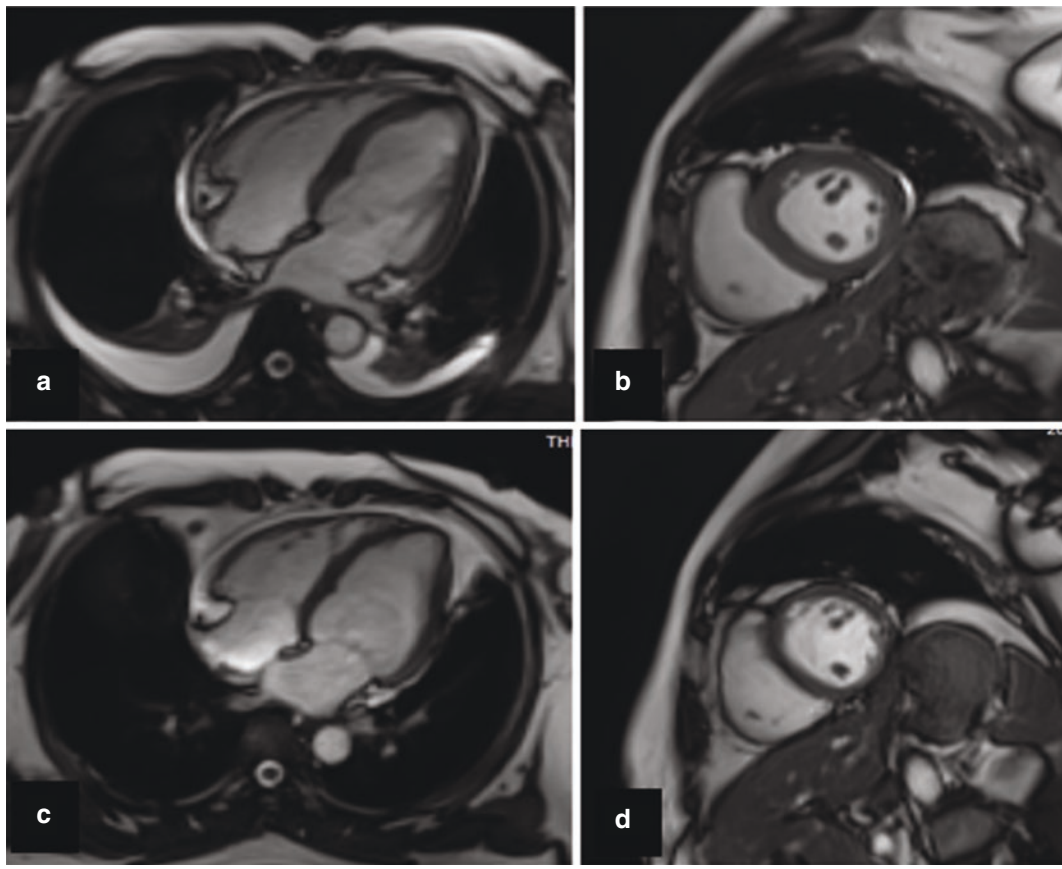

Fig. 12.4 Structural and functional abnormalities showed by CMRI in a 55-year-old woman with clinical diagnosis of FM. The four-chamber and short-axis views were shown. (**a** and **b**) were initial CMRI during hospitalization, and (**c** and **d**) were repeated CMRI at 3 months follow-up. The patients had reduced LVEF (47%) that recovered to 56% at 3 months follow-up. The interventricular septum was thickened at a wall thickness of 1.2 cm initially (**a** and **b**) and decreased to normal (0.9 cm) at following-up (**c** and **d**). In addition, pericardial and bilateral pleural effusion were present initially (**a** and **b**) and disappeared at the follow-up (**c** and **d**)

septum in AM than in non-FM [42]. Overall, compared with acute non-FM, patients with FM have a greater reduction in left ventricular systolic function and greater thickness in the interventricular septum. Furthermore, patients with FM are more likely to have pericardial effusion and pericardial inflammation. In our unpublished data, 85% of patients with FM had pericardial effusion (Fig. 12.3a, b), which usually disappeared during the healing stage (Fig. 12.4c, d).

12.9 Prognostic Value of CMRI in Myocarditis

CMRI is not only used as an excellent diagnostic tool, but it can also provide prognostic information for patients with myocarditis. However, studies on CMRI measurements as prognostic indicators of myocarditis are also mainly in nonfulminant AM, and the prognostic role of CMRI in FM is less investigated. In uncomplicated AM, the presence and extent of LGE may be a powerful predictor of cardiac events, and LGE located in the septum is considered to have the worst prognosis [11, 25, 43]. Another study involving 670 patients with suspected myocarditis with a median follow-up period of 4.7 years showed that septal and midwall LGE had the strongest associations with major adverse cardiovascular events (MACE) and LGE extent (per 10% increase) corresponding to a 79% increase in the risk of MACE [44]. In contrast, a normal CMR corresponded to a low annual MACE and death rate [44]. In addition to LEG, T1 and T2 mappings provide excellent performance to differentiate acute from healed myocarditis, and abnormal T2 mapping correlated with adverse outcomes [45, 46]. ECV may also have incremental value in the risk stratification of patients with suspected myocarditis [47]. A CMRI is suggested to be repeated in the follow-up in athletes with myocarditis before restarting active training [48], and the absence of edema on CMRI may be an indicator of physical activity reintroduction, as suggested by Ammirati et al. [7].

12.10 Limitations of CMRI in FM

CMRI scans take a long time to complete and cannot be performed at the bedside. Patients with FM are often hemodynamically unstable or with severe heart failure on admission. They are often treated with mechanical assistance devices in the acute stage, making it unlikely to perform CMRI scans in FM. Therefore, CMRI is not usually the initial diagnostic tool for FM. In our study, most CMRI examinations were performed in the convalescent period before discharge and therefore cannot represent true myocardial injury in the acute phase of FM. Therefore, the early clinical diagnostic value of CMRI examinations for patients with FM may be limited. For the same reason, CMRI cannot be repeated frequently and is unsuitable for dynamic monitoring of disease changes in the acute stage of bedside echocardiography. Furthermore, CMRI cannot identify the histological type of myocarditis, which has prognostic and therapeutic implications in FM [49]. In the case of FM, EMB is still recommended to characterize the histological type of FM, thus guiding optimal medical treatment [5].

12.11 Conclusion

In conclusion, CMRI can be used to "image" myocardial histological characteristics, including edema, hyperemia/capillary leakage, myocardial necrosis, and subsequent fibrosis, which means that CMRI can provide pathophysiological information on myocardial injury in myocarditis and thereafter has been a noninvasive diagnostic tool in myocarditis. New CMRI techniques, such as T1 and T2 mapping, have the advantage of quantitatively evaluating features of myocardial tissue and can provide incremental evidence of inflammatory activity. Currently, CMRI has been widely used in clinical practice as a substitute "gold standard" for EMB in the diagnosis of myocarditis. CMRI can also be used in the differential diagnosis of myocarditis and has a certain value in predicting the prognosis of the

disease. Combined with elevated myocardial injury markers, such as troponin and other suspicious clinical manifestations, CMRI presentation in accordance with the diagnostic criteria of myocardial inflammation, a clinical diagnosis of myocarditis can be made.

Key Points

1. Evidence of active myocardial inflammation by CMRI: First, T2 imaging suggests myocardial edema, including enhanced regional myocardial signal in T2WI, ratio of myocardial signal to adjacent skeletal muscle signal ≥2.0, or increased T2 relaxation time suggested by quantitative T2 mapping; Second, T1 imaging suggests myocardial injury, including increased LGE, T1 relaxation time, and ECV, indicating myocardial necrosis and fibrosis, myocardial hyperemia or capillary leakage, and intracellular and extracellular edema.
2. Meeting two of the above criteria has the highest specific diagnostic value for AM; meeting one of the two criteria supports the diagnosis of AM in certain clinical settings.
3. Other CMRI findings, including abnormal left ventricular function, pericardial effusion, pericardial thickening, as well as pericardial hyperintensity in T2WI, increased pericardial T1/T2 relaxation time, and abnormal pericardial LGE, may be supporting evidence of the presence of myocarditis.
4. The characteristic manifestations of AM on CMRI can provide diagnostic evidence of myocardial inflammation and allow the diagnosis of myocarditis in patients with clinically suspected FM, and help distinguish FM from myocardial infarction.
5. Although CMRI is the imaging gold standard and has a higher specificity for the diagnosis of AM, it is of limited value in early diagnosis and monitoring the dynamic changes of myocardial injury in the case of FM due to the intrinsic requirements to perform CMRI scans and the unstable status of patients with FM.

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13 Diagnosis and Differential Diagnosis of Fulminant Myocarditis

Weijian Hang and Dao Wen Wang

Fulminant myocarditis can occur in patients without a specific age preference. According to literature reports, patients aged between 2 and 82 years were reported to suffer from fulminant myocarditis [1, 2], with even cases of infants being reported. However, most patients with fulminant myocarditis are usually previously healthy young adults.

Fulminant myocarditis is the most severe and specific type of myocarditis. It is a cardiac inflammatory disease with rapid onset of severe hemodynamic disturbance in <2 weeks, usually 3–5 days. Fulminant myocarditis is characterized by a quick onset and extremely rapid progress, which can cause hemodynamic abnormalities, including pump failure, circulation failure, and refractory arrhythmia in patients in a short time, with complications such as respiratory failure or liver and kidney failure [3]. Fulminant myocarditis patients usually show an extremely high mortality rate in the early phase, but can have a good prognosis if the patient receives proper treatment [3–6].

Fulminant myocarditis is usually caused by viruses and shows little difference from common viral myocarditis in terms of histology and pathology. Therefore, it is a clinical diagnosis. It is considered that fulminant myocarditis can be diagnosed when a myocarditis patient shows sudden onset and rapid progression, and rapidly falls into refractory heart failure with hypotension and cardiac shock, and large doses of positive inotropic or vasoactive drugs and mechanical circulation support devices are needed to maintain blood pressure.

13.1 Clinical Diagnosis of Fulminant Myocarditis

1. Prodromal symptoms of fulminant myocarditis

   The etiology of fulminant myocarditis is complex and not well understood. Infectious factors, non-infectious factors, and toxic factors are thought to contribute to the development of fulminant myocarditis. Pathogenic infection, especially viral, is the predominant etiology of fulminant myocarditis. It can assist in the diagnosis of fulminant myocarditis and explain the underlying pathogenesis.

   Attention should be paid to the likelihood of myocarditis or fulminant myocarditis when patients with common cold-like symptoms, such as fatigue, loss of appetite, and breathlessness, do not show any improvement after receiving treatments against the common cold, and even show progression of such symptoms [7].

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Symptoms of non-viral infection and toxicity can be referred to Chap. 5.

2. Obvious hemodynamic disturbances (hypotension, shock, or decreased pulse pressure), which require vasoactive agents or mechanical circulation support devices.
3. Obvious elevation of cardiac injury markers (cTnT, cTnI, or CK-MB) and an obvious increase in BNP or NT-pro-BNP.
4. Significantly decreased ejection fraction, massive or left ventricular hypokinetic state. These changes can occur in a short time, complicated by significant hypertrophy caused by edema.
5. Massive epicardium or medium edema confirmed by cardiac magnetic resonance (CMR).

According to our experience, a clinical diagnosis of fulminant myocarditis can be made if the patient satisfies rule 1 plus any one or more of the rules from 2 to 5 above. The following auxiliary examinations can help in diagnosis, if available: first, cardiac injury markers, such as cTnT, cTnI, CK-MB, and cardiac function markers such as BNP or NT-pro-BNP. Second, heart function assessment using echocardiography. Third, the intensive outer and middle layer of myocardium edema confirmed by CMR.

No obvious changes in heart shape can be found on physical examination in most patients with fulminant myocarditis, but several can show cardiomegaly. However, blunt heart sounds, third heart sounds, or gallop rhythms may be heard. ECG typically shows abnormal changes, including low voltage QRS waves, prolonged QRS wavelengths, low or dismissed T waves, suppressed ST segment, or multiple leads ST segment enhancement, which mimic the ECG manifestation of acute myocardial infarction. In addition, elevation of cTnI, cTnT, and BNP or NT-pro-BNP, and decrease in ejection fraction, which indicates hypokinesis of the left ventricle can also be observed. Under these circumstances, acute myocardial infarction requires urgent exclusion, which can be immediately achieved by coronary artery angiography. Thus, clinical diagnosis of fulminant myocarditis is easy to make if the physician has thought of this possibility. Table 13.1 shows suggestions for auxiliary examinations.

Table 13.1 Suggestions regarding auxiliary examinations in case of suspected myocarditis or fulminant myocarditis [4]

Auxiliary examinations	Suggestions
Laboratory examinations	Measurement of cardiac troponins is useful for detection of myocyte injury for the diagnosis of fulminant myocarditis, and for risk or prognostic evaluation
	Plasma NP level (BNP, or NT-proBNP) should be measured in all patients with acute dyspnea and suspected fulminant myocarditis to help in the differentiation from non-cardiac causes
	The following laboratory assessments of the blood should be performed: BUN (or urea), creatinine, electrolytes (sodium, potassium), glucose, complete blood count, liver function tests at admission and every 1–2 days, TSH, ESR or CRP
	Test for autoantibody to myocardium can be considered when available
ECG	A 12- or 18-lead ECG should be used to identify the myocardial injury and should be monitored every 1–2 days
Chest X ray/CT	Chest X-ray examination should be used to assess signs of pulmonary congestion and identify other cardiac or non-cardiac diseases that may cause or contribute to the patient's symptoms; Chest CT can be performed when the status is stable
Echocardiogram	Immediate echocardiography should be considered in all patients suspected of fulminant myocarditis to evaluate cardiac function
	Transthoracic echocardiogram should be repeated during hospitalization if there is any worsening of hemodynamics
Coronary arteriography	Immediate coronary arteriography should be performed to differentiate myocarditis from acute infarction when patients have changes in ECG ST segment, especially in old patients

Table 13.1 (continued)

Auxiliary examinations	Suggestions
Invasive hemodynamic monitoring	PICCO or invasive hemodynamic evaluation with a pulmonary artery catheter should be done to evaluate state of illness and judge effects of treatments
Cardiac magnetic resonance/CMR	Transthoracic echocardiogram should be repeated during hospitalization if there is any worsening of hemodynamics.
	It can provide evidences in a noninvasive way, and is possible to substitute percutaneous endomyocardial biopsy.
Percutaneous endomyocardial biopsy	It can be considered when patients are clinically suspected of fulminant myocarditis
	It is still considered as a "gold standard" of diagnosis of myocarditis
	It should be performed when patients are clinically suspected of specific type of myocarditis such as giant cell myocarditis to guide clinical treatment
Detection of pathogen	Tests of serum special antibodies can help early diagnosis Viral gene detection can be done to help identify pathogen if available

13.2 Pathological Classification of Fulminant Myocarditis

Pathological diagnosis is usually considered the "gold standard" in the diagnosis of fulminant myocarditis. If pathological samples, including endomyocardial biopsy (EMB) samples, can be acquired in time for subsequent pathological analysis, it will greatly help in the treatment of fulminant myocarditis.

Characteristics of different pathological classifications of fulminant myocarditis:

1. Lymphocytic fulminant myocarditis

   In China, most cases of fulminant myocarditis are categorized as lymphocytic fulminant myocarditis according to pathological analysis, which is quite different from those in America. Recently, Professor Zhou Yiwu from the forensic medicine department of HUST conducted an analysis of 50 samples from postmortem samples of patients who died from clinically diagnosed or suspected fulminant myocarditis and revealed that all the samples showed massive lymphocytic infiltration and were diagnosed as lymphocytic fulminant myocarditis. EMB was also performed in six patients diagnosed with fulminant myocarditis at our center, and 100% (6/6) of these samples were confirmed to have lymphocytic fulminant myocarditis. These six patients showed rapid onset of disease manifestation and were transmitted to our department within 3–5 days, and four out of six patients showed prodromal syndromes such as infection, fatigue, and loss of appetite.
2. Giant-cell fulminant myocarditis

   This pathological classification shows higher frequency in case reports from Western countries, especially USA. Giant-cell fulminant myocarditis has been reported in patients with no age preference [8]; however, this is still rare. Professor Cooper from the Cardiology Department of the Mayo Clinic reported that after pathological analysis of 36 cardiac tissue samples obtained from postmortem examinations or from heart failure center patients undergoing EMB, cardiac assistance device implantation, or heart transplantation, it took an average of 21 months to find one case of giant-cell myocarditis, and it was even more rarer to find a fulminant manifestation [9]. Immune organ diseases, such as thymoma, lymphoma, or thymic and autoimmune diseases including SLE, Crohn's disease, and ulcerative colitis, have been reported to be closely related to giant-cell myocarditis [8]. It usually shows relatively slow progress and takes about 1 month from prodromal symptom onset to obvious clinical manifestations, and new-onset heart failure is more frequently reported. It is uncommon to see

fulminant manifestation, although several case reports can be found [10–13].

3. Eosinophilic fulminant myocarditis

   It is quite rare to see eosinophilic myocarditis, let alone eosinophilic fulminant myocarditis; however, it is quite dangerous and shows rapid progress. The common reason for eosinophilic fulminant myocarditis is drug hypersensitivity [14, 15] or food allergies. Idiopathic hypereosinophilia, parasitic infection [16], vaccination, and autoimmune diseases have all been reported to trigger eosinophilic fulminant myocarditis as well. Food or drug allergies show higher potency to trigger fulminant myocarditis [17]; for example, it was reported that eosinophilic fulminant myocarditis rapidly took place after penicillin injection [15]. Eosinophilic fulminant myocarditis shows extremely rapid progress and can occur in only 1–2 h after drug treatment, and patients usually die from circulatory failure. Blood routine usually shows an elevation of the eosinophil count. The treatment regimen for eosinophilic fulminant myocarditis is similar to other kinds of fulminant myocarditis, but it requires more rapid decision and treatment that is more prompt; otherwise, the patient may not survive [18].

4. Cancer treatment related fulminant myocarditis.

   First, it should be confirmed that cancer treatment-related fulminant myocarditis is not a pathological classification of fulminant myocarditis, which includes two categories. The first category is cardiotoxicity caused by chemotherapy during cancer treatment. It is rather common and under certain circumstances, severe cardiac injury can lead to cardiogenic shock and occurrence of fulminant myocarditis. The second category includes checkpoint inhibitors (CTLA-4, PD-1, or PD-L1 inhibitor) that trigger fulminant myocarditis. Recently, with the application of checkpoint inhibitors in the clinical treatment of several types of cancers, the prevalence rate of checkpoint inhibitor-induced fulminant myocarditis is increasing. It is estimated that 1% of checkpoint inhibitor treatment can be complicated by fulminant myocarditis, and it may increase to 2% if combined with cardiotoxicity chemotherapy treatments [19]. The exact pathogenesis is not yet fully understood, and it is believed related to the disturbance of immune homeostasis. The application of checkpoint inhibitors may suppress peripheral immune tolerance towards the heart and, therefore, activate intrinsic cytotoxic T cells to attack the heart. Another explanation for this phenomenon is that several kinds of cancer antigens show similarities with cardiac antigens, which attract cancer-targeting T cells infiltrating into cardiac tissue and lead to cardiotoxicity [20]. Pathological analysis of checkpoint inhibitor-induced fulminant myocarditis revealed massive lymphocyte infiltration in the myocardium, and immunohistochemical staining showed that they were predominantly CD3+CD4+ or CD3+CD8+ T cells, which indicates the activation of immune response toward cardiac tissue [20, 21].

   Although the prevalence rate of checkpoint inhibitor-induced fulminant myocarditis is much lower than that of other side effects of checkpoint inhibitors, it is quite concerning that the mortality rate is extremely high and some reports indicate even higher mortality rates compared with other kinds of fulminant myocarditis. According to a clinical registry, the mortality rate of checkpoint inhibitor-induced fulminant myocarditis is 46%, and it can increase to 76% in long-term follow-up [19, 21]. However, this terrible result may lead to several doubts, such as lack of knowledge and insufficient treatment, which may greatly hinder clinical treatment.

   In addition, several toxic natural medicines, such as monkshood and snake gall bladder, can also trigger fulminant myocarditis [22, 23]. Direct cardiac toxicity may contribute more to the development of fulminant myocarditis, complicated by immune cell infiltration. Chronic drug toxicity can lead to dilated cardiomyopathy (DCM).

However, it is not recommended to excessively depend on pathological examination to delay treatment of fulminant myocarditis for several reasons: First, most patients with fulminant myocarditis are in quite severe condition and need emergency treatment, and performing EMB is not appropriate in such a condition. Second, it takes several days from getting EMB samples to final pathological diagnosis owing to sample preparation and examination; however, patients cannot survive this period if not treated immediately. Third, the pathological injury of fulminant myocarditis is not equally distributed within the heart, but is more concentrated in the myocardium beyond the epicardium. In other words, endomyocardial biopsy may not have access to real pathological injuries and thus may mislead clinical diagnosis. Fourth, although there are mainly three different types of pathological classification of fulminant myocarditis, the majority of infiltrated immune cells are lymphocytes. Even in giant-cell or eosinophilic fulminant myocarditis, these two types of cells are rather less compared to massive infiltration lymphocytes. Hence, even with an accurate pathological diagnosis, little guidance can be provided regarding the clinical treatment decisions. However, several studies have indicated that pathological diagnosis can provide information about long-term prognosis; for example, giant-cell fulminant myocarditis shows worst prognosis, but needs further confirmation. In addition, eosinophilic fulminant myocarditis showed specific clinical characteristics that can be used for differential diagnosis. Therefore, EMB is still an important tool for the treatment and diagnosis of fulminant myocarditis. Multiple aspects of research on fulminant myocarditis should be carried out to gain more knowledge about it, while EMB still being an important method. CMR is useful for diagnosis and confirmation of fulminant myocarditis, but it is not possible to perform CMR in the acute phase due to the severity of the disease. Instead, when the situation of the patient improves, CMR can be considered to obtain more information about the function and morphology of the heart. In conclusion, it is vital for clinical treatment initiation to make diagnosis in time [11, 24].

13.3 Differential Diagnosis of Fulminant Myocarditis

Fulminant myocarditis should be differentiated from several diseases. Although epidemic data indicate higher likelihood of healthy young individuals and children to get fulminant myocarditis, it can indeed attack individuals of any age. What makes situation worse is that the lack of specific characteristics of fulminant myocarditis and multiple organ complications further impede accurate diagnosis [4, 25]. However, the rapid progress and severe condition of fulminant myocarditis patients calls for accurate diagnosis as soon as possible. In fact, if physicians consider the possibility of fulminant myocarditis, it can be quickly diagnosed using several differential diagnoses and auxiliary tests [4].

1. Coronary artery disease and myocardium infarction

   On the one hand, fulminant myocarditis and coronary artery disease show similar symptoms, including significant T-wave and ST-segment changes, which are lead-specific or extensive lead changes, and elevation of myocardial injury markers such as BNP and NT-pro-BNP. On the other hand, the treatment regimen and prognosis of these two diseases are quite different; therefore, it is important to make wise and quick decisions. Apart from the above-mentioned history record, physical examination, and laboratory tests, echocardiography can also help in making the diagnosis, as echocardiography in fulminant myocarditis cases usually shows massive hypokinesis and myocardial edema. Emergency coronary angiography should be performed to rule out myocardial infarction. If a patient is well prepared and coronary

angiography is conducted with less contrast reagent as quickly as possible, the risk of performing angiography can be minimized. In our center, over 100 fulminant myocarditis patients first underwent coronary angiography, and only two of them had ventricular fibrillation onset and were successfully defibrillated. No deaths were caused by emergent angiography [25].

2. Viral pneumonia

   Severe viral pneumonia such as COVID-19 pandemic from the winter of 2019 to spring of 2020 can not only lead to heart infarction but also different degrees of cardiac injury, with incidence rate reported to be 20% or even higher [26]. The mechanisms underlying viral pneumonia-induced cardiac injury include several aspects [27, 28]. First, direct invasion of the virus into the myocardium can lead to an immune response and further damage to the myocardium. Massive lymphocyte infiltration can be seen in cardiac tissue, and cardiac injury markers, such as cTnI, BNP, and NT-pro-BNP, can be elevated. If the injury is too severe resulting in left ventricular dysfunction and induced ejection fraction, circulation homeostasis may not be able to sustain, and finally normal circulation will collapse and lead to fulminant myocarditis. However, the incidence rate is <1%. Second, toxic effects of virus can directly injury myocardium. A cytokine storm can be triggered in severe pneumonia similar to fulminant myocarditis. Cytokine storms not only injure the lungs, but also inhibit myocardial contraction ability and eventually lead to ventricular dilation due to elevated proinflammatory cytokines during the cytokine storm. NT-pro-BNP and cTnI levels can be slightly elevated on laboratory tests. Third, persistent hypoxia can impede myocardial viability and cause elevation of NT-proBNP levels, which further deteriorates heart function. However, if oxygen saturation is rectified by appropriate treatment, such as VV-ECMO, abnormalities in heart function can be prevented. What needs further attention is that if severe pneumonia is complicated by myocarditis or heart injury, the risk of death will be significantly elevated. Hence, special attention should be paid to prevent cardiac injury in advance, observe and treat any abnormality in time, and reduce the risk.

3. Septic myocarditis

   Severe bacterial infection can cause sepsis, which is marked by dramatic elevation of bacterial toxicity, such as LPS, as well as proinflammatory cytokines. Cardiac injury can be caused by sepsis and toxic shock, and can increase the severity of the condition. Massive immune cell infiltration into the myocardium can also be observed in sepsis; hence, the immune response participates in the development of septic myocarditis [29]. Patients usually have a history of some pathogen infection and fever, and pathogenic bacteria can be found on blood culture, which is of great help in clinical diagnosis and treatment. After diagnosis, prevention and treatment of myocardial injury should be noted in addition to routine antibiotic treatments. Assessment of heart injury can rely on laboratory tests for cTnI and NT-pro-BNP, as well as echocardiography. If there is evidence to support severe cardiac dysfunction or even heart failure, treatment regimens for fulminant myocarditis, including mechanical circulation support and immunomodulation therapy, should be administered in a timely manner.

4. Stress cardiomyopathy

   Stress cardiomyopathy, also known as takotsubo syndrome, takotsubo cardiomyopathy, or broken heart syndrome, because of obvious apex dilation, which resembles baskets used to capture octopus by Japanese fishermen on echocardiography or left ventricular radiography after onset. It is also termed apical ballooning syndrome due to apex dilation [30]. Stress cardiomyopathy has a rapid onset, and the severe type can cause cardiac shock. Coronary angiography must be conducted first to rule out the possibility of coronary artery disease, because stress cardiomyopathy can also lead to severe chest pain (in 75% of

the patient), dyspnea (in 50% of the patient), ST-T changes on ECG, and elevation of cTnI and NT-pro-BNP as in case of acute coronary artery disease [30, 31]. However, no or little obvious artery occlusion can be found in stress cardiomyopathy, but the specific manifestation of left ventricular radiography can help in the diagnosis of stress cardiomyopathy. Stress cardiomyopathy should also be differentiated from fulminant myocarditis because of similar clinical manifestations. Ninety percent of stress cardiomyopathy patients are postmenopausal females, and is triggered by strong mental stress. In addition, heavy sport exercise, epileptic seizure [32] and pheochromocytoma [33] are all reported to trigger stress cardiomyopathy, and all of these causes are related to extreme sympathetic excitation. Although cardiac injury markers such as cTnI and BNP or NT-pro-BNP can all be elevated in stress cardiomyopathy, BNP or NT-pro-BNP usually shows higher elevation than cTnI, which indicates more severe heart dysfunction. In conclusion, stress cardiomyopathy can be diagnosed if these conditions are met: postmenopausal women with a history of severe mental stress but not infection, with normal coronary angiography and specific takotsubo-shape on left ventricular radiography. Most patients with stress cardiomyopathy show whole-left ventricular involvement, but several only show mid- ventricular involvement [34].

5. Acute myocarditis

   Prodromal infection can usually be found in fulminant myocarditis patients, and these patients usually show sudden onset, rapid progression, and severe heart function deterioration. cTnI and BNP or NT-pro-BNP levels are significantly elevated and show rapid changes. In contrast, acute myocarditis is the most common type of myocarditis, and acute myocarditis patients usually do not show the above-mentioned characteristics, and the situation of patients' changes with immune response and infections. Heart function deterioration and elevation of cTnI or BNP levels are not as severe as those of fulminant myocarditis are. Acute myocarditis has a better short-term prognosis than fulminant myocarditis.

6. Fulminant myocarditis caused by specific trigger

   As mentioned above, fulminant myocarditis induced by autoimmune diseases, drug toxicity or allergy, and checkpoint inhibitors are all related to abnormal immune activation or disturbance of immunohomeostasis [3, 31]. It is easy to diagnose this kind of fulminant myocarditis with history taking and laboratory tests, and the treatment regimen is consistent with "life support based comprehensive treatment regimen" introduced in this chapter. In addition, drug toxicity-induced fulminant myocarditis, or acute toxic cardiomyopathy, is related to toxic drug usage history; hence, it is important to treat toxicity and remove drugs through dialysis.

7. Cardiomyopathy

   Fulminant myocarditis can lead to severe inflammatory edema of the myocardium, and ventricular wall thickness can increase to 12–13 mm, and in severe myocarditis it can even increase to 15–25 mm. Thickening of the ventricular wall can be observed at the apex or free wall of the ventricle, but mostly in the interventricular septum (IVS), which requires careful differential diagnosis of hypertrophic cardiomyopathy. However, echocardiography revealed that the hypertrophic apex showed reduced but not increased contraction, similar to hypertrophic cardiomyopathy. Global longitude strains analysis can further reflect motion of myocardium. After proper treatment, the edematous myocardium can return to normal within 1 week to 1 month period [35]. Obvious massive or concentrated left ventricular wall edema can also be observed using CMR. In addition, few fulminant myocarditis patients show significant ventricular dilation at admission, which may lead to a misdiagnosis of dilated cardiomyopathy complicated by fulminant myocarditis. This can be differentiated by rapid normalization of the ventricle diameter after proper treatment.

Hence, it is important to make a quick and correct diagnosis in a short time for successful treatment. The diagnosis procedures have been summarized as a picture illustration as shown below.

Key Points in Diagnosing Fulminant Myocarditis

We noticed that most of the patients only received delayed treatment, which is possibly related to the misdiagnosis of the disease in the early stage and rapid progression of the disease into the late stage. Some patients did not receive a clear diagnosis until they passed away. There are also circumstances that, although the patients are diagnosed, little attention is paid to the monitoring of heart function due to lack of knowledge of the clinical features of the disease. As the heart function of the patient can deteriorate in a short period, for example, the ejection fraction can decrease from 50% to <20% in 2–3 h, the situation of the patient can be very critical. Hence, we proposed the idea of "very early recognition, very early diagnosis, very early prediction, very early treatment" to treat fulminant myocarditis patients in order to save their lives and improve their prognosis. The concept of "very early prediction" refers to the acknowledgement of rapid changes in the situation once the patient is diagnosed with fulminant myocarditis. The heart function of the patient can deteriorate rapidly; as a result, the patient must be treated or transferred to a superior hospital immediately, rather than only receiving symptomatic treatments because of temporary stability.

In conclusion, when dealing with suspected fulminant myocarditis patients, the key is to make an accurate diagnosis in a short time. To make it convenient for clinicians to refer to, we conclude the diagnosis procedure into the following points (Fig. 13.1).

1. Fulminant myocarditis can attack patients at any age, but the young patients are more susceptible. It is a cardiac inflammatory disease

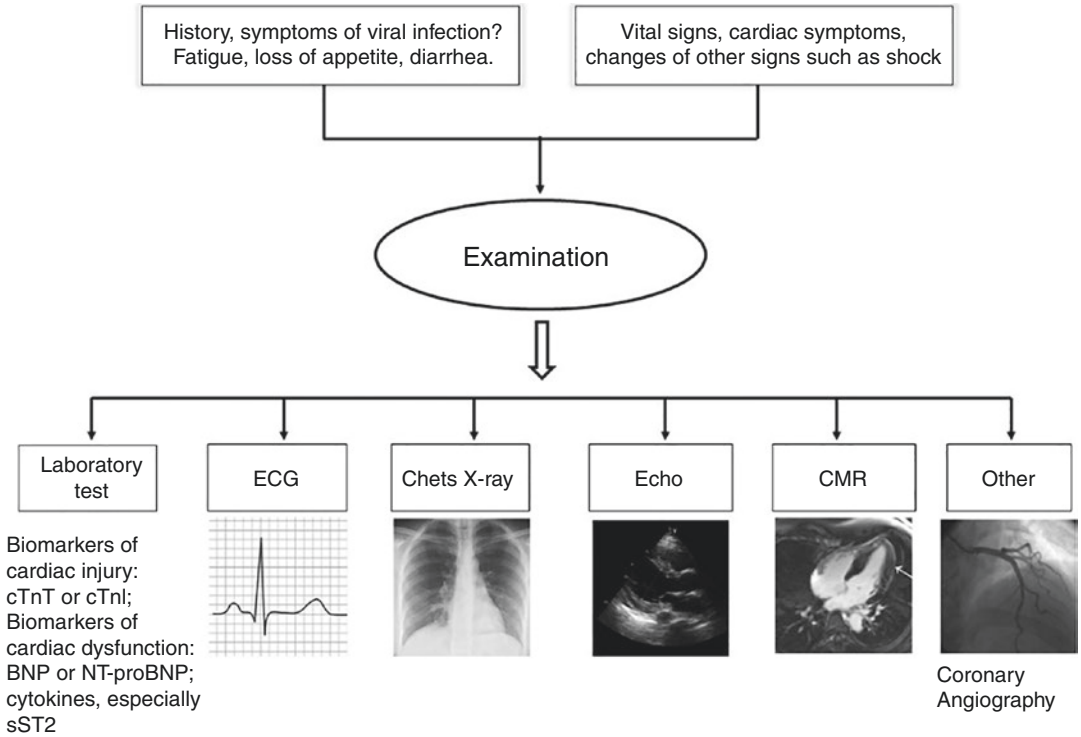

Fig. 13.1 Flow chart for diagnosis of fulminant myocarditis. *cTnT* cardiac troponin T, *cTnI* cardiac troponin I, *BNP* brain natriuretic peptide, *NT-proBNP* N terminal of pro-BNP; *Echo* Echocardiography, *CMR* cardiac magnetic resonance

with rapid onset and obvious hemodynamic disturbances.

2. It must be clear that fulminant myocarditis is a clinical diagnosis rather than a pathological or pathophysiological diagnosis. If the patient has prodromal signs such as a common cold and does not recover after proper treatment, attention should be paid to rule out the possibility of fulminant myocarditis. Careful physical examinations and targeted auxiliary examinations should be performed, including biomarkers of cardiac injury and heart function, echocardiography, ECG, and CMR. If significant elevation of cTnI and NT-proBNP along with obvious hypokinetic ventricle by echocardiography can be confirmed, and acute myocardial infarction or takotusbo cardiomyopathy can be excluded, the clinical diagnosis of fulminant myocarditis can be made. Endomyocardial biopsies can be performed in equipped clinical centers.
3. The pathological classifications of fulminant myocarditis include lymphocytic, giant cell, and eosinophilic fulminant myocarditis. However, the significance of endomyocardial biopsy to guide diagnosis or treatment during the acute phase is limited, and proper treatment cannot be delayed for the result of pathological classification.
4. Fulminant myocarditis should be differentially diagnosed from acute myocardial infarction, viral pneumonia, septic cardiomyopathy, takotusbo cardiomyopathy, acute myocarditis, special kinds of cardiomyopathy, and other cardiovascular diseases. Acute myocardial infarction requires a special differential diagnosis due to completely different treatment protocol. Immediate coronary angiography can be performed to confirm the differential diagnosis.
5. In treating fulminant myocarditis, the concept of "very early recognition, very early diagnosis, very early prediction, very early treatment" is emphasized.

The flow chart for diagnosis of fulminant myocarditis is shown in Fig. 13.1.

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14 Novel Conceptions in Treatments of Fulminant Myocarditis

Chen Chen, Hongyang Shu, and Dao Wen Wang

Fulminant myocarditis has a rapid onset and progression. Severe arrhythmia (or even fatal arrhythmia), cardiogenic shock, heart failure, and sudden death occur at the onset of illness. Owing to an inadequate understanding of the pathophysiology and pathogenesis of the disease, there has been no correct treatment regimen for a long time; thus, its mortality rate exceeds 50%. Based on clinical observations, a team led by Professor Wang Dao Wen from Tongji Hospital of Huazhong University of Science and Technology proposed that "the overactivation of immune response and inflammatory waterfall" is the core cause of heart damage, pump failure, and circulatory collapse in patients, as well as formulated the "life support-based comprehensive treatment regimen" based on this theory. Clinical practice has confirmed that this regimen reduces the mortality rate of fulminant myocarditis to less than 5%. Commissioned by the Chinese Society of Cardiology, Professor Wang Dao Wen led the team to formulate the "Chinese Expert Consensus on the Diagnosis and Treatment of Fulminant Myocarditis in Adults" which is the world's first expert consensus on fulminant myocarditis [1]. Recently, the American AHA published the "Recognition and Initial Management of Fulminant Myocarditis: A Scientific Statement from the American Heart Association," which further affirmed the key role of the life support regimen in the treatment of fulminant myocarditis [2].

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14.1 New Understanding of Pathophysiology of Fulminant Myocarditis

The pathology of fulminant myocarditis shows that there is a large amount of inflammatory cell infiltration in the myocardium. Lymphocytes and monocytes/macrophages are the main cell types associated with lymphocytic myocarditis. In eosinophilic myocarditis, there is a large number of eosinophils, neutrophils, lymphocytes, and giant cell types. In addition to the infiltration of inflammatory cells, necrotic myocardium, myocardial edema, and fibrosis have been observed. Additionally, the analysis of the serum inflammatory factors proved that a variety of cytokines and inflammatory mediators in the patient's serum increased significantly, and some even exceeded the normal value by more than 1000 times. Under the stimulation of pathogens or antigen molecules, the expression of pattern recognition receptors in cardiomyocytes is significantly upregulated, thereby enhancing the responsiveness to pathogen-related molecules and injury-related molecules and generating inflammatory

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responses through downstream signals, which further promotes the formation of inflammatory storms. Finally, various pathogen-related molecules not only stimulate myocardial cells to secrete inflammatory factors, but also significantly decrease contractility. Culturing cardiomyocytes with patient serum containing a large amount of inflammatory mediators promoted the death of cardiomyocytes, and the results also revealed that the contractility of viable cardiomyocytes and the intracellular level of Ca2+ were significantly reduced.

Based on the above introduction and that of previous chapters, we propose a new mechanism for the onset of fulminant myocarditis as the pathophysiological basis of a new treatment regimen. Pathogen-related molecules (viruses, bacteria, proteins, or drug molecules) and injury-related molecules stimulate the myocardium and/or inflammatory cells, which infiltrate the myocardial cells through chemotaxis. Excessively activated inflammatory cells and cardiomyocytes secrete a large number of cytokines and inflammatory mediators, forming an inflammatory storm, acting on the cardiovascular system and others. For example, dendritic cells and T cells attack and B lymphocytes produce antibodies. These immune activation and inflammatory storms result in myocardial damage and necrosis inhibition, leading to hypotension, cardiogenic shock, arrhythmia, and sudden cardiac death.

14.2 Design of Treatment Regimen

Based on the analysis of the above-mentioned pathogenesis, if cardiotonic agents such as levosimendan are used to increase myocardial contractility, or vasoactive drugs such as norepinephrine and pituitrin are used to increase blood pressure when dealing with fulminant myocarditis with hypotension, cardiogenic shock, extremely low heart sounds, third heart sound galloping rhythm, and peristaltic beats, they not only increase the burden on the failing heart, but also increase myocardial ischemia, which eventually causes poor clinical outcomes. The correct approach is to allow the failing heart to rest and maintain blood pressure and organ blood perfusion through mechanical circulatory support devices. In this process, the preload and afterload of the left ventricle must also be considered. Additionally, we should also make it possible to reduce the heart load, including assisted breathing.

Maintaining hemodynamic stability and temporarily saving the patient's life through mechanical circulation support is a strategy for alleviating symptoms. The active control of excessive immune activation and inflammatory storms and treatment of myocardial inflammation and edema are strategies for treating illness.

Cytotoxic drugs and immunosuppressive treatments, which are widely used in most case reports and literature, have unsatisfactory therapeutic effects. We propose the concept of "immunomodulatory therapy", which includes the use of sufficient doses of glucocorticoids (GCs) and adequate doses of immunity globulin. Continuous renal replacement therapy (CRRT) is used to filter inflammatory factors, which can be used as an auxiliary to rapidly suppress inflammatory storms.

14.3 Treatment Regimen

14.3.1 Mechanical circulation device support
- 14.3.1.1 Intra-aortic balloon pump (IABP)
- 14.3.1.2 Extracorporeal membrane oxygenation (ECMO)
- 14.3.1.3 Heart assist device
- 14.3.1.4 Other mechanical support: ventilator

14.3.2 Immunomodulatory therapy

14.4 Life Support Treatment

Patients with fulminant myocarditis rapidly develop severe arrhythmia, heart failure, and cardiogenic shock, which require active life support treatment.

14.4.1 ECMO

ECMO is a type of extracorporeal life support technology used for continuous external support therapy for patients with heart and lung failure. The core of this technology is to draw blood from the inside to the outside of the body, which is then oxygenated by a membrane oxygenator (membrane lung) and injected into the body with a centrifugal pump to partially or completely replace the patient's heart and lungs, thereby rapidly providing stable hemodynamic support for patients with acute respiratory or circulatory failure and ensuring that the oxygen supply and circulating blood volume of critically ill patients are in a long-term stable state [3, 4]. ECMO can be divided into venous-arterial ECMO (V-A ECMO) and venous-venous ECMO (V-V ECMO) [5]. V-V ECMO mainly provides respiratory support, whereas V-A ECMO provides respiratory and circulatory support simultaneously. V-A ECMO is mainly used for the treatment of fulminant myocarditis. The non-oxygenated blood is drawn from the right atrium or venous system by the V-A ECMO line through the drainage tube and enters the oxygenator driven by the pump head for gas exchange. The oxygenated blood is then pumped into the arterial system through the perfusion tube (Fig. 14.1a). ECMO can be divided into two types according to the position of the intubation: central and peripheral. Adult V-A ECMO commonly uses femoral vein-femoral artery cannulation (Fig. 14.1b). This method can drain most of the heart blood, effectively reducing the pre-load of the right ventricle, thereby reducing the pre-load of the left ventricle, increasing cardiac output, and improving tissue perfusion. However, because the blood returning to the body is retrogradely perfused by a catheter inserted into the descending aorta through the femoral artery, it resists the blood pumped out by the heart, causing an increase in the left ventricular end diastolic pressure, left atrial pressure, and pulmonary capillary wedge pressure. Therefore, there is a potential risk of pulmonary edema and aortic valve opening. Additionally, V-A ECMO has complications, including bleeding, hemolysis, thrombosis, infection, and liver and kidney damage [6].

ECMO is one of the most important life support devices in the treatment of patients with fulminant myocarditis, and its therapeutic effect has been supported by a large number of clinical data [7–9]. The main feature of VA ECMO is the "bridge" effect, i.e., "bridging" critical states

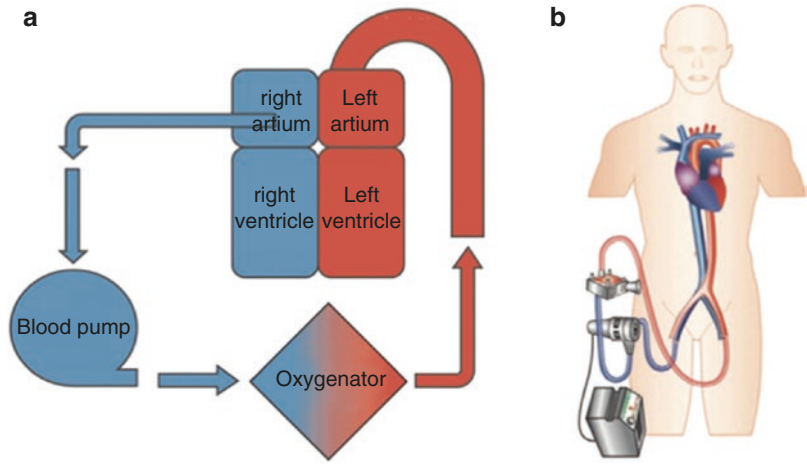

Fig. 14.1 V-A ECMO schematic diagram. Femoral vein-femoral artery cannulation V-A ECMO. (**a**) cited from Maya Guglin, Mark J Zucker, Vanessa M Bazan, et al. Venoarterial ECMO for Adults: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2019 Feb 19;73(6):698–716. https://doi.org/10.1016/j.jacc.2018.11.038. (**b**) Cited from Anne Freund, Steffen Desch, Janine Pöss, et al. Extracorporeal Membrane Oxygenation in Infarct-Related Cardiogenic Shock. *J Clin Med.* 2022 Feb 25;11(5):1256. https://doi.org/10.3390/jcm11051256

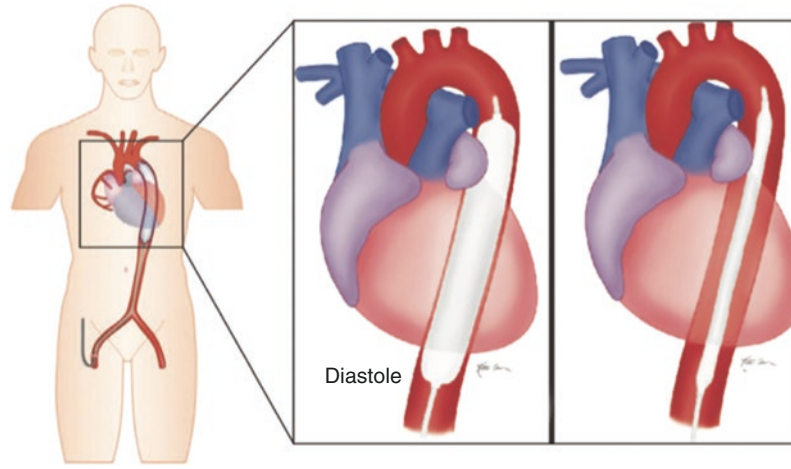

Fig. 14.2 IABP schematic diagram

such as refractory ventricular arrhythmia, cardiac arrest, and cardiogenic shock to a hemodynamically stable state, to wait for long-term mechanical circulation assist devices or other next step treatments such as heart transplantation [5, 10]. Fulminant myocarditis is acute, dangerous, and has a high mortality rate. However, if ECMO treatment can be implemented quickly and effectively, it can provide sufficient rest time for the patient's heart and lungs, ensure the recovery of hemodynamics in patients with fulminant myocarditis, help patients survive the dangerous period, and increase the rescue success rate of patients with fulminant myocarditis and multiple organ failure.

14.4.2 IABP

The IABP is the most common ventricular mechanical assist device. A catheter with a balloon is placed in the descending aorta, 1–2 cm distal to the opening of the left subclavian artery through the arterial system. In the early diastolic period, the airbag is inflated to increase the diastolic pressure, increase coronary perfusion pressure, and improve myocardial blood supply. At the beginning of the systole, the balloon is deflated immediately before the aortic valve opens, and the aortic pressure drops to reduce the afterload, thereby reducing the wall tension and myocardial oxygen consumption, increasing forward blood flow, and improving peripheral perfusion (Fig. 14.2) [11–13]. IABP can improve the hemodynamics of patients with fulminant myocarditis in a short period of time and can help patients survive the acute phase [14]. IABP should be used as soon as possible in patients with hemodynamically unstable fulminant myocarditis [1, 15, 16].

IABP also has limitations. It is a passive assistive device that relies on the electromechanical activity of the patient's heart to trigger a mechanical pump. It cannot replace the function of the heart. Therefore, the effect of IABP treatment on patients with severe myocardial damage or cardiac arrest is often poor. For severe fulminant myocarditis with cardiogenic shock, the decrease in myocardial contractility is mainly due to the extensive damage of myocardial cells by viruses and inflammation. Cytokines such as TNF-α, IL-1β, IL-6, and IL-18 affect myocardial contractility through a variety of signaling pathways, and there is no obvious damage to the coronary blood supply.

In this case, the therapeutic effect of IABP on pump failure is relatively limited. Therefore, when patients with fulminant myocarditis are critically ill, early ECMO-assisted circulatory therapy should be used to help patients survive the dangerous period. Because IABP can reduce cardiac afterload, it theoretically helps to reduce the risk of pulmonary edema caused by V-A ECMO, increasing the cardiac afterload. If necessary, for patients with severe fulminant myocarditis combined with cardiogenic shock, V-A ECMO and IABP can be combined to correct heart failure and shock, thereby saving patients' lives and improving prognosis.

14.4.3 Percutaneous Left Ventricular Assist Device

The percutaneous left ventricular assist device (Impella) consists of a console, a ventricular assist device, and a purification system. Its working mechanism simulates the original function of the heart, i.e., blood flows from the left ventricle into the ventricular assist device and is pumped out from the aortic root. The pumped blood flows through the descending aorta to the whole body while providing coronary blood supply through the entrance of the coronary arteries, increasing the systemic blood flow output and myocardial oxygen supply (Fig. 14.3).

The outflow part of the Impella device is located at the aortic root, and the axial flow pump provides forward flow of blood, thereby increasing the output power of the heart [17, 18]. Because the pumped blood comes directly from the left ventricle, the end-systolic volume and pressure of the ventricle are reduced, thereby reducing the work of the heart and reducing myocardial oxygen consumption. The increase in blood flow and pressure and decrease in heart wall tension are conducive for increasing coronary blood flow and myocardial oxygen supply and improving myocardial viability [19]. Additionally, the myocardium of fulminant myocarditis has a large number of activated inflammatory cells. The inflammatory response leads to an imbalance of the myocardial Ca2+ balance, affects the function of titin, which causes myocardial hypertrophy, and activates fibroblasts that promote fibrosis, which ultimately results in an increased cardiac load and cardiac dysfunction. Reducing the cardiac load using Impella can block these processes through integrin-mediated mechanical conduction pathways and improve cardiac function (Fig. 14.4) [20].

Similar to IABP, Impella can also be used for continuous left ventricular decompression, which can reduce pulmonary edema caused by V-A ECMO, increasing the left ventricular afterload. As a new ventricular assist device, Impella theoretically has advantages over IABP in short-term circulation support. Several small clinical trials have also confirmed that Impella is superior to IABP in terms of stabilizing hemodynamics and reducing the incidence of adverse events (Tables 14.1 and 14.2) [21]. Impella is currently widely used in Europe and the United States.

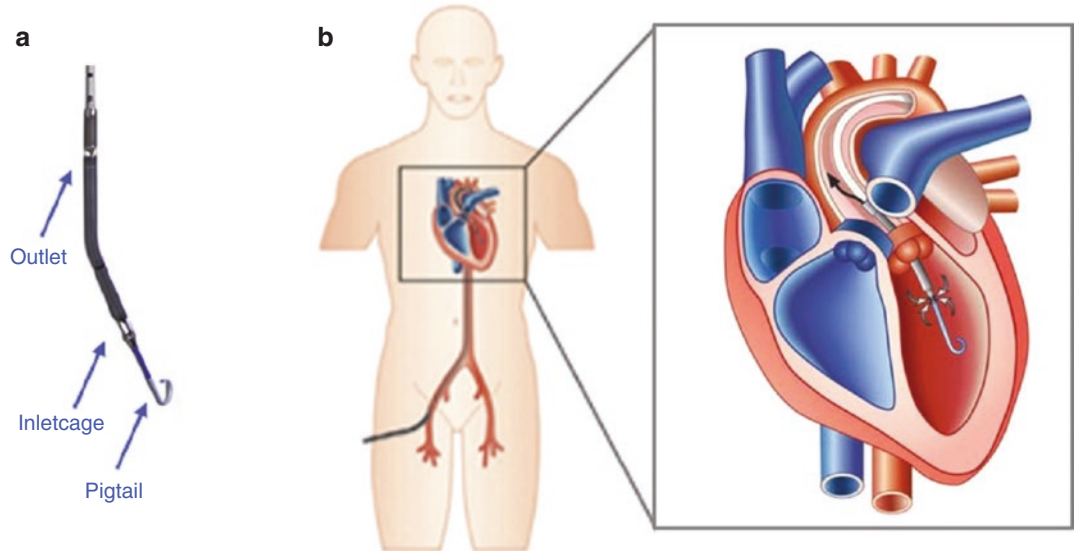

Fig. 14.3 Impella left ventricular assist device. (**a**) Impella installation schematic diagram. (**a**) modified from Balthazar T, Vandenbriele C, Verbrugge H, et al. Managing Patients With Short-Term Mechanical Circulatory Support JACC Review Topic of the Week. *J Am Coll Cardiol.* 2021 Mar 9;77(9):1243–1256. https://doi.org/10.1016/j.jacc.2020.12.054. (**b**) modified from Gilotra N, Stevens G. Temporary mechanical circulatory support: a review of the options, indications, and outcomes. *Clin Med Insights Cardiol*. 2015 Feb 3;8(Suppl 1):75–85. https://doi.org/10.4137/CMC.S15718

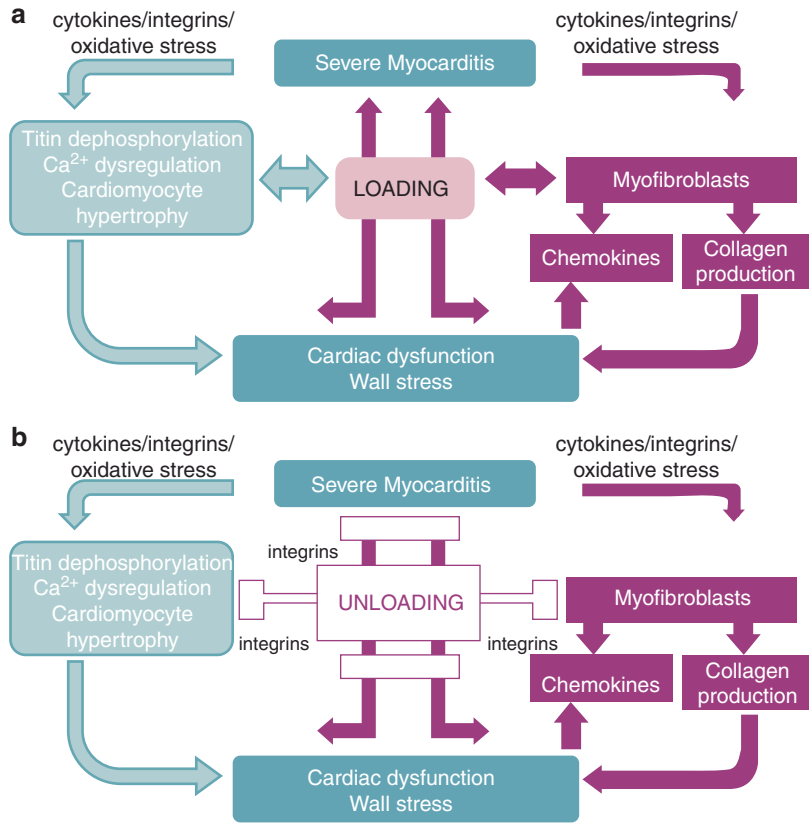

Fig. 14.4 The influence of cardiac load on the pathophysiological process of severe myocarditis. Cited from Spillmann F, Van Linthout S, Schmidt G, et al. Mode-of-action of the PROPELLA concept in fulminant myocarditis. Eur Heart J. 2019;40(26):2164–2169. https://doi.org/10.1093/eurheartj/ehz124

Table 14.1 Comparison of the effects of VA-ECMO, IABP and Impella on cardiac function

Equipment	VA-ECMO	IABP	Impella (2.5; CP; RP)
Flow rat/L·min^{-1}	4–6	0.5–1	2.5–5
Continuous support time (FDA standard)	6 h	9 day	4 day (2.5. CP) 14 day (RP)
Supporting ventricle	Left ventricle and Right ventricle	Left ventricle	Left ventricle/Right ventricle
Post-load	↑↑↑	↓	↓
MAP	↑↑	↑	↑
Heart contractility	↑↑	↑	↑↑
LVEDP	↔	↓	↓↓
PCWP	↓↓	↓	↓
Left ventricular preload	↓	—	↓↓
Coronary blood supply	—	↑	↑
Myocardial oxygen consumption	↔	↓	↓↓

Note: *MAP* mean arterial pressure, *LVEDP* left ventricular end-diastolic pressure, *PCWP* pulmonary capillary wedge pressure

Table 14.2 Comparison of the advantages and disadvantages of VA-ECMO, IABP and Impella

Equipment	VA-ECMO	IABP	Impella (2.5; CP; RP)
Advantages	• Higher cardiac output • Complete cardiopulmonary support (Including oxygenation and CO2 scavenging)	• Easy to install • Higher security • Few side effects	• More model options
Disadvantages	• Higher requirements for equipment • Increased afterload • Vascular complications • Thrombocytopenia may occur	• Limited hemodynamic support • Severe aortic reflux is contraindicated	• Highly invasive • Compared with IABP, implantation is complicated • Often accompanied by hemolysis • Vascular complications are common

14.5 Immunomodulatory Therapy

The excessive activation of the immune system plays an important role in the pathogenesis of fulminant myocarditis. Therefore, immune regulation therapy is essential to calm the cytokine storm, reduce heart damage, and improve prognosis. Current clinical studies on the application of different immunomodulatory drugs in fulminant myocarditis are limited, and more evidence-based medical evidence is required.

14.5.1 Intravenous Gamma Globulin

Intravenous immunoglobulin (IVIG) refers to blood products rich in IgG (≥95%) preparations, which are separated from the fresh plasma of healthy adults and contain billions of idiotypic antibodies in the serum of healthy people. It is widely used in various autoimmune and inflammatory diseases [22, 23].

Animal experiments have shown that IVIG can effectively reduce inflammatory infiltration in the mouse heart [24, 25]. A series of case reports showed that IVIG treatment can help improve the left ventricular function in patients with myocarditis [26, 27]. IVIG has dual antiviral and anti-inflammatory effects. Its main component, the IgG molecule, can be divided into two functional fragments: the F(ab′)2 segment with antigen-binding activity and the Fc segment with immunomodulatory function. Both play an important role in the anti-inflammatory and immune regulation of IVIG. The underlying mechanism of the F(ab′)2 segment includes killing target cells through antibody-dependent cell-mediated cytotoxicity, blocking cell-surface interactions mediated by cell surface receptors such as CD95 and CD95L, directly neutralizing cytokines and autoantibodies, and clearing allergic toxins C3a and C5a, among other actions. Fc-segment-dependent pathways act via the following mechanistic routes: promoting the proliferation of Treg cells, blocking the binding of immune complexes to low-affinity Fcγ receptors (FcγRs), activating dendritic cells through FcγRIII, and regulating the expression of activating and inhibitory FcγR on immune effector cells and B cells (Fig. 14.5) [23].

The underlying mechanism of IVIG in the treatment of fulminant myocarditis is as follows.

1. Direct antiviral mechanisms

   Antibodies can directly bind to the surface protein of the virus outside the cell, block the virus from binding to the cell surface receptors, invade the host cell, and inhibit the spread of the virus in the body.

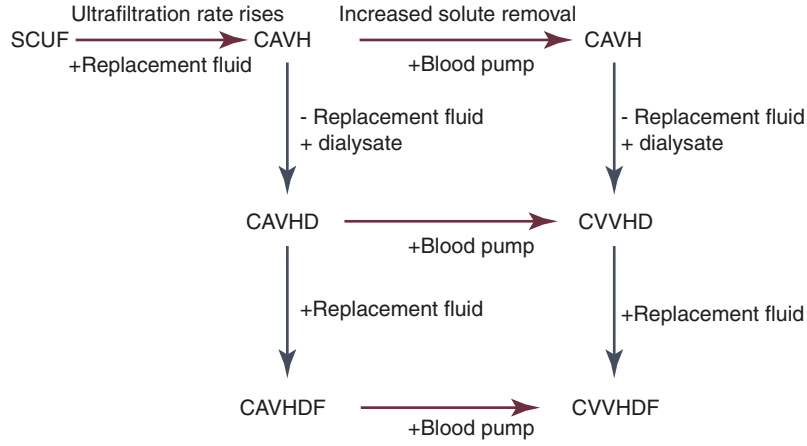

Fig. 14.5 F(ab′)2-and Fc-dependent pathways of IVIG activity. Cited from Schwab I. Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol.* 2013;13(3):176–189. https://doi.org/10.1038/nri3401

2. Regulation of immune system and eliciting an anti-inflammatory effect

IVIG can inhibit the proliferation of over-activated T cells, B cells, and antigen-presenting cells; reduce the attack of cytotoxic T cells on cardiomyocytes; promote Treg cell activation and exert anti-inflammatory effects; up-regulate the synthesis and release of IL-1 receptor antagonists TNF-α, IL-1, and IL-6, as well as other anti-inflammatory factors; and inhibit the production of pro-inflammatory factors such as IL-1, IL-6, IFN-γ, and TNF-α. IVIG can also down-regulate a variety of important adhesion molecules such as the intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and chemokines such as monocyte chemotactic protein-1 (MCP-1). The expression of the macrophage colony stimulating factor and granulocyte-macrophage colony stimulating factor inhibits the proliferation of endothelial cells and chemotaxis of inflammatory cells. In summary, IVIG regulates the immune system and inflammatory response through multiple routes, thereby reducing cardiomyocyte damage and improving heart function (Fig. 14.6) [28–30].

14.5.2 GCs

GCs are steroid hormones secreted by the adrenal cortex, which play an important role in regulating the growth, development, metabolism, and immune function of the body under physiological conditions. GCs also have a wide range of effects, such as anti-inflammatory, immunosuppressive, anti-allergic, and anti-shock effects when super-physiological doses (pharmacological doses) are used. The effectiveness of GCs in the treatment of fulminant cardiomyositis currently lacks the results of large-scale multicenter clinical studies. However, existing clinical practice suggests that their effectiveness and safety are good.

In fulminant myocarditis, the treatment target for GC treatment is not a virus. Instead, GCs control the over-activated systemic inflammatory response and results in tissue damage. GCs have strong anti-inflammatory and immunosuppressive effects, but the underlying mechanism is not fully understood. In the past, it was considered that GCs play a role through a genomic effect mediated by the GC receptor (GR). Liposoluble GCs pass through the cell membrane and combine with GRs in the cytoplasm to form a complex and ectopic nucleus. Such a complex

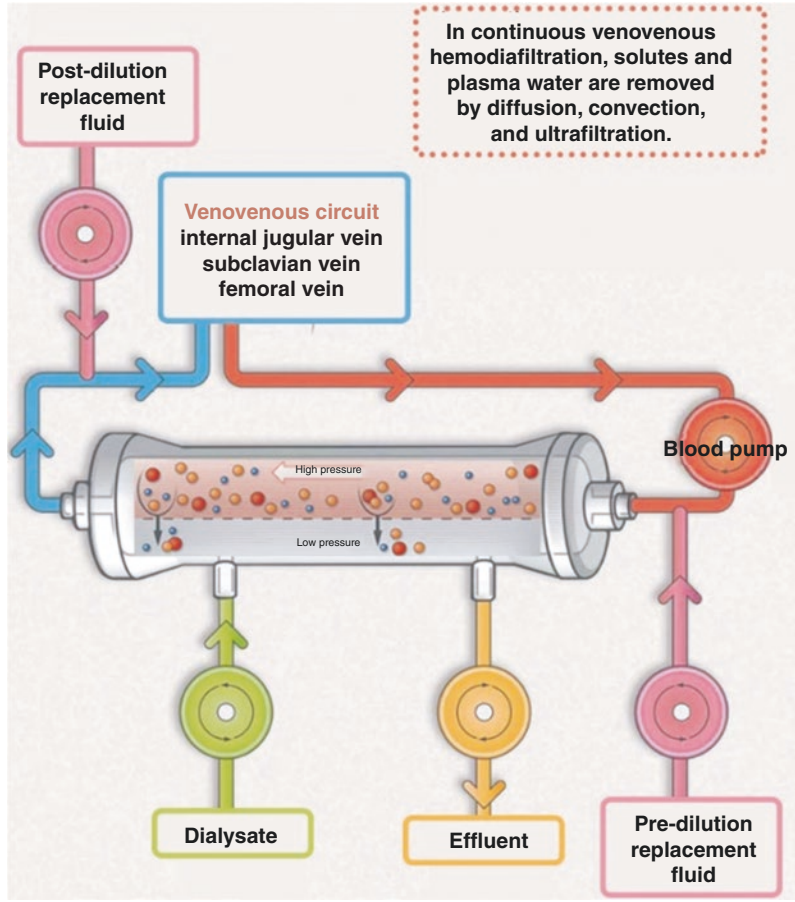

Fig. 14.6 IVIG's regulation of the immune system. Cited from Durandy A, Kaveri SV, Kuijpers TW, et al. Intravenous immunoglobulins—understanding properties and mechanisms. *Clin Exp Immunol.* 2009;158 Suppl 1(Suppl 1):2–13. https://doi.org/10.1111/j.1365--2249.2009.04022.x

functions through a variety of ways. (1) It directly inhibits the activator protein-1, as well as activates nuclear factor of activated T cell (NFAT), nuclear factor κB (NF-κB), signal transducer and activator of transcription, and other pro-inflammatory transcription factors. (2) It combines with the negative GC response element to inhibit the transcription of inflammatory molecular genes such as IL-1β and IL-2. (3) It combines with the positive GC response element and promotes the transcription of a variety of immunosuppressive genes, such as inhibitory kappa B (IκB), IL-10, lipocortin-1, and annexin-1 to exert an immunosuppressive effect. The first two effects can only occur when the body's original pro-inflammatory proteins and factors are degraded; thus, they are relatively slow. Recent studies have shown that non-genomic effects also play an important role in the mechanism of action of GCs. By combining with membrane GR, cytosolic GR, or non-specific GR, a GC can affect cell transmembrane current within a few minutes and inhibit TCR and MAPK signal transduction pathways, thereby affecting the mobilization of intracellular Ca2+ ions and exerting an immunomodulatory effect (Fig. 14.7) [31–33].

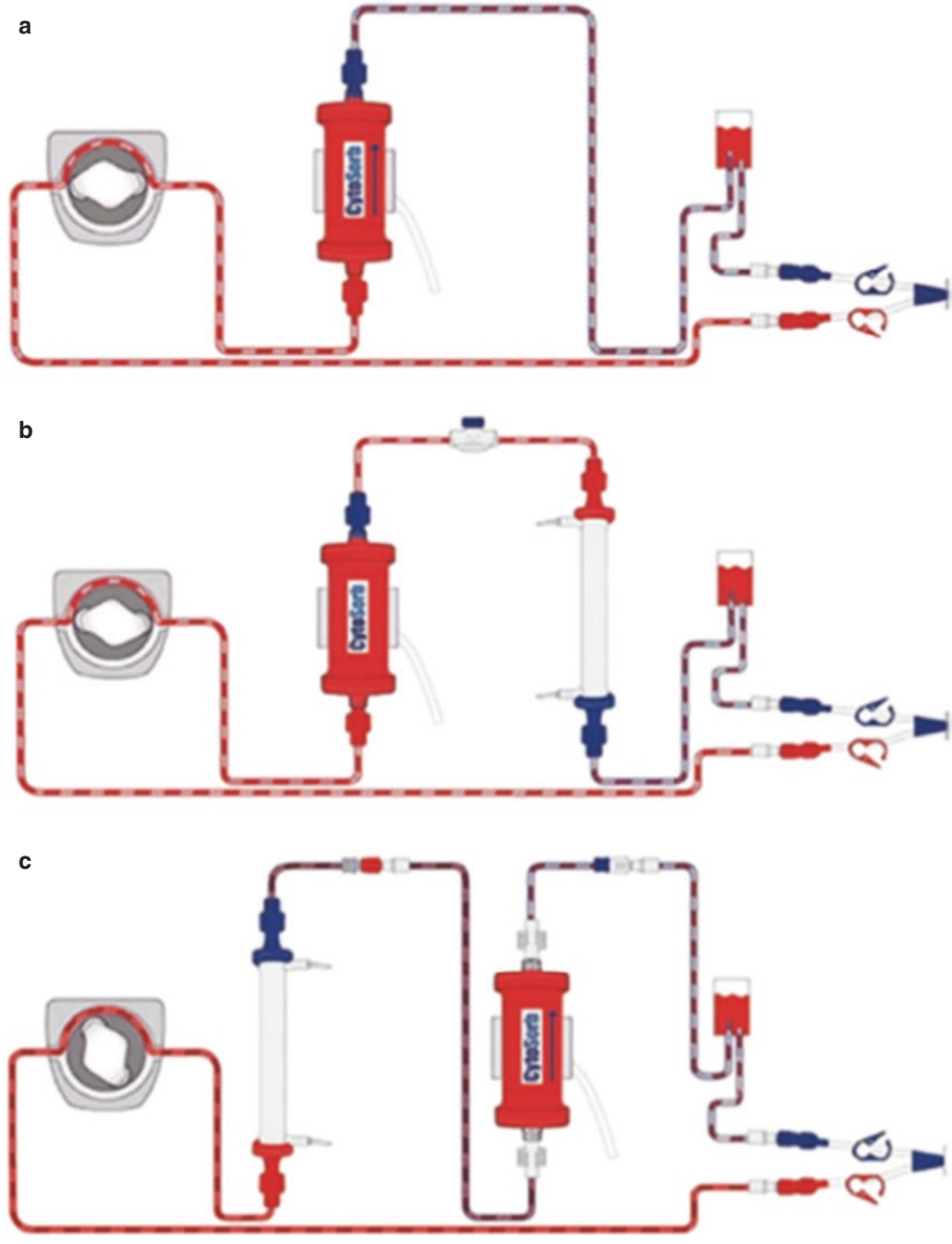

Fig. 14.7 Genomic and nongenomic immunoregulation by glucocorticoids. Cited from Löwenberg M, Verhaar AP, van den Brink GR, Hommes DW. Glucocorticoid signaling: a nongenomic mechanism for T-cell immunosuppression. *Trends Mol Med.* 2007;13(4):158–163. https://doi.org/10.1016/j.molmed.2007.02.001

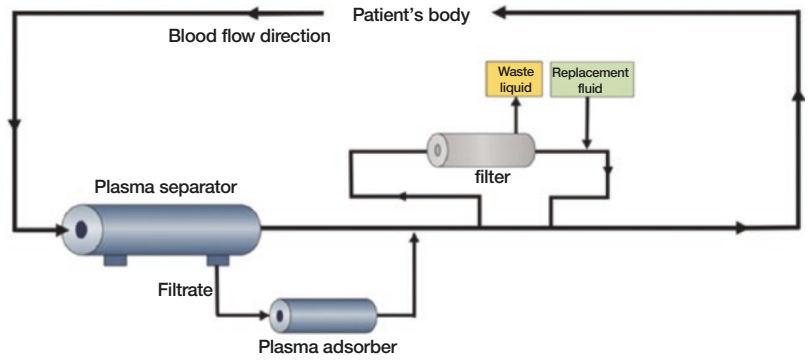

Fig. 14.8 Regulation of glucocorticoids on immune cells and non-immune cells

The inflammation-inhibiting effect of GC is manifested in the following aspects.

1. Regulation of inflammation-related chemical mediators

   GC can affect the metabolism of arachidonic acid; reduce the production of prostaglandins and leukotriene inflammatory mediators; and block the production of NO, prostaglandin E2, and related inflammatory mediators by inhibiting the expression of nitric oxide synthase and cyclooxygenase-2. Additionally, GC can promote the production of epoxyeicosatrienoic acid, which is the product of the CYP epioxidase pathway, to resist inflammation and myocardial damage.
2. Regulation of cytokines

   GC can inhibit the expression of TNF-α, IL-1, IL-2, IL-5, IL-6, IL-8, and other pro-inflammatory factors, while promoting the expression of NF-κB inhibitory proteins (IκB1), IL -10, IL-12, IL-1RA, and other pro-inflammatory mediators.
3. Regulation of inflammatory cells

   GC can inhibit the phagocytosis and processing of antigens by macrophages; inhibit the proliferation of lymphocytes by down-regulating the expression of c-myc, c-myb, and other cell proliferation-related genes; and block the recruitment of mononuclear macrophages induced by activated T lymphocytes. Large doses of GC can also inhibit the conversion of B cells into plasma cells, thereby reducing antibody production and disrupting humoral immunity. Additionally, GC promotes the apoptosis of various inflammatory cells such as monocytes, macrophages, granulocytes, and lymphocytes by inducing intracellular DNA degradation, activating caspases and specific endonucleases, and inhibiting the expression of the adhesion molecules (Fig. 14.8) [31, 34, 35].

GC can also treat fulminant myocarditis by enhancing the body's stress-resistance ability, improving the body's tolerance to toxins, exerting anti-shock effect, and regulating metabolism. It is worth noting that because GC extensively inhibits the body's defense function, a high-dose use of GC may aggravate or further induce infection in viral-induced fulminant myocarditis. Therefore, in the treatment of fulminant myocarditis, attention should be paid to the timing and dosage of administration.

14.5.3 Cytotoxic Immunosuppressive Drugs

Currently, immunosuppressive therapies such as cyclosporine and azathioprine are mostly used for patients diagnosed with autoimmune myocarditis without contraindications, including giant cell myocarditis, cardiac sarcoidosis, and

myocarditis associated with known extracardiac autoimmune diseases [2, 36]. Endocardial biopsy should be performed to rule out viral infections before using these drugs.

1. Cyclosporine A (CsA)

   CsA is a neutral cyclic peptide isolated from fungal metabolites. It has a highly selective inhibitory effect on the humoral immunity of thymus-dependent antigens and can inhibit the production of IL-2 and IL-2-dependent T cell proliferation and cytokine production. CsA inhibits the calcineurin's catalytic effect on NFAT dephosphorylation after binding to cyclosporin receptor, thereby inhibiting NFAT from entering the nucleus and preventing the induction of gene transcription. Moreover, CsA can reduce the production of inflammatory factors in macrophages and neutrophils and inhibit the expression of cytokines such as IL-1 and anti-apoptotic proteins, thereby suppressing immunity [37].
2. Azathioprine

   Azathioprine is a common anti-metabolism purine drug. It is a derivative of 6-mercaptopurine. It inhibits the synthesis of purine nucleotides by interfering with the link of purine metabolism, thereby inhibiting the synthesis of cellular DNA, RNA, and proteins, and thus, inhibiting T lymphocytes, B lymphocytes, and NK cells. Simultaneously, it can inhibit cellular immunity and the humoral immune response but does not inhibit the phagocytic function of macrophages.

   Owing to the potential risk of virus spread, immunosuppressive agents such as cyclosporine and azathioprine are not recommended for virus-positive fulminant myocarditis.

   In summary, with respect to the histopathology of fulminant myocarditis, a large number of lymphocytes and macrophages exhibit infiltration and excessive immune activation. It is undoubtedly reasonable to use cytotoxic drugs to suppress immunity. However, cytotoxic immunosuppressive drugs do not seem to have significant clinical effects in clinical practice. Although there are recent opinions that the prognosis of patients with giant cell fulminant myocarditis is poor and the use of immunosuppressive agents may be more beneficial, further research is necessary [38].

14.5.4 CRRT

CRRT is a general term for the continuous and slow removal of water and solutes using the principles of ultrafiltration, diffusion, convection, and adsorption, and it is also referred to as "artificial kidney." The main components of CRRT include single-needle double vena cava catheters, extracorporeal loops, blood filters, blood pumps, and outflow pumps [39]. It may also involve the use of dialysate and/or replacement fluid pumps. Commonly used modes include SCUF, CVVH, CVVHD, and CVVHDF (Fig. 14.9).

In the most common CVVH mode, the solutes and plasma pass through a semi-permeable membrane with a high ultrafiltration rate. Simultaneously, the replacement fluid penetrates the blood under the action of the replacement pump. The replacement fluid replenishes the filtered water and electrolyte. The replacement fluid can be placed before the semi-permeable membrane (pre-dilute replacement fluid) or behind the semi-permeable membrane (post-dilute replacement fluid). In the CVVHD mode, the solutes and plasma enter the blood filter by permeation or ultrafiltration, and the dialysate enters the blood under the action of a controlled pump (Fig. 14.10).

In patients with fulminant myocarditis, the immune system is overactivated, and cytokines are released in large quantities. CRRT can continuously remove excess cytokines, water, and metabolites from the body, thereby maintaining

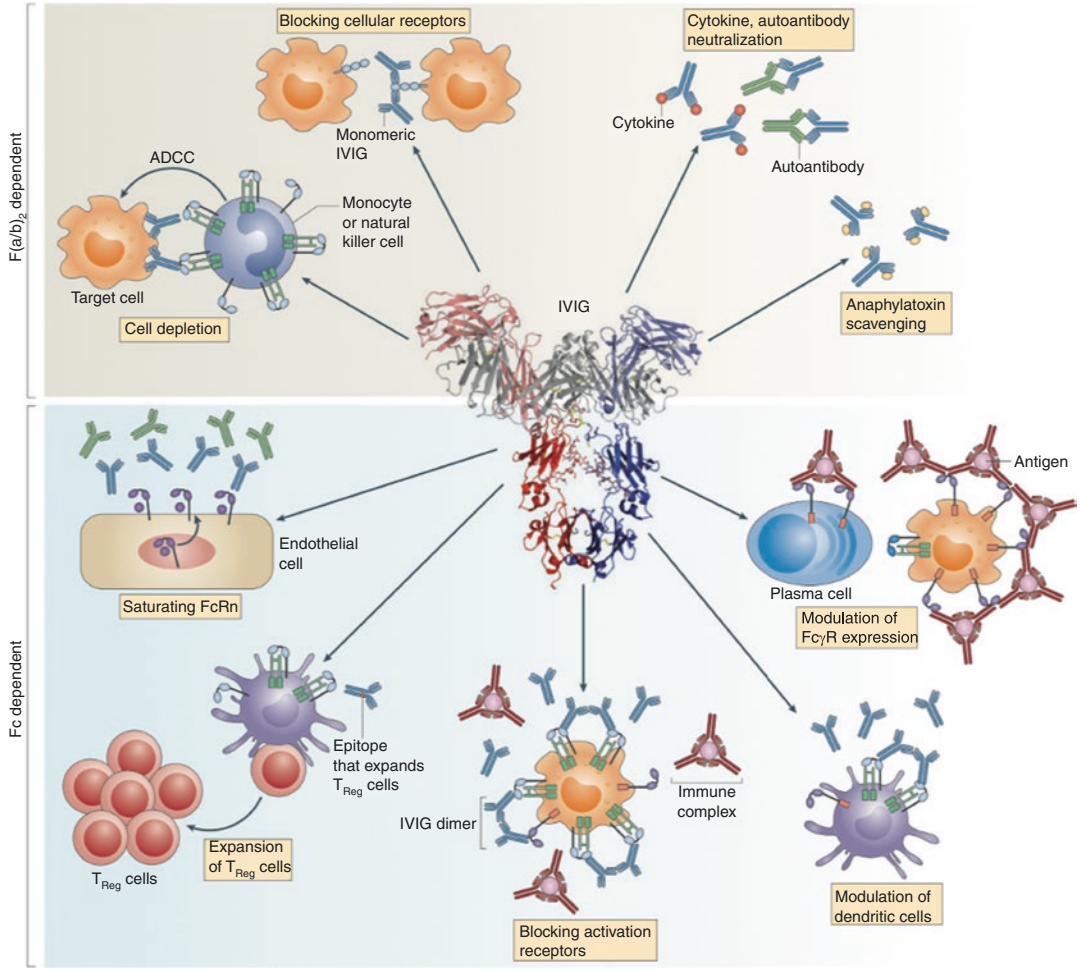

Fig. 14.9 Common CRRT mode and its conversion

the stability of the body's hemodynamics and acid-base balance and reducing secondary immune damage. Patients with fulminant myocarditis often experience kidney damage. The early application of CRRT can effectively stabilize the hemodynamics of patients with fulminant myocarditis, protect heart and kidney function, and improve prognosis. However, some studies have shown that CVVH has a limited ability to clear some cytokines in plasma, such as TNF-α and IL-6 [40, 41]. The molecular weight of many inflammatory cytokines exceeds the cut-off molecular weight of the dialysis membrane and is difficult to remove effectively. Moreover, CVVH mainly removes cytokines through adsorption, and its removal capacity is limited by the saturation of the dialysis membrane.

A plasma immunosorbent device can also be placed in the CRRT loop. Immunoadsorption (IA) is a new type of blood purification technology, similar to adding a "purifier" to plasma. IA technology uses highly specific antigen-antibody reactions or adsorption materials to remove blood

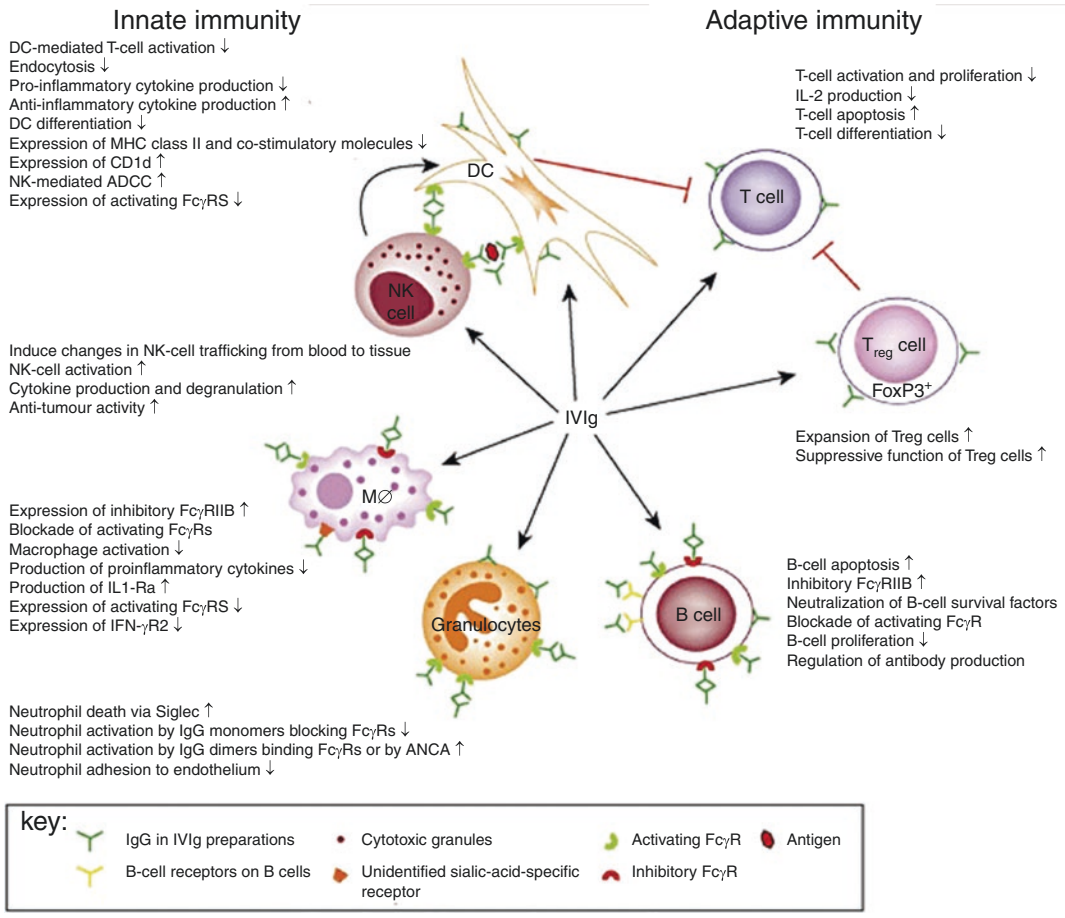

Fig. 14.10 The main component of the CRRT loop

related to immune-related pathogenic factors and then returns the purified blood to the patient's body, thereby purifying the blood and alleviating the illness. Compared with CRRT, IA is not restricted by membrane permeability and dialysis membrane saturation and can completely remove pathogenic cytokines in patients with fulminant myocarditis. Moreover, there is almost no loss of beneficial components in the patient's body, and theoretically, it has more advantages than CRRT. Common clinical IA technologies include staphylococcal protein A IA column, CytoSorb (CS) and other cytokine adsorption columns, and coupled plasma filtration adsorption (CPFA).

SPA is currently the most widely used immunoadsorbent. It is a protein component of the cell wall of certain Staphylococcus aureus strains. The binding rate of the active part of the amino terminal of SPA to IgG was approximately 95%. The carboxyl end of SPA is a non-immunoglobulin binding region, which can be covalently cross-linked to various scaffold structures such as bead agarose and silica gel. Its combination is stable to changes in temperature, pH, and denaturant, and it is not easy to lose [42]. SPA has a good effect on alleviating some active immune diseases and has been applied in various immune-related diseases.

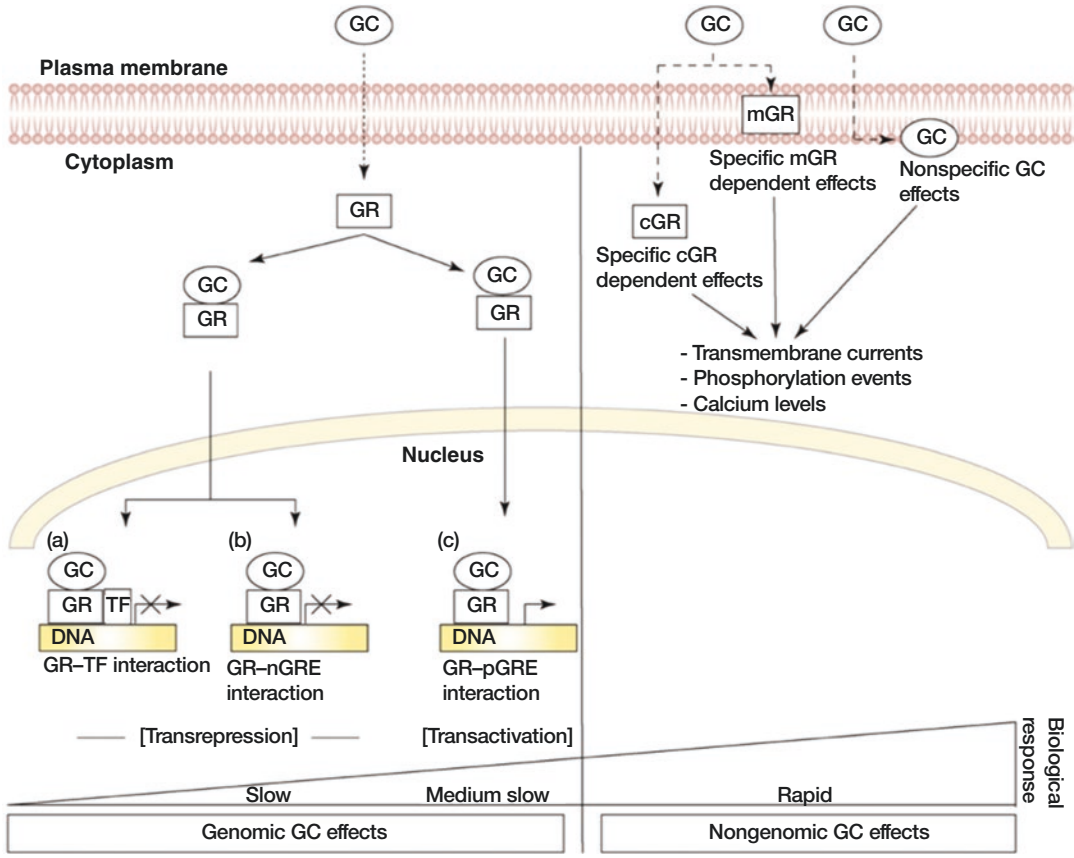

Fig. 14.11 CytoSorb loop. CytoSorb Independent treatment (**a**); Pre-dialyzer mode (**b**); Post-dialyzer mode (**c**)

The CS cytokine adsorption column is composed of polystyrene-divinylbenzene polymer beads with good biocompatibility, high porosity, and polyvinylpyrrolidine coating. Compared with the existing dialyzer, its large surface area has a stronger removal ability. It mainly uses pore capture and surface adsorption to remove substances from blood. It can be used as an independent treatment method or combined with an extracorporeal tube (Fig. 14.11) [43]. The safety and effectiveness of CS have been proven in the treatment of septic shock with severe immune imbalance [44–46]. Studies have shown that for patients with cytokine release syndrome caused by CAR-T treatment, CS treatment can effectively reduce the levels of multiple cytokines such as IFN-γ, IFN-α, IL-1, IL-2, IL-5, and CCL2/MCP1 [47]. Similar to CS, there are adsorption columns, such as oXiris and Toraymyxin. Their working principles are similar, except for differences in the removal efficiencies of cytokines and endotoxins.

CPFA is also referred to as "continuous plasma filtration adsorption," which combines technologies including plasma separation, plasma adsorption, and CRRT and is often used in the treatment of sepsis. The plasma is separated from whole blood using a plasma separator, and the adsorbed plasma is mixed with blood cells and then subjected to continuous hemofiltration and/or hemodialysis. The adsorbents are mostly resins, which are mainly used clinically to remove inflammatory mediators, such as small molecule toxins and cytokines (Fig. 14.12).

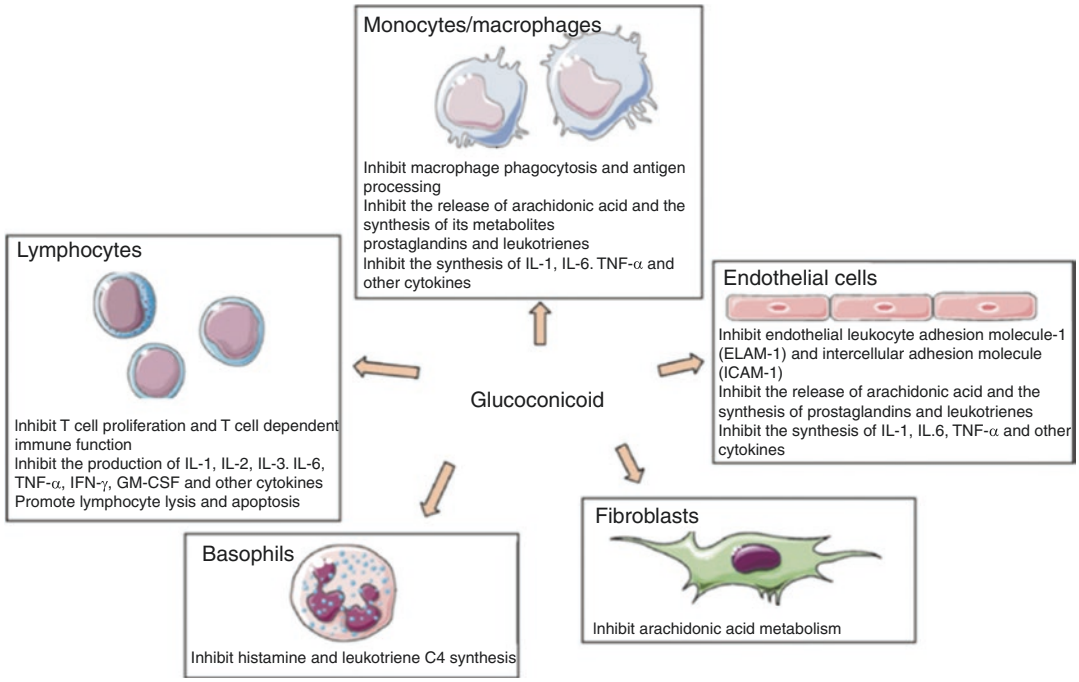

Fig. 14.12 CPFA schematic diagram

14.6 Antiviral Treatment

Presently, the most common cause of fulminant myocarditis is viral infections, such as coxsackie virus B3 and human parvovirus B19. Therefore, antiviral drugs may have therapeutic effects. In theory, all patients with viral fulminant myocarditis should undergo combined antiviral therapy early in the pathogenesis; however, there is currently no approved antiviral therapy for enterovirus and parvovirus infections. Drugs commonly used clinically for antiviral treatment of fulminant myocarditis include oseltamivir and ganciclovir.

Oseltamivir is a prodrug of neuraminidase (NA) inhibitors, and its active metabolite is a potent and selective NA inhibitor of influenza A and B viruses. Its main antiviral mechanism is to inhibit viral NA and block the release of newly formed virus particles from infected cells (Fig. 14.13). However, the cause of fulminant myocarditis in most patients is not influenza virus infection, and the mechanism of action against influenza virus is not an effective treatment. However, studies have shown that myocardial cells may release NA and *N*-acetylneuraminic acid during myocardial injury, which may cause changes in the sialylation of a variety of proteins, thereby affecting cardiac function. Therefore, oseltamivir may reduce myocardial damage while suppressing the virus [48].

Ganciclovir is a derivative of acyclovir and a common antiviral drug. It is phosphorylated by specific thymidine kinase encoded by HSV and other viral genes in the cell to generate the triphosphate type, which can inhibit the DNA polymerases of herpes virus and cytomegalovirus and can incorporate it into viral DNA to inhibit viral DNA synthesis.

Because the myocardial damage caused by the virus invading the body is common in the early course of fulminant myocarditis, antiviral treatment should be implemented as soon as possible.

Fulminant myocarditis is dangerous and has a high mortality rate. The "Consensus of Chinese Experts on the Diagnosis and Treatment of

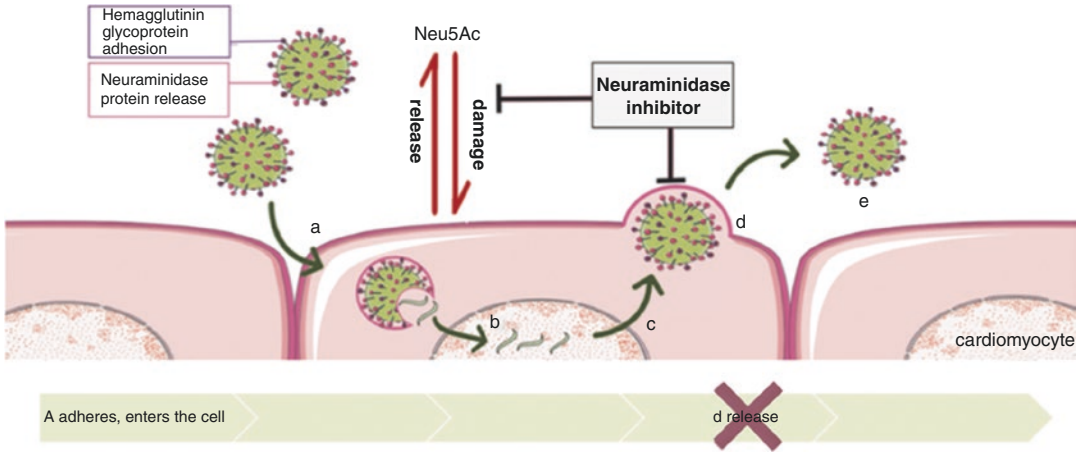

Fig. 14.13 Underlying mechanism of neuraminidase inhibitors

Fulminant Myocarditis in Adults" proposed a "life support-based comprehensive treatment regimen" to reduce the mortality rate of fulminant myocarditis from 50% to less than 5%. In the future, new treatment methods, such as treatments targeting Treg cells and Th17 cells, treatment with monoclonal antibodies against various cytokines, use of S100A9 inhibitors, global immunomodulation, and nanocarrier treatments, will be potentially suitable options for the treatment of fulminant myocarditis [49, 50].

Key Points

1. Immune response overactivation and inflammatory storms are the core causes of heart damage, pump failure, and circulatory collapse in patients.
2. The "life support-based comprehensive treatment regimen" has reduced the mortality rate of fulminant myocarditis to less than 5% in clinical practice.
3. The "life support-based comprehensive treatment regimen" includes mechanical circulatory support treatments, immunomodulatory treatments using substantial doses of both GCs and immunoglobins, and NA inhibitor treatments.

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15 Treatments of Fulminant Myocarditis in Acute Phase

Jiangang Jiang and Dao Wen Wang

Fulminant myocarditis usually has a sudden onset, rapidly progresses, and has a high mortality rate in the early phase, and the long-term prognosis of fulminant myocarditis patients is relatively good once the patients have survived the dangerous period after proper initial treatment [1]. Therefore, attention should be paid to early diagnosis and the timely treatment of fulminant myocarditis, and various possible measures should be taken to save the patient's life. In the acute phase, active comprehensive treatment methods should be adopted as soon as possible. General treatments (such as strict bed rest; nutritional support) and standard pharmacological therapy (including neutralizing the myocardium, reducing heart load, protecting functions of the stomach, the kidney, the liver, and the brain) is required. In addition, and most importantly, treatment during the acute phase also includes immunomodulation therapy using sufficient doses of glucocorticoids and of immunoglobulin, and mechanical circulatory support using intra-aortic balloon counter pulsation (IABP) and if necessary, addition of extracorporeal membrane oxygenation (ECMO). Other symptomatic and supportive treatments, such as temporary pacemaker implantation, ventilator-assisted breathing, etc. are used if necessary. Taking these comprehensive measures is aimed at stabilizing vital signs, reducing the work load of the heart as much as possible, lessening the frequency of complications to enable survival during the acute phase, and ultimately preventing the transformation into dilated myocardium disease in the chronic phase.

The high mortality and morbidity of fulminant myocarditis are related to its rapid progression, which usually leads to acute heart failure, malignant arrhythmias and cardiogenic shock complicated by dysfunction of hepatic, renal or hematologic systems in some patients. The prognosis following the traditional treatment regimen based on vasoactive drugs such as noradrenaline, dopamine and dobutamine is extremely poor. Therefore, none of these drugs is an ideal treatment option for patients with fulminant myocarditis. Based on the in-depth understanding and research findings of the pathogenesis and pathophysiology of fulminant myocarditis and of our clinical experiments, it is particularly important to actively use life support devices along with effective pharmacological treatment aimed at the cause in the early phase of fulminant myocarditis. Therefore, we have proposed a "Life-support based comprehensive treatment regimen" [2, 3]. Based on the pathogenesis and characteristics of fulminant myocarditis and its curability, the regimen emphasizes the importance and necessity of mechanical life support devices for circulatory

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support and immunomodulation for therapy of the causes, including severe myocardial inflammation and systemic cytokine storm, and reflects the comprehensive application of multiple treatment methods.

15.1 Treatment in Acute Phase: Core Treatments

1. Principles of treatment

   First, mechanical life support should be used to maintain hemodynamic stability and vital signs to allow the severely injured heart to rest rather than the administration of vasoactive and inotropic drugs forcing the heart to work hard;

   Second, immunomodulation therapy rather than immunosuppression should be applied to treat severe myocardial inflammation and oedema, and inflammatory storm induced by overactive immune responses;

   Third, neuraminidase inhibitors should be administered to reduce cardiac desialylation and to help reduce myocardium damage.

   The core treatment is a life-support based comprehensive treatment regimen [2].
2. Methods of treatment:

   First, substantial circulation should be maintained actively using mechanical circulatory support techniques including intra-aortic balloon counter-pulsation (IABP), extra corporeal membrane oxygenation (ECMO) or Impella, and if necessary, a respirator should be used to reduce oxygen consumption and cardiac workload because of respiratory stress. Vasoactive drugs should be avoided, especially norepinephrine, to maintain blood pressure. Thus, it is important to allow the severely injured heart to get some rest.

   Second, immunomodulation therapy should be actively administered to the patients, including substantial doses of glucocorticoids and substantial doses of intravenous immunoglobin G (IVIG), to treat severe myocardial inflammation, oedema, injury, and severe cardiogenic shock and to inhibit overactive immune reaction and cytokine storm.

   Third, injured myocardium releases a large number of neuraminidases, which cleave N-acetylneuraminic acid (NANA) of cell surface glycoprotein and induce further cardiac injury [4]. Application of neuraminidase inhibitors will help reduce myocardial injury.
3. Implementation of treatments

   Mechanical circulatory support treatment: Effective modes of mechanical life support treatment, especially those that provide mechanical circulatory support, are extremely important for the treatment of fulminant myocarditis and should be considered top priority in the clinical management strategy. Because the myocardium of patients with fulminant myocarditis is extensively and severely damaged, the pump function is severely impaired, resulting in hypotension, cardiogenic shock, and potentially fatal arrhythmia, complicated with pulmonary congestion and pulmonary inflammatory damage. Hence, it is difficult to maintain basic arterial blood pressure and satisfy the blood and oxygen requirements of the whole body. In the past, due to the lack of a correct understanding of the pathophysiology of fulminant myocarditis, traditional modes of treatment were symptomatic and were similar to dealing with shock due to other causes, such as use of cardiotonic treatment, volume expansion and vasoactive drugs (especially the use of norepinephrine, pituitrin, etc.). The new cardiotonic drug levosimendan (myocardial calcium sensitizer) is widely used in patients with fulminant myocarditis in Western countries such as in the United States and Germany [5]. These agents undoubtedly increase the load on the heart and make the situation of the already severely damaged heart even worse as the critically ill patient is faced with an extra burden when he/she is at the end of the tether. On the other hand, persistent large doses of norepinephrine will further decrease organ perfusion, and exacerbate organ injury and augment hypoxia. Although blood pressure can be maintained for a short period of time, the cardiovascular system cannot sustain effective functionality in the long run. According to our experience, long-term

usage of large doses of vasoactive agents (such as norepinephrine or pituitrin) will lead to hepatic necrosis, renal injury and disseminated intravascular coagulation (DIC) that can be difficult to reverse. The inotropes dopamine and dobutamine are likely to cause arrhythmia including a variety of tachyarrhythmias. The correct treatment should be to reduce the workload of the heart as much as possible and allow it to rest. This principle of optimal therapy is to maintain basic breathing and circulation through mechanical life support devices, so that the heart can fully recover, and at the same time its function can be restored with comprehensive systemic treatment. According to research by Carsten et al. [6], mechanical circulatory support can reduce cardiac inflammation. This is not difficult to infer because stress and sympathetic stimulation can promote inflammation via IL-18 [7]. Cardiotonic drugs or catecholamines, especially norepinephrine is the only alternative, and only used for a short time when the brain is still obviously hypoperfused after other drugs have failed and mechanical life support treatment is unavailable. Therefore, a "life-support based comprehensive treatment regimen" is specially proposed. Life support treatment includes respiratory support (using a ventilator), circulatory support (including intra-aortic balloon counterpulsation (IABP) and extracorporeal membrane oxygenation (ECMO)) and blood purification treatment.

15.2 Mechanical Circulation Support

The currently available clinical circulation support system includes IABP, ECMO, Impella and other left ventricular assist devices. IABP and ECMO are commonly used due to their quick and easy implementation and have a much higher efficiency:cost ratio.

1. Intra-aortic balloon pump or intra-aortic balloon counter-pulsation (IABP):

A balloon catheter is inserted from the arterial system to the descending aorta below the opening of the left subclavian artery and above the opening of the renal artery, and the size of balloon for an adult is about 30~50 mL. The balloon is continuously and rhythmically inflated and deflated during the diastolic period of the cardiac cycle to reduce the burden on the heart. When the balloon is inflated quickly during the diastolic phase, it occupies the dilated lumen of the aorta to increase the diastolic pressure by enhancing the recoil of the elastic tissue in the tunica media, so that an increase the circulatory perfusion of important organs such as heart, kidney and brain, as well as peripheral organs results; when the balloon is deflated immediately before systole, the pressure in the aorta decreases, reducing the afterload and the work performed by the heart when it is contracting, increasing the stroke volume, the forward blood flow, and perfusion of the entire body. In fulminant myocarditis patients with unstable hemodynamics, the application of IABP can reduce the usage and dosage of vasoactive drugs to help patients pass through the acute phase. Clinical experience from our group and others abroad has proven that IABP has obvious adjuvant therapy effect on severe myocardial injury in treating fulminant myocarditis, and systolic blood pressure is usually elevated by 20–25 mmHg with reduction in heart rate of about 10 beats per minute. Once patients with fulminant myocarditis display cardiogenic shock, hypotension, and other signs of hemodynamic instability such as the need for vasoactive drugs to maintain blood pressure or to alleviate elevation of heart rate, the implantation of IABP should be initiated immediately rather than administration of vasoactive drugs [8, 9]. If IABP is not sufficient to support an adequate circulation, ECMO should be added promptly, that is, the combined application of both IABP and ECMO [10]. ECMO can decrease preload but increase afterload, while IABP can decrease afterload. Hence, the combined application of IABP and ECMO can minimize their

respective shortcomings and maximize their auxiliary effects, and can meet the patient's demand for cardiorespiratory support treatment [11, 12]. Intra-aortic balloon counterpulsation (IABP) is composed of a cylindrical balloon fixed to a catheter and placed in the thoracic aorta. The proximal end of the catheter is located at the end of the left subclavian artery, and the distal end is located above the renal artery. The balloon inflates when the heart relaxes and deflates when the heart contracts. This results in a double hemodynamic effect: the diastolic inflation driving the blood flow forward, and increasing the diastolic blood pressure and coronary perfusion. The balloon is deflated before the heart contracts to reduce the systolic pressure by reducing cardiac afterload and improve left ventricular ejection function (LVEF). The balloon can be programmed to inflate and deflate once in each cardiac cycle (1:1 mode) or once every two cardiac cycles (1:2 mode) based on heart rate (Fig. 15.1). The size of the balloon can also be adjusted according to the amount of gas entering the balloon. One of several different models of IABP is selected by the physician according to the patient's height and weight (Table 15.1).

Diagnostic criteria for cardiogenic shock: (1) Heart index < 2L/(min·m^2); (2) Mean arterial pressure (MAP) < 60 mmHg or systolic blood pressure <90 mmHg or reduction in systolic blood pressure of over 20 mmHg from the baseline level; (3) Left atrial pressure

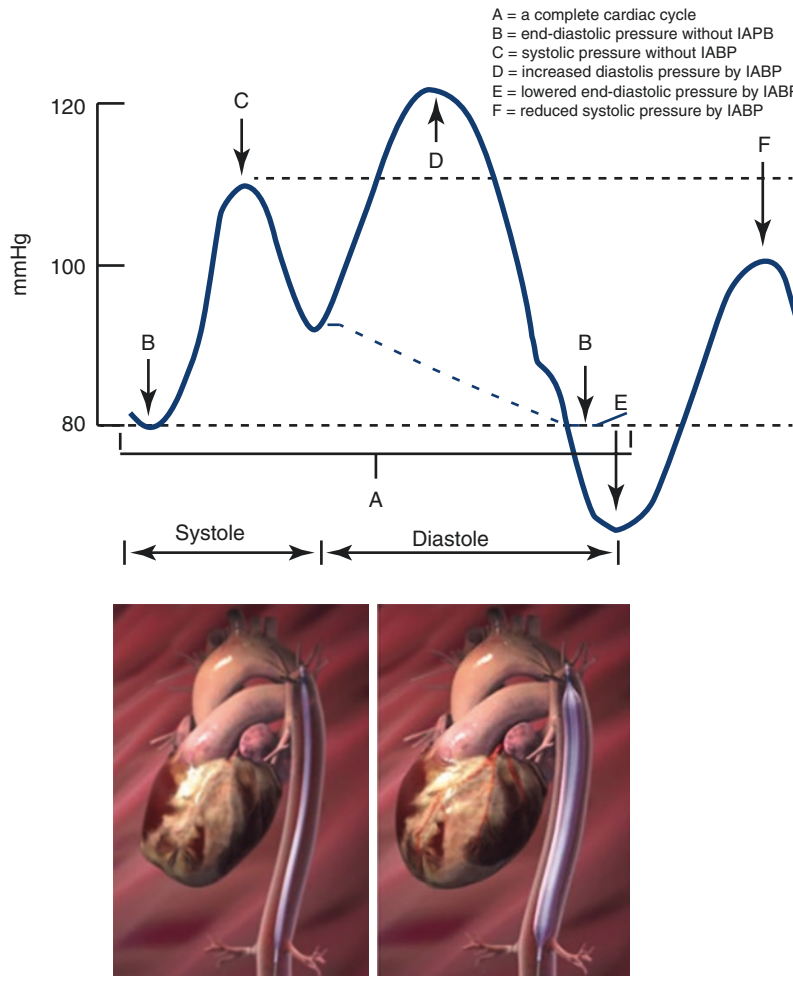

Fig. 15.1 Illustration of working mechanism of IABP (upper panel). Lower panel is a schematic diagram of IABP working in cardiac systole and diastole, respectively

Table 15.1 Selection of the sizes for counter-pulsation balloon and catheter/sheath based on patient height

Specs	Sensation plus	Sensation	Sensation plus	Sensation
Balloon size	40 mL	34 mL	50 mL	40 mL
Patient height	152–162 cm	152–162 cm	≥162 cm	162–183 cm
Catheter/sheath size	7.5 Fr	7 Fr	8 Fr	7 Fr
Balloon diameter	16 mm	15 mm	17.4 mm	15 mm
Balloon length	229 mm	221 mm	258 mm	258 mm
Guidewire	0.63 mm	0.45/0.63 mm	0.63 mm	0.45/0.63 mm
Inner lumen	0.69 mm	0.51 mm	0.69 mm	0.51 mm

(LAP) or pulmonary capillary wedge pressure (PCWP) > 20 mmHg; (4) Urine volume < 20 mL/h for an adult, cold periphery, cyanosis, and weak peripheral circulation; (5) Heart rate of over 100 per minute or the need to use dopamine or even norepinephrine or (6) Physician's opinion that the heart is hypodynamic and requires mechanical assistance.

The above criteria are defined in the literature including in textbooks. Undoubtedly IABP should be implanted when these criteria are met. However, in the treatment of fulminant myocarditis, it is not necessary to use IABP unless all these criteria are met. We emphasize early usage of mechanical circulatory support. When the patient has the above-mentioned conditions or a state of hypotension or shock, IABP should be implanted as early as possible. Our experience has demonstrated that the use of IABP can increase the systolic blood pressure by more than 20 mmHg, permitting significant reduction of the dosage of vasoactive drugs required, and lowering the increased heart rate. Most clinical observations in China proved that the earlier the treatment is started, the greater the benefit derived by patients with the above-mentioned indications. More than 70% of patients with fulminant myocarditis are able to maintain an effective circulation after IABP application in the timescale that we suggest [13, 14]. Therefore, we advocate starting this treatment as early as possible.

For patients with fulminant myocarditis, the indications for weaning the patient off IABP are as follows: (1) stable hemodynamics; (2) heart index > 2.5 L/min·m^2; (3) systolic blood pressure > 100 mmHg, MAP > 80 mmHg; (4) PCWP < 18 mmHg; (5) Urine volume > 1 mL/kg·h; (6) conscious state and good peripheral circulation, and a dose of dopamine of less than 5 μg/kg·min.

The contraindications for IABP are: (1) coexistence of aortic dissection, aortic aneurysm, or aortic sinus aneurysm; (2) aortic regurgitation, especially moderate or severe; (3) severe aortic-iliac artery disease; (4) coagulation dysfunction; (5) other conditions such as severe anemia, acute cerebral hemorrhage, etc. Complications of IABP include: acral ischemia (5–47%), thrombosis or embolism (1–7%) [15]. Other complications such as arterial perforation, bleeding, infection, aortic dissection, thrombocytopenia, etc. are also common. Thromboembolism caused by IABP is usually attributed to the following mechanisms: vortex formation in the arterial lumen leading to platelet aggregation driven by the centrifugal effect of the vortex; balloon flapping causing atherosclerotic plaque fragmentation and shedding. The balloon can precipitate terminal thrombosis and dislodgment of emboli. Some patients have a hypercoagulable state. Therefore, prophylactic anticoagulants should be administered to patients receiving IABP. The common anticoagulation measures taken in China include: heparin 0.5–1 mg/kg intravenously every 6–8 h; monitoring of ACT every 2 h to maintain ACT time > 180 s; or monitoring APTT to maintain 1.5–2 times to its normal state; infusion of 100 mg heparin diluted in 50 mL normal saline at a rate of 2–4 mL/h uniformly and slowly with a micro pump, with the same

monitoring indicators as above. No extra monitoring is needed when low molecular weight heparin b.d. is used. Low molecular weight dextran is used at a rate of 1–20 mL per hour.

IABP pipeline flushing: diluting 12,500 U heparin in 500 mL normal saline, flushing the pipeline with 5 mL of it each time every hour, and totally flushing the pipeline with about 200–250 mL in 24 h to infuse 3000–5000 U heparin. If IABP is implanted before or during intervention, intravenous heparin should be continued after intervention to maintain activated clotting time (ACT) at 250–300 s. Low molecular weight heparin should not be used because of significantly increased incidence of embolism and ischemic events. If clotting factor IIb/IIIa receptor antagonists are used, intravenous heparin should not be used for anticoagulation considering the elevated risk of bleeding. If IABP implantation is needed for a long time, heparin should be added to extend the activated partial thromboplastin time (APTT) to 50–70 s after discontinuing the IIb/IIIa receptor antagonist.

2. Extracorporeal Membrane Oxygenation (ECMO)

ECMO is usually used in combination with IABP. It can help the severely injured and failing heart to rest as well as aid pulmonary function, and save time for treatment and functional recovery of myocardial inflammation and shock. Because patients with fulminant myocarditis are in a more serious state than those with common myocarditis, the shock and pump failure may become worse in just a few hours. ECMO should be applied immediately when IABP is insufficient to maintain the basic circulation and shock is refractory to treatment. Critically ill patients, such as those with cardiogenic shock, heart index less than 2.0 L/min·m^2, and blood lactate greater than 2 mmol/L, can benefit greatly from ECMO treatment. For such patients, ECMO treatment should be used actively and as soon as possible, and it can save the lives of these critically ill patients. Our experience demonstrated that in some fulminant myocarditis patients (about 20–25% of the total admitted patients) who are unstable and whose circulation is sub-optimal even after IABP implantation, supplementation with ECMO can result in reversion to stable hemodynamics.

ECMO originated in the 1970s. The main design idea is to replace the open oxygenation method in conventional cardiopulmonary bypass with closed membrane oxygenation to overcome the shortcomings of conventional open cardiopulmonary bypass such as complexity of equipment, high rate of complications, heavy bleeding, and limited bypass duration. After decades of continuous improvement, ECMO has gradually become a portable extracorporeal mechanical assist device that is simple and convenient to operate at the bedside, requiring no surgical intervention, and providing longer-term life support. ECMO is mainly composed of three parts: (1) the piping system that draws blood from the body and returns it to the body; (2) the power pump (artificial heart) that keeps the blood flowing fast; (3) the closed membrane oxygenator that subjects the blood to gas exchange (membrane lung). Other auxiliary devices include constant temperature water tanks, oxygen supply pipelines, and various monitoring systems.

The treatment of fulminant myocarditis by ECMO has been supported by a large amount of clinical data [12, 16]. The median number of ECMO treatment days is reported to be 5–9, and the survival and discharge rate is 55–66% [12, 17]. A meta-analysis showed that the survival rate of patients with fulminant myocarditis receiving circulatory support, especially ECMO, was significantly higher than those treated by other means (Table 15.2) [18, 19].

Although ECMO can provide sufficient circulatory support to severe cardiogenic shock patients, its complications should also be borne in mind. Complications such as extremity ischemia, intracranial hemorrhage, thromboembolism, infection of ECMO tube and long-term depression are all possible dur-

Table 15.2 Analysis of clinical outcome of adult fulminant myocarditis

Author, year	Number of cases	Pathogen	Myocardium infiltration	Treatment	Survival rate (%)
Saji 2012	64	Virus	Lymphocyte, Eosinophil	IVIG, GC, MCS	52
Ning 2013	5	–	–	ECMO	80
Ukimura 2013	29	Influenza virus A	–	MCS	72
Polito 2015	6	–	–	MCS	67
Lin 2016	18	–	–	ECMO	78
Okada 2016	8	1 patient of mumps virus and 7 patients with undefined pathogen	–	ECMO	63
Vigneswar 2016	11	Parvovirus B19	Lymphocyte	IVIG	54
AN 2016	43		–	ECMO	
Inaba 2017	42		–		85
Chin 2018	13	Tsutsugamushi Disease	–	GC	84.50
Hekimian 2018	4	Influenza B Virus		ECMO	100
Liao 2018	33			ECMO	79
Ammirati 2019	165	Virus	Lymphocyte, eosinophil, macrophage	IVIG, GC, MCS	72

IVIG intravenous immunoglobulin, *MCS* mechanical circulation support, *ECMO* extracorporeal membrane oxygenation, *GC* glucocorticoid

ing ECMO implementation. Besides careful monitoring of coagulation function to avoid thromboembolism or bleeding, it is important to make a thorough and comprehensive nursing plan for patients receiving ECMO treatment [20, 21].

15.3 Immunomodulation Therapy

The pathophysiological mechanism of myocardial injury in the development of fulminant myocarditis includes direct damage to the myocardium by viruses or other pathogens or allergens in the early stage, and excessive immune activation triggered by the infiltration of a large number of inflammatory cells, including neutrophils, monocytes/macrophages, and lymphocytes. These inflammatory cells themselves and local tissue cells release large quantities of cytokines, inflammatory mediators and antibodies including autoantibodies, leading to myocardial damage, necrosis, inflammatory exudation, edema, inhibition of myocardial function and shock (discussed in detail in Chap. 4). An important part of our "Life-support based comprehensive treatment regimen" is to use both sufficient doses of glucocorticoids and adequate doses of immunoglobulin to modulate the pathophysiology of excessive immune activation and inflammation storm. In theory, it can block the pathogenesis, relieve shock, and reduce symptoms, preserve the myocardium, and improve prognosis. Although there is a shortage of large-scale multi-center clinical trials, the existing evidence from our multicenter work suggests its effectiveness and safety. We do not suggest "immunosuppressive" treatment with cytotoxic drugs as used in western countries.

1. Sufficient dose of glucocorticoids.

   We suggest intravenous infusion of 200–500 mg methylprednisolone daily in the first few days, and close observation of changes in the patient's condition, especially changes in circulatory status and cardiac function. In our patients LVEF reached a minimal level but then rebounded after 3–5 days of treatment. The dosage can be gradually reduced after the obvious improvement, and glucocorticoid should be maintained for 2 weeks.

   Why is sufficient dosage of glucocorticoid vitally important in treatment of fulminant

myocarditis? The basis of using glucocorticoid entails several key points: First, the pathophysiological basis of fulminant myocarditis is an overactive immune system and formation of cytokine storm. From pathological examination of endomyocardial biopsy samples, massive lymphocyte and macrophage infiltration can be observed. Hence, applying glucocorticoids can inhibit activated lymphocytes and decrease production of antibodies to suppress antigen-antibody reaction. Second, glucocorticoids exert anti-inflammatory and anti-allergic effects. Third, they also alleviate shock. Fourth, because obvious oedema of the myocardium is evident in fulminant myocarditis, glucocorticoid treatment is useful to reduce inflammatory exudates and alleviate oedema. Fifth, glucocorticoids can upregulate the expression as well as the activity of nitrite oxide synthase (NOS) in cardiomyocytes and in the endothelium, thereby maintaining the viability of myocardium [22]. Sixth, our recent work demonstrated great alteration of arachidonic acid metabolism under septic shock, which results in significantly decreased production of eicosatrienoic acids (EETs). In addition, glucocorticoids can modulate the metabolism of arachidonic acid and preserve the level of EETs to enhance the production of interferon and bring about immunomodulation effects.

The concern regarding promotion of virus replication by glucocorticoids is a fallacy. First, under the emergency posed by cardiogenic shock, the overriding problem is risk of death. The primary aim is to save life. Besides, although viral infection is the trigger of disease, when the myocardium is already severely damaged, the subsequent cytokine storm is the principal life-threatening factor rather than viral infection [22]. Theoretically, glucocorticoids should be used in the second stage of viral myocarditis, that is, the immune-mediated damage stage, and should be avoided in the first stage, namely the virus replication and viral damage stage, because glucocorticoids may lead to increased virus replication. However, for fulminant myocarditis, the first stage is quite short. When the patient has obvious symptoms, he or she may already enter the second stage, namely the cytokine storm and overactive immune response stage. Therefore, for severely ill patients, early use of glucocorticoids in sufficiently high doses is recommended. Concern regarding enhancement of virus replication is not warranted. An initial bolus of 10–20 mg dexamethasone intravenously can be given, followed immediately with methylprednisolone by intravenous infusion to induce an expedient response.

A previous Cochrane meta-analysis summarized 4 effective clinical trials using glucocorticoids for the treatment of viral myocarditis involving 719 cases [23, 24]. The results showed that although there was no significant difference in mortality between the treatment group and the control group, the LVEF of the treatment group was significantly higher than that of the control group during the 1–3-month follow-up period (Table 15.3).

It is worth noting that glucocorticoid treatment did not cause increased virus replication or exacerbation of disease. Therefore, the safety of glucocorticoid treatment can be confirmed at least in our practice [3, 25]. There are no large-scale clinical studies on the use of glucocorticoids in fulminant myocarditis and only a few cases have been reported. In 2016, Bjelakovic et al. reported two cases of successful treatment of high-dose methylprednisolone in children with fulminant myocarditis [26]. Both children suffered cardiogenic shock, metabolic acidosis, hypoxemia and hyperlactic acidemia, requiring high doses of dopamine and dobutamine, but their condition continued to worsen. After the application of high-dose methylprednisolone 10 mg/kg·h, the condition improved significantly. Blood pressure and oxygen saturation returned to normal 10 h after treatment, and left ventricular function completely returned to normal within 2 weeks. Our multi-center studies have also shown that the efficacy of glucocorticoids in sufficient doses is definite, and further experimental studies have found that glucocorticoid treatment in fulminant myocarditis did not continuously increase

Table 15.3 Meta-analysis of clinical randomized controlled trials of administration of glucocorticoid in myocarditis

Protocol design	Main endpoint	Outcome
Randomized controlled trial of 102 patients with idiopathic dilated cardiomyopathy (prednisolone vs. placebo)	Changes in LVEF and LVDD at 3 months	There was improvement of 4.3 ± 1.5% in LVEF in prednisolone group ($P < 0.054$)
Randomized controlled trial of 111 patients with myocarditis (prednisolone vs. placebo)	Change in LVEF after 28 weeks	No significant changes
Randomized controlled trial of 84 patients with inflammatory dilated cardiomyopathy (prednisolone vs. placebo)	Rate of death, heart transplantation or readmission at 2 years	No significant changes
Randomized controlled trial of 84 patients with inflammatory and virus-negative dilated cardiomyopathy (prednisolone vs. placebo)	Change in LVEF after 6 months	Significant elevation of LVEF in prednisolone group compared with placebo group

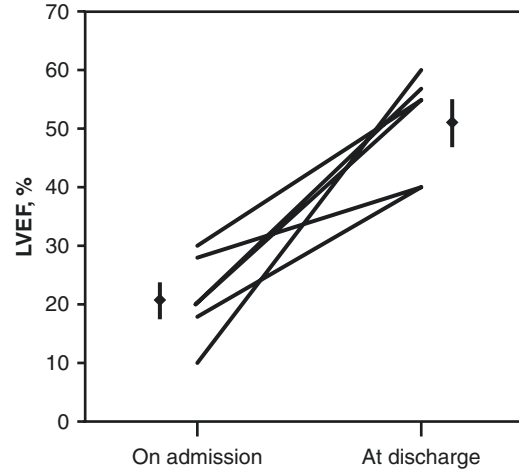

Fig. 15.2 Comparison of left ventricular ejection fraction of patients at admission (21.7 ± 7.5%) and discharge (50.3 ± 8.6%), $P = 0.005$

virus replication; on the contrary, it even inhibited its replication [3]. The mechanism may be related to the activation of arachidonic acid metabolism to produce epoxyeicosatrienoic acids (EETs), which can promote interferon production.

2. Sufficient dose of immunoglobulin (IVIG)

We recommend intravenous infusion 20–40 g per day for 3–4 days, then 10–20 g per day for 5–7 days or longer for adults.

Immunoglobulin can not only neutralize pathogens such as viruses, but more importantly, it is an immunomodulator and anti-inflammatory agent. Immunoglobulin can bind to Fcγ receptors, regulate the functions of antigen-presenting cells (dendritic cells) and T helper cells, reduce the number of cytotoxic M1 macrophages and promote the number of anti-inflammatory M2 macrophages, inhibit excessive activation of cellular immunity, reduce the attack launched by cytotoxic T cells on cardiomyocytes, prevent cytokine production and inhibit the formation of inflammatory storms, thereby reducing the myocardial damage and improving left ventricular function, ultimately reducing the occurrence of malignant arrhythmias and death [27].

Although there is still a lack of large-sample prospective randomized controlled clinical studies, some small-sample studies have confirmed that IVIG has a favorable therapeutic effect in fulminant myocarditis. An early observational study [28] in the United States of six patients with fulminant myocarditis with LVEF < 30% treated with high-dose of IVIG showed that LVEF increased from 21.7 ± 7.5% before treatment to 50.3 ± 8.6% after treatment ($P = 0.005$). After an average follow-up of 13.2 months, the LVEF was still maintained at 53 ± 6%, and no patient required rehospitalization during the follow-up period (Fig. 15.2).

The results of a controlled study [29] of 21 children with acute myocarditis who were treated with high-dose IVIG (2 g/kg, injected within 24 h) showed that compared with 26 cases in the control group, there was a significant improvement of the left ventricular end

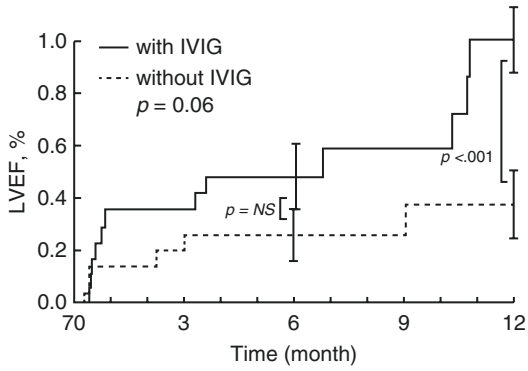

Fig. 15.3 Analysis left ventricular function of patients receiving and not receiving immunoglobulin

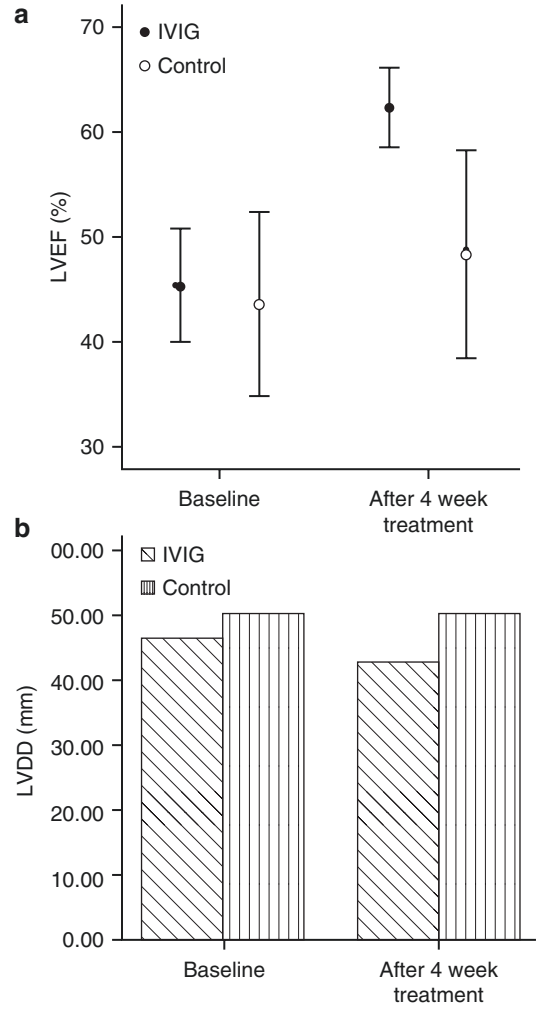

Fig. 15.4 Tendency of the differences in left ventricular ejection fraction (**a**) and left ventricular diastolic diameter (**b**) at baseline and after 4 weeks of immunoglobulin treatment. *LVEF* left ventricular ejection fraction, *LVDD* left ventricular diastolic diameter

diastolic diameter (LVEDD) in the treatment group during follow-up ($P = 0.008$ from 3 to 6 months; $P = 0.072$ from 6 to 12 months). Left ventricular function improved significantly after 6 months (Fig. 15.3).

A recent clinical multicenter controlled study of 41 patients with acute myocarditis in Japan [30] showed that high-dose IVIG (1–2 g/kg body weight/day, applied for 2 days) can significantly improve the patients' survival curve ($P < 0.01$), The first month mortality rate had a downward trend (20.0% in the treatment group vs. 34.6% in the control group), and the inflammatory mediators in the peripheral blood such as TNF and IL-6 were significantly lower in the treatment group ($P < 0.01$). A retrospective study of 58 children with fulminant myocarditis in Guangdong23 showed that patients treated with IVIG 400 mg/kg body weight/day for 5 days showed significantly improved LVEF and end-diastolic diameter compared with the control group (without IVIG) after 4 weeks (P values were 0.011 and 0.048, respectively) (Fig. 15.4). The incidence of ventricular tachycardia and ventricular fibrillation was significantly reduced after IVIG treatment ($P = 0.025$) but not significantly changed in the non-treatment group ($P = 0.564$); the mortality rate was 6% in the treatment group but 27% in the control group, although due to the small sample size, it did not show significant statistical difference ($P = 0.072$), but the downward trend is obvious. It is worth noting that 33% of patients in the treatment group received IABP treatment due to heart failure/cardiogenic shock, while only 16% in the non-IVIG treatment group, suggesting that patients in the treatment group may have been more severely ill, but here, too, there was no statistically significant difference due to small sample size (P = 0.073) [31].

The total dose of IVIG should be adequate and should be applied as soon as possible. A retrospective analysis published in 2015 did not support the view that the use of IVIG

treatment in fulminant myocarditis can reduce mortality during hospitalization [24]. However, after careful analysis it was found that, first, most patients in the treatment group failed to receive IVIG at a total dose of 2 g/kg body weight; insufficient dosage may be a cause of poor efficacy. Second, the study only included patients who were treated with IVIG after mechanical circulatory support, and excluded patients who had been treated with IVIG before mechanical circulatory support. Obviously, by the time the application of mechanical assist devices is needed, the patient's condition is already quite severe. At this time, it may be too late to start IVIG treatment to attain maximal beneficial effects. Therefore, the dose and timing of IVIG administration may be the key to the current controversy about the inconsistency of its efficacy, and it needs to be further confirmed by high-quality larger clinical trials.

15.4 Administration of Neuraminidase Inhibitors and Antiviral Drugs

Neuraminidase inhibitors are used to treat influenza by inhibiting type I neuraminidase of influenza virus to suppress virus spread and exhibit an anti-viral effect. Early administration can result in a more potent effect. Some reports indicate that earlier administration of the neuraminidase inhibitor oseltamivir was associated with an improved outcome, lowered mortality rate by 50% (hazard ratio (HR) = 0.49; 95% CI 0.28–0.87; $P = 0.01$) in influenza-induced fulminant myocarditis compared to later administration [32].

However, fulminant myocarditis is usually sporadic, can be caused by different viruses, and other pathogens, chemicals, toxins or even checkpoint inhibitors. It is clear that expression of type I to IV neuraminidase can be detected in human myocardium. When myocardium is damaged, expression of neuraminidase, especially type III neuraminidase, is significantly upregulated and released into the circulation. Circulatory neuraminidase can digest neuraminic acid at the extracellular domain of membrane proteins, causing instability of membrane proteins and exacerbating cardiac injury [33]. We have observed significant upregulated level of plasma acetylneuraminate in fulminant myocarditis, and treatment with oseltamivir (75 mg, bid for 7 days) can significantly improve clinical outcomes.

There are also some concerns regarding the use of other nonspecific anti-viral agents. Because precise determination of a viral etiology is not possible in the majority of patients, the use of anti-viral agents such as acyclovir and ganciclovir are not recommended. Recently, Veronese et al. reported several viruses including parvovirus B19, adenovirus, human herpes virus type 6 and enterovirus in myocardial biopsy samples in 165 cases of fulminant myocarditis and 55 cases of non-fulminant myocarditis. According to this research, 34% European, 17% American and 3% Japanese patients were virus-positive, and 22% of the positive samples from patients with lymphocytic myocarditis had PVB19 [34]. Considering these results, it might be of benefit to use non-specific anti-viral therapy. Large prospective studies are warranted to address the role of virus identification and effect of specific antiviral therapy on clinical outcomes [35].

1. Neuraminidase inhibitors

   oseltamivir and peramivir inhibit the neuraminidase of influenza virus, thereby inhibiting the release of newly synthesized virus particles from infected cells and the replication of the virus in the human body, showing efficacy in myocarditis caused by type A or B influenza viruses [36]. Oseltamivir phosphate (Tamiflu) capsules are recommended when needed, and the dosage is 75 mg orally bid. Peramivir injection is the first intravenous neuraminidase inhibitor licensed in China. The dosage is 300–600 mg by intravenous infusion for 1–5 days. In fact, most doctors are not aware of the mechanism of action of neuraminidase inhibitors, and it may not be related to antiviral effects. Neuraminidase (including four subtypes) is widely present in human cells and tissues including the myocardium. When tissue is damaged, its expression

increases, and neuraminidase is released out of the cell into the circulation, digesting the neuraminic acid at the glycosylated end of the cell surface protein, thereby leading to the myocardial damage [4]. Our research has shown that the plasma levels of N-Acetylneuraminic acid and neuraminidase proteins are significantly higher in patients with fulminant myocarditis, and the use of oseltamivir is benefitial [3], which further supports this hypothesis. Thus, use of non-specific inhibitors of neuraminidase may be beneficial in all patients with severely injured myocardium.

2. Acyclovir

Acyclovir, a guanylate analogue, is effective against DNA viruses such as Epstein-Barr virus, and may be effective in patients with myocarditis caused by Epstein-Barr virus [37]. Ganciclovir (0.5–0.6 g/day intravenously) is effective against cytomegalovirus. Since the exact type of virus causing myocarditis is not confirmed in most patients, a combination of antiviral drugs can be considered.

3. Interferon

Interferon can be tried, especially for patients infected with enterovirus. A small-sample study from Germany showed that after continuous administration of interferon therapy (106 IU/week) for 24 weeks, the patient's heart size and cardiac function were effectively improved (Fig. 15.5) [38]. However, more clinical evidence is still needed to support the clinical application of interferon in acute myocarditis [39].

Research on the treatment of parvovirus B19 with telbivudine is currently in progress. Finally, Chinese Journal of Cardiology published several clinical studies showing that as long as this treatment regimen was used, excellent therapeutic effect is obtained [40, 41].

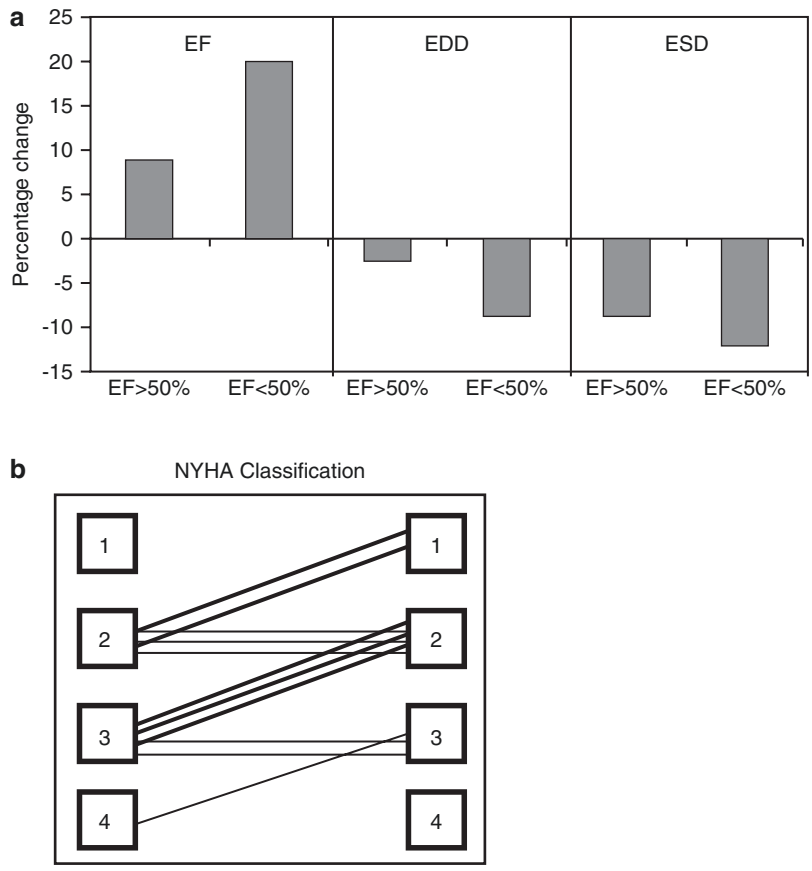

Fig. 15.5 Hemodynamic changes in patients with global (EF 50%) versus regional (EF 50%) LV dysfunction (**a**) and heart function class (**b**) before and after IFN-γ therapy. *EF* left ventricular ejection fraction, *EDD* end diastolic diameter, *ESD* end systolic diameter. (Modified from Kühl et al. [38])

15.5 Assessment of Treatment Effects

With the improvement in physicians' awareness of the disease and the diversification of diagnostic methods, most patients with myocarditis can be diagnosed based on clinical symptoms, signs, and appropriate auxiliary investigations. However, different treatment methods determine the prognosis of patients. Clinical data of 169 patients diagnosed as fulminant myocarditis was used to analyze the effect of various modes of treatment on the prognosis [3]. The traditional treatment group refers to those treated with conventional medications such as high-dose vasoactive drugs, especially dopamine and noradrenaline as first-line treatment of heart failure and cardiogenic shock to maintain hemodynamic stability. If traditional medication is not sufficient to improve the deranged hemodynamics, then life-support devices, such as intra-aortic balloon pump (IABP) and, continuous renal replacement therapy (CRRT) are applied. Antiviral drugs, intravenous immunoglobulins, and glucocorticoids are used according to the doctor's personal experience. However, the mechanical life support-–based comprehensive treatment regimen needs to meet the following criteria: (1) Using glucocorticoids immediately after admission (immediately give dexamethasone 20 mg bolus intravenously once, followed by intravenous injection of methylprednisolone 200–500 mg od for 5 days); (2) Sufficient doses of intravenous immunoglobulin (over 20 g/day for 5–10 days). Glucocorticoids plus immunoglobulin can be administered; (3) Applying neuraminidase inhibitor for 5–7 days; Mechanical life-support treatment, mainly mechanical circulatory support, is essential for all patients with fulminant myocarditis. For circulatory support, immediately use IABP. If IABP still does not help make the patient hemodynamically stable, implement extracorporeal membrane oxygenation (ECMO) immediately. Respiratory support should be used according to the patient's condition. For patients with difficulty in breathing and reduced or elevated (>20 breaths/min) breathing rate, biphasic positive airway pressure ventilation is preferred. If dyspnea cannot be improved or the patient cannot tolerate it, endotracheal intubation and ventilator assisted ventilation can be considered. Vasoactive drugs such as dopamine, norepinephrine, etc. are only used during the preparation phase for IABP or ECMO, maintaining the systolic pressure at around 86–90 mmHg until IABP or ECMO is successfully installed. All patients are closely monitored for vital signs and receive general treatment, including invasive blood pressure, ECG, and oxygen saturation monitoring. Absolute bed rest is advised, avoiding any mental stimulation and sympathetic system stimulation. The amount of water intake and urine output are closely controlled.

Other adjunctive drugs: improving myocardial metabolism including by the use of coenzyme Q10, or trimetazidine is recommended, as well as supplements of water-soluble and fat-soluble vitamins which may help the injured liver and prevent DIC. We start CRRT treatment immediately for 8–20 h a day for 3–7 days which helps regulate fluid balance and also helps excrete some cytokines.

The results of the study are as follows: There was no significant difference between the traditional treatment group and the life support treatment group in terms of baseline conditions (age, gender, visit time, symptoms, myocardial injury markers, liver and kidney function, and peak left ventricular ejection fraction), but the main endpoint of the observation was the in-hospital mortality rate, which was 59.6% in the traditional treatment group but only 5.6% in the life-support treatment group and the difference was statistically significant ($P < 0.01$) (Fig. 15.6). The average length of hospital stay in the traditional treatment group was 14 days, whereas it was 12.5 days in the life-support treatment group ($P < 0.05$), suggesting that the length of hospital stay was shortened by life-support treatment. The mortality and length of hospital stay in the mechanical life support treatment group were significantly better than those in the traditional treatment group ($P < 0.05$). In particular, the difference in mortality rate confirmed the advantages of life-support treatment (Fig. 15.6).

The subgroup analysis involved performing independent statistical analysis on the individual special treatment modalities such as antiviral drugs, intravenous immunoglobulin, high-dose glucocorticoids, IABP and CRRT. The results indicated that the use of IABP, antiviral drugs, immunosuppressive agents, CRRT, and high-dose glucocorticoid all exhibited a tendency to reduce the in-hospital mortality rate, and especially the use of IABP and the use of antiviral drugs showed statistical significance when compared with not using them (all $P < 0.05$) (Fig. 15.7).

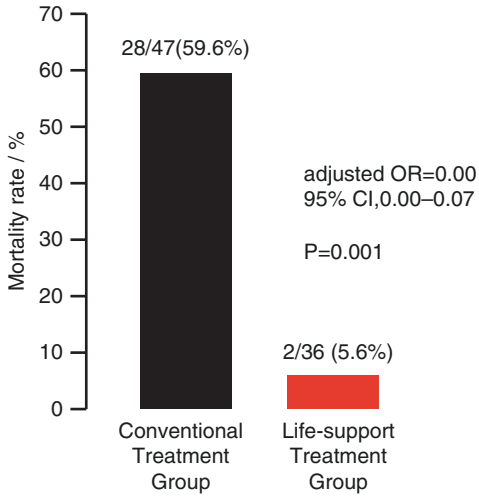

Fig. 15.6 In-hospital mortality rate of traditional treatment group and life support treatment group

15.6 Auxiliary Care

1. Respiratory support-mechanical ventilation

   It has been reported that a ventilator can be used as an auxiliary treatment for acute left ventricular failure, which can improve lung function, reduce cardiac workload and importantly, save energy and relieve the burden placed on the failing heart [2, 10]. According to the "rest the heart" principle, a ventilator can be actively used even before the confirmation of hypoxemia under normal oxygen inha-

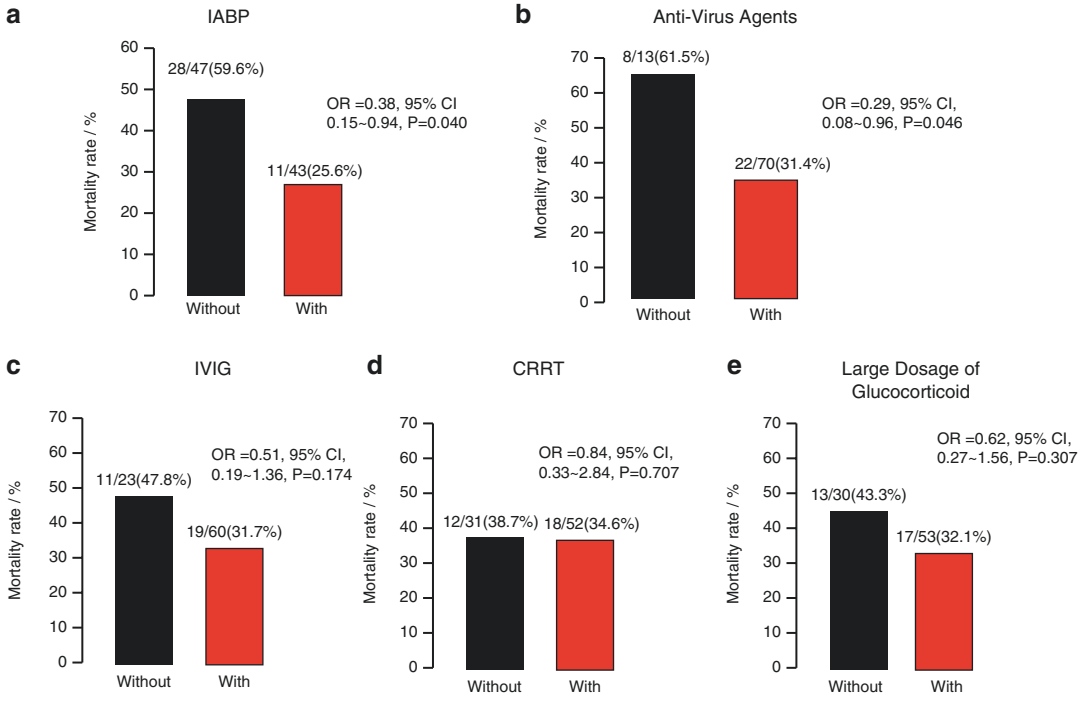

Fig. 15.7 Independent analysis of the relationship of in-hospital mortality rate between use and non-use of each component of special treatment

lation. When the patient has dyspnea, and increased breathing rate or tachycardia, positive pressure inhalation is recommended to reduce the burden on the patient and the workload of the heart. There are two ways to afford respiratory support. One is the provision of non-invasive ventilator-assisted ventilation, which is divided into two modes: continuous positive airway pressure ventilation and biphasic intermittent positive airway pressure ventilation. It is recommended for patients who have difficulty in breathing or have a breathing rate of >20 breaths/min or respiratory distress, and who can cooperate with the operation of ventilator ventilation. The second is endotracheal intubation and artificial mechanical ventilation: indications for this modality include cardiopulmonary resuscitation or respiratory failure, especially for patients with obvious respiratory and metabolic acidosis that affect their consciousness. We encourage the active use of mechanical ventilation in fulminant myocarditis patients with the above-mentioned clinical features. Endotracheal intubation and mechanical ventilation should not be withheld when there are relative counterindications to its use e.g., certain respiratory diseases. Taken together, a ventilator should be used as soon as possible to give some respite to the patient and reduce the burden on the heart, even if the blood oxygen saturation is still normal but the breathing is fast and laborious [42].

2. Blood purification

The main purpose of blood purification is to continuously filter and remove cytotoxins and inflammatory factors. It should be actively implemented in the early phase when cardiopulmonary dysfunction is combined with renal impairment. Blood purification treatment can also reduce the load on the heart through ultrafiltration, ensuring good water, electrolyte, and acid-base balance, and restoring the response of blood vessels to vasoactive drugs to treat heart failure, which is of great help to patients with fulminant myocarditis. It is worth noting that this therapy needs to be carried out continuously, for at least 8–12 h a day, to remove toxic substances. Another important point is that blood drainage and reinfusion must be very slow at the beginning and during termination because of extremely fragile cardiac function of the patient at this time, so as not to induce heart failure.

An inflammation storm occurs due to infiltration of a large number of inflammatory cells including monocytes, lymphocytes, and neutrophils, in response to viral or other microbial infections, which activate cellular immunity and humoral immunity, and stimulate the production of cell adhesion molecules and cytokines accompanied by antibody production. Local inflammation helps to remove pathogens and necrotic tissues, but the inflammatory storm (a large number of inflammatory factors and cytokines) will further damage the heart, blood vessels and other tissues, and plays the most important role in the occurrence and progress of the disease [43]. In addition to maintaining the balance of the internal environment in the body, blood purification treatment can also help to remove inflammatory mediators, which is of great benefit to patients with fulminant myocarditis. Studies have shown that early and effective stabilization of the hemodynamics of patients with fulminant myocarditis and reduction of subsequent immune damage can significantly improve the prognosis.

(a) Continuous veno-venous hemodiafiltration (CVVHDF): Renal replacement therapies (RRTs) are widely used in chronic heart failure, one of which is CVVHDF. It is often used in critically ill patients. CVVHDF uses a blood pump to drive blood out of the venous end of the circulation. After passing through the filter, it flows back into the body. The process balances sodium and water levels in the body continuously, slowly, controls blood osmolality, and removes inflammatory mediators from the blood. Its main functions include: disposition of various small molecule toxins through convection, diffusion, and adsorption, quick

removal of various water-soluble inflammatory mediators, downregulation of inflammation and reduction of organ damage; correction of water, electrolyte and acid-base disorders, reduction of blood temperature, and maintenance of the stability of the internal environment. It effectively reduces tissue edema, improves tissue oxygen supply and organ function; and provides enough fluid to ensure the effectiveness of other necessary drug treatment and parenteral nutrition support [44]. During CVVHDF treatment, due to the small changes in blood volume and colloidal osmotic pressure, sufficient tissue perfusion can be maintained. Therefore, hemodynamics is not adversely affected during the process of reducing lung and peripheral tissue edema and improving lung function, but there are still a few studies reporting the occurrence of hypotension and hemodynamic instability during RRT [45].

Although the traditional indications for RRT are oliguria, anuria, hyperkalemia, severe metabolic acidosis (pH < 7.1), azotemia (blood urea nitrogen >30 mmol/L), etc., it is particularly important that it is carried out in patients with fulminant myocarditis and acute left ventricular insufficiency as early as possible. Circulatory failure and shock are not contraindications to this treatment. On the contrary, these symptoms indicate a serious condition and warrant urgent use of RRTs.

(b) Immunoadsorption (IA): IA therapy is a blood purification technology developed in the past 15 years. It combines highly specific antigens, antibodies, or substances (ligands) with specific physical and chemical affinity to adsorption materials (carriers) to make an adsorbent column, which selectively or specifically removes pathogenic substances such as interleukin-6 (IL-6) in the blood, thereby purifying the blood, and hence reducing the damage caused by the inflammatory storm. Both humoral and cellular immune processes occur during the pathophysiological process of fulminant myocarditis, and the goal of immunoadsorption is to selectively remove pathogenic factors in the plasma. Although there is no evidence based on large-scale clinical trials to support this technique, the results of small clinical studies show that IA therapy can improve cardiac function, clinical features, and hemodynamic parameters (cardiac output, stroke volume, peripheral Vascular resistance), etc., and reduce the level of indicators of the severity of heart failure (such as exercise intolerance, NT-proBNP, etc.). In addition, IA can also reduce myocardial inflammation [46]. Patients with myocarditis display improved left ventricular systolic function after receiving protein A immunoadsorption therapy. We recommend clinicians to use a therapeutic trial when possible.

3. Strict monitoring, admission to the cardiac intensive care unit with 24-h special care, mainly including:
   (a) Strictly monitor and control the inflow and outflow of water, recording and reporting the volume every hour as a reference for rehydration.
   (b) Strictly monitor any changes in the ECG, blood oxygen saturation and hemodynamics index to keep abreast of the progress of the disease.
   (c) Routinely monitor blood chemistry, myocardial enzymes, blood gas analysis, liver and kidney function, blood lactic acid, electrolytes, blood coagulation function and other laboratory results to help prevent multiple organ dysfunction.
   (d) Conduct bedside chest radiographs and bedside cardiac B-mode ultrasound once a day or every other day. In order to understand the progress of the disease and evaluate the effectiveness of treatment, such measures can be conducted even multiple times a day.

(e) Perform non-invasive or invasive hemodynamic testing to monitor blood volume and cardiac function based on central venous pressure and pulmonary capillary wedge pressure, accordingly adjusting the volume of fluid infusion and inflow, and monitor arterial blood pressure.

4. Active supportive treatment, which is extremely important for fulminant myocarditis patients, including:
   (a) Absolute bedrest, reduction of visits and emotional stimulation, and the provision of sedatives if necessary. Let the patient rest and relax as much as possible, avoid sympathetic system stimulation caused by emotions and other stimuli, which may increase the workload and oxygen consumption of tissues and organs and ultimately promote deterioration of the condition.
   (b) High-flow and positive pressure oxygen inhalation can effectively ensure sufficient oxygen supply to the whole body. and improve cardiopulmonary function.
   (c) A light, digestible and nutritious diet. Eat small and frequent meals with supplements of various water-soluble and fat-soluble vitamins to reduce gastrointestinal burden and avoid reduced synthesis of coagulation factors due to impaired liver function.
   (d) Improve myocardial energy metabolism and increase the energy supply of the myocardium by giving creatine phosphate and coenzyme Q10.
   (e) Antipyretic drugs are generally not recommended if the body temperature is lower than 38.5 °C. Physical cooling can be performed if the patient cannot tolerate pyrexia. If body temperature exceeds 38.5 °C, antipyretic drugs can be considered. Glucocorticoids are recommended, but non-steroidal anti-inflammatory drugs are not.
   (f) Proton pump inhibitors are given to protect the gastric mucosa and prevent gastrointestinal bleeding, given the stress of critical illness and the side effects of glucocorticoid usage.
   (g) If tracheal intubation or an invasive operation of an artery has been undertaken, antibiotics are needed to prevent infection.
   (h) Maintenance of fluid volume. Fluid intake and output of patients with fulminant myocarditis should be meticulously recorded, and the total daily fluid intake generally should not exceed 2500 mL. At the same time, avoid excessive intake of saline in the process of maintaining basic fluid balance. The daily volume of fluid input and output should be closely monitored. A healthy fluid balance should be achieved by making sure that the input and output are equal. If fluid loss exceeds fluid intake, a negative balance results, and the opposite signifies a positive balance. Patients with fulminant myocarditis and severe pump failure often have coexistent pulmonary and systemic congestion. Under the premise of no obvious factors that promote low fluid volume (hemorrhage, severe dehydration, profuse sweating, etc.), the total daily requirement of a normal person is 2000–2500 mL, while patients with heart failure should generally consume less than 1500 mL; A negative balance of approximately 500 mL a day should be maintained, while in patients with severe pulmonary edema the negative balance should be 1000–2000 mL. The exact amount needs to be determined based on clinical evaluation. Generally, after 3–5 days, pulmonary congestion and pulmonary edema will decrease, and the volume of negative balance should be gradually reduced to eventually equate input and outflow. Care should be taken to prevent hypovolemia, hypokalemia (e.g. resulting from the use of loop diuretics), and hyponatremia during this period.
   (i) Psychological intervention. Due to the severe condition of patients with fulmi-

nant myocarditis, most patients have a sense of psychological fear or anxiety. Psychological intervention should be carried out in a timely manner to resolve the psychological obstacles faced by the patients.

5. Detection of abnormal fluid volume: PICCO rehydration technology is recommended when conditions permit. Guidance under PICCO on fluid volume is especially useful for patients with cardiac insufficiency who require fluid replacement, and the technique can avoid blind fluid rehydration, which could deteriorate the situation. The only disadvantage is the high cost. If PICCO is not available, the following indicators can also help:
   (a) Physical examination. Inspection can reveal any edema, such as bulbar conjunctival edema, and bilateral edema of the lower limbs.
   (b) Central venous pressure (CVP): Central venous pressure refers to the pressure in the right atrium and thoracic segments of the superior and inferior venae cavae. It can reflect the overall situation of the patient's blood volume, cardiac function, and vascular resistance. The normal value of CVP is 5–12 cm H_2O. It is important to improve cardiac function first before rehydration therapy, and adjust the rate of rehydration according to CVP. It should be noted that CVP cannot be judged solely on the basis of absolute values, but also needs to be assessed by dynamic development.
   (c) Pulmonary capillary wedge pressure (PCWP). The normal range is 6–15 mmHg. If PCWP increases while CVP is normal, excessive infusion should be avoided to prevent aggravating pulmonary edema, and reduction of pulmonary vascular resistance should be considered. When the PCWP is less than the lower limit of the normal range, it indicates insufficient blood volume, and the sensitivity is greater than that of CVP.
   (d) Heart output index (CI). The heart index is equal to (heart rate × stroke volume)/body surface area. It represents the cardiac output per minute per square meter of body surface area and is a non-continuous indicator with the normal range of 3–5. A low value indicates poor cardiac function.

   In contrast with shock caused by other conditions, the heart pump function of patients with fulminant myocarditis is severely impaired. Therefore, the intake and output of fluid should be calculated according to cardiac and renal function during the course of treatment, and fluids should not be infused or eliminated, especially when there is no circulation support.
6. Treatment of complications
   (a) Medical treatment of shock and acute left heart failure. Fulminant myocarditis combined with shock is very common, and acute left ventricular failure or congestive cardiac failure is seen in almost every patient. The mechanisms of shock include pump failure, systemic toxic effects, and insufficient volume. The severely impaired pump function is the fundamental difference from shock due to other etiologies, and also underlies the difference in treatment methods. Therefore, if conditions permit, life support treatment should be carried out, and pharmacological therapy can be added if the hemodynamics do not improve.

   Medication for shock: treat according to the cause of shock. When fulminant myocarditis is accompanied by excessive sweating, nausea, vomiting, diarrhea, etc., which can all cause insufficient blood volume, appropriate fluids can be given. Determine the rate and dose of fluid replacement medication according to actively monitored indicators. First, give dopamine and sodium bicarbonate, and if necessary, add alamin to maintain the basic vital signs and buy time for further treatment. In addition to obvious fluid loss, fluid rehydration treatment needs to be progressive and never too fast.

α-receptor agonists should only be used for a short period. Long-term usage can lead to increased hypoxia and even irreversible damage to tissues and organs and death. The use of dopamine can also easily lead to a significant increase in heart rate and ventricular arrhythmias such as premature beats, ventricular tachycardia and even ventricular fibrillation, which increase the burden on the heart. Care should be taken to minimize the use of dopamine. As part of anti-shock treatment, glucocorticoids should be used as soon as possible.

Drugs for acute left heart failure. The intravenous use of diuretics can be considered. Digitalis should be avoided when the heart rate is significantly increased, and monoamine cardiotonics used as little as possible, so as not to increase cardiac oxygen consumption and risk of arrhythmia. Because of low blood pressure, vasodilators should be used with caution. In order to reduce the occurrence of acute left heart failure, the amount of fluid intake and output should be determined daily according to fluid balance and hemodynamic conditions. For patients with severe heart failure or even cardiogenic shock, it is necessary to actively use life support treatment to maintain hemodynamic stability, in order to ensure the perfusion of important organs such as the heart, brain and kidney, which can ultimately help the heart to get adequate rest and help the patient survive the acute phase.

(b) Treatment of arrhythmias: Patients with fulminant myocarditis often have hypotension or shock. If a severe arrhythmia occurs, hemodynamic instability will be aggravated and might become life-threatening. The treatment principle should follow the existing arrhythmia guidelines, and should fully consider the patient's cardiac function and blood pressure to determine which specific drugs or treatment strategies should be employed.

Prediction of malignant arrhythmia: sinus bradycardia, QRS complex widening, echocardiogram showing deterioration of left ventricular function, continuous increase or fluctuation of cardiac troponin level, or non-sustained ventricular tachycardia are all indicators of the occurrence of malignant arrhythmia [47]. In addition, it is especially emphasized that severe hypotension is the most important causative factor in fatal arrhythmia, so it should be corrected in time. Vasoactive drugs such as dopamine, alamin or norepinephrine to may be required to maintain an appropriate blood pressure, during the transfer process to the tertiary hospital, so that systolic blood pressure can be kept above 70 mmHg to avoid fatal arrhythmias such as ventricular tachycardia and ventricular fibrillation.

(c) General treatment principles:
  (i) Quickly identify and correct hemodynamic disorders. Severe hemodynamic disorders caused by arrhythmia should be corrected immediately. For tachyarrhythmias such as ventricular tachycardia or ventricular fibrillation, synchronous or asynchronous electrical cardioversion should be applied immediately. If tachyarrhythmias cannot be corrected or recur after correction, concurrent drug therapy is required, such as 150 mg amiodarone dissolved in 5% glucose solution for slow intravenous injection, and then 300 mg in 50 mL of 5% glucose intravenously pumped at the rate of 10 mL/h for the first 6 hours and tapered to 5 mL/h later. If the arrhythmia cannot be terminated, use IABP + ECMO with the goal of stabilizing hemodynamics and improving symptoms.
  (ii) For patients with relatively stable hemodynamics, appropriate treatment strategies and antiarrhythmic

drugs, usually intravenous amiodarone, should be selected according to the clinical symptoms, cardiac function and the electrocardiographic features of the arrhythmia. Sympathetic storm is possible if sympathetic system stimulation is high. A β-blocker should be used if necessary, such as esoprolol 50 mg slowly intravenously, and maintained at a small dose. Preventive measures to reduce the risk of recurrence should be taken after the arrhythmia is corrected.

(iii) Actively improve cardiac function and hypotension, correct and deal with electrolyte disturbances, blood gas and acid-base balance disturbances and make other corrections in homeostasis.

(iv) Patients with myocarditis often have cardiac insufficiency, cardiogenic shock, and hypoperfusion of tissues and organs. Patients with tachyarrhythmia should not take β-receptor blockers, non-dihydropyridine calcium antagonists and other negative inotropic and negative chronotropic drugs. These negative inotropic drugs can further reduce constriction of heart, which is detrimental to patients at acute phase. However, once the patients survive the acute phase and enter into chronic phase, these drugs can be considered whenever necessary. Intravenous infusion of amiodarone is the first choice of therapy, but rapid intravenous bolus injection is not suitable. Patients with atrial fibrillation can be given digoxin to control the rapid ventricular rate.

(v) A temporary pacemaker should first be considered in patients with bradycardia. If it is unavailable, drugs that increase heart rate such as isoproterenol or atropine can be used.

(vi) Most patients with myocarditis can convalesce after surviving the acute phase. In patients with bradycardia, a permanent pacemaker is not recommended during the acute phase. Observation is required for at least 3–4 weeks. If the conduction block has not recovered after stabilization of the systemic condition, then permanent pacemaker implantation can be considered. For patients with ventricular tachycardia and ventricular fibrillation in the acute phase, an implantable cardioverter defibrillator (ICD) is not recommended during the acute phase or after recovery.

(d) Treatment of abnormalities of the digestive tract. Because prophylactic anticoagulants are needed during invasive procedures in the acute phase, patients with fulminant myocarditis usually have high risk for suffering from gastrointestinal bleeding. High-dosage of glucocorticoid therapy also contributes to this tendency. However, some patients urgently need life support treatment in this scenario, under which circumstances adequate anticoagulation treatment is inevitable. If the patient's own blood coagulation function is impaired, the patient may suffer from gastrointestinal bleeding. Anticoagulants should be stopped immediately if gastrointestinal bleeding occurs. Blood transfusion should be immediately commenced according to the severity of bleeding. Hemostatic drugs should be used with caution because the excessive use will cause thrombosis in the management of life support equipment and affect the treatment effect of them such as ECMO. After the patient's bleeding status has been fully evaluated, intravenous anticoagulants should be used immediately for low-dose anticoagulation management. Patients with fulminant

myocarditis often require high-dose glucocorticoid therapy, which necessitates regular gastroprotective treatment. The intensity of gastro-protective treatment should be increased in patients with a history of gastrointestinal disease.

In addition to the management of gastrointestinal bleeding, attention should also be paid to the treatment of other coincident gastrointestinal disease. Fulminant myocarditis is often accompanied by shock. Some patients require supportive treatment such as sedation and immobilization, which can lead to, abdominal distension or constipation resulting from lack of exercise (muscular activity aids peristalsis]. Diarrhea as well as other gastrointestinal symptoms can also occur. Appropriate treatment should be given for symptoms of such iatrogenic gastrointestinal dysfunction.

(e) Treatment of coagulation dysfunction: There is a balance between coagulation factors and anticoagulation mechanisms in the normal human body. Patients with fulminant myocarditis often need a variety of bedside clinical procedures, and often have multiple organ dysfunction such as that due to infections and shock. At this time, the endogenous and exogenous coagulation pathways are often activated. Sudden emergencies arise, such as extensive bleeding at multiple sites accompanied by manifestations of DIC, which cannot be explained by the primary disease, Progressive liver and kidney dysfunction can also ensue. Prompt active and effective treatment of sub-optimal coagulation function can prevent progression to DIC. Therefore, treatment of the primary disease is a fundamentally crucial measure. Coagulation disorders can be improved by supplementation with coagulation factors, infusion of blood products, and anti-free radical treatment.

(f) Prevention and treatment of limb ischemia caused by invasive procedures: Patients with fulminant myocarditis and severe cardiogenic shock often need timely and effective life-support treatment, such as IABP and ECMO, which are invasive and involve insertion of catheters into the patient's body. After insertion of these "foreign bodies", some patients may develop ischemia of the relevant limb, more commonly the lower limbs, as with ischemia from other causes. Treatment of this complication includes: (1) extracorporeal reperfusion therapy on the ipsilateral ischemic limb; (2) application of warmth to the limb; (3) appropriate use of drugs that improve the circulation, such as prostaglandins.

(g) Preservation of brain function and treatment of brain injury: Patients with severe cardiogenic shock and fulminant myocarditis often require endotracheal intubation, and some patients even suffer from cardiac arrest that requires cardiopulmonary resuscitation to prevent cerebral infarction. Under these situations, the brain function of these patients may be impaired or hypoxic-ischemic encephalopathy may occur. Ensuring normal brain function is essential for recovery. Therefore, it is necessary to actively conduct timely assessment and interventional action to avoid ischemic hypoxic encephalopathy. First, timely and effective cardiopulmonary resuscitation is essential to ensure adequate cerebral blood flow, which is the basis for avoiding ischemic hypoxic encephalopathy. Second, the brain should be protected using hypothermia, by placing ice wool caps to reduce brain metabolism and hence oxygen requirement. Dehydrating agents and glucocorticoids, as well as neuroprotective agents can be considered according to the clinical condition.

In summary, fulminant myocarditis is a special type of myocarditis with rapid onset and critical course, and is usually associated with unstable hemodynamics,

which is a state that is difficult to correct solely with drugs. Compared with other critical illnesses, mechanical life support therapy is extremely useful in assisting patients to pass through the acute phase. It is of great significance that clinicians should pay diligent attention to early identification of the disease and prediction of changes in the clinical picture, and implement multi-system treatment as early as possible. Patients should be rigorously monitored and clinicians should exercise perseverance in trying to save their lives. The latest rescue measures such as CRRT and ECMO should be employed whenever possible. Treatment of in line with the guidance outlined in "Life-support based comprehensive treatment regimen" and racing against time, can ultimately enable us to save lives.

Key Points

1. Fulminant myocarditis progresses rapidly and needs expedient treatment. The core treatment concept is "to allow the heart to rest" with mechanical life support devices.
2. Circulatory homeostasis is maintained by mechanical circulatory support devices including IABP and ECMO, rather than vasoactive and inotropic agents. IABP can be implanted initially, followed by ECMO implementation if IABP cannot meet the demand of the circulation.
3. Overactive immune response and triggered cytokine storm are the core pathophysiological mechanisms of fulminant myocarditis. Immunomodulation therapy including using sufficient doses of both glucocorticoids and IVIG is the key to normalizing immune reactions and attenuating cytokine storm induced cardiac injury, as well as cardiogenic shock.
4. Neuraminidase inhibitors such as oseltamivir can be administered to protect the cardiomyocyte from desialylation and restricts cardiac injury. Other non-specific anti-viral agents can be used considering that viral infection is the most common etiology of fulminant myocarditis.
5. "Life support based comprehensive treatment regimen" consists of high-level mechanical life support especially circulatory support and immunomodulation therapy as well as neuraminidase inhibitors. Symptomatic treatment is also needed.

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16 Prevention and Treatment of Arrhythmias Complicated by Fulminant Myocarditis

Yan Wang

Fulminant myocarditis progresses rapidly. Some patients may develop a complete atrioventricular block within several hours. Other patients may have frequent atrial tachycardia, premature ventricular contractions, ventricular tachycardia, or/and electrical storms, which are important causes of sudden cardiac death. Hence, timely diagnosis and treatment of fulminant myocarditis complicated by arrhythmia are essential [1–3].

16.1 Prediction and Prevention of Lethal Arrhythmias

Patients with fulminant myocarditis can easily develop various types of arrhythmias, even lethal arrhythmia. Many situations can induce or aggravate those arrhythmias, which requires clinicians' attention to avoid the occurrence in advance [3].

16.1.1 Hypotension

Severe hypotension, especially systolic pressure less than 70 mmHg, is an important risk factor for lethal arrhythmia, including ventricular tachycardia and ventricular fibrillation. Hence, attention should be paid to maintaining proper blood pressure, especially during patient transfer. Vasoactive agents, such as norepinephrine or dopamine, can be administered during transfer.

16.1.2 Usage of Catecholamines

Dopamine and dobutamine, which are routinely used to raise blood pressure via their cardiotonic effects, are likely to trigger arrhythmias. Hence, it is important to avoid unnecessary large dosages. Close monitoring of arrhythmias during administration is also recommended. In this way, dopamine and dobutamine can be used together with α-receptor agonists, such as norepinephrine or M-hydroxylamine, to maintain blood pressure.

16.1.3 Long-Term Usage of α-Receptor Agonists

Norepinephrine and other α-receptor agonists can decrease myocardial perfusion. When used over a long period, the drug can also trigger lethal arrhythmia. Hence, long-term and continuous use of α-receptor agonists should be avoided. Instead, the timely use of mechanical circulatory-support devices may improve patients' outcomes.

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16.1.4 Sustained Shock

Sustained shock is potentially arrhythmogenic and should be corrected as soon as possible. The use of mechanical life-support devices and immunomodulation therapy in the early stage should be advocated.

16.1.5 Prolonged QRS Interval

It is a hallmark of intraventricular block and this situation is at risk of malignant arrhythmia.

16.1.6 Female Patients

Female patients are more likely to develop malignant arrhythmia, partially due to the lower sensitivity of women to glucocorticoids. Hence, a larger dosage of glucocorticoids is needed.

16.1.7 Hypokalemia

Hypokalemia is related to vomiting, a loss of appetite, or the administration of diuretics.

16.1.8 Hypoxemia

Fulminant myocarditis complicated by pulmonary infection or pulmonary congestion can cause myocardial hypoxemia and may trigger arrhythmias.

16.2 Treatments to Bradyarrhythmia

If a patient with fulminant myocarditis has a first-degree atrioventricular block, the doctor should be vigilant of the successive occurrence of high-degree atrioventricular block. Antiarrhythmic drugs are recommended while myocarditis is being treated with a positive, timely and even foresighted strategy. Temporary pacemakers should also be planned or prepared for possible implantation.

16.2.1 Drug Treatment

1. Atropine: 0.5–1 mg administered as an intravenous injection. Repeat injection, up to 1–2 mg, if necessary. A temporary pacemaker should also be considered.
2. Isoprenaline: administered by dissolving 1 mg isoprenaline into 50 ml of 5% glucose or normal saline for intravenous injection via a controlled mini-pump. The dosage should be adjusted according to the patient's heart rate. It should be noted that isoprenaline can trigger tachyarrhythmia. If premature contractions begin to emerge, the dosage of isoprenaline should be decreased, or isoprenaline should be withdrawn and replaced by a temporary pacemaker.

16.2.2 Temporary Pacemaker

1. Indication
   (a) A temporary pacemaker can be implanted in advance in patients with type I second-degree atrioventricular block (AVB) if the situation may deteriorate after assessment, even though these patients have no amaurosis or syncope at the time.
   (b) Even though sinus arrest only lasts for 2 s, pacemaker implantation should be considered for patients with sinus arrest complicated by symptoms of bradyarrhythmia. Here bradyarrhythmia-related symptoms is of concern more than the duration of sinus pause.
   (c) Patients with type I or type II second-degree AVB or third-degree AVB should consider temporary pacemaker implantation. Under normal conditions, these patients may not experience significant bradycardia. However, in the presence of fulminant myocarditis, severe hemodynamic dysfunction may arise.

(d) Frequent ventricular tachycardia
(e) Patients who need a large dose of antiarrhythmia drugs.

These indications are based on the American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. However, due to the likelihood of rapid deterioration in fulminant myocarditis cases, any complicated severe cardiac arrhythmia may be lethal. Hence, foresighted decision for temporary pacemaker implantation is required [4].

2. Choice for implantation approach
   (a) For patients with an extremely slow heart rate or patients experiencing cardiac arrest, the quickest and most convenient approach should be used for implantation to avoid cerebral injury. For example, a floating electrode can be prepared in the ward and used for temporary pacing through the superior vena cava at the bedside. When there is no floating electrode in the ward, you can choose a softer electrode. The distal end is shaped as C, the tail is connected to high-voltage pacing, and the electrode is slowly and gently advanced at a suitable length, generally 25–35 cm. Whether the tip of the electrode can capture the heart is observed with the ECG monitoring. Even without X-ray guidance, a temporary pacemaker can be implanted in most cases.
   (b) If the patient is in the interventional catheterization lab, the femoral access can be used to guarantee recovery of the patient's heartbeat.
   (c) If the patient has severe heart failure, pulmonary congestion, and/or hypoxia but the patient does not suffer from severe slow heartbeat, the axillary vein can be used with priority. The subclavian vein and internal jugular vein punctures should be conducted with caution because pneumothorax or hemothorax is potentially lethal in this situation. If available, an echography-guided puncture can be performed.
   (d) For severe patients with ventilator or extracorporeal membrane oxygenation (ECMO) assistance and who are difficult to transfer, a temporary pacing electrode can be implanted at the bedside by three-dimensional navigation without fluoroscopic guidance [5–6].
3. Choice and management of electrode
   (a) Most electrodes for temporary pacemaker implantation, including floating electrodes, are not stable enough to be retained in the ventricular chamber. This is especially so if they have been implanted through the superior vena vein, which may result in unstable pacing and cause irregular rhythm in patients receiving intra-aortic balloon pumping (IABP). Unsynchronized counterpulsation does not provide a satisfactory treatment effect [7].
   (b) Some severely ill patients receiving IABP or ECMO through the lower limbs are difficult to turn over and their pipeline systems are challenging to nursing if they have received temporary pacing via the lower limbs.

   In these two situations, a permanent pacemaker electrode can be implanted through the superior vena vein and connected to a permanent pacemaker (in vitro) or connected to a temporary pacemaker through a transductor. In this way, the electrode is more stable, thus providing more stable pacing [8–9].
4. Permanent pacing

   After active treatment and the normalization of cardiac troponin, if the patient still has sinus arrest or an unrecovered transduction block for 2 weeks, permanent pacemaker implantation should be considered according to the relevant guidelines [4].
5. Pacing frequency management
   (a) For patients with severe heart failure, pacing frequency can be adjusted by invasive

blood pressure monitoring. The frequency can be gradually increased every 2–3 min. The initial frequency can be set at 70–110 bpm, according to the blood pressure, or the patients' objective feelings.

(b) For patients without heart failure or at the recovery stage of heart failure and who are exhibiting transduction block, the pacing frequency can be set at 50–70 bpm to meet the lowest need for life as well as decrease the cardiac workload.

(c) As for patients with frequent ventricular premature contractions or ventricular tachycardia, which leads to unstable hemodynamics, pacing frequency can be increased and adjusted to inhibit the arrhythmias.

16.3 Tachycardia

Due to massive myocardial injuries, the sudden death risk of patients with fulminant myocarditis is very high. Electrolytes should be monitored according to the guidelines for sudden death, and anti-arrhythmia drugs should be administered whenever necessary to treat or prevent malignant tachycardia. Ventricular premature contractions are frequent in patients with myocarditis. Considering the Lown and Wolf system for grading ventricular premature beats is valuable for risk assess in patients with coronary artery disease (Table 16.1), this assessment can be referred when treating fulminant myocarditis.

A higher risk is likely if the morphology of the QRS wave of the ventricular premature beat shows the following features: (1) widened QRS wave, such as longer than 0.14 s; (2) low voltage, such as less than 1.0 mV; (3) notch at the QRS wave; (4) equipotential line at the beginning of the ST segment, symmetrical high sharp T wave, and the orientation of the T wave is the same as that of the QRS wave; and (5) a ventricular premature beat index of approximately 0.6–0.85 (ventricular premature beat index = time period of ventricular premature beat's QR/QT).

Table 16.1 Lown and Wolf grade of ventricular premature beat

Grade	Definition
0	No ventricular premature beat
I	Less than or equal to 30 beats/h
II	More than 30 beats/h
III	Multiform ventricular premature beat
IV-A	Coupled ventricular premature beat
IV-B	Three or more ventricular premature beats to form short burst velocities
V	Early ventricular premature beat (R on T)

16.3.1 Electrolytes Management

1. Blood potassium

   Monitor blood potassium every day to keep it higher than 4.0 mmol/l. If Torsade de pointes (Tdp) occurs, keep it between 4.5 and 5 mmol/l.

2. Blood magnesium

   If Tdp occurs, magnesium should be supplemented with 25% magnesium sulfide diluted to 20–40 ml and administered slowly via intravenous injection or drip [10, 11].

16.3.2 Monitor the QTc Interval

If the QTc interval of patients gradually increases over 20%, especially in patients with Tdp, avoid using drugs that have the potential to elevate QTc, including macrolide antibiotics, quinolone antibiotics, amiodarone, sotalol, and chlorpromazine, etc. [10, 11].

16.3.3 Anti-arrhythmia Drugs

1. Amiodarone

   Amiodarone is the most commonly used drug. For patients with frequent atrial tachycardia, ventricular premature contractions, and ventricular tachycardia without significantly prolonged QTc, amiodarone can be given with a pump. Usually, 300 mg of amiodarone is dissolved into 50 ml with 5% glucose solution and infused intravenously at 10 ml/h over 6 h and then, slowed down to

5 ml/h for maintenance. For patients with ventricular tachycardia, 150 mg amiodarone is dissolved in 50 ml 5% glucose solution and slowly injected intravenously first, followed by infusion with a controlled pump.

2. Nifekalant

   Nifekalant is indicated for patients with refractory ventricular tachycardia or VF without a prolonged QTc interval. Nifekalant does not have a negative chronotropic effect or a negative inotropic effect, and it takes effect very quickly. Nifekalant produces the greatest pharmacological effect 3 min after injection, and its effect fades 30 min after withdrawal.

   Detailed application:

   2.1 Single intravenous injection with a preloaded dose. For adults, the dosage is 0.3 mg/kg. Nifekalant is dissolved into 10–20 ml of normal saline or 5% glucose solution and injected in 5 min under continuous electrocardiogram (ECG) monitoring. Dosage can be enhanced slightly but a dose over 0.5 mg/kg is not recommended.

   2.2 Intravenous infusion. For adults, the dosage is usually 0.4 mg/(kg·h) and infused under continuous ECG monitoring. The concentration of solution should not exceed 2 mg/ml, and the dose should not exceed 0.8 mg/(kg·h). According to a report in the literature, approximately 3% of patients receiving nifekalant infusion suffer from Tdp. Hence, for patients with refractory atrial fibrillation or atrial tachycardia, the risk-to-benefit ratio must be assessed before using nifekalant, considering its potential to trigger Tdp [11–15].

16.3.4 Electrical Cardioversion

If the arrhythmia manifests as sudden onset and sudden termination and lacks warm-up or acceleration, it should be diagnosed as reentrant atrial tachycardia or ventricular tachycardia. If the ventricular rate is too fast and influence hemodynamics, electrical cardioversion should be applied promptly. Antiarrhythmic drugs should also be used to reduce recurrence and the potential injuries to cardiomyocytes caused by multiple electrical cardioversion. Electrical cardioversion is not suitable for automatic atrial tachycardia or ventricular tachycardia. In those cases, medications should be preferred.

16.3.5 Electrical Storms

1. Administer analgesia and sedation, consider a hibernate mixture if necessary. Midazolam can be considered for sedation because of its weak cardiac inhibitory effect. For patients in the intensive care unit or critical care unit, 2–3 mg midazolam can be injected intravenously and maintained with 0.05 mg/(kg·h) to achieve sedation. Midazolam is catabolized by hepatic microsomal enzymes. Hence, the half-life can be prolonged in patients with congestive heart failure or hepatic dysfunction. The dosage of midazolam should be reduced in these patients. Attention should be paid to the possibility of respiratory inhibition and oropharyngeal tube ventilation or flumazenil should be used as necessary [16–17].
2. If the heart failure is not severe or the hemodynamic situation is guaranteed by mechanical life-support devices, beta-blockers can be considered. Esmolol has a very short half-life and can be considered as the first choice. Esmolol is catabolized mainly by lipases in the cytoplasm of erythrocytes. Hence, its half-life is minimally influenced by hepatic or renal functions. The half-life of esmolol is only 9 min, and its acidic catabolite is mainly excreted by the kidneys. If a large dose of esmolol is administered to patients with renal failure for a long period, the dosage should be mitigated, and esmolol should be changed to moderate- or long-acting beta-blockers. Esmolol is administered intravenously by injecting over 30 s at a dosage of 1 mg/kg, and maintained at a dosage of 0.15 mg/(kg·min). The maximum maintenance dosage is 0.3 mg/(kg·min) [18–19].
3. Isoprenaline can be temporarily applied during the acute phase in patients with repeated

Tdp occurrence and without congenital long-QT syndrome, especially in those whose Tdp is triggered by bradycardia [20].

4. If the arrhythmia is life-threatening and difficult to control, such as ventricular tachycardia or electrical storm of ventricular fibrillation, a huge dosage of amiodarone or nifekalant can be used to treat the arrhythmia with pacing-protection after assessment.

16.3.6 Traditional Chinese Medicine

For refractory and recurrent arrhythmia, Wenxin Granules, or Shensongyangxin Capsules can be used as adjunctive therapy or alternative [11, 21].

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17 Prevention and Treatment of Disseminated Intravascular Coagulation in Fulminant Myocarditis

Guanglin Cui and Dao Wen Wang

During life support treatment of patients with fulminant myocarditis, bleeding, embolism, and other coagulation-related complications are still one of the main factors affecting patient morbidity and mortality. Proper anticoagulation during life support is very important. It is also a major problem during life support therapy. Disseminated intravascular coagulation (DIC) is one of the most serious complications associated with life support therapy.

DIC is an acquired clinical syndrome characterized by activation of coagulation factors and platelets, increased thrombin, and extensive microthrombosis.

Patients with fulminant myocarditis are prone to DIC if they are not treated in time or if they are treated improperly. During life support, the initial DIC is due to the release of many inflammatory factors throughout the whole body, forming an inflammatory storm. When a large number of procoagulant substances enter the blood circulation, the coagulation system is activated, resulting in the imbalance of the coagulation-anticoagulant function. In the process of widely forming microthrombosis (mainly composed of fibrin (FBN) and aggregated platelets in microvessels), numerous coagulation factors and platelets are consumed. Secondary fibrinolysis is also enhanced. In addition, anticoagulants are used during life support. These factors lead to obvious bleeding, shock, organ dysfunction, and anemia [1].

17.1 Etiology of DIC Secondary to Fulminant Myocarditis

Among the common causes of DIC, infectious factors account for approximately 30%. Fulminant myocarditis is usually caused by viral infection. The most common pathogens are viruses, including enteroviruses (especially Coxsackie B virus), adenoviruses, cytomegalovirus, EB virus, and the influenza virus. These viruses cause damage to the myocardium by mainly invading and replicating. In the subacute phase, the main pathophysiological changes are immune-related. A few patients enter the chronic phase, which is characterized by the chronic persistent and sudden aggravation of inflammatory activities, weakening of myocardial contractility, myocardial fibrosis, and cardiac enlargement [2].

Prolonged shock and prolonged use of vasoconstrictors, such as m-hydroxylamine, norepinephrine, or pituitrin, are the most common and important risk factors for inducing DIC in patients with fulminant myocarditis.

During fulminant myocarditis, the occurrence of an inflammatory storm, hypoxia, acidosis,

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antigen-antibody complex, free fatty acids, and lipids, as well as the successively activated fibrinolysis system, kinin system, complement system, and other factors may trigger the coagulation system and promote the onset and development of DIC.

17.2 Pathogenesis of DIC Secondary to Fulminant Myocarditis

17.2.1 Activation of the Coagulation System

1. Severe tissue damage

   In addition to severe inflammatory injury, of myocardium, patients with fulminant myocarditis are often complicated with inflammatory injury of multiple organs, even tissue necrosis, which can promote the release of tissue factor (TF) into the blood within a short time, leading to the activation of the coagulation system, and subsequently, DIC. TF is a transmembrane glycoprotein composed of 263 amino acid residues, which mainly exists in the endoplasmic reticulum of cells. TF can be constantly expressed in smooth muscle cells, fibroblasts, pericytes, astrocytes, and podocytes in the outer layer of blood vessels. When tissues and blood vessels are damaged, TF is released from damaged cells into the blood. TF contains negatively charged γ-carboxyl glutamic acid and γ-carboxyglutamate (GLA) can interact with Ca^{2+} combinations. Factor VII forms a complex (VIIa-TF) by combining Ca^{2+} with TF. VIIa-TF, in turn, activates factor X (classical pathway), resulting in the factor Xa-Va-Ca2+-PL complex. The IXa-VIIa-Ca2+-PL complex can also be formed by factor IX activation (alternative pathway). In both pathways, the prothrombin activator is produced, leading to thrombin production. Thrombin can also positively feedback and accelerate the activation of factor V, factor VIII, and factor IX, which, in turn, accelerates the generation of thrombin, which accelerates the coagulation reaction, platelet activation, and the aggregation process, leading to a large number of microthrombosis in microvessels [3].
2. Vascular endothelial cell injury

   Shock and an inflammatory storm in patients with fulminant myocarditis leading to a substantial accumulation of bacteria, viruses, endotoxin, and antigen-antibody complexes within a short time, followed by persistent hypoxia and acidosis. These factors can damage vascular endothelial cells, especially microvascular endothelial cells. The mechanism is as follows. (1) The injured vascular endothelial cells express and release a large amount of TF and activate the coagulation system, leading to the occurrence of DIC. (2) The injury exposes subendothelial collagen, and other tissues can directly activate factor XII or factor XI to start the endogenous coagulation system. (3) Platelet activation occurs, which produces adhesion, aggregation, and release reactions, and aggravates the microthrombosis.

   In patients with fulminant myocarditis, there is substantial inflammatory cell infiltration in the myocardial tissue as well as multiple organ tissues of the whole body. The various inflammatory cells release cytokines such as TNF α, IL-1, IFN, endothelial adhesion molecules, platelet-activating factor (PAF), complement components C3a, C5a, and oxygen-free radical. These cytokines, in turn, aggravate vascular endothelial cell (VEC) injuries and stimulate TF expression, thereby further promoting and accelerating coagulation reactions [4].
3. Blood cells are destroyed, and platelets are activated

   Most patients with fulminant myocarditis need the assistance of powerful life support equipment. At present, the main popular life support equipment available in China are IABP, ECMO, Impala ventilator, and TandemHeart advanced hemodynamic support device. Current clinical evidence shows that IABP has little impact on the hematological system. However, platelets adhere easily

to the silica gel membrane and pipe surface during ECMO bypass, resulting in continuous destruction and consumption of platelets. Therefore, the most damage to the blood system by ECMO is platelets. Red blood cell destruction and hemolysis can also occur easily, especially when the centrifugal pump is running at high speed. The ECMO artificial device and its control process cannot avoid damaging the integrity of red blood cells to varying degrees, and thus, hemoglobin escapes and hemolysis results. The main clinical manifestations are the decrease in hemoglobin concentration, the increase in plasma-free hemoglobin concentration (1.0 g/L) (100 mg/dL), and hemoglobinuria. The severity increases with the increase of auxiliary flow, auxiliary time, and Hct [5].

4. Other ways to activate the clotting system are as follows. (1) In some patients with fulminant myocarditis and digestive tract symptoms, a large amount of trypsin enters the blood when the inflammation involves the pancreas. Due to the direct activation of prothrombin by trypsin, a large number of microthrombosis are caused. (2) In cases of toxin-related myocarditis caused by bee venom and snake venom, these exogenous toxins are efficient procoagulant substances. They can directly activate factor X and prothrombin, or directly convert fibrinogens (FBG) into fibrin monomers. (3) In tumor-associated myocarditis, some tumor cells can secrete specific procoagulant protein (CP), which can directly activate factor X, leading to the activation of the coagulation system.

17.2.2 Fibrinolysis Dysfunction

The fibrinolytic function (fibrinolytic function) is an important anticoagulant function of the human body. It plays an important role in removing FBN from blood vessels and gland excretion pipelines, thereby preventing thrombosis.

During the provision of life support treatment to patients with fulminant myocarditis, due to the release of a large number of inflammatory factors and a large amount of procoagulant substances into the blood, the coagulation system is activated, resulting in the imbalance of coagulation and anticoagulant functions. Secondary fibrinolytic dysfunction and the use of anticoagulants during life support can subsequently lead to obvious bleeding, shock, organ dysfunction, and anemia [6].

1. Decreased fibrinolytic function

   In patients with fulminant myocarditis, vascular endothelial function is seriously impaired, especially vascular endothelial-dependent relaxation function [7]. VEC damage is critical to the initiation and development of DIC. The injured VEC, without its normal anticoagulant function, is conducive to the local deposition of FBN and microthrombosis. For example, as the surface electronegativity of VEC decreases, the generation of TFPI and adsorption of AT-III and other anticoagulant substances also decrease, resulting in reduced local anticoagulant function of the microvessels. Similarly, as the expression of thrombomodulin (TM) on the damaged VEC membrane decreases, its ability to promote protein C (PC) activation also decreases, resulting in reduction in local anticoagulation and fibrinolysis functions. The affected VEC produces increased plasminogen activator inhibitor (PAI-1) and decreases tissue plasminogen activator (t-PA), which, in turn, reduces the fibrinolytic function, leading to the local deposition of FBN and microthrombosis. Moreover, fibrinolytic activities at the microvascular site may not be significantly reduced, but due to the hyperactive coagulation and the formation of a large amount of FBN in the microvessels, the ability of plasmin to be cleared in time is exceeded, leading to FBN precipitation and microthrombosis. The reduction in anticoagulant and fibrinolytic activities is another important condition for the formation and retention of transparent microthrombosis [8].
2. Secondary fibrinolysis enhanced

   Secondary fibrinolysis (secondary fibrinolysis) refers to the activation of the fibrinolytic

system after the coagulation system is activated. Secondary fibrinolysis is important for dissolving FBN and FBG. Secondary enhancement of fibrinolysis can occur simultaneously with hypercoagulability. It can also occur successively after hypercoagulability. Therefore, secondary hyperfibrinolysis not only promotes the dissolution of microthrombosis in microvessels, but also aggravates the obstacles of hemostasis and coagulation function, resulting in bleeding.

17.3 Factors Affecting the Occurrence and Development of DIC

In addition to inflammatory damage to myocardial tissue and even multiple organs of the whole body, patients with fulminant myocarditis also have a decline in systemic immune regulation. These comprehensive factors can make patients with fulminant myocarditis prone to develop DIC.

17.3.1 Impaired Function of the Monocyte-Macrophage System

Monocytes and macrophages phagocytose and remove bacterial endotoxin, tissue cell debris, immune complexes, cytokines, ADP, and other procoagulant substances. In fulminant myocarditis, the cardiomyocytes swell and degenerate, myocardial fibrous interstitial edema arises, and a large number of inflammatory cell (mainly monocytes) infiltrates. Therefore, when the function of the monocyte-macrophage system is seriously impaired (such as long-term and high doses of glucocorticoids or serious liver diseases), or cell function is blocked due to excessive phagocytosis (such as bacteria, endotoxin, lipids and necrotic tissues), the clearance of procoagulant substances in the blood by monocyte-macrophages is reduced and a large amount of procoagulant substances are accumulated, which easily induces DIC. At the same time, the ability of the monocyte~macrophage system to phagocytose activated coagulation factors is reduced and endotoxins cannot be inactivated. Endotoxins can activate coagulation factors, damage VEC, promote platelet aggregation, and constrict blood vessels, leading to DIC-like pathological changes.

17.3.2 Severe Liver Dysfunction

Fulminant myocarditis easily leads to acute liver damage, which is mostly caused by severe infection, insufficient cardiac output, liver congestion and insufficient perfusion. Long shock time and chronic use of vasoactive drugs, especially potent vasoconstrictors, such as m-hydroxylamine, norepinephrine, and pituitrin, can further aggravate tissue and liver ischemia. Furthermore, inflammatory factors can also directly inhibit the synthesis of hepatocytes and participate in the pathogenesis of DIC [9].

1. Reduction of synthetic anticoagulant substances in the liver: anticoagulant substances, PC, AT-III, and flg are synthesized by the liver. In cases of chronic migratory hepatitis and liver cirrhosis, the synthesis of anticoagulant substances in the liver is reduced, and the blood is in a hypercoagulable state, which easily induces DIC.
2. Reduction of activated coagulation factors that are inactivated by the liver: during the activation of the coagulation system, activated coagulation factor IXa, XIa, Xa, TAT, and PAP are cleared and inactivated in the liver. In acute severe hepatitis and liver cirrhosis, inactivation of the activated coagulation factors decreases, and the blood is in a hypercoagulative state, thereby enhancing the risk of inducing DIC.
3. TF may be released in large quantities in acute liver necrosis.
4. Some causes of liver dysfunction, such as viruses and certain drugs, can activate coagulation factors.

These factors play a certain role in the occurrence and development of DIC.

17.3.3 Hypercoagulative State of the Blood

Hypercoagulative state of the blood refers to a state in which blood coagulation increases under some physiological or pathological conditions, which is conducive to thrombosis. Patients with fulminant myocarditis often have secondary hypercoagulability due to systemic severe infection and acidosis.

1. Primary hypercoagulative state

   The primary hypercoagulative state is seen in hereditary AT-III, PC, PS deficiency, and PC resistance caused by the abnormal structure of factor V.
2. Secondary hypercoagulative state

   Patients with fulminant myocarditis often have secondary hypercoagulability due to severe systemic infection and acidosis. The mechanism is as follows.
   (a) VEC injury initiates the coagulation system and induces the occurrence of DIC.
   (b) A decrease in blood pH increases the enzyme activities of the coagulation factors and weakens the anticoagulant activity of heparin.
   (c) Promotion of platelet aggregation occurs. After aggregation, platelets can release a series of procoagulant factors that cause the blood to be in a hypercoagulative state.

17.3.4 Microcirculation Disturbance

Fulminant myocarditis complicated with cardiogenic shock is common. When the cardiogenic shock cannot be corrected in time, serious microcirculation disorder results. Blood flow in the microcirculation is slow. Blood vortex or stasis occurs, and blood cells gather. These promote the development of DIC.

The occurrence and development of DIC in fulminant myocarditis are also related to the quantity, speed, and route of procoagulant substances entering the blood. In chronic myocarditis or mild viral myocarditis, the entry of procoagulant substances into the blood is small and slow. If the body's compensatory function (phagocytosis) is normal, DIC does not usually occur, or only chronic DIC with no obvious symptoms arises. In patients with fulminant myocarditis, when too much coagulants enter the blood within a short time or they enter too fast, the body's compensatory ability is exceeded, and acute DIC results. Moreover, the route of procoagulant substances entering the blood has an important relationship with the site of microthrombosis. When procoagulant substances enter the blood through the venous system, DIC is mainly distributed in the lungs. In contrast, DIC is mainly distributed in the kidneys, when procoagulant substances enter the blood through the arterial system [3].

17.4 Main Clinical Manifestations of DIC Secondary to Fulminant Myocarditis

The main clinical symptoms of DIC are bleeding, multiple organ dysfunction, microcirculation disorder (shock), and anemia. The first three symptoms are more common in acute DIC.

Importantly, patients with fulminant myocarditis are prone to multiple organ failures. For example, (1) When combined with viral pneumonia, extensive microthrombosis in the lungs can cause alveolar capillary membrane damage and clinical symptoms of acute respiratory failure, such as adult respiratory distress syndrome (ARDS); (2) If there is extensive microthrombosis in the kidneys, it can cause bilateral renal cortical necrosis and acute renal failure. The clinical manifestations are oliguria, hematuria, and proteinuria; (3) DIC in the digestive system can cause nausea, vomiting, diarrhea, and gastrointestinal bleeding; (4) Intrahepatic microthrombosis can cause portal hypertension, liver dysfunction, gastrointestinal congestion, edema, jaundice, and other related symptoms; (5) Myocarditis results in decreased myocardial contractility, decreased cardiac output, decreased cardiac index, and significantly increased creatine phosphokinase and lactate dehydrogenase;

(6) Neurological diseases show nonspecific symptoms, such as unconsciousness, drowsiness, coma, and convulsion [9].

17.5 Treatment of DIC Secondary to Fulminant Myocarditis

When DIC occurs in patients with fulminant myocarditis, it indicates that the patient's condition is serious, dangerous, and rapidly developing. Active rescue must be initiated. Otherwise, irreversible damage is imminent. Fulminant myocarditis, cardiogenic shock, and DIC are the cause and effect of each other. Consideration must be given to both the treatment, and the clinical changes. Clinical manifestations and laboratory test results must also be closely monitored.

Treatment principle. The current view is that the treatment of fulminant myocarditis is the most critical and fundamental treatment for mitigating the pathological process of DIC.

Main treatment measures are as follows. (1) Alleviate the basic diseases causing DIC. (2) Block the process of intravascular coagulation. (3) Restore normal platelet and plasma coagulation factor levels. (4) Antifibrinolytic therapy. (5) Symptomatic and supportive treatment.

1. **Treatment of the primary disease to reduce and prevent the onset of DIC** The use of glucocorticoids in patients with fulminant myocarditis increases the risk of systemic infection. Therefore, infection prevention strategies should be implemented from the beginning of treatment. Infection should be treated actively. Antimicrobials should be commenced early, and the choice should be broad-spectrum and provided at a sufficiently high dose. Empirical medication should adopt the principle of "descending the ladder" to reduce the damage of infection to the microvascular system as soon as possible. This is completely consistent with the treatment concept of fulminant myocarditis (see the chapter on treatment of fulminant myocarditis for details). On the contrary, if the primary infection is not removed or difficult to control, DIC will also be difficult to control or it may relapse easily. Infection, shock, acidosis, and hypoxia are important factors that contribute to and promote DIC. Actively eliminating these inducing factors can prevent the occurrence and development of DIC and create conditions to facilitate the recovery of normal coagulation-anticoagulation balance.

   Mechanical circulation should be used to support the active treatment of shock. Strong vasoconstrictors and blood pressure raising drugs, such as m-hydroxylamine, norepinephrine, and pituitrin should be avoided as far as possible to reduce the organ blood supply and minimize the risk of inducing irreversible DIC. If the local hospital needs to transfer patients with DIC to a tertiary hospital, the above vasoactive drugs can be used for a short time during the transfer process to maintain the blood pressure [10].

   Due to poor nutritional intake and absorption during illness, vitamin deficiency is common. Therefore, water-soluble and fat-soluble vitamins are routinely supplemented in the critical stage to facilitate the synthesis of liver coagulation factors.
2. **Therapeutic measures for intervening in the pathophysiological process of DIC** The condition of patients with fulminant myocarditis develops and changes rapidly. Even in the same case, different treatment measures must be taken according to the changes in the patient's condition. It should be pointed out that the clinical stages of patients with fulminant myocarditis complicated with DIC overlap to some extent, so treatment should be closely assessed in combination with the patient's clinical process and laboratory test results. Comprehensive measures should be taken [11].
   (a) Early stage (diffuse microthrombotic stage): It is mainly microthrombotic. The purpose of this treatment is to inhibit extensive microthrombotic formation and prevent further consumption of platelets and various coagulation factors. Therefore, the treatment mainly involves anticoagulants.

(b) Metaphase (consumptive hypocoagulant phase): Microthrombosis is still in progress at this stage. Therefore, anticoagulant treatment is still essential. However, due to the progressive consumption of coagulation factors, clinical bleeding is common. Therefore, based on complete anticoagulation, alternative treatment with platelet and coagulation factors should be considered. Currently, the recommended alternative therapeutic agents include infusion of plasma (including fresh plasma, fresh frozen plasma, cryoprecipitation, and prothrombin complex) and platelets.

- Fresh plasma: The blood coagulation factors contained in fresh plasma are similar to fresh whole blood. Plasma can also reduce the total amount of input liquid and avoid the destruction of red blood cells, to produce membrane phospholipids and other coagulation-promoting factors. Hence, it is an ideal supplementary preparation of coagulation factors for patients. Furthermore, plasma input may help in correcting shock and improving the microcirculation.
- Fibrinogen: It is suitable for patients with acute DIC, obvious low fibrinogen, or extremely serious bleeding. The first dose is 2–4 g by intravenous infusion. Subsequent supplementation can be provided according to the content of plasma fibrinogen, so that the content of plasma fibrinogen reaches more than 1.0 g/L. Since the half-life of fibrinogen is 96–144 h, it generally does not need to be readministered after 24 h, especially in patients whose fibrinogen plasma concentration returns to more than 1.0 g/L or there is no obvious hyperfibrinolysis.
- Platelet: For patients with no bleeding, whose platelet count is lower than (10–20) × 10^9/L, or patients with active bleeding and whose platelet count is lower than 50 × 10^9/L, urgently transfusion of platelet suspension is required. Platelets must be provided in sufficient quantity, and the first dosage should be at least one adult unit.
- Late-stage (secondary fibrinolytic hyperactivity): At this stage, microthrombosis has basically stopped, and secondary hyperfibrinolysis is the main contradiction. If it is clinically confirmed that hyperfibrinolysis is the primary cause of bleeding, an appropriate amount of antifibrinolytic drugs can be used. At the same time, fibrinogens should also be actively supplemented due to the consumption of coagulation factors and platelets. Main indications for fibrinolytic inhibitors are as follows. (1) Fulminant myocarditis has been effectively controlled and has been treated with effective anticoagulant therapy and supplemental platelets and coagulation factors. However, bleeding is still difficult to control. (2) DIC with fibrinolytic hyperactivity. (3) In the late stage of DIC, hyperfibrinolysis becomes the main pathological process and the main cause of recurrent bleeding or aggravation of bleeding. (4) During DIC, fibrinolytic laboratory indexes confirmed that there is obvious secondary hyperfibrinolysis.
- Patients with fulminant myocarditis are prone to secondary DIC, which is also an important factor leading to patient death. According to our clinical experience, hypotension or prolonged shock, long-term use of norepinephrine, meta-hydroxylamine, or pituitrin to maintain blood pressure are the most important risk factors for DIC. Therefore, early use of treatments such as mechanical circulatory support and immune regulation, while effectively preventing and treating infections, and early supplementation of water-soluble and fat-soluble vitamins may help prevent DIC. During

treatment, the coagulation state must be monitored, to ensure that any abnormalities are detected promptly to facilitate correction and treatment.

Key Points

1. Patients with fulminant myocarditis are at risk of DIC due to infections and the inflammatory storm, and prolonged hypotension or shock.
2. Tissue ischemia caused by long-term use of norepinephrine, m-hydroxylamine, or pituitrin for maintaining blood pressure, is the most important risk factor for inducing DIC.
3. Anticoagulants should be used during life support therapy. Monitoring coagulation function is an important measure for preventing DIC.
4. Early use of mechanical circulatory support and immunomodulatory therapy, effective prevention and treatment of infection, monitoring of bleeding and coagulation-related indicators, and early supplementation of water-soluble and fat-soluble vitamins may help to prevent DIC.

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18 Rehabilitation Treatment for Myocarditis

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18.1 Overview

Myocarditis patients can be divided into the acute period, sub-acute period, and chronic period. The acute phase generally lasts about 3–5 days, mainly due to virus invasion and replication of myocardial damage. In the subacute stage, immune response is the main pathophysiological change. A few patients enter the chronic stage, presenting with chronic persistent and suddenly aggravated inflammatory activities, weakened myocardial contractility, myocardial fibrosis, and heart enlargement [1]. About 50% of patients with acute myocarditis will gradually recover within 2–4 weeks, about 25% of patients still have persistent cardiac function impairment, and 12–25% of patients will suddenly deteriorate, resulting in death or end-stage dilated cardiomyopathy, requiring heart transplantation [2]. The chronic progression of myocarditis to dilated cardiomyopathy has become an international consensus [1–8]. Studies have found that 30% of patients with myocarditis diagnosed by myocardial biopsy gradually develop dilated cardiomyopathy, presenting with heart failure [2].

At present, there is no sensitive or specific examination method to determine whether the process of myocardial inflammatory response is over. For acute myocarditis related to dilated cardiomyopathy, it generally takes more than 6–12 months for the disappearance of inflammatory response [8]. International guidelines agree that all patients with acute myocarditis should avoid competitive or leisure sports within 6 months of onset after discharge from the hospital, regardless of the patient's age, gender, severity of symptoms, and whether they are taking drugs or not. After clinical reassessment by doctors, the patient can gradually resume exercise [2, 8, 9].

The American Heart Association (AHA) lists three requirements for myocarditis patients to participate in exercise after 6 months: (1) ventricular systolic function has returned to the normal range; (2) blood samples show that the markers of myocardial injury, inflammation, and heart failure returned to normal; and (3) no clinically relevant arrhythmia, such as frequent or complex ventricular or supraventricular ectopic activity, was seen in the Holter and stress ECG. The view that "the loss of LGE associated with myocarditis as suggested by cardiac magnetic resonance is one of the criteria for participating in strenuous exercise" needs further discussion. However, the presence of myocardial scars still carries the risk of arrhythmia [8, 10, 11].

In patients with myocarditis within 6 months of onset, in addition to rest, taking medication is also necessary. The thickening of the left ventricular wall in patients with myocarditis is often a

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manifestation of active inflammation, which can be gradually reduced in a few weeks [12]. Cardiac magnetic resonance can be used to assess the situation of myocardial edema and inflammation in patients [13–17]. In addition, the use of echocardiography for systematic spot tracking analysis can also easily find and assess the state of cardiac inflammation and functional recovery [18]. For patients who still have myocardial edema and inflammatory activity after discharge, appropriate oral glucocorticoids can improve cardiac function [19–22]. For patients with high myocardial injury markers but normal cardiac function after discharge, it is recommended to return to the clinic after 1–2 weeks, focusing on the changes in the patient's troponin and cardiac function [12], and it is necessary to perform endocardial myocardial biopsy for histological evaluation. Patients with low left ventricular ejection fraction or abnormal ultrasound spot tracking should be treated with β-blockers, angiotensin converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB), which not only help improve heart function but may also help to reduce inflammation. Most patients with myocarditis with impaired cardiac function respond well to standard heart failure therapy [2, 8, 12].

Patients with myocarditis who still have impaired cardiac function 6 months after onset should follow the guidelines for chronic heart failure. ACEI/ARB and β-blockers should be used as early as possible (unless conjunctive or intolerant). Trimetazidine can attenuate inflammation and improve cardiac function for myocarditis patients [23, 24]. Diuretics should be used first to reduce fluid retention in patients with heart failure with symptoms and/or signs of congestion. If symptoms persist, aldosterol receptor antagonists or angiotensin receptor enkephalinase inhibitors (ARNI) instead of ACEI/ARB are recommended. If the dosage of β-blocker has reached the target dose or the maximum tolerated dose but the heart rate is still greater than 70 beats/min and LVEF is less than 35%, evabradine may be considered. It should be recommended if it conforms to the indications of CRT/ICD [25]. For patients with poor results and without endocardial biopsy, endocardial biopsy should be performed to determine the pathological type of myocarditis [26]. The rehabilitation treatment process for patients with myocarditis is shown in Fig. 18.1.

If the patient still has poor cardiac function after normal anti-heart failure treatment after discharge, endocardial biopsy is required to further guide treatment.

All patients with myocarditis need to rest for 3–6 months after disease onset to avoid load exercise. Patients were followed up in the outpatient clinic at the first, third, and sixth month after discharge, and their conditions were evaluated comprehensively, including symptoms, medication, living habits, mental and psychological status, nutritional status, and quality of life, as well as

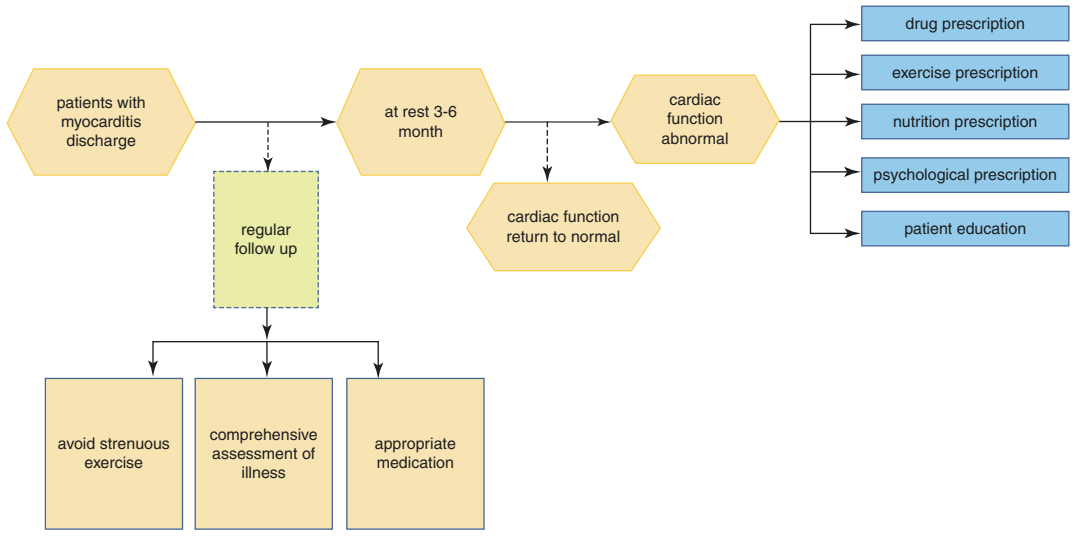

Fig. 18.1 Flow chart of rehabilitation treatment for patients with myocarditis

undergoing physical examinations and normal examinations such as blood routine, liver and kidney function, electrolytes, inflammatory indexes, cardiac enzymes, markers of heart failure, electrocardiogram, ultrasonic cardiogram, and so forth. Cardiac magnetic resonance examination is recommended 3 months after discharge to assess cardiac structure, myocardial edema, and fibrosis. If myocardial edema is still present, oral steroids are recommended. Patients with high levels of troponin are recommended to be re-visited 1–2 weeks later to observe changes in troponin and cardiac function. Patients with left ventricular ejection fraction below 40% should be treated with ACEI, β-blockers, or ARBs in accordance with international guidelines for stage B heart failure. If symptoms improve and ultrasound spot tracking shows that cardiac function has returned to normal, the drug can be stopped for observation. If the patient's symptoms or test results do not improve, endocardial biopsy may be considered for further determination of cardiac pathological changes. For patients with decreased cardiac function, it is suggested to refer to chronic heart failure for cardiac rehabilitation therapy, including drug, exercise, nutrition, psychological, and patient education prescriptions.

18.2 Cardiac Rehabilitation

Patients with myocarditis should pay special attention to exercise restriction after discharge. According to the condition that cardiac function is not restored to normal or cardiac structure is enlarged, patients are advised to undergo cardiac rehabilitation in accordance with the guidelines for heart failure 6 months to 1 year later [25, 27, 28]. Multiple studies have shown that chronic heart failure resulting from various causes can benefit from cardiac rehabilitation [29–31].

Cardiac rehabilitation/secondary prevention is a professional prevention and treatment system integrating biomedicine, sports medicine, nutrition medicine, psychosomatic medicine, and behavioral medicine. It refers to the systematization, structuring, digitization, and individualization of cardiovascular disease prevention and management measures based on an overall medical evaluation and intervenes in risk factors through a comprehensive model of five core prescriptions (drug, exercise, nutrition, psychological (including sleep management), and smoking cessation and alcohol restriction prescriptions), aiming to provide cardiovascular disease patients with comprehensive physical, psychological, and social management services and care during the acute, recovery, and maintenance phases, and the entire life process [32, 33].

Specific components of cardiac rehabilitation/secondary prevention include:

1. System evaluation. Initial, stage, and outcome evaluations are the premise and basis of cardiac rehabilitation.
2. Evidence-based drug therapy. Cardiovascular risk factors should be controlled.
3. Change unhealthy lifestyles, including smoking cessation, proper diet, and scientific exercise.
4. Mood and sleep management. The adverse effects of psychopharmacology and sleep quality on quality of life and cardiovascular outcomes should be noted.
5. Change of health education behavior. Instructing patients to learn self-management is the ultimate goal of cardiac rehabilitation.
6. Improve quality of life and return to society and careers [32].

The five prescriptions of cardiac rehabilitation are drug, exercise, nutrition, psychological (including sleep management), and patient education (risk factor management and smoking cessation) prescriptions. The combined effect of comprehensive evaluation and the "five prescriptions" provides long-term comprehensive management of psychology, biology, and society for patients with cardiovascular disease in the acute, recovery, and maintenance phases, and the entire life process [32].

The clinical path of cardiac rehabilitation can be divided into six steps:

1. Patients with myocarditis who still have impaired cardiac function 6 months after discharge are recommended to receive cardiac rehabilitation therapy.
2. The physician performs the initial patient evaluation.

3. Physicians make personalized cardiac rehabilitation prescriptions according to the evaluation results.
4. Patients are instructed by physicians to complete 36 prescriptions of cardiac rehabilitation in hospital or at home.
5. Physicians evaluate the outcome of cardiac rehabilitation and provide an analysis report on the effect of cardiac rehabilitation.
6. Physicians provide long-term out-of-hospital treatment plans to patients based on evaluation results [32].

18.2.1 Cardiac Assessment

Cardiac assessment is conducted throughout cardiac rehabilitation. It is very important to conduct a comprehensive evaluation of cardiac rehabilitation patients, which should start from the first contact with patients and run through the whole process of cardiac rehabilitation, and is the primary and important content of cardiac rehabilitation [34].

1. Comprehensive cardiac assessment. Including biological history, lifestyle habits, risk factors, cardiovascular function and exercise risk, mental and psychological status, nutritional status, quality of life, and systemic status and disease perception (Table 18.1). Through assessment, the patient's overall status, risk stratification, and various factors affecting treatment effects and prognosis can be understood, so as to formulate optimal treatment strategies for patients in acute and chronic stages, and achieve comprehensive and whole-course medical management [34].

   Patients with myocarditis who agreed to participate in cardiac rehabilitation were assessed at five time points: initial assessment, pre-exercise assessment for each exercise treatment, emergency assessment for new or abnormal signs/symptoms, reassessment every 30 days of the cardiac rehabilitation treatment cycle, and 90-day outcome assessment.

   The assessment included history, symptoms, signs, medication status, cardiovascular risk factors, and routine adjunctive examinations. Routine adjunctive examinations include resting electrocardiogram (ECG), echocardiography (detection of atrial enlargement, left ventricular ejection fraction), and blood tests (such as lipids, blood glucose, and markers of myocardial injury).
2. Exercise risk assessment. The contraindications for exercise prescriptions include unstable angina, systolic blood pressure >200 mmHg or diastolic blood pressure >110 mmHg at rest, blood pressure drop >20 mmHg after presenting with symptoms, severe aortic stenosis, acute systemic disease or fever, uncontrolled severe atrial or ventricular arrhythmia, uncontrolled obvious sinus tachycardia (>120 beats/min), uncontrolled heart failure, third degree atrioventricular block without pacemaker implanted, active pericarditis or myocarditis, thrombophlebitis, recent thromboembolism, ST segment depression or elevation (>2 mm) at rest, severe motor system abnormalities that can limit exercise capacity, and other metabolic abnormalities, such as acute thyroiditis, hypokalemia, hyperkalemia, or hypovolemia [35].

   Exercise risk assessment should be performed before patients are prescribed exercise. The assessment contents include the following: a history of cardiovascular disease and other organ diseases; a physical examination, focusing on the heart, lung, and musculoskeletal system; recent cardiovascular examination results, including blood biochemical examination, 12-lead electrocardiogram, coronary angiography, echocardiography, exercise stress test, pacemaker, or implantable cardioversion defibrillator function; drugs currently taken, including dosage, method of administration, and adverse reactions; whether the control of cardiovascular disease risk factors is up to standard; and daily eating and exercise habits [36].

The exercise load test and risk stratification are the key contents in exercise risk assessment, which require clinicians to master relevant professional knowledge. All patients need to be stratified according to risk before cardiac rehabilitation (Table 18.2). Low-risk patients can participate in exercise under ECG monitoring

Table 18.1 Contents of comprehensive evaluation of patients in cardiac rehabilitation

Project	Contents
History	Diagnosis, complications, comorbidities, and past history related to the current cardiovascular event
Physical examination	Assessment of cardiopulmonary function
	Assessment of musculoskeletal system function, especially extremities and loin
Resting electrocardiogram	Whether the ECG ST-T changes, serious arrhythmia, etc.
Medication	Drug type, name, dose, and frequency
Risk factors of cardiovascular disease	Uncorrectable risk factors
	Age, sex, family history of cardiovascular disease
	Modifiable risk factors
	Smoking status, including primary and secondary smoke
	History and control of hypertension
	History and control of dyslipidemia: 6–8 weeks lipid profile, including total cholesterol, low density lipoprotein cholesterol and high density lipoprotein cholesterol, triglycerides
	Dietary structure, particularly dietary fat, saturated fat, cholesterol, and calorie intake
	Body composition: weight, height, body mass index (BMI), waist circumference, waist-to-hip ratio, body fat content (%)
	Fasting blood glucose, glycated hemoglobin, diabetes history, and blood glucose control
	Physical activity status: leisure sports, favorite form of exercise, daily sitting time
	Assessment of psychosocial functioning: depression, anxiety, family history of mental illness
	Other questionnaire data: such as sleep disorders and sleep apnea (Pittsburgh Sleep Quality Scale (PISQ))
Athletic ability	Exercise testing
	Cardiopulmonary exercise test
	The 6-min walk test
Markers of myocardial necrosis	Serum troponin concentration
Echocardiography	Heart cavity size, left ventricular ejection fraction

From The Chinese Guidelines for Cardiac Rehabilitation and Secondary Prevention (2018 edition) [34]

Table 18.2 Risk stratification of cardiovascular events during exercise

Factor		Risk stratification		
		Low risk	Median risk	High risk
Exercise test factors	Angina	No	Yes or no	Yes
	Asymptomatic but with ischemic changes on the ECG	No	Yes, but ECG ST segment down <2 mm	Yes, ECG ST segment down ≥2 mm
	Other obvious uncomfortable symptoms, such as shortness of breath, dizziness, etc.	No	Yes or no	Yes
	Complex ventricular arrhythmias	No	No	Yes
	Hemodynamic response (with the increase of exercise load, heart rate increases and systolic blood pressure increases)	Normal	Normal	Abnormality, including poor function of heart rate or decreased systolic blood pressure with increased exercise load
	Functional reserve	≥7 Mets	5.0–7.0 Mets	≤5 Mets
Non-exercise test index	Left ventricular ejection fraction	≥50%	40–50%	<40%
	History of sudden death	No	No	Yes
	Complex ventricular arrhythmias at rest	No	No	Yes
	Complications of myocardial infarction or revascularization	No	No	Yes
	Myocardial ischemia after myocardial infarction or revascularization	No	No	Yes
	Congestive heart-failure	No	No	Yes
	Clinical depression	No	No	Yes

between 6 and 18 times, middle-risk patients can participate in exercises under ECG monitoring between 12 and 24 times, and high-risk patients can participate in exercises under ECG monitoring between 18 and 36 times. The types of exercise load tests include the instrumental exercise load test and the unarmed 6-min walking test [36]. The contraindications of the exercise load test are the same as exercise prescriptions.

It is worth clinicians' attention that the principle of individuation should be observed in the formulation of cardiac rehabilitation programs. Due to differences in patients' cognition, behavior, psychology, motivation, physiology, and environment, rehabilitation goals and treatment plans need to be formulated in consultation with the patient and appropriate family members according to the actual patient situation. Every assessment in the process of cardiac rehabilitation should be adjusted according to the patient's condition, and a stable rehabilitation plan should gradually be formulated [35].

18.3 Five Prescriptions for Cardiac Rehabilitation

Cardiac rehabilitation includes five prescriptions: drug, exercise, nutrition, psychological (including sleep management), and patient education (risk factor management and smoking cessation) prescriptions.

1. Drug prescriptions

   Evidence-based medication to control cardiovascular risk factors. Cardiac rehabilitation physicians should master and update the core content of drug therapy guidelines for cardiovascular diseases in a timely manner and master the control objectives of cardiovascular risk factors as well as the selection and treatment targets of cardiovascular protective drugs. The control objectives of major cardiovascular disease risk factors and related drugs are shown in Table 18.3 [32]. In addition to controlling risk factors, ACEI and

Table 18.3 Control targets and related drugs for major cardiovascular disease risk factors

Risk factor	Control targets and related drugs
Dyslipidemia	• LDL-c <2.6 mmol/L (100 mg/dL) (high-risk patients); <1.8 mmol/L (70 mg/dL) (extremely high-risk patients, including ACS or coronary heart disease with diabetes)
	• TG <1.7 mmol/L (15 mg/dL)
	• Non-HDL-c <3.3 mmol/L (130 mg/dL) in high-risk patients; <2.6 mmol/L (100 mg/dL) (extremely high-risk patients)
	• Statins are the first choice for lowering cholesterol. When the LDL-C of moderate intensity statins is not up to the standard, ezetimibe 5–10 mg/day can be added orally.
Hypertension	• Ideal blood pressure: 120/80 mmHg
	• Blood pressure control target: <140/90 mmHg. If tolerated, blood pressure can be further controlled to 120–130/70–80 mmHg. In healthy elderly, blood pressure can be controlled to 130–140/70–80 mmHg, and in weak elderly, it can be relaxed to 150/90 mmHg.
	• All patients received guidance on healthy lifestyles, and attention is paid to detect and correct sleep apnea; β-blockers, ACEI, or ARB are preferred for patients with coronary heart disease or heart failure complicated with hypertension, and other antihypertensive drugs are added when necessary.
Diabetes	• Control objective: HBA1c ≤7.0%
Heart rate control	• The resting heart rate of patients with coronary heart disease should be controlled at 55–60 beats/min.
	• The preferred drugs for heart rate control are the β-blockers metoprolol, bisoprolol, and carvedilol.
	• Evabradine is indicated for patients with chronic stable angina with sinus rhythm >70 beats/min after β-blocker application.
Weight and waist circumference	• Body mass index (BMI) of 18.5–23.9 kg/m^2. Waist circumference should be no more than 90 cm for men and 85 cm for women.

β-blockers can be used to prevent and delay the progression of heart failure. Angiotensin II receptor blockers (ARBs) may be used in patients who cannot tolerate ACEI. Clinicians adjust medications and dosages according to patients' conditions [25].

2. Exercise prescriptions

For patients who meet the indications of exercise prescription and exclude contraindications, an individualized exercise prescription should be formulated according to exercise risk assessment. The elements of exercise prescription include exercise type, intensity, duration, and frequency, among which exercise intensity is an important factor in the formulation of exercise prescription, which is directly related to the safety and efficacy of exercise.

Aerobic exercise is the main form of exercise rehabilitation for patients with chronic heart failure [28, 37]. Aerobic exercise includes walking, using a treadmill, swimming, cycling, stair climbing, tai chi, and so on. The principle of the progressive adjustment of aerobic exercise prescription is to "gradually increase the amount of exercise by adjusting the duration, frequency and/or intensity of exercise until the desired goal is reached; Impedance training is adjusted by increasing resistance and/or increasing the number of repetitions, and/or increasing the frequency of each set" [32].

The American Society of Cardiopulmonary Rehabilitation puts forward specific suggestions on a progressive exercise program as follows: (a) develop a personalized progressive exercise program for each patient; (b) adjust the exercise program once a week; (c) generally, only one exercise content (duration, frequency, intensity) is adjusted each time; (d) increase the duration of aerobic exercise about 1–5 min each time until the patient has reached the target value; (e) an increase in exercise intensity and duration of 5–10 each time is generally well tolerated; and (f) first increase the duration of aerobic exercise to the desired goal, and then increase the intensity and frequency [35].

3. Nutrition prescriptions

When providing nutritional advice to patients, it is necessary to understand and evaluate the daily intake of energy, saturated fatty acids, cholesterol, sodium, and other nutritional elements in their diets [35]. Patients should be evaluated for their dietary habits, adherence to cardiovascular protective diets, knowledge of nutrition, and misperceptions of nutrition. Nutritional prescription recommendations for patients should be formulated according to the patients' culture, the patients' preferences, and the principles of a cardiovascular protective diet [32]. Weight, body mass index (BMI), and waist circumference should be regularly monitored. Overweight and obese patients are advised to reduce their BMI by 5–10% within 6–12 months to maintain a BMI of between 18.5 and 23.9 kg/m^2. Waist circumference should be controlled for males ≤90 cm and females ≤85 cm [38].

4. Psychological prescriptions (including sleep management)

The general emotional response of patients should be understood through consultation, and patients' anxiety and depression should be assessed using a psychological screening self-rating scale. For patients with anxiety and depression, symptomatic treatment can be given first, including correct disease cognitive education, exercise therapy, and symptomatic treatment of antidepressant drugs. Patients' evaluation of their own sleep quality should be understood through consultation; patients' sleep quality should be evaluated by the Pittsburgh Sleep Quality Scale. Understanding the sleep behavior of patients is vital to correct their incorrect insomnia cognition and sleeping habits [32]. In the process of cardiac rehabilitation, patients may experience fluctuations in their psychology, and patient communication is needed to enable analysis and rational treatment; patients need to be encouraged to complete their rehabilitation program independently.

5. Patient education (risk factor management and smoking cessation)

Patients' good cognition of disease and rehabilitation treatment plays a very important role in the smooth progress of rehabilitation treatment and improved benefits. Patients should be educated individually by combining their cognitive ability, behavioral characteristics, psychological characteristics, environment, and other factors. Patients should be instructed to learn self-management. All cardiac rehabilitation professionals should receive doctor–patient communication skills training. Evidence-based health behavior change models and intervention techniques should be used to guide patients to improve unhealthy behaviors. Clinicians should routinely ask patients about their smoking history and passive smoking. Smoking patients should be advised to quit smoking in a clear manner. Drugs combined with behavioral interventions improve the success rate of quitting. All patients are advised to avoid exposure to environmental tobacco smoke at work, at home, and in public places.

Cardiac rehabilitation is not a simple exercise, but has clear indications, contraindications, adverse reactions, and "toxic side effects." The exercise of cardiac rehabilitation should be standardized, and the exercise of cardiovascular patients should be strictly restricted and guided. Therefore, to conduct cardiac rehabilitation, professional cardiovascular disease rehabilitation teams should be established, including cardiologists, rehabilitation physicians, rehabilitation therapists, nurses, dietitians, psychologists or consultants, clinical pharmacists, and so forth. To ensure the safety of cardiac rehabilitation, it is necessary to jointly conduct exercise risk assessments on patients under the leadership of cardiologists, formulate reasonable secondary prevention and exercise prescriptions, and strengthen supervision and guidance.

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19 Follow-Up and Long-Term Prognosis of Myocarditis and Fulminant Myocarditis

Jiangang Jiang and Dao Wen Wang

The clinical manifestations of myocarditis vary from mild dyspnea or chest pain, which can gradually disappear without special treatment for cardiogenic shock leading to death [1]. The prognosis can also vary. A prospective study including 174 cases of myocarditis confirmed by endocardial biopsy with a median follow-up of 23.5 months found that the positive polymerase chain reaction (PCR) detection of viral genes on endocardial biopsy was a factor contributing to poor prognosis [2]. Another study of 222 patients diagnosed with viral myocarditis by endocardial biopsy with a median follow-up of 4.7 years reported a mortality rate of 19.2% [3]. The prognosis of myocarditis is related to its etiology, clinical manifestations, and disease stages [2, 4, 5]. This chapter describes the prognosis of patients with viral myocarditis with different pathological tissue types, clinical symptoms, auxiliary examination findings, and clinical treatments.

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19.1 Histopathological Type and Prognosis

The histological examination of endocardial biopsy in myocarditis shows cellular infiltration (Fig. 19.1), usually of tissue cells and mononuclear cells, and possibly with myocardial cell damage [6]. The specific histopathological types of myocarditis are mainly divided into lymphocytic myocarditis, eosinophilic myocarditis, and giant cell myocarditis.

Viral infection, the most common cause of lymphocytic myocarditis [1, 7, 8], usually begins within 3–5 days or up to 2 weeks of infection. Its course varies. The disease can be subclinical, indolent, or fulminant. When the disease is indolent, it gradually progresses to dilated cardiomyopathy (DCM); when it is fulminant, it may lead to death, or the patient may fully recover after reasonable treatment such as short-term hemodynamic support [9]. A study of 27 patients with lymphocytic myocarditis or critical myocarditis confirmed by endocardial biopsy reported a 5-year survival rate of 56%, which did not differ significantly from that of specific DCM [10]. In an earlier retrospective study of 112 patients with histopathologically diagnosed myocarditis, 66 (59%) had lymphocytic myocarditis. The 1- and 5-year follow-up rates of the total population without heart transplantation were 79% and 56%, respectively. A multivariate regression analysis suggested that histopathological

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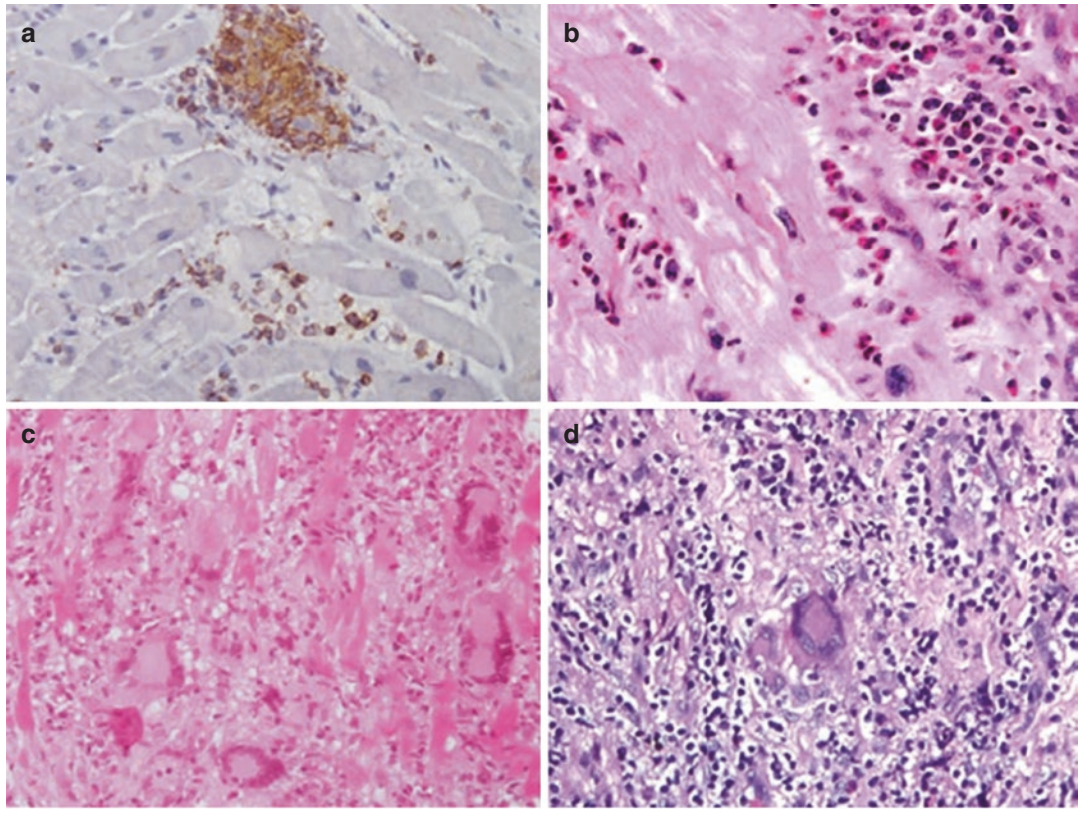

Fig. 19.1 Endocardial biopsies of four types of myocarditis. (**a**) Lymphocytic myocarditis (CD45RO immunoperoxidase stain, 200×); (**b**) eosinophilic myocarditis (250× with HE staining); (**c**) giant cell myocarditis (HE staining, 200×); (**d**) granulomatous myocarditis (HE staining, 200×) [6]. *HE* hematoxylin and eosin

findings (lymphocytic, granulomatous, or giant cell myocarditis) are among the factors predicting patient death or need for heart transplantation [11].

Giant cell myocarditis is a rare and severe autoimmune myocarditis that is virus-negative and usually fatal for which immunosuppressive therapy may be effective [12]. Compared with other pathological myocarditis, giant cell myocarditis has a higher mortality and heart transplantation rate [13]. Eosinophilic myocarditis, characterized by eosinophilic infiltration of the myocardium, is seen in malignancies, parasitic infections, allergic myocarditis, endocardial fibrosis, and idiopathic hypereosinophilic syndromes. In a meta-analysis of 264 patients with eosinophilic myocarditis, the average left ventricular ejection fraction (LVEF) at admission was 35%, 16.8% of patients required transient cardiopulmonary bypass, and the in-hospital mortality rate was 22.3% [14]. In recent years, immune checkpoint inhibitors have been widely used in tumor treatment and achieved significant effects. However, it cannot be ignored that 20–30% of patients have myocardial injury, 1–2% of patients develop fulminant myocarditis, and the risk of death is as high as 46–75% [15].

However, the above results were all reported by Western scholars and published before our report entitled "Life-support based comprehensive treatment regimen." Therefore, it does not represent the latest research conclusions.

19.2 Clinical Manifestations and Prognosis

Fulminant myocarditis, the most serious and special type of myocarditis, is characterized by sudden-onset and extremely rapid disease progression. The patient rapidly develops abnormal hemodynamics and severe arrhythmia that may be accompanied by respiratory failure and liver and kidney failure, and the early mortality rate is extremely high. It is worth noting that some studies have found that, although the hospital mortality rate of this disease is high, once the acute crisis is passed, the long-term prognosis is good.

An 11-year follow-up study in 2000 (Fig. 19.2) showed that, among patients diagnosed with myocarditis by endocardial biopsy, 14 patients with fulminant myocarditis had a significantly higher survival rate than 132 patients with normal acute myocarditis (93% and 45%, respectively), and the long-term survival rate was similar to that of the general population [16]. However, two articles published in 2017 and 2019 reported the opposite conclusion. In a previous study (Fig. 19.3), myocarditis was diagnosed by endocardial biopsy or cardiac magnetic resonance, and 34 patients with fulminant myocarditis and 96 patients with acute viral myocar-

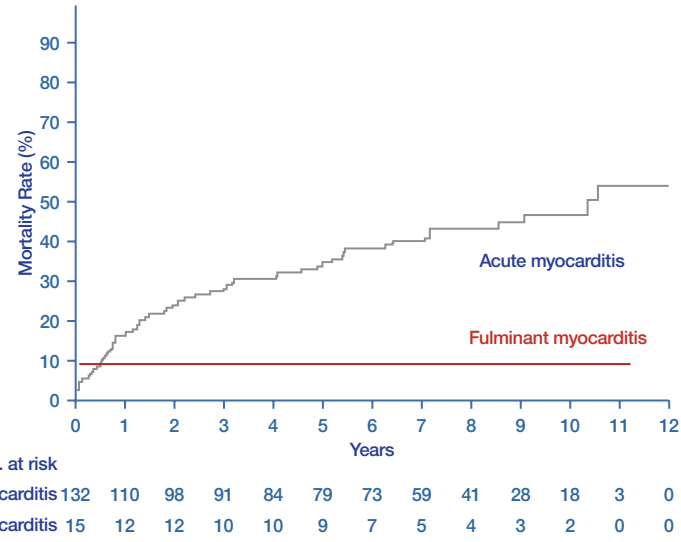

Fig. 19.2 Survival of fulminant myocarditis versus acute lymphocytic myocarditis groups [16]

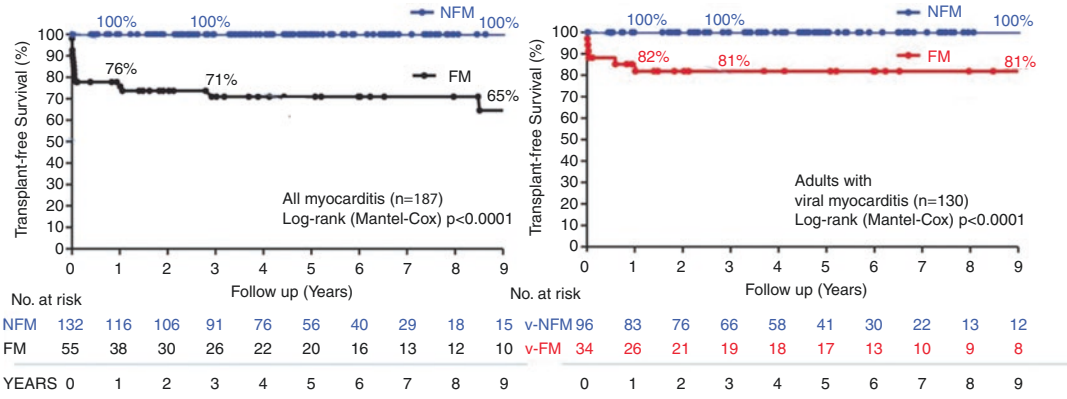

Fig. 19.3 Survival of fulminant myocarditis versus non-fulminant myocarditis groups [17]

ditis were followed for 9 years [17]. In the latter study, myocarditis was diagnosed by histological examination, and 165 patients with fulminant myocarditis and 55 patients with acute viral myocarditis were followed for 60 days and 7 years, respectively [12]. Both studies showed that the survival rate without heart transplantation in patients with fulminant myocarditis was significantly lower than that in patients with acute viral myocarditis [12, 17]. The difference in results was related to the fact that all patients in the study published in 2000 were diagnosed with lymphocytic myocarditis by endocardial biopsy, whereas few patients were assisted with extracorporeal mechanical circulation for fulminant myocarditis at that time.

In a study published in 2017, only some patients underwent endocardial biopsy, and the pathological types of myocarditis were not classified and compared [18]. In a study published in 2019, although all of the patients underwent endocardial biopsies and lymphocytic myocarditis pathological types were compared, the changes in treatment methods for myocarditis (such as the use of external mechanical circulation assistance in patients with fulminant myocarditis) and differences in etiology led to somewhat different conclusions [19] (Fig. 19.4).

Ammirati's two studies also suggested that a QRS duration greater than 120 ms on admission is also a predictor of poor prognosis in patients with myocarditis [12, 17]. A prospective study of 174 patients with biopsy-diagnosed myocarditis found that biventricular dysfunction severity was a major predictor of death or heart transplantation in patients with myocarditis [18]. A follow-up study in Germany of 77 patients diagnosed with viral myocarditis by endocardial biopsy (EMB) reported that the presence of late gadolinium enhancement (LGE) of cardiac magnetic resonance was the most independent predictor of all-cause and cardiogenic death in patients [19]. A follow-up study in 2018 enrolled 443 patients with acute myocarditis diagnosed by endocardial biopsy or biomarker elevation plus meeting two cardiac magnetic resonance criteria for myocarditis (edema and late gadolinium enhancement in non-ischemic mode) reported that patients with complex acute myocarditis (defined as an initial LVEF of less than 50%, persistent ventricular arrhythmia, or low cardiac output syndrome requiring positive inotropic drugs or mechanical circulation support) had significantly higher mortality and heart transplant rates than patients with uncomplicated acute myocarditis [20]. Secondary pulmonary hypertension is a predictor of a poor outcome. In another study, 93 patients with myocarditis who underwent right heart catheterization and EMB were followed up for 4.4 years, and mean arterial pressure was the most important predictor of death [21].

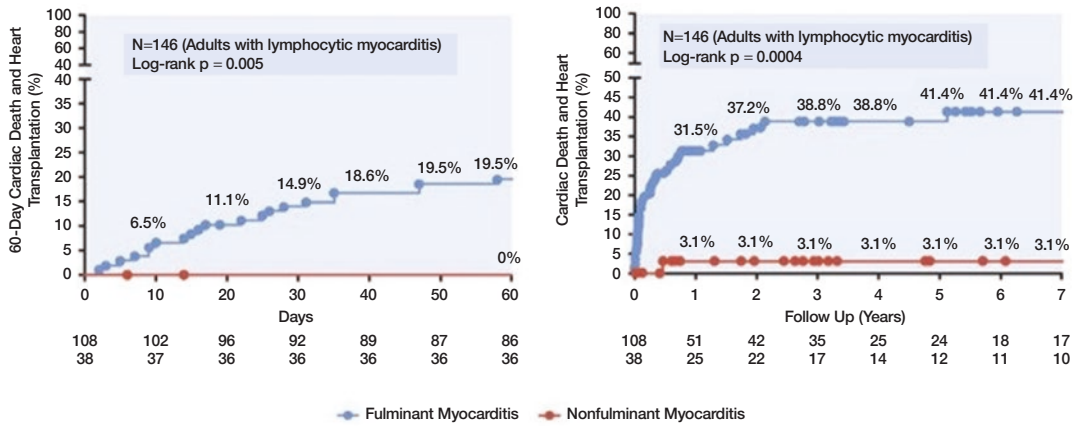

Fig. 19.4 Short-term (left) and long-term (right) follow-up results of lymphocytic fulminant versus non-fulminant myocarditis [12]

The persistence of viral genomes in the myocardium may be an important factor in predicting the outcome of viral myocarditis. In one study, 172 patients with viral myocarditis diagnosed by biopsy were included, of whom 151 were infected with only one virus. After a median follow-up of 6.8 months, endocardial biopsy was repeated. Of them, 55 had spontaneous clearance of the virus genome and a significant increase in LVEF but a significant decline in LVEF was found in patients with persistent viral genome [22]. However, another follow-up study showed that the viral genome detected by endocardial biopsy at admission was not associated with poor prognosis, suggesting that the viral genome may sometimes reflect latent rather than active viral infection [23].

Serological markers, particularly soluble Fas ligands and interleukin-10 (IL-10), may be helpful for predicting the outcomes of acute severe myocarditis. A case series showed that the serum concentrations of soluble Fas and Fas ligand in patients with acute myocarditis were significantly higher than those in normal subjects or patients with old myocardial infarction, and the concentrations of Fas and Fas ligands in patients with myocarditis who died during hospitalization was significantly higher than that in patients with myocarditis who were discharged after recovery [24]. Another study included 20 patients with recently onset idiopathic DCM and the results further support the role of Fas [25]. A higher serum IL-10 concentrations at admission in patients with fulminant myocarditis may indicate cardiogenic shock and death [26].

Cardiac-specific autoantibodies can be identified in patients with acute or chronic myocarditis. The presence of autoantibodies is associated with an increased risk of chronic myocarditis progressing to DCM [27]. A case series of 33 patients with chronic myocarditis showed that patients with anti-α-myosin autoantibodies were less likely to have improved left ventricular systolic and diastolic function. Patients with this antibody showed no improvement in LVEF at 6 months, while those without this antibody showed a 9% absolute increase in LVEF. Similarly, in relatives of patients with idiopathic DCM, the presence of anti-cardiac antibodies predicts future left ventricular dilatation [27].

In summary, we found that the difference between myocardial enzyme spectrum changes in patients with myocarditis and myocardial infarction is that there is no obvious enzyme peak, indicating that the lesion is a gradual change, while the continuous increase indicates that the myocardium is continuously damaged and aggravated, indicating a poor prognosis. The levels of brain natriuretic peptide (BNP) or N-terminal proBNP are usually significantly increased, indicating that cardiac function is seriously impaired, and it is an important indicator for diagnosing cardiac insufficiency, evaluating its severity, and judging its progression and outcome. Neutropenia is a sign of poor prognosis, as is persistent thrombocytopenia.

19.3 Clinical Treatment and Prognosis

The treatment of patients with viral myocarditis can be divided into three parts: symptomatic and supportive treatment, immunosuppressive therapy, and immunomodulatory therapy [28]. Some clinical studies have discussed the effects of these treatments on the prognosis of patients with viral myocarditis. When hemodynamically stable heart failure with a reduced LVEF is present in patients with myocarditis, diuretic therapy on demand, diuretic therapy should be used as needed, angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers should be started as soon as possible, and beta-blockers should be used on an evidence-based basis. ACEI and beta-blockers have been shown to reduce complications and death in patients with systolic heart failure [29]. Animal experiments have shown that ACEI can improve myocardial necrosis and adverse outcomes caused by myocarditis [30, 31].

Cardiopulmonary bypass devices are necessary for patients with myocarditis and severe hemodynamic disorders. Although studies have found that intra-aortic balloon pumping (IABP) cannot improve the prognosis of patients with

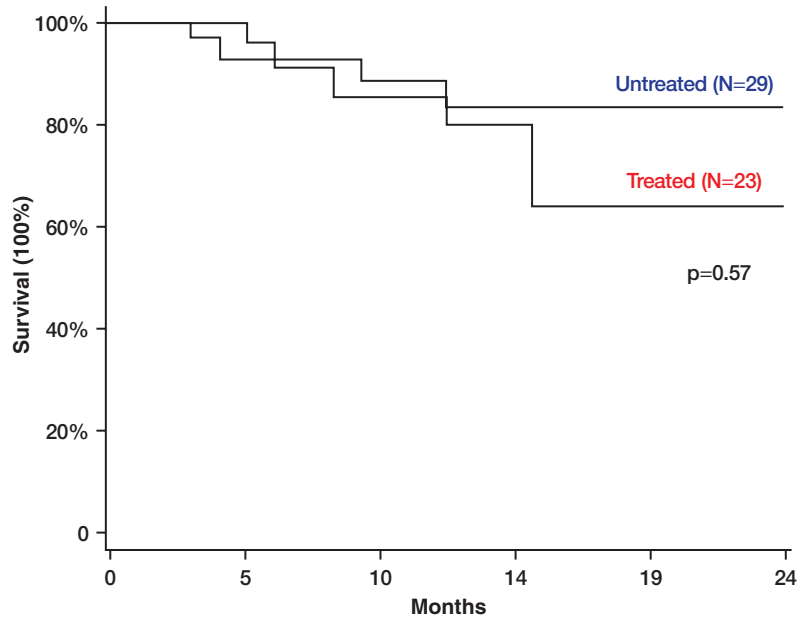

Fig. 19.5 Effect of prednisone on survival of patients with acute myocarditis [41]

myocardial infarction [32], and large randomized controlled studies on the efficacy of IABP in patients with myocarditis are currently lacking, some retrospective studies or case reports have found that IABP can help patients with fulminant myocarditis in the acute phase [33–35]. The therapeutic effect of extracorporeal membrane oxygenation (ECMO) on fulminant myocarditis has been supported by a large number of clinical data [36–40]. In a study of 57 patients with fulminant myocarditis who received adjuvant ECMO therapy, 41 (71.9%) survived and were discharged from the hospital with a 5-year follow-up survival rate of 65.2% [36]. A statistical analysis of 3846 patients with cardiogenic shock treated with veno-arterial ECMO from January 2003 to December 2013 showed that 1601 patients (42%) survived and were discharged from the hospital, while chronic renal failure, hypotension, and low bicarbonate ion levels were associated with high mortality rates [38].

The widespread use of glucocorticoids in clinical practice is largely based on the doctors' clinical experience [8]. Preliminary studies reported that immunosuppressive agents may be beneficial for certain patients with chronic myocarditis, but the effectiveness of immunosuppressive therapy for acute lymphocytic myocarditis of unknown etiology has not been proven. In 1989, two controlled studies showed that glucocorticoids did not improve the survival rate of patients with myocarditis (Fig. 19.5) [41]. One study included 102 patients with myocarditis and reported that the LVEF in the glucocorticoid treatment group was significantly improved compared with that of the control group within 3 months [42]. Long-term follow-up found no significant intergroup difference in LVEF [43]. Glucocorticoids combined with azathioprine therapy benefits the prognosis of patients with chronic myocarditis [43, 44]. In a study in 2001, 84 patients diagnosed with DCM more than 6 months prior with chronic inflammation confirmed by biopsy were randomly divided into hormone treatment and control groups, and the former was treated with steroids and azathioprine. After a 2-year follow-up, the hormone treatment group had significant improvements in LVEF and cardiac function classification compared with the control group (Fig. 19.6) [43].

In 2009, the TIMIC study included 85 patients with chronic stable DCM who were confirmed to have myocarditis by endocardial biopsy, the viral genome was not found on endocardial biopsy, and the patients were randomly divided into hormone treatment and control groups. The hormone treatment group was treated with prednisone and azathioprine. After 6 months of follow-up, the

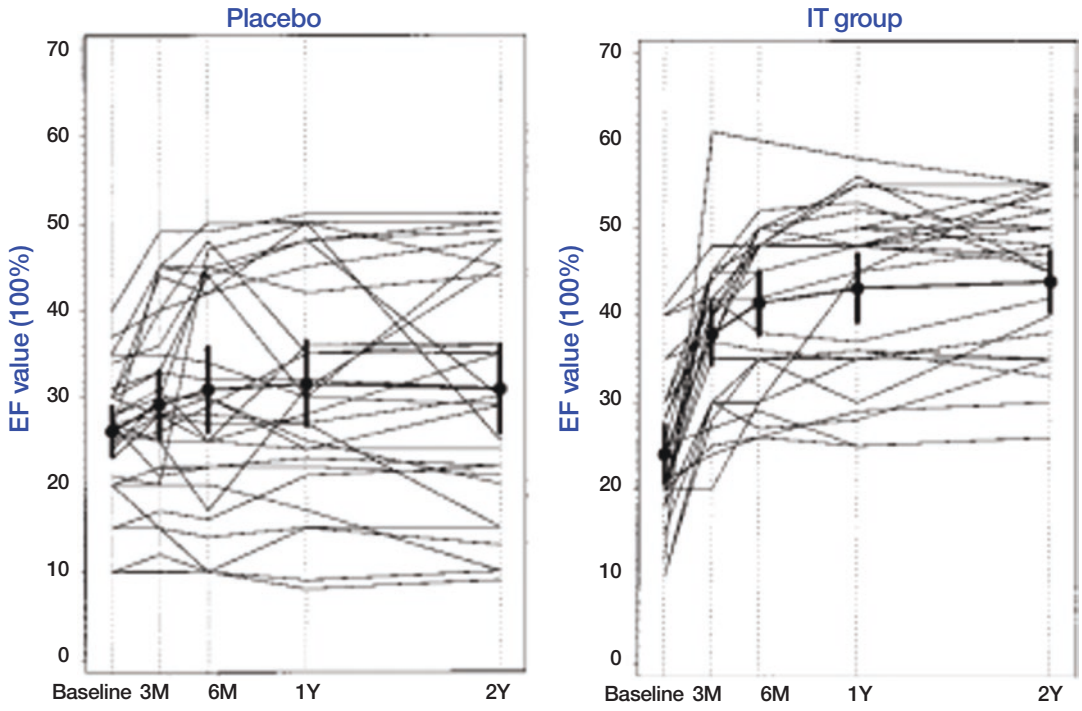

Fig. 19.6 Comparison of cardiac function between the immunosuppressive therapy and control groups of patients with chronic inflammatory dilated cardiomyopathy [43]

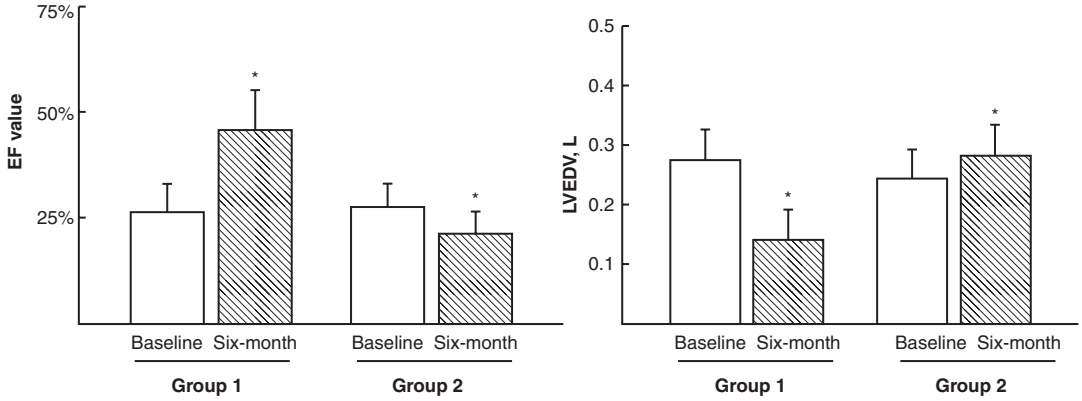

Fig. 19.7 TIMIC study [44] of patients with chronic stable dilated cardiomyopathy who had myocarditis confirmed by endocardial biopsy and had no viral genome detected by endocardial biopsy. Group 1 was the hormone therapy group (n = 43; prednisone and azathioprine), and group 2 was control group (n = 42). *Indicates a statistically significant difference. The black shadow indicates the data after 6 months of follow-up, while the white shadow indicates the baseline data. The follow-up for 6 months showed that the ejection fraction of the hormone treatment group increased significantly after 6 months and the cardiac structure recovered. The results were worse in the control group

hormone treatment group had significantly improved cardiac function and cardiac outcome than the control group (Fig. 19.7) [44]. The Myocarditis Treatment Trial is a randomized controlled trial that included 111 patients with an LVEF of less than 45% and histopathologically diagnosed myocarditis of unknown cause, and there was no significant difference in cardiac

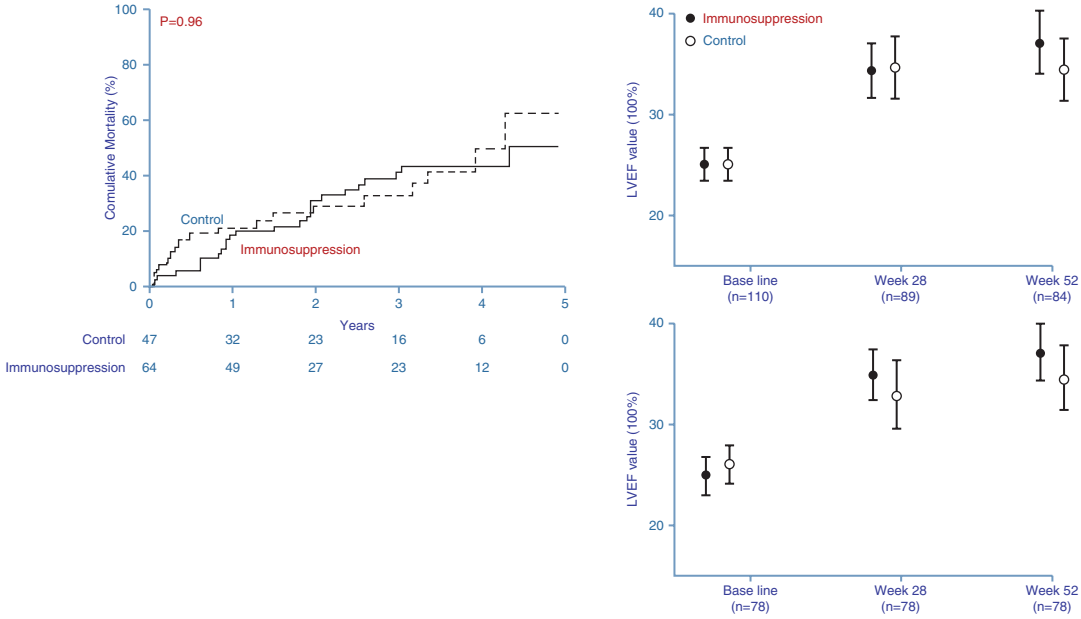

Fig. 19.8 The Myocarditis Treatment Trial [45]. The left figure compares the cumulative mortality, with the dashed line as the control group and the solid line as the immunosuppressive treatment group. The figure on the right compares the left ventricular ejection fractions of the two groups. The figure above compares the total population, while the follow-up data of some groups are missing. The figure below compares the follow-up data of the three groups. The results showed no significant difference in cardiac function and survival in patients with a left ventricular ejection fraction of less than 45% and histopathological diagnosed myocarditis of unknown cause received hormone and cyclosporine or azathioprine treatment compared with the control group

function improvement or survival between the hormone treatment group treated with glucocorticoids and cyclosporine or azathioprine and the control group (Fig. 19.8) [45]. A meta-analysis published in 2013 with a total of 719 patients summarized 8 clinical trials on the use of glucocorticoids in the treatment of viral myocarditis and found that, although there was no intergroup difference in mortality, the LVEF of the treatment group was significantly better than that of the control group during 1–3 months of follow-up [46].

Immunoglobulin has antiviral and immunomodulatory effects, suggesting that it may be helpful in the treatment of viral myocarditis. A multicenter clinical study in Japan on 41 patients with acute myocarditis showed that high-dose intravenous immunoglobulin (IVIG; 1–2 g/kg body weight for 2 days) significantly improved patient survival, the 1-month mortality rate showed a downward trend, and the inflammatory factors in the peripheral blood were significantly reduced [47]. A retrospective study of 58 patients with explosive myocarditis in Guangdong, China, showed that IVIG 400 mg/kg for 5 days can significantly improve the patient's LVEF and left ventricular end diastolic diameter after 4 weeks, and significantly reduce malignant arrhythmias and mortality [48]. However, a systematic review concluded that the current rigorous data are insufficient to enable recommendation of routine immunoglobulin therapy in patients with acute myocarditis [49]. Preliminary data suggest that antiviral therapy with interferon β may be beneficial in patients with chronic dilation who have viral genomes in endocardial biopsy confirmed by PCR. A study included 143 patients with biopsy-diagnosed viral myocarditis complicated with symptoms of heart failure who were randomly divided into an antiviral therapy group

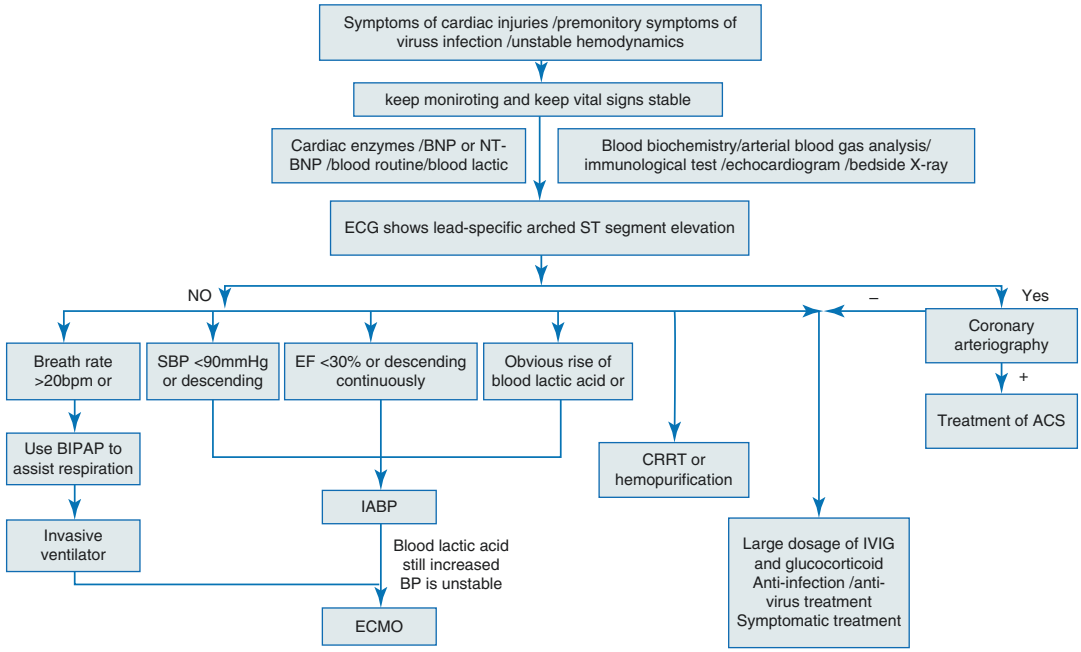

Fig. 19.9 Flowchart of clinical decision-making process in the treatment of fulminant myocarditis [50]

(interferon β1b) and a control group. The results showed that antiviral therapy could improve viral clearance and cardiac function in chronic viral myocarditis [50].

In 2017, the Chinese Society of Cardiology Expert Consensus Statement on the Diagnosis and Treatment of Adult Fulminant Myocarditis put forward a "life-support based comprehensive treatment regimen" which emphasized the early treatment of mechanical life support therapy, immunoregulatory therapy, and neuraminidase inhibitor therapy (Fig. 19.9) [15]. A multicenter controlled trial showed that treatment in accordance with the "comprehensive treatment plan" can significantly reduce the in-hospital mortality of fulminant myocarditis from 50% to 3.7%, and the use of cardiopulmonary bypass devices, antiviral therapy, and immunoglobulin were associated with improved outcomes for fulminant myocarditis [51]. In another multicenter study further confirmed its effacacy [52]. In our study center (Tongji Hospital), myocarditis patients were followed up for an average of 12 months, and we only found 24.2% fulminant myocarditis patients had sustained LVEF <55% after discharge but no cases of cardiac death or heart transplantation in 66 discharged patients with fulminant myocarditis were reported [53]. Related research is ongoing, and the current follow-up situation is shown in Fig. 19.9.

19.4 Follow-Up of Fulminant Myocarditis Patients

Although the association between troponin, BNP, CRP, and the prognosis of fulminant myocarditis is controversial, monitoring these indicators can help clinicians assess the patient's condition, so as to timely adopt aggressive treatment and adjust the medication regimen. Therefore, for patients with fulminant myocarditis, we recommend that cardiac troponin (CTN), BNP, and CRP be tested, and cardiac ultrasound and magnetic resonance

examination be performed regularly. It is recommended that patients be tested 1, 6, and 12 months after discharge. If all indicators and cardiac ultrasound were normal, the follow-up reexamination time could be extended.

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Clinical Nursing for Patients with Fulminant Myocarditis

20

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Precision Medicine Group of the Chinese Society of Cardiology issued "An Expert Consensus on Diagnosis and Treatment of Fulminant Adult Myocarditis" in 2017 [1]. The panel proposed a new treatment regimen termed "life support-based comprehensive treatment regimen" as a theoretical evidence for clinical diagnosis and treatment. The core content of this treatment regimen includes: (a) mechanical life support (applications of mechanical respirators and circulatory support systems, including intra-aortic balloon pump and extracorporeal membrane oxygenation); (b) immunological modulation using sufficient doses of glucocorticoids and immunoglobulins; and (c) antiviral reagents using neuraminidase inhibitors, combined with other symptomatic treatments such as acute left heart failure therapy, antishock therapy, antiarrhythmia therapy, and real-time monitoring.

Early transfer to the cardiac intensive care unit, installed with circulatory respiratory monitoring and mechanical life support devices, is a priority for all patients with fulminant myocarditis for continuous monitoring. When the patients received life support devices such as intra-aortic balloon pump (IABP) and extracorporeal membrane oxygenation (ECMO), a professional medical team was recommended to respond. The multi-disciplinary medical team consisted of a leader (a cardiovascular specialist/critical care physician), a coordinator (the head nurse/nursing expert of the critical care unit), and other core members such as expert nurses in continuous renal replacement therapy (CRRT). With the special care mode with a nurse-patient ratio of 2:1 or 1:1, and 24-h continuous bedside care, the multidisciplinary team struggled to save patients with fulminant myocarditis in the critical phase and improve the survival rate.

20.1 Basic Nursing

20.1.1 Pressure Ulcer Prevention

To avoid long periods of locally sustained pressure, repositioning the patients by following the axis every 2–3 h is an essential element of pressure ulcer prevention [52]. A variety of constant low-pressure devices such as air-filled mattresses, cushions, and pillows should be placed on skin areas prone to ulcer formation to reduce the pressure ulcer incidence. Bedsheets of the patients should be soft, clean, dry, and void of any contamination from urine and stool. The oxygen saturation (SpO_2) measuring sensor could be switched to a different finger every hour for reducing the long-term compression. Additionally, patients in a coma after cardiac arrest require close observation of the patient's

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ears and headrest when using ice cap as brain protection. A nurse would reposition the head and limbs with all joints at a functional position and perform a regular massage of normal limbs. Raise the head side of the bed to 30° is considered as an effective measure for preventing ventilator-associated pneumonia (VAP).

20.1.2 Keeping Warm

Poor peripheral circulation and a complaint of cold are common in patients with fulminant myocarditis. There are two main contributors to the symptoms: (a) inadequate intake of calories at an early stage, that resulted due to the impact of the rapid progress of fulminant myocarditis on the gastrointestinal tract; (b) mobility limitation due to protective constraint, that resulted from unplanned extubation of life-support catheters. To improve the patient's body temperature, room temperature and humidity are set at an appropriate range and the patients are offered soft uniforms and cotton quilts. The nurse shift handover needs to concentrate on all the invasive catheters of patients and to decrease skin exposure to the environment.

20.1.3 Continuous Monitoring

1. A nurse would observe and record the patients' body temperature, heart rhythm, arterial blood pressure, respiration rate, consciousness, SpO_2, and other parameters of life-support devices in real-time.
2. Continuous electrocardiography (ECG) and 12-lead or 18-lead ECG provided evidence to trace the signs of arrhythmia among the patients. Pharmacotherapy and electrocardioversion therapy were administered in response to adverse cardiac events. When signs of bradycardia are observed on ECG, temporary pacemakers were a priority for patients. Pharmacotherapy such as isopropyl epinephrine or atropine could be used temporarily to improve the heart rate.
3. Accurate volume management is essential for planning the patient's fluid therapy. A nurse needs to record the amount of patient's fluid input and output every 1–2 h, and would report about the fluid imbalance to a doctor, if necessary.
4. Biochemical indexes are significant indicators for the effectiveness of fulminant myocarditis treatment, including the levels of creatine kinase MB isoenzyme (CKMB), B-type natriuretic peptides (BNP) or N-terminal fragment brain natriuretic peptides (NT-pro-BNP), blood lactate, C-reactive protein, cytokines, electrolytes; arterial blood gas (ABG) analysis; blood routine indexes; liver and kidney function indexes; erythrocyte sedimentation rate; and other inflammatory markers. Nurses would dynamically track these biochemical indexes and report critical values to the corresponding doctor immediately.
5. A "Safety checklist for patients with fulminant myocarditis" was developed and put into practice to enhance the quality of care and improve the treatment (the checklist attached at the end of the chapter).

20.2 Nursing of Life-Support Devices

Mechanical life support therapy (including respiratory support, circulation, and CRRT, which allows the heart to get enough rest under systemic therapy to restore its normal function), is one of the most important aspects of a "comprehensive life support-based treatment program" [2, 3].

20.2.1 ECMO

ECMO offers physiologic rest, which is equivalent to providing the patient with bed rest and oxygen. It improves myocardial compliance, restores cardiac conduction, and increases coronary blood flow to promote ventricular recovery. In addition, it can effectively increase the perfusion of vital organs including the lungs and brain.

20.2.1.1 Catheter Care

1. Unblock catheter

   Catheters connected to ECMO should be prevented from occlusion, damage, rupture, or breakage. ECMO patients must lie strictly in bed with the elevation angle of the head of the bed should not exceed 30°, and their implanted limbs cannot bend at their hips [4]. Protective restraint should be used when the patient becomes agitated. The nurse managing the ECMO should assess the external loop every hour, including correct catheter connection, reasonable alarm setting, and clotting formation in external ECMO catheters and membrane lung through light flush. The formation of a clot in the external ECMO catheters and membrane lung is defined by a visually dark color that settles on the catheters and membrane lung and does not flow with the blood [5]. Replacement of ECMO catheters is recommended, as more mobile clotting >5 mm are found. Nurses need to secure IABP catheters while repositioning patients following the axis every 2–4 h. ECMO catheters are forbidden to be used for intravenous (IV) infusion, blood transfusion, and blood sample collection. Immediate action needs to be taken under the shake in ECMO catheters resulting from obstruction and inadequate volume of circulation.
2. Secure catheters

   Subcutaneous sutures are used to secure the V-A catheter and the insertion site is covered with adhesive anchors and an additional large transparent film dressing [4]. The external catheter of ECMO is positioned parallel to the patient's axis and secured at the end of the bed without tension. Nurses monitoring ECMO must examine all connections of the catheter every 1 h to prevent distortion, displacement, or prolapse. The length of the ECMO external catheter should be measured at nurse shift handover and recorded on the medical system.

20.2.1.2 The Monitoring of ECMO Patients

Nurses need to regularly monitor indexes and parameters related to ECMO which include the following: revolutions per minute, flow rate, air oxygen mixed concentration, air flow, the vascular active drug dosage, temperature, the actual temperature of the water tank, SpO_2, urine output and color, and the circulation of lower limb (temperature and color) that is inserted into the femoral arteriovenous catheter.

Speed and Flow Rate

1. Speed: The initial speed is >1500 r/min, and the maximum speed for the treatment is ≤4000 r/min.
2. Flow rate: The initial flow rate is set at 20 mL/(kg min), and the maximum flow rate is increased to 120 mL/(kg min) in 20–30 min to repay the oxygen debt. Thereafter, blood flow should be gradually reduced to the minimum level of adequate support, with adult ECMO-assisted flow usually maintained at 60 mL/(kg min). During the treatment, the flow rate was closely observed in accordance with the rotational speed, and the perfusion flow was adjusted timely according to the venous oxygen saturation, mean arterial pressure, blood lactic acid level, urine volume, etc.

Oxygenation Monitor

Arterial blood gas changes should be closely monitored, every 2 h at the beginning of treatment and every 4–6 h after stabilization. Gas flow and oxygen concentration should be dynamically adjusted according to the results of blood gas analysis to maintain arterial oxygen partial pressure above 90 mmHg and mixed venous SpO_2 should reach approximately 75% [6]. The ventilator parameters, ECMO flow, and ventilation were adjusted according to acid-base balance. In addition, maintaining hematocrit >40% and hemoglobin >120 g/L optimizes oxygen delivery at the lowest allowed blood flow. The SpO_2 of the right hand reflects the patient's cardiopulmonary function and the SpO_2 of the left hand reflects the SpO_2 of ECMO [7]. The dynamic changes of the peripheral blood SpO_2 of the left and right hands should be observed and compared regularly.

Gas Management

The initial membrane oxygen concentration is adjusted to 70–80%, the gas-blood flow ratio is 0.5:1 to 0.8, and the membrane oxygen concentration is adjusted to 30–40% in the stable period.

The blood at the inlet and outlet of the membrane lung is taken for blood gas analysis, the working condition of the membrane lung is judged, and the air flow and oxygen concentration are adjusted dynamically.

Pressure Monitor

The pressure at the inlet and outlet of the oxygenator is monitored when the conditions permit. The pressure in front of the power pump is ≤300 mmHg, the pressure behind the power pump is ≤400 mmHg, and the negative pressure of venous suction should be less than 30 mmHg, otherwise it may be easy to cause hemolysis. When the pressure at both points increases, it indicates that the arterial cannula end of the oxygenator is blocked, and the oxygenator thrombosis is suggested when the pressure difference between the two points increases when the two-point pressure increases.

Temperature Management

The temperature of the water tank is set at 36–37 °C, and the patient's body temperature is maintained close to 37 °C and monitored continuously. Very low temperature will lead to the disorder of hemodynamics and blood coagulation mechanism. However, very high temperature will increase the oxygen consumption of the body, which is not conducive for the recovery of cardiopulmonary function [8]. If the patient is placed under the condition of suspected hypoxic-ischemic brain damage, the brain hypothermia (central temperature, 32–34 °C) should be maintained within the first 24–72 h to avoid neurological complications.

Volume Management

The nurse should closely monitor the amount of water intake and output, control the speed of infusion, maintain mean arterial pressure (MAP) at 50–70 mmHg, central venous pressure (CVP) at 5–10 mmHg, and maintain blood lactic acid <1.5 mmol/L using diuretics until patients reach normal dry weight after their hemodynamics is stable. If the patient has diuretic resistance or acute renal injury, the initiation of CRRT as soon as possible is important.

Anticoagulation Monitor

Continuous heparin infusion [20–50 U/(kg h)] is administered to fulminant myocarditis with ECMO. At the onset of ECMO-assistance, the activated coagulation time (ACT) is tested every time at bed and then could be measured at intervals of 2–3 h after the stabilization of patient. The ACT is recommended to be maintained at 160–220 s [9, 10], and activated partial thromboplastin time (APTT) maintained at 50–70 s is tested every 4–6 h. The dose of heparin is reduced or increased depending on the patient's procoagulant status. The ACT should be maintained at 150–170 s when active bleeding is reported, while it should be maintained at 200–220 s when less auxiliary flow and a high risk of clot are present. In addition, fresh frozen plasma or fibrinogen is required to be administered when patient's hemodynamics are not within the following criteria: the amount of platelet is required to be $>50 \times 10^9$/L and fibrinogen should be maintained at 250–300 mg/dL. Antithrombin III (ATIII) level needs to be monitored when ATIII deficiency is suspected. Fresh frozen plasma, cryoprecipitate, or recombinant ATIII could be administered to the patient when ATIII level below 50% of normal value is observed. Agaltreban is recommended as a replacement or thromboelastography is given to patients diagnosed with heparin-induced thrombocytopenia. It is noted that ACT should be performed after 30 min when the transfusion of blood products such as platelets, plasma, and clotting factors, and protein is completed.

Indicators for Weaning ECMO [11–13]

Standardized indicators and procedure to optimize the weaning process is disputable. Experts consider that successful weaning from patients with fulminant myocarditis is a multifactorial process, which requires to sufficiently restore the function of the heart and other organs, including signs of recovery at 1-week ECMO support, hemodynamically stable, the volume of cardio-

pulmonary bypass support <30% demand for patient, left ventricular ejection fraction with the administration of positive inotropic drug >35–45%, and patient's cardiopulmonary function provide sufficient circulation and oxygen. The decisive factor for fulminant myocarditis patients to wean ECMO is the recovery of myocardial injury and long-term arrhythmia [14]. Before VA-ECMO is completely withdrawn, more than one test of weaning ECMO should be performed on the patient [15], clamp the arteriovenous catheter temporarily, make the ECMO circuit circulate by itself through the bridge between the artery and the venous catheter for 0.5–4 h, and continuously flush the cannula with heparin saline or manually every 10 min to prevent thrombosis in the ECMO circuit and the cannula. The standardized procedure for weaning of adult patients on ECMO follows the below steps: Firstly, the arteriovenous catheter is temporarily clamped which makes the ECMO circulate through the bridge between the artery and the venous catheter for 0.5–4 h. Then, the setting catheters are kept under high flow of heparin sodium every 10 min to minimize the risk of clot formation.

20.2.2 IABP

The IABP increases myocardial oxygen supply and reduces myocardial oxygen demand by inflating and deflating the IAB in synchrony with cardiac contraction via an external drive console. When blood stops discharging from the heart, the IAB is inflated at the beginning of diastole; balloon deflation makes the aorta partially empty, so as to reduce afterload and maximize left ventricular ejection fraction. IABP reduces cardiac workload to decreases myocardial oxygen consumption.

20.2.2.1 Effective Trigger

Daily chest X-ray and B-ultrasound should be obtained to confirm the position of the IABP catheter tip. To achieve effective trigger, the site of IAB should be located inferior to the origin of the left subclavian artery and superior to the renal arteries, and the top of the catheter should be at the level of the left and right main bronchial bifurcation. ECG trigger mode is preferred with the full assistance of 1:1 to partial assistance (IABP assistance less than every cardiac contraction).

20.2.2.2 Continuous Observation

Some experts suggest that hemodynamic variables require assessment, including heart rate, peak diastolic pressure (PDP), average arterial pressure, pulmonary capillary wedge pressure, and cardiac output [16]. Increased blood pressure, decreased heart rate, reduction of vasoactive drug use, improvement in tissue perfusion, and PDP systolic pressure ≥10–20 mmHg should be considered as evidence of IABP effectiveness. Especially for evaluation in perfusion, conscious recovery, dyspnea relief, the disappearance of skin spot, warm limbs, and increased urine output are indicators for adequate perfusion. Nurses managing IABP must continually detect the arterial pressure waveform and heart rate which is synchronized with the ECG trigger mode, ensuring that the arterial pressure waveform follows a regular pattern. Adequate helium is necessary for IABP to function well. Arterial pressure waveform at regular inflation and deflation of IAB is demonstrated in Fig. 20.1, and arterial pressure waveform at irregular inflation and deflation of IAB is demonstrated in Fig. 20.2.

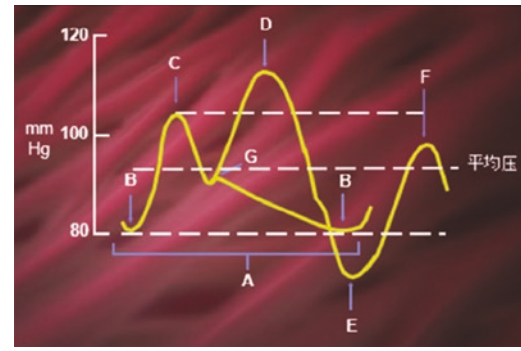

Fig. 20.1 Blood pressure changes during balloon counterpulsation. (A) A complete heart cycle; (B) unaided end diastolic pressure; (C) unaided systolic blood pressure; (D) diastolic pressurization (counterpulsation pressure); (E) end diastolic pressure after adjuvant; (F) post adjuvant systolic blood pressure; (G) double beat notch

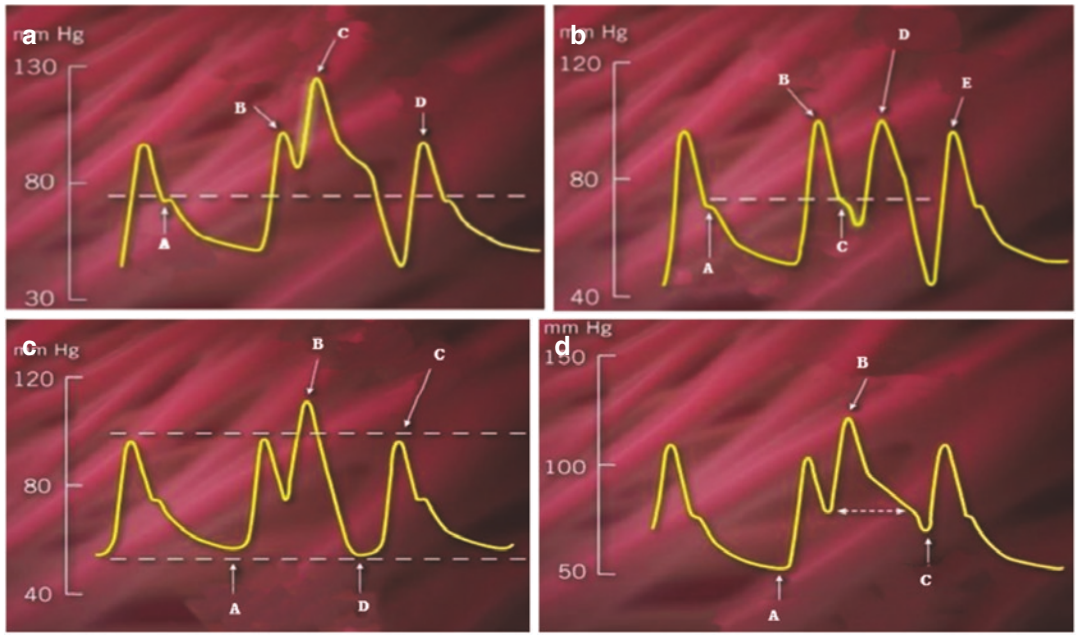

Fig. 20.2 (1) Phase error—premature balloon inflation. (A) Recoil notch; (B) unaided systolic blood pressure; (C) diastolic pressurization (counterpulsation pressure); (D) premature balloon inflation after assisted systolic pressure is common before aortic valve closure. The waveform is characterized by balloon inflation and diastolic pressure "invading" the systole before the stroke notch. The physiological effect is that the aortic valve may close prematurely. It is possible to increase LVEDV/LVEDP/PCWP; increase left ventricular wall pressure or afterload, aortic blood reflux, and increase myocardial oxygen demand

(2) Phase error—balloon inflated too late. (A) Aortic notch closed; (B) unaided systolic blood pressure; (C) double beat notch; (D) diastolic pressurization (counterpulsation pressure); (E) it is common that the balloon inflates too late after aortic valve closure. The waveform features that the balloon inflates after the stroke notch, lack of sharp "V", and insufficient counterpulsation pressure. The physiological effect is insufficient coronary perfusion

(3) Phase error—premature balloon deflation. (A) Unaided end diastolic pressure; (B) diastolic pressurization (counterpulsation pressure); (C) post adjuvant systolic blood pressure; (D) premature balloon deflation after assisted end diastolic pressure is often seen in premature balloon deflation in diastole. The waveform is characterized by the rapid decline of counterpulsation pressure immediately after it appears. Insufficient counterpulsation pressure, the end diastolic pressure with counterpulsation may be equal to or lower than that without counterpulsation. Systolic blood pressure may increase with counterpulsation. The physiological effect is insufficient coronary perfusion. Coronary and carotid blood may have reflux. Coronary blood reflux may lead to angina pectoris. The effect of afterload reduction is undesirable and increases myocardial oxygen demand.

(4) Phase error—balloon deflation too late. (A) Unaided end diastolic pressure; (B) diastolic pressurization (counterpulsation pressure); (C) it is common to start deflation when the main valve begins to open. The waveform characteristic is that the end diastolic pressure with counterpulsation may be equal to the end diastolic pressure without counterpulsation. The rise time of systolic blood pressure in counterpulsation was prolonged and the appearance of the counterpulsation pressure part is widened. The physiological effect was that the afterload did not decrease at all. The increase of left ventricular ejection resistance and the prolongation of isovolumic systole lead to the increase of myocardial oxygen consumption. Balloon may obstruct left ventricular ejection and increase afterload

20.2.2.3 Catheter Care

1. Secure catheters

   Sutures, adhesive anchors, and additional large transparent film dressings are used to secure the IABP catheter. The external catheter of IABP is positioned parallel to the patient's axis. Nurses monitoring IABP must examine all connections of catheter every 1 h to prevent distortion, displacement, or prolapse. The length of IABP external catheter should be measured at nurse shift handover and recorded on the medical system.

2. Unblock catheter

   Catheters connected to IABP should be protected from damage, rupture, or breakage, especially for the pressure sensor monitor catheter that detects accurate DPD. Patients with femoral IABP must remain in bed, with the head of the bed not elevated more than 30°, and the implanted limb must not flex at the hip. The pressure sensor monitor catheter could be placed at the same horizon with the patient's heart and calibrated to zero every 4 h. Nurses need to secure IABP catheter while repositioning the patients following the axis every 2–4 h.

20.2.2.4 Surveil Anticoagulant

All patients need to receive an intravenous infusion of heparin (sodium chloride 500 mL + heparin sodium 2500 U) to prevent blood clots in the IABP with a small dose per hour. The heparin IV is compressed by 300 mmHg pressure bag and rapidly flushes the IV catheter for 15 s to prevent the effect of catheter occlusion on pressure indicators.

Nurse should pay close attention to the compression of pressure bag and maintain the heparin IV infusion at a specific rate. ECMO anticoagulation guideline is recommended when patient undergo IABP and ECMO.

20.2.2.5 Indicators for Weaning IABP [17, 18]

Evidence demonstrates that the withdrawal of IABP support depends on stable hemodynamics, cardiac index >2.5 L/(min m^2), average arterial pressure >80 mmHg, conscious status, sufficient peripheral circulation, urine output >1 mL/(kg h); minimisation of pharmacological assistance such as the dose of dopamine <5 μg/(kg min), no signs of arrhythmia or myocardial ischemia on ECG, and normal arterial blood gas results. The withdrawal of IABP support may be achieved by either frequency weaning or volume weaning or both.

20.2.2.6 Care After Weaning IABP

Keeping an eye on the patient's response to IABP is critical in nursing practice. Nurses must continually assess the patient's response to discontinuation of IABP support and identify early cardiac decompensation. Hemodynamics stability, insertion site, pulse on dorsal foot artery of both lower limbs, muscle tension and circumference of thigh and calf, skin color, and temperature are required for real-time assessment.

20.2.3 Care for Temporary Pacemaker

Pacing heart rate, output voltage, and sensory sensitivity parameters are set based on the personal cardiac function. Nurses should closely monitor the patient's heart rate in consistent with pacing heart rate, independent rhythm, and temporary pacemaker work mode. Doctors and nurses must be present at the time of adverse cardiac events, such as cardiac arrest, to replace the pacemaker battery.

20.2.4 Care for Invasive Ventilator

20.2.4.1 Respirator-Assisted Ventilation

Respiratory support should be given to all patients with fulminant myocarditis as soon as possible to improve pulmonary function and reduce heart load [1, 2, 19]. There are the two types of respiratory support, non-invasive assisted ventilation and endotracheal intubation and manual control of mechanical ventilation. The former is recommended for patients with respiratory rate exceeding 20 bpm, $PaO_2 < 60$ mmHg, or $SaO_2 < 90\%$. If it is ineffective or the patient cannot tolerate it, endotracheal intubation should be used. The latter that provide full respiratory support, is suitable for patients with respiratory failure, especially those with significant respiratory or metabolic acidosis and disturbance of consciousness. Not all patients with external life support receive endotracheal intubation and manual control of mechanical ventilation [20, 21]. After many years of improvements in components and technology, ECMO has become a portable mechanical support device that is safe to use [3].

Table 20.1 Richmond agitation–sedation scale(RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior towards staff
+2	Agitated	Frequent nonpurposeful movement or patient–ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
−1	Drowsy	Not fully alert, but has sustained (more than 10 s) awakening, with eye contact, to voice
−2	Light sedation	Briefly (less than 10 s) awakens with eye contact to voice
−3	Moderate sedation	Any movement (but no eye contact) to voice
−4	Deep sedation	No response to voice, but any movement to physical stimulation
−5	Unarousable	No response to voice or physical stimulation

Table 20.2 Sedation-agitation scale (SAS)

Score	State	Behavior
7	Dangerous agitation	Pulling at ET tube, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very agitated	Dose not calm despite frequent verbal reminding, requires physical restrains
6	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands
1	Unarousable	Minimal or no response to noxious stimuli, dose not communicate or follow commands

Domestic and overseas scholars have researched the feasibility of "conscious" ECMO treatment with spontaneous ventilation and have recommended the "conscious" ECMO treatment to the clinic [22–24]. Experts have explored the potential benefits of "conscious" ECMO, including reduction of adverse events related to mechanical ventilation, decrease in unplanned extubation, minimization of the demand for analgesia, facilitation in oral intake, enhancement of communication, improvement of patient's comfort, and recovery [25, 26].

20.2.4.2 Tracheal Cannula

Appropriate analgesia and sedation are important in mechanically ventilated patients to ensure patient comfort and safety while reducing excessive compensatory oxygen consumption and protecting all organs. It is necessary to understand sedation strategies and available therapeutic agents [27]. All sedation strategies should start with real-time assessment and ensure adequate pain control. As the currently most precise and reliable sedation assessment tools for measuring quality and depth of sedation in adult patients [27–30], the Richmond agitation-sedation scale (RASS, Table 20.1) and Sedation-agitation scale (SAS, Table 20.2) have been strongly recommended by domestic and overseas guidelines, and has good validation for ICU patient with mechanical ventilation, agitation, and delirium [27, 31, 32]. Light sedation corresponds to the score of RASS (−2 to +1), the score of SAS (3–4), moderate/deep sedation corresponds to the RASS (−4 to −3), the score of SAS (2), sedation with neuromuscular blockers corresponds to the score of RASS (5), the score of SAS (1). The nurse should dynamically adjust the sedate target to reduce drug accumulation in the body and maintain the optimal sedation state of patients [33].

20.2.4.3 Mechanical Ventilation

A protective lung ventilation strategy is implemented, the ventilator parameters are reduced, and the minimum level of support is maintained,

so that the lung could obtain adequate recovery [6]. The strategy is designed to reduce the ventilator parameter settings to avoid barotrauma and volutrauma [34]. Nurses should continuously observe the respiratory rate, rhythm, and oxygen saturation. The ventilator parameters are dynamically adjusted according to the blood gas analysis [35]. The recommendations for ventilator parameters include the tidal volume (3–5 mL/kg), respiratory rate (<8 beats/min), positive end-expiratory pressure (5–5 cmH_2O), pause pressure (<25 cmH_2O), and FiO_2 (30–40%) [12, 34]. The arterial and venous oxygen saturation should be continuously monitored, keeping the arterial oxygen saturation more than 95% and maintaining the mixed venous oxygen saturation at 65–75% [36, 37].

20.2.4.4 Respiratory Tract Nursing

Airway humidification, closed endotracheal suctioning, and physical therapy is adopted for clearing respiratory secretions, keeping airway open, ensuring aseptic suction, and improving ventilation. Cluster nursing is implemented to prevent ventilator-associated pneumonia [38], including daily assessment of extubation indications and early extubation. In addition, sequential ventilation is adopted, referring to the gradual transition to non-invasive positive pressure ventilation, face-mask ventilation, high-flow nasal cannula, or nasal cannula.

20.2.5 CRRT Nursing

CRRT is beneficial for patients with fulminant myocarditis and is widely used in its treatment [3]. Its functions usually include: (a) continuous elimination of toxins and cytokines from circulation; (b) volume overload decrease via ultrafiltration; (c) maintaining water-electrolyte and acid-base [39, 40]; and (d) recovery of vessel response to vasoactive drugs [11]. When complicated with renal injuries, CRRT should be used actively in the early stage [41].

20.2.5.1 CRRT Mode [42]

The common modes are continuous veno-venous hemofiltration and continuous veno-venous hemodiafiltration. Pre-dilution is preferred, using a filter with adsorption function.

20.2.5.2 Vascular Access

The blood purification tube was recommended to coupling to the ECMO loop [43]. The common connections include: (a) connecting the inlet line (artery) and the outlet line (vein), the inlet line is after the centrifugal pump and the outlet is before the oxygenator; (b) connecting the inlet line (artery) and the outlet line (vein), the inlet line is before the centrifugal pump and the outlet is before the oxygenator. For the patients without ECMO support, an independent and temporary hemodialysis catheter could be established. The right internal jugular vein catheter should be placed under the guidance of ultrasound, and the chest X-ray should be taken immediately after catheterization and before the first use. Evaluation of the catheter includes: (a) patient temperature; (b) tube type; (c) indwelling time; (d) dressing; (e) exposed length; (f) local skin of puncture point; and (g) tube function (the syringe can fill up to 10 mL in 3 s).

20.2.5.3 Parameters Setting

The speed of the replacement fluid is 4000–6000 mL/h, the duration of continuous treatment is 8–12 h or longer, and blood flow is 150–200 mL/min. According to the patient's intake, output, and vital signs, the ultrafiltration rate should be adjusted at any time based on fluid balance.

20.2.5.4 Anticoagulation for CRRT

The risks and benefits of anticoagulation therapy should be comprehensively evaluated to determine whether to proceed with anticoagulation and to determine the intensity of anticoagulation.

Nurses should choose the appropriate anticoagulant and infusion rate, and dynamically monitored the blood coagulation to keep APTT or

ACT within 1.5 times the normal value. For the patients treated with IABP and/or ECMO, the use of additional anticoagulants is not required.

20.2.5.5 Commencing Treatment

The initial flow speed was controlled at 30–50 mL/min, and gradually adjusted to 100 mL/min for 3–5 min after the blood was drained. When the blood pump gradually adapted to the heart and ECMO, the speed of the blood pump was adjusted to 150–200 mL/min for 30 min. There was no change in the patient's condition and the treatment was started.

20.2.5.6 Volume Management

A three-level management was adopted [44]. Combined with the monitoring of CVP and invasive arterial blood pressure, the nurses adjust the ultrafiltration rate according to the volume of intake and output per hour to achieve fluid balance and avoid fluid retention and excessive ultrafiltration.

20.2.5.7 Disconnection

1. Planned weaning

   Indications for stopping CRRT treatment include: (a) the patient has no manifestations of volume overload, which is assessed by chest X-ray and echocardiography; (b) water-salt and acid-base are balanced; (c) the dose of vasoactive drugs is not large; (d) there is no serious infection; and (e) daily urine output is more than 500 mL.
2. Unplanned weaning

   Treatment should be stopped when: (a) the filter is blocked by coagulation at level 2 or above and the transmembrane pressure (TMP) continues to be more than 250 mmHg; (b) the CRRT machine continues to alarm which could not be eliminated; (c) the venous pressure is consistently higher than 300 mmHg.
3. Method of flushing blood back to patient

   The following methods was adopted step-by-step [45]: (a) the blood flow rate was set at 180 mL/min, lasting for one quarter. (b) It was adjusted to 150 mL/min. At the same time, the replacement volume was reduced and the ultrafiltration fraction was controlled at 20%, continuing for one quarter. (c) The blood flow rate was adjusted to 100 mL/min and the ultrafiltration was turn off, lasting for 15 min. (d) The blood flow speed was set at 50 mL/min and blood was then flushed back to patient.

20.2.5.8 Supplement

For monitoring during treatment, please refer to *Standard Operating Procedures for Blood Purification (2010 Edition)* [40].

20.3 Nursing of Drug Therapy

Patients with fulminant myocarditis are often treated with antiviral therapy in the early stage. At the same time, the patients were given high doses of glucocorticoids and sufficient amounts of immunoglobulin for immunomodulatory treatment. In addition, there are other drug treatments, such as anti-arrhythmia, vascular activation, improvement of myocardial energy metabolism, symptomatic therapies (such as high fever, oliguria, anuria, and gastrointestinal bleeding), sedation, and anticoagulation. A central venous catheter before systemic heparinization and more than two venous channels should be established to ensure the subsequent venous treatment. At the same time, vascular punctures should be minimized for reducing the rate of vessel-related complications, such as bleeding and thrombosis during mechanical assistance.

The nursing staff arranged the administration sequence and strictly controlled the infusion speed with infusion pump or micropump to avoid heart overload. A micro pump is used to inject vasoactive drugs intravenously. When replacing vasoactive drugs, nurses should change the pump in order to prevent the fluctuation of blood pressure. In addition, nurses should master the types, usage and incompatibility taboos of common drugs. Drugs should be administered safely and accurately following the doctor's advice, and the efficacy and adverse drug reactions should be monitored.

20.4 Nursing of Complications

Patients with fulminant myocarditis are prone to bleeding, embolism, infection, and renal failure when receiving life support treatments [46–48].

1. Hemorrhage

   Hemorrhage is a common complication. The causes of hemorrhage include: (a) defects in surgical techniques, unstable tube fixation, and bleeding of puncture site caused by the activity of patients; (b) systemic heparinization to avoid blood coagulation and thrombosis because of the contact with a large number of non-physiological foreign bodies; (c) severe consumption of platelets; and (d) the damage of platelet function and coagulation mechanism because of the blood cell destruction [49]. Therefore, nurses should closely monitor ACT, APTT and PLT to observe the thrombosis in the circulatory system of ECMO.
2. Embolism

   Embolization is mainly related to intubation. The damage of the centrifugal pump and oxygenator due to blood cells is inevitable. In addition, it is also related to cardiac output, vessel/catheter diameter, intimal damage, insufficient anticoagulation, and embolus shedding, mainly including cerebral embolism, limb embolism, and massive left atrial thrombosis. During the treatment, it is necessary to closely monitor the blood supply of the distal lower extremities. Nurses should evaluate the sensory responsiveness, skin color, and temperature of the affected limbs per hour, compare the pulsation of dorsalis pedis arteries bilaterally, and mark the obvious pulsation. If the patient has symptoms such as numbness and pain in the puncture limbs, pale and cool skin, and the disappearance of dorsalis pedis artery pulsation, the nurse should notify the physician immediately. Nurses should observe the patient's consciousness, pupils, and physical activity to prevent cerebral embolism. Nurses should pay special attention to the high-risk period of lower extremity thrombosis due to the dosage reduction of heparin and venous stasis when ECMO and IABP support are withdrawn, and the wounds are compressed with elastic bandage. In addition, nurses should accurately monitor the pipe connections to avoid the pipe detachment and air embolism.
3. Infection

   Infection is another high-incidence complication during ECMO support, that is mainly related to surgical trauma and long-time intubation. Infection can reduce the survival rate of patients and is a common cause of death [50]. In order to prevent infection, there is a need to take protective isolation measures and place patients in a CCU where air disinfection and hospital infection surveillance should be maintained. A ventilator-related bundle was implemented measured by a special ECMO nursing team. Nurses pay attention to aseptic procedures and strength the isolation. Moreover, family visitation is not permitted.

   (a) Strict aseptic procedures are required during intubation, dressing change, interventional treatment, and tube withdrawal. (b) Nurses need to replace contaminated dressings timely to keep incisions dry and clean. (c) Hand hygiene should be maintained and hands should be washed before any operations. (d) All wounds should be disinfected with iodine and covered daily. (e) The blood transfusion set should be replaced if used for more than 4 h. (f) Aseptic technique should be incorporated strictly when carrying out intravenous infusion, arterial blood collection, ECMO and IABP tube replacement, medication administration, and sample collection [51]. (g) It is better if blood sampling is reduce as much as possible and infusion pipes and tees are replaced daily. (h) Nurses should continuously monitor and record the patient's temperature in a timely manner. WBC should be detected daily, and blood, urine, fecal, sputum culture, and drug susceptibility should be tested timely. Physicians should adjust antibiotics according to WBC and culture results. (i) Nurses should implement airway management and basic nursing. A nasogastric tube is used for enteral nutrition. When necessary, the doctor should give the patient immunos-

Table 20.3 Clinical indicators and outcomes of patients with fulminant myocarditis treated with ECMO and IABP

Variable		Total (n = 21)	Survival group (n = 16)	Mortality group (n = 5)	Z	P valve
Sex	Male	10 (47.6)	9 (56.3)	1 (20.0)	–	0.311
	Female	11 (52.4)	7 (43.8)	4 (80.0)		
Age[a] (years)		27.0 (16.0)	27.00 (16.0)	29.00 (15.0)	0.37	0.709
Weight[a] (kg)		55.0 (21.0)	54.50 (23.0)	56.00 (17.0)	0.25	0.804
ECMO support time[a] (h)		52.0 (62.4)	52.0 (55.0)	50.0 (212.0)	0.08	0.934
Type of complication						
Renal failure		10 (47.6)	5 (31.3)	5 (100.0)	–	0.012
Cerebral hemorrhage		2 (9.5)	0 (0.0)	2 (40.0)	–	0.048
Gastrointestinal complications		5 (23.8)	0 (0.0)	5 (100.0)	–	0.000
Lower limb ischemia		3 (14.3)	0 (0.0)	3 (60.0)	–	0.008
Multiple organ failure		4 (19.0)	0 (0.0)	4 (80.0)	–	0.001
Septicemia		6 (28.6)	5 (31.3)	1 (20.0)	–	1.000

[a]These data were reported with non-normal distribution as median and interquartile range (IQR) and the Wilcoxon signed rank test were used to compare the two groups. Statistical analysis was performed using Fisher's exact probability test without χ^2. The data in the bracket represents percentage

timulants to enhance immunity. (j) Nurses should strictly implement the disinfection and segregation system and strengthen hand hygiene, and hands should be washed before and after contact with the patients. (k) Nurses should observe redness, swelling, bleeding, and exudation at the puncture site, and should keep it clean and dry to prevent infection.

4. Renal failure

Renal failure is a common complication of fulminant myocarditis and the result of IABP combined with ECMO, especially when improper placement of IABP catheter causes renal artery compression. Li et al. retrospectively analyzed the clinical data of 21 cases with fulminant myocarditis and cardiogenic shock undergoing ECMO combined with IABP, including the data before combined application, during treatment, and after combined application [52]. The results indicated that the main complications were renal failure (n = 10), septicemia (n = 6), cerebral hemorrhage (n = 2), lower limb ischemia (n = 3), gastrointestinal complications (n = 5), and multiple organ failure (n = 4). Renal failure, cerebral hemorrhage, lower limb ischemia, gastrointestinal complications, and multiple organ failure were the risk factors affecting the prognosis (Table 18.1).

Therefore, when implementing IABP treatment, nurses should establish an indwelling catheter and closely monitor the urine volume per hour. Combined with the relevant indicators of ECMO, nurses could timely identify circulatory volume deficiency or acute renal failure, and give corresponding treatment once oliguria or anuria occurs. Table 20.3 shows relation between major complications and clinical outcomes.

20.5 Rest and Nutrition

(a) In the acute stage, patients should take strict bed rest, maintain a comfortable position and use air cushions bed to reduce heart load. (b) Physicians administer sedative-hypnotic drugs to ensure that patients rest fully and reduce mood swings. (c) According to the patients' specific conditions, they receive fasting and intravenous feeding, and then make the transition to a heart-healthy diet when the health status improves. (d) During the recovery period, instructions regarding physical activity for the patients according to the cardiac function should be provided [53]. (e) Patients could choose liquid or semi-liquid food and eat frequent small meals (50–100 mL per meal and 3–4 meals per day). It is better to finish meals before 8 p.m. to ensure that the patients get sufficient sleep. (f) Nurses should instruct patients to defecate correctly and regularly.

Patients promote gastrointestinal motility through abdominal massage from right to left. Laxatives should be administered when patients have habitual constipation. Patients in the acute stage of fulminant myocarditis are prone to constipation as a result of impaired gastrointestinal motility and restricted physical activity. Exertion could induce arrhythmia and heart failure.

20.6 Psychological Nursing

Fulminant myocarditis has the characteristics of sudden onset, high mortality and rapid progress. The disease and economic burden have brought serious psychological distress to patients, such as tension, anxiety, and fear. Nurses should pay special attention to the establishment of a trusting doctor-patient relationship, and communicate treatment plans, health conditions, and successful cases with family members in a timely manner to increase patient confidence. In the course of treatment, the nurse should provide information to the awake patient including the current time, place, family mood, disease information, and the importance of various treatments on time. Nurses should also meet the psychological needs of patients to reduce anxiety/fear and enhance self-confidence. At the same time, the family members should have a basic understanding of the life support, such as ECMO and IABP. They should understand that despite the apparent improvements of the patient's condition, the heart and lung may still not function. Moreover, family members should correctly face crisis situations that may arise. The nurse should ask the patients' needs and subjective feelings in time and implement strict isolation. Clothes and cotton quilts should be given to the patients to keep them warm.

In conclusion, fulminant myocarditis is the most serious and special type, and its mortality rate is 40–80% after drug and mechanical support [54]. Therefore, nurses should immediately notify the critical care team to rescue the patient. Nurses should also work together to ensure effective treatment for rescuing patients, including: (a) the patency of airway and venous access; (b) proper installation and operation of IABP and ECMO; (c) hemodynamic data and vital signs monitoring. During the treatment, nurses should carry out critical care and continuous vital signs monitoring, and also ensure the operation of instruments to improve the treatment success rate.

Appendix Fulminant myocarditis patient recording sheet.

Date/time (per hour)	
Vital signs	T
	HR
	SpO_2 (%)
	IBP (mmHg)
ECMO	Rotation speed (r/min)
	Blood flow (L/min)
	FiO_2 (%)
	Air flow (L/min)
	Actual water temperature (°C)
Blood supply	Potency of oxygenator and tube
	Leg circumference (cm)
	Lower extremity skin temperature (°C)
IABP	Trigger mode
	Counterpulsation rate
	PDP (mmHg)
	MAP (mmHg)
	Pulsations of the dorsalis pedis artery
Invasive mechanical ventilation	Mode
	VT (mL)
	FiO_2 (%)
	PEEP (cmH_2O)
	Breathing rate (times/min)
Temporary pacemaker	P/O/S
Cardiac ultrasound	EF(%)
Coagulation indexes	ACT(s)
	APTT(s)
Blood gas analysis	PO_2 (mmHg)
	PCO_2 (mmHg)
	PH
	SaO_2 (%)
Laboratory data	LA (mmol/L)
	ALT (U/L)
	AST (U/L)
	CTNI (pg/mL)
	WBC (*10^9/L)
	Hb (g/L)
	K (mmol/L)
Drug concentration and dose	Dopamine (mL/h)
	Metaraminol (mL/h)
	Dexmedetomidine (mL/h)
	Heparin (mL/h)

Date/time (per hour)	
Intake and output	Total intake (mL)
	Total output (mL)
	Urine output (mL)

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21 Introduction of Clinical Courses of Typical Cases of Fulminant Myocarditis (Including Six Cases)

Ning Zhou, Yu Han, and Dao Wen Wang

21.1 Typical Case 1

Ms. Yang, female, 25 years old.

21.1.1 Clinical Features

21.1.1.1 Chief Complaint

Fever, fatigue, and chest tightness with shortness of breath for 3 days.

21.1.1.2 Present Medical Information

The patient developed fever after overworking 3 days previously. The highest recorded body temperature of the patient was 39 °C, and she experienced general fatigue and weakness, precordial discomfort, shortness of breath, anorexia, nausea, vomiting, and dizziness. She had no obvious symptoms such as cough, expectoration, abdominal pain, diarrhea, and muscle soreness. She received treatment in a community hospital for 2 days, but the symptoms worsened. Due to frequent nausea, vomiting, mental illness, and drowsiness, she visited the emergency department of our hospital. Since the onset of the disease, her mental state and appetite had been poor, with normal defecation and obvious fatigue.

21.1.1.3 Medical History

She denied a history of chronic diseases, such as hypertension, coronary heart disease, and diabetes. She had no history of congenital heart disease or familial disease.

21.1.1.4 Physical Examination

Her blood pressure (BP) and oxygen saturation (SpO_2) were 86/50 mmHg and 96%, respectively, and she had an extremely poor mental state and was lethargic. The jugular vein was not filling. Her heart rate was 150 bpm, and she had a low heart sound, an audible gallop rhythm, and no heart murmurs. The breathing sounds of both lungs were low, without dry or wet rales. The abdomen was flat and soft. There was no tenderness or rebound pain. The liver and spleen were not palpable under the ribs, and the lower limbs were not swollen.

Regarding the outpatient data, the cardiac troponin I (cTnI) level was 4.9 (reference range, 0–0.03) ng/mL. The levels of the myocardial enzymes lactate dehydrogenase and creatine kinase and creatine kinase isoenzyme were 360, 695.0 ng/mL, and 58.5 (0–25) U/L, respectively. Her blood routine and arterial blood gas examination results were normal but marked abnormality of electrocardiograms (Figs. 21.1 and 21.2).

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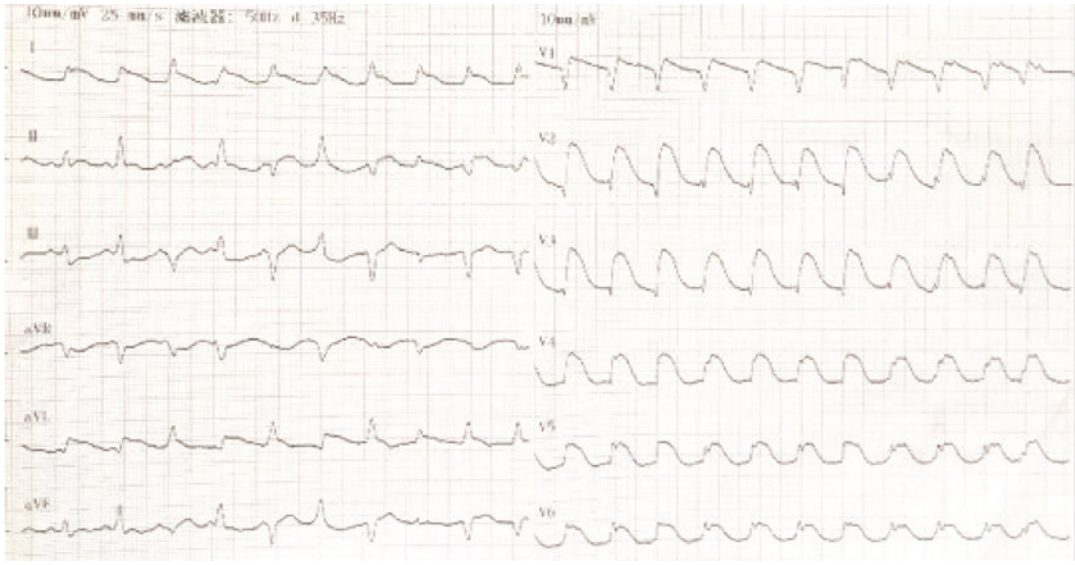


Fig. 21.1 Outpatient electrocardiogram showing polymorphic ventricular tachycardia with a widened QRS duration. The ST segment of the entire anterior lead is elevated. The ventricular rate is 150 bpm

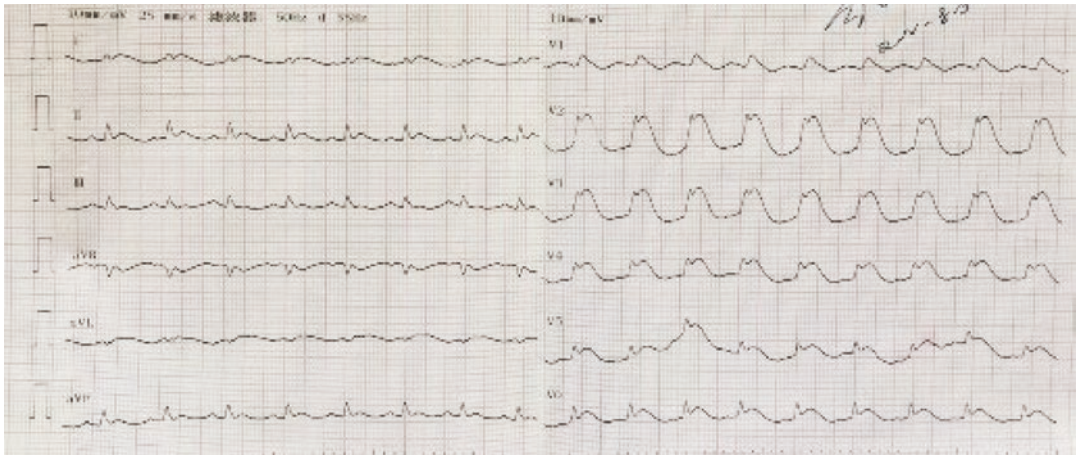


Fig. 21.2 Re-examination of the electrocardiogram after admission. (1) Sinus rhythm with a heart rate of 100 bpm. (2) The ST segment of the chest lead is elevated (back upward). (3) Low voltage and widened QRS wave

21.1.2 Diagnosis

Fulminant myocarditis with cardiogenic shock.

21.1.3 Physical Examination and Tests

21.1.3.1 Day 1 of Admission

The patient was admitted to the hospital in a very poor mental state, with recurrent nausea and discomfort, inability to eat, lethargy, and cold extremities. The pulse rhythm was irregular and weak, the cardiac border was normal, and the cardiac sound was very weak with a third heart sound gallop rhythm.

Bedside Echocardiography

The ascending aorta and aortic diameter were normal, and the inner diameter of each heart cavity was normal. The ventricular septum was 12 mm thick; the posterior wall of the left ventricle was approximately 9 mm thick, and the apex of the heart was approximately 5 mm thick. The septum and posterior wall of the left ventricle moved in the reverse direction. The movement of the posterior wall of the left ventricle was diffused and uneven, and no obvious reverse movement was observed. A small amount of pericardial effusion was observed. The left ventricular ejection fraction (LVEF) was 57%.

Laboratory Tests

Her cTnI and N-terminal pro brain natriuretic peptide (NT-proBNP) levels were 9.17 ng/mL and 7.852 pmol/L, respectively.

Chest computed tomography (CT) was performed immediately after hemodynamics was slightly stabilized.

Treatments and Course After Admission

The patient was diagnosed with fulminant myocarditis. Immunomodulatory and anti-neuraminidase treatments were immediately initiated. Importantly, circulatory support was also used. Subclavian vein catheterization was performed to monitor central venous pressure and strictly control the liquid balance of inflow and outflow. Treatment was started immediately after admission as follows:

1. Intravenous immunoglobulin (20 g/day) together with methylprednisolone (200 mg/day) was administered after intravenou injection of 20 mg dexamethasone.
2. An intra-aortic balloon pump (IABP) was implanted through the right femoral artery in the cardiac catheterization room immediately after admission. The counter pulsation pressure was approximately 85–95 mmHg.
3. Oseltamivir capsules (75 mg bid) were administered. Additionally, proton pump inhibitors were used to protect the gastric mucosa (Figs. 21.3, 21.4 and 21.5).

21.1.3.2 Day 2 of Admission

Bedside Ultrasound Examination

No significant enlargement was observed in the atrial and ventricular lumens of the heart. The anterior and posterior diameters of the left ventricle were 4.2 cm. The movement of the left ventricular wall was not coordinated or diffusely weak. The thickened septum was reduced, and few pericardial effusions were observed in the pericardial cavity. The LVEF was 48%. The left ventricular wall movement was uncoordinated and diffusely reduced. The systolic and diastolic functions were significantly reduced.

The patient was still lethargic, with an extremely poor mental state. The symptoms of frequent nausea and vomiting were not significantly relieved. With the support of the IABP, the systolic and diastolic blood pressure could be between systolic blood pressure 90 and 100 mmHg and diastolis blood pressure 60 and 70 mmHg, respectively. Immunomodulatory treatments and other medications were maintained in the original regimen.

21.1.3.3 Day 3 of Admission (Fig. 21.6)

Although the patient's mental state improved, she still experienced intermittent nausea and retch-

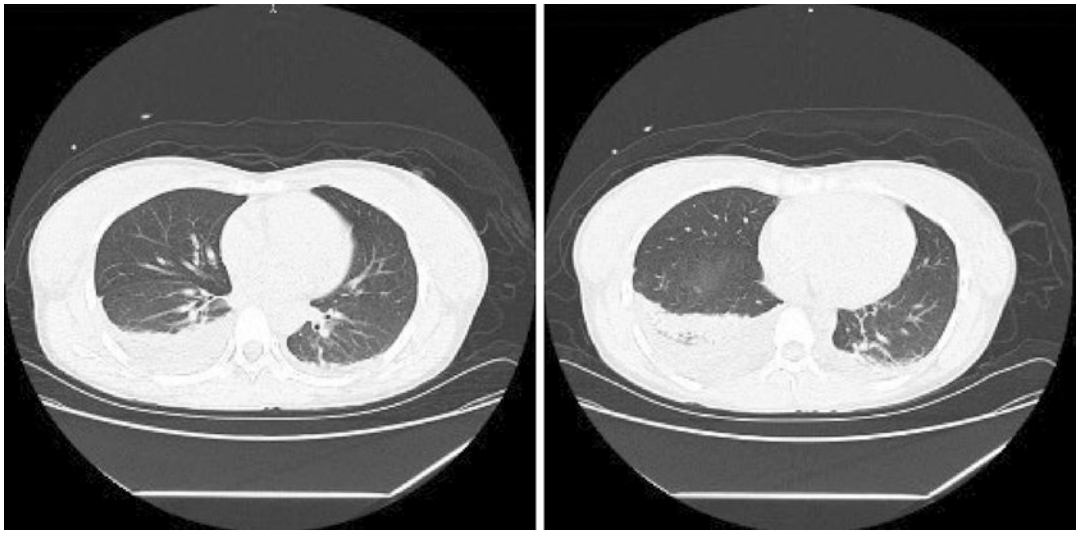


Fig. 21.3 Chest CT showing bilateral interstitial lung inflammation. Bilateral pleural effusion, with partial expansion of both lower lungs

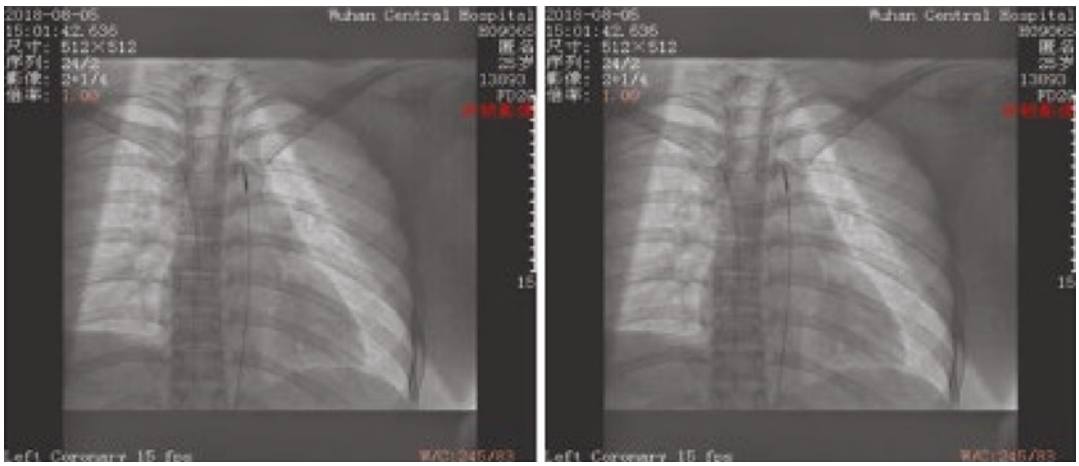


Fig. 21.4 The chest radiographs show that the heart shadow is small

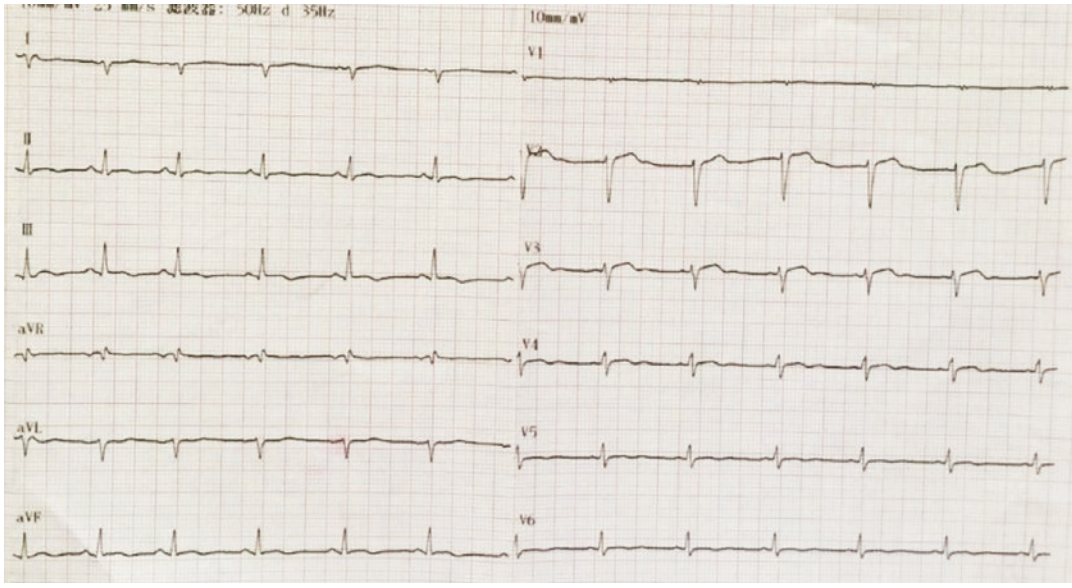


Fig. 21.5 Re-examination of the electrocardiogram. (1) Sinus rhythm. (2) QRS wave low voltage, T wave is low voltage and flat in wide-range of leads, which looks better than previous two electrocardiogram records

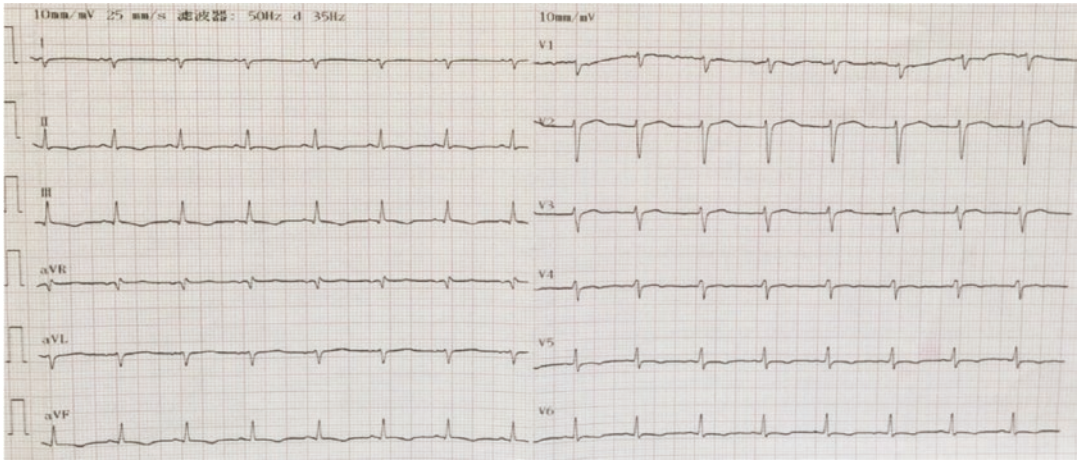


Fig. 21.6 Re-examination of the electrocardiogram: (1) Sinus rhythm. (2) ST-T changes in the inferior wall and the anterior lead. (3) Ventricular rate of 98 bpm

ing. She could consume a small amount of liquid diet and continued to be supported by the IABP and vasoactive drugs. Her vital signs remained stable, and the immunomodulatory treatment regimen (including methylperone and gamma globulin) remained unchanged.

21.1.3.4 Days 4–7 of Admission

On the fourth day, the patient's mental state improved. Gastrointestinal symptoms gradually subsided. The immunomodulatory therapy drugs were gradually reduced. She still received human blood immunoglobulin (10 g/day) with methylprednisolone (80 mg/day) and discontinued it 4 days later; oseltamivir capsules (75 mg bid) were discontinued after a total of 5 days. The IABP was removed on the fifth day after admission.

On the fourth day, re-examination of cardiac color Doppler ultrasound showed no significant enlargement of all atrial and ventricular lumens and no abnormality of the ventricular wall movement. The LVEF was 60%. These parameters improved significantly (Figs. 21.7, 21.8 and 21.9).

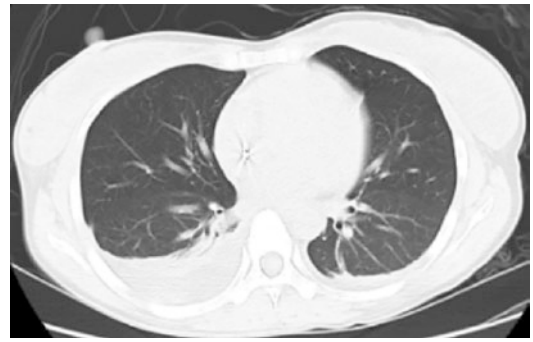


Fig. 21.8 Both lower lung inflammation and effusion are not observed

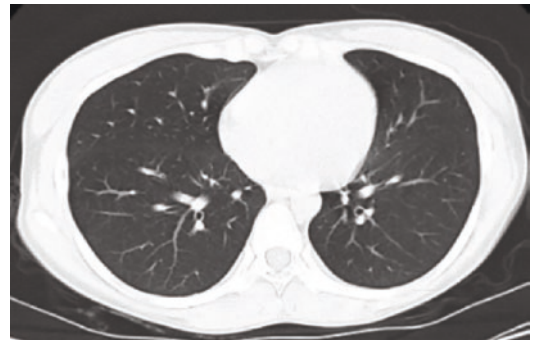


Fig. 21.9 Pulmonary infection and pleural effusion have completely disappeared

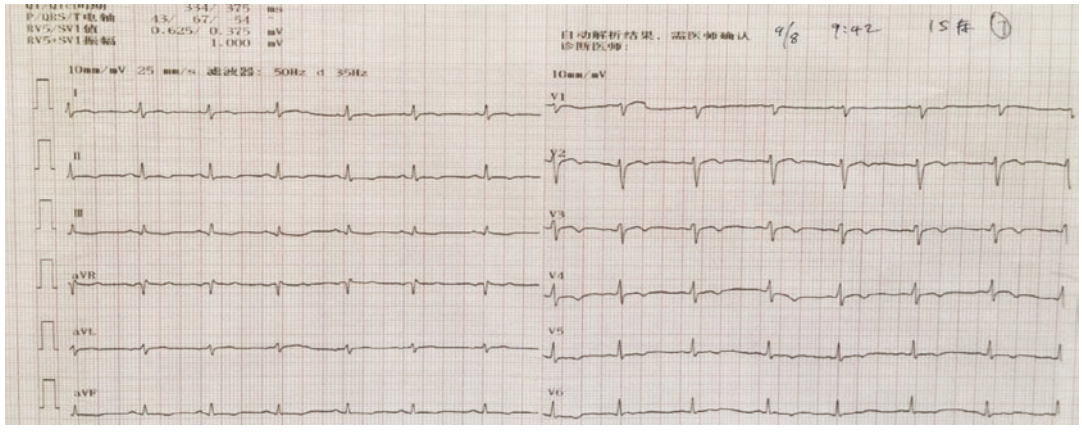
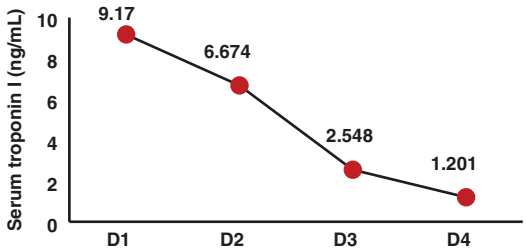


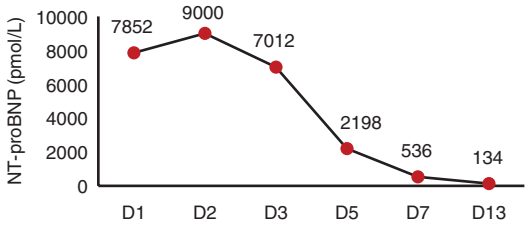
Fig. 21.7 Re-examination of the electrocardiogram showed basically the same results as it did the previous day

21.1.4 Variation Trend of the Main Indicators During Admission



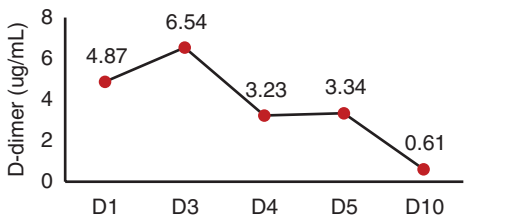
Trend chart of serum troponin Iafter admission (pmol/L)

Trend chart of serum troponin I after admission (pmol/L)



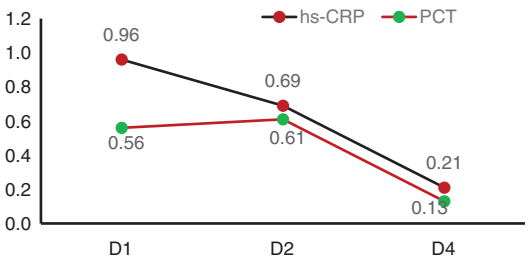
Trend chart of NT-proBNP after admission (pmol/L)

Trend chart of NT-proBNP after admission (pmol/L)



Change trend chart of D-dimer after admission (ug/mL)

Change trend chart of D-dimer after admission (μg/mL)



Trends of high sensitivity C reaction protein (hs-CRP) and procalcitonin (PCT) after admission(ug/mL)

Trends of high sensitivity C reaction protein (hs-CRP) and procalcitonin (PCT) after admission (μg/mL)

21.1.5 Case Review

The patient was a young woman with typical respiratory and digestive prodromal symptoms of respiratory virus infection and cardiogenic shock, which were consistent with the course of fulminant myocarditis. The diagnosis and treatment at the primary hospital were timely and effective; therefore, the patient was immediately pulled out of danger.

Upon reviewing this case, the following historical features were found to be consistent with the diagnostic characteristics of typical fulminant myocarditis:

1. ***Young woman with no underlying history of heart disease.***
2. ***There were obvious prodromal symptoms of virus infection 3 days before onset.***
3. ***Onset of acute illness, a few days into the state of shock.***
4. ***Myocardial injury markers, electrocardiogram (ECG), and color Doppler echocardiography all suggested serious heart damage and cardiogenic shock combined with malignant arrhythmia.***

Therefore, the diagnosis of this case was not difficult. With good understanding of the characteristics of fulminant myocarditis, it should not be difficult to make a diagnosis based on the Chinese Society of Expert Consensus Statement on the Diagnosis and Treatment of Adult Fulminant Myocarditis. Patients with fulminant myocarditis often have fever, fatigue, and poor appetite, as well as respiratory or digestive tract symptoms. The prodromal symptoms last 3–7 days and then suddenly develop into severe hemodynamic dysfunction. Laboratory tests show that the cardiomyocytes are severely damaged. An ECG shows a variety of malignant arrhythmia, ventricular tachycardia, ventricular fibrillation, high-grade atrioventricular block, and sinus arrest. On echocardiography, visible diffuse ventricular wall motion decreases. Coronary angiography can be used to identify acute myocardial infarction and fulminant myocarditis when the condition is per-

mitted. However, the prodromal symptoms of fulminant myocarditis are often nonspecific in the clinical setting; therefore, it is easily misdiagnosed as a "cold" or "upper respiratory tract infection." The natural course of the prognosis is very poor. Timely and correct management, especially advanced mechanical life support, can greatly reduce mortality and improve long-term outcomes.

The patient had obvious prodromal symptoms of viral infection 3 days before admission, with obvious fatigue after slight physical activity, obvious digestive tract symptoms, frequent nausea and vomiting, rapid progression and deterioration of the disease, as well as hemodynamic disorders and persistent polymorphic ventricular tachycardia only 2 days after the onset of the disease. After arriving at the hospital, the myocardial injury marker and NT-proBNP levels were abnormally increased. Bedside cardiac Doppler ultrasound suggested diffuse weakening of the ventricular wall movement and LVEF decline. Fulminant myocarditis was diagnosed for the first time after admission.

According to the Chinese Expert Consensus on the Diagnosis and Treatment of Fulminant Myocarditis in Adults, drafted and written by Professor Wang Daowen in 2017, the patients are administered a timely full dose of glucocorticoids and immunoglobulin for immunoregulatory therapy and IABP-assisted life support. During treatment, the patients' respiratory function is closely monitored. If there is any sign of dyspnea or respiratory failure, the healthcare provider should be prepared to actively manipulate the ventilator. After positive and accurate treatment, the patients will abruptly recover on the third day after admission and consequently be discharged from the hospital.

In terms of the treatment plan, the expert consensus points out that the treatment of fulminant myocarditis emphasizes "extremely early identification, extremely early diagnosis, extremely early prediction, and extremely early treatment." The foundation for the successful treatment of this patient lies in an extremely early diagnosis and the correct treatment plan for the decisive implementation of mechanical life support and immunomodulatory treatment. In addition, by the time of discharge, if the patient has not completely recovered and the ECG does not show a low-voltage state, rest, follow-up, and the use of β-blockers and low-dose angiotensin-converting enzyme inhibitor treatment for 6 months to 1 year are advised, and follow-up is maintained according to the situation of treatment adjustment.

21.2 Typical Case 2

Ms. F, female, 25 year–old.

21.2.1 The Clinical Features

21.2.1.1 Chief Complaint

Chest tightness and fatigue for 1 week, aggravation for 3 days.

21.2.1.2 Present Medical History

The patient developed chest tightness, fatigue, cough, and other discomfort after common cold a week ago. She took automedication for cold, but the symptoms did not improve. Her chest tightness and fatigue worsened over the past 3 days. She arrived at a local hospital at 21:00 (February 5, 2019). At 21:22, electrocardiogram (ECG) suggested ventricular tachycardia. The patient received continuous intravenous infusion of amiodarone and immediate cardioversion. However, this condition was not attenuated. She was then transferred to the emergency department at 00 o'clock (February 6, 2019) where another ECG showed ventricular tachycardia. Her blood pressure could not be measured. Electrical cardioversion and treatment such as noradrenaline, lidocaine, and magnesium sulfate were administered several times. Her cardiac rhythm returned to sinus rhythm at 0:10. She was sent to the Coronary Care Unit (CCU) and admitted to the emergency department with a primary diagnosis of fulminant myocarditis.

Since the onset of the disease, the patient's mental state, diet, and sleep were very poor without obvious change in her body weight. Her urine and feces were normal.

21.2.1.3 Past Medical History

She had an induced abortion 1 month previously. She denied a history of hypertension, diabetes, hepatitis, and tuberculosis. She had a history of cesarean section. She denied a history of trauma, blood transfusion, or known drug and food allergy.

21.2.1.4 Physical Examination

Temperature (T) 36.0 °C, blood pressure, and pulse were undetectable. She was in the supine position, and respiration (R) was 28 bpm. She was unconscious and lacks cooperation in physical examination. Systemic skin sclera with yellow stain, enlarged superficial lymph node were not noted. She presented cold and dry limbs without dilated jugular vein. Her neck was soft, and clear breath sound auscultation in both lungs, without moist or dry rales. The heart rate was 165 bpm, with an irregular rhythm. Her heart sounds were low and blunt. The galloping was obvious, and no obvious murmur was heard. The abdomen was flat and soft, and there was no tenderness or rebound pain in the entire abdomen.

There was no edema in both lower limbs and no percussion pain in either kidney.

Laboratory Tests

Blood potassium 2.79 mmol/L, N-terminal pro-brain natriuretic peptide (NT-pro BNP): 7260 pg/mL, hypersensitive troponin I, >50,000 pg/mL (over the detectable up-limit).

21.2.2 Diagnosis

Fulminant myocarditis complicated with persistent ventricular tachycardia

Evidence: Young woman, chest tightness and fatigue for 1 week, aggravation for 3 days, and shock and malignant arrhythmia as the main onset. Extensive lead ST-segment changes revealed on ECG. Significant increase in NT-pro BNP and myocardial injury marker hypersensitive troponin I levels.

21.2.3 Treatment

At 2:14 on February 6th, 2019, her blood pressure and pulse were undetectable. She was delirious, and ECG revealed ventricular tachycardia. She was treated with anti-shock, potassium supplement, anti-arrhythmia (amiodarone, lidocaine, and esmolol), and immunomodulatory therapy (dexamethasone 10 mg IV, followed by methylprednisolone 200 mg iv, gamma globulin 10 g iv.). After repeated electrical cardioversion, sinus rhythm was restored. However, her blood pressure and pulse were still undetectable. The patient immediately underwent endotracheal intubation, and a bedside intra-aortic balloon pump (IABP) was implanted on February 6, 2019. The counterpulsation pressure was approximately 60 mmHg. The patient's blood pressure remained very unstable, and she had repeated episodes of ventricular tachycardia.

Bedside venoarterial-extracorporeal membrane oxygenation (VA-ECMO) implantation was completed at 2:31 on February 06, 2019, and the initial ECMO parameter was set at a rotational speed of 3500 rpm and flow rate of 3.5 L/min. Her blood pressure gradually stabilized to 86/64 mmHg.

Her hypersensitive (hs)-cardiac troponin I level was over 50,000.0 pg/mL in the morning, BP 88/59 mmHg, pulse rate (P) 66 bpm, R 20 times/min. She was sedated. The level of hs-cardiac troponin I was still over 50,000.0 pg/mL, myoglobin 887.0 ng/mL (normal range <106 ng/mL), creatine kinase-MB type (CK-MB) isoenzyme 71.0 ng/mL (normal range <3.4 ng/mL), blood glucose (GLu) 17.75 mmol/L (normal range 4.11–6.05 mmol/ L).

Three consecutive cardiac color ultrasound examinations were performed within 24 h after admission:

21.2.3.1 Bedside Echocardiography

The right ventricular outflow tract and the aortic root were not widened, and the aortic valve was normal and open. There was no enlargement of the

atrial and ventricular chambers. The septal wall thickness increased to 1.4 cm. The activity of the anterior lobe of the mitral valve showed bimodal activity, the distance between the EE was shortened, anterior and posterior lobes showed reverse movement, and valve echo was normal and open. The interventricular septum and posterior wall of the left ventricle were not thickened. There were no obvious segmental wall motion abnormalities. The left ventricular ejection fraction (LVEF) was 55%.

However, the LVEF dropped to 40% only 3 h later. It continued to decrease to 14% at 09:45, 2019-02-06 (Fig. 21.10).

Summary of medical advice on admission day

1. ***Continuous IABP Applications***
2. ***VA-ECMO assistance***
3. ***Continuous renal replacement therapy (CRRT) treatment***
4. ***Invasive-assisted ventilation for tracheal intubation***
5. ***Immunomodulatory therapy: methylprednisolone 200 mg/day × 4 days + 80 mg/day × 2 days + 40 mg/day × 2 days IV drip, then prednisone orally, 40 mg/day, reduced 5 mg per week until withdrawal; Gamma globulin 20 g/day × 3 days + 10 mg/day × 4 days, iv.***
6. ***Neuraminidase inhibitor: oseltamivir 150 mg/day × 7 days, orally.***
7. ***Improve myocardial metabolism treatment: trimetazidine 70 mg/day × 11 days oral + coenzyme Q10 30 mg/day × 11 days oral. After discharge, oral administration was continued for 1 month until the return visit.***
8. ***(a) Esomeprazole sodium 40 mg/day × 8-day intravenous drip + fat-soluble vitamin, (b) water-soluble vitamin for injection 1 box/day × 3 days, intravenous drip, nasal feeding nutrition.***
9. ***Antibiotics application: cefotaxime sodium sulbactam sodium 6 g/day × 5 days, intravenous drops to prevent infection.***

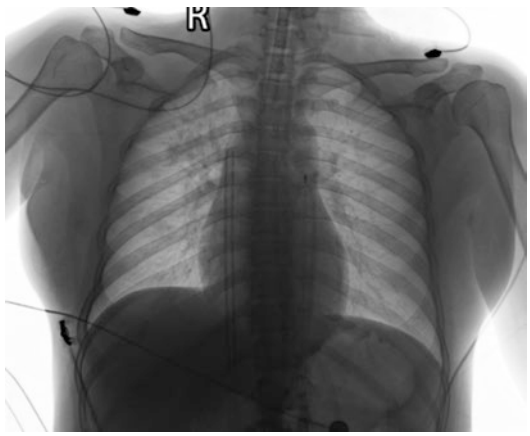


Fig. 21.10 Chest radiograph: double lung texture enhancement, right middle and upper lung fields. A VA-ECMO venous drainage catheter was observed at the upper end of the right atrium vena cava. The IABP balloon catheter was observed in the descending aorta. A tracheal tube was observed in the main trachea

21.2.3.2 Day 2 After Admission

During endotracheal intubation, the patient was under mild sedation without obvious discomfort, such as cough, expectoration, fever, and so on. Electrocardiogram monitoring suggested sinus rhythm, with no obvious malignant arrhythmia. Oxygen saturation of 100%. Continuous VA-ECMO was applied at a speed of 3490 rpm, a flow rate of 2.39 L/min, a gas flow rate of 5 L/min, and a fraction of inspired oxygen (FiO_2) of 50%. The tank temperature was 36.8 °C. The operation of the ECMO instrument was normal. Continuous IABP application with a counterpulsation ratio of 1:1, using an ECG trigger mode.

21.2.3.3 Physical Examination

The blood pressure was 88/47 mmHg, and heart rate (HR) 69 bpm with regular rhythm. The heart sound was low and blunt, and no obvious murmur was heard.

Laboratory Tests

White blood cell count 14.97 × 10^9/L, neutrophil (%) 80.9%↑, neutrophil (#) 12.11 × 10^9 /L, red blood cell count 3.56 × 10^{12}/L, hemoglobin 108.0 g/L↓, Procalcitonin 2.11 ng /mL↑, NT-pro BNP 1190 pg/mL, hs-cardiac troponin I 41743.0 pg/mL, and serum electrolyte level was normal.

Due to the patient's stable circulation and improved respiratory function, tracheal intubation was removed and the rotational speed of ECMO was gradually reduced. Concentrated red blood cells were injected to improve oxygen carrying capacity, and immunoregulation, anti-infection, myocardial metabolism improvement, gastric protection, and energy supplementation were continued.

Bedside Echocardiography (10 a.m., Feb 7, 2019)

The interventricular septum was no longer thick (0.8 cm), and the posterior wall of the left ventricle was not thick (0.8 cm). The diffuse wall motion of the left ventricle decreased, especially in the inferior wall and anterior septal wall. The LVEF increased to 20%. The visceral and parietal pericardium were separated, and the maximum liquid area was 0.5 cm in the lateral wall of the left ventricle.

21.2.3.4 3–5 Days After Admission

After tracheal intubation was removed, the patient recovered spontaneous breathing and consciousness, no recurrent ventricular tachycardia or other malignant arrhythmia, with occasional premature beats. The circulation was gradually stabilized, and the blood pressure remained stable at 80–100/50–65 mmHg. Her HR was 95 bpm, and the oxygen saturation of the left finger was 100% after the gradual reduction of ECMO parameters. The CRRT was stopped on day 4 after admission, and ECMO assistance was removed on day 5. Since the hemodynamics of the patient were stable after the removal of life assistance devices, drugs were administered to improve myocardial remodeling: perindopril 2 mg/day + metoprolol 23.75 mg/day, which gradually increased depending on blood pressure.

Bedside echocardiography showed no thickening of the interventricular septum and left ventricular posterior wall. The LVEF increased to 56% and was preserved until the fifth day after admission (Fig. 21.11).

Cardiac magnetic resonance perfusion imaging One week after admission.

There was no left ventricular hypertrophy (end-diastolic diameter: 4.3 cm, end-systolic diameter: 3.3 cm, shortening rate: 23.2%), the diameter of the left atrium was 2.4 cm, and the myocardial thickness of each segment of the end-diastolic left ventricle was normal (the anterior wall of the middle segment 10.5 mm, lower lateral wall 5.3 mm), the overall systolic movement of the left ventricle was normal with a proximal ascending aorta diameter of 3.2 cm. No right ventricular hypertrophy was present (long diameter 6.6 cm, short diameter 4.3 cm), the transverse diameter of the right atrium was 4.0 cm, and the overall contractile movement of the right ventricle was normal. Mild to moderate regurgitation was observed in the aortic valve. No obvious regurgitation signal was observed in the tricuspid valve. DOUBLE and TRIPLE T2 increased myocardial

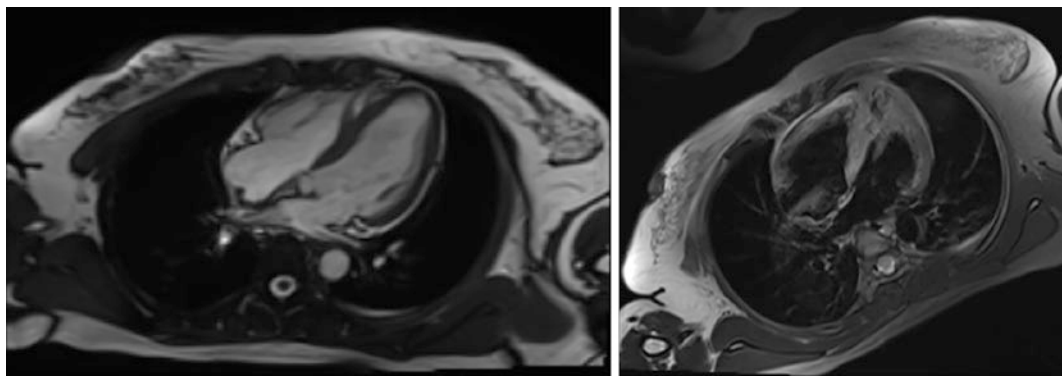


Fig. 21.11 One week after admission, cardiac magnetic resonance image showing myocardial edema and necrosis in the ventricular septum, and anterior and inferior wall of left ventricle

signals in the superior interventricular septum and anterior and inferior walls of the left ventricle. The pericardium was not thick. A small amount of fluid signal was observed in the pericardium, and no fluid signal shadow was observed in either thorax. Left ventricular function: LVEF 63%, CO 4.9 L/min, end diastolic volume index (EDVi): 69 mL/m^2. Cardiac perfusion: No obvious abnormal filling defect signal was observed in the myocardium after initial perfusion. Strip and sheet enhancement were observed in the outer myocardium from the basal segment to the middle segment of the ventricular septum during delayed enhancement. Conclusion/diagnosis: Myocardial edema and necrosis in the ventricular septum and the anterior and inferior walls of the left ventricle were noted. Combined with the clinical findings, acute myocarditis and mild to moderate aortic insufficiency were considered, with small pericardial effusion.

21.2.3.5 Holter 1 Week After Admission

1. Sinus rhythm, with a minimum heart rate of 49 beats per minute, occurred at 02:45. The maximum heart rate was 99 bpm at 18:27. The average heart rate was 71 bpm.
2. Accidental atrial premature beats were 1/whole course.
3. There were 21 accidental ventricular premature contractions (PVCS) and 2 PVCS in pairs.
4. Leads V1 and V2 were observed during monitoring, ischemic ST-T abnormalities were observed in the inferior wall and anterior wall, and myocardial infarction was combined with clinical observation.
5. The patient did not record any uncomfortable symptoms for the whole day (Figs. 21.12 and 21.13).

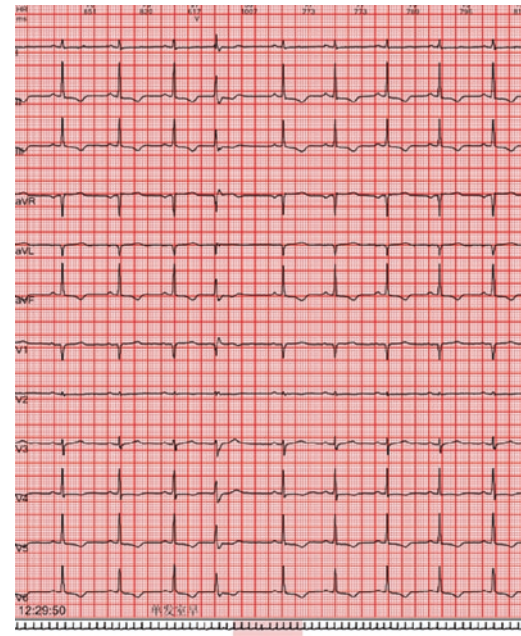


Fig. 21.12 Holter showed no obvious arrhythmia 1 week after admission, but there were still extensive ST-T changes in leads

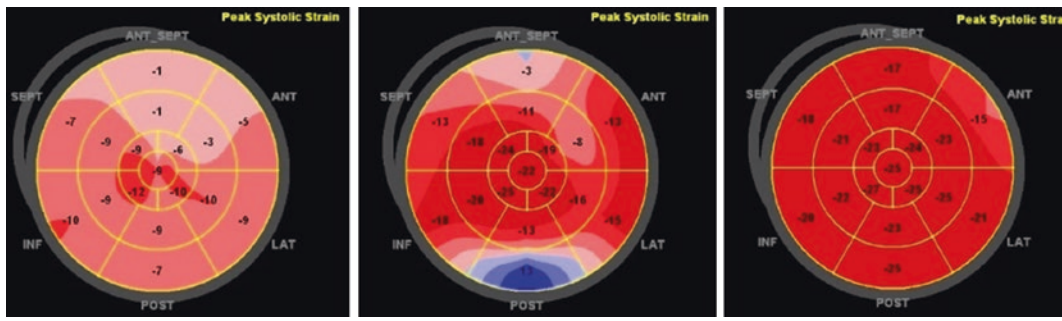


Fig. 21.13 "Bull's eye pattern" of ventricular wall movement by cardiac ultrasound spot tracer on days 1, 3, and 8 after admission. The lighter the red color is, the weaker the chamber wall movement and the darker the chamber wall movement. Blue indicates that the ventricle wall is moving in the opposite direction. Dynamic echocardiographic spot tracer indicated a decrease in diffuse ventricular wall movement, accompanied by weaker local movement or even reverse movement. After 8 days of treatment, only part of the anterior wall of the left ventricle was weakened, while the rest of the ventricular wall was basically restored

21.2.4 Variation Trend of Main Biomarkers and Cardiac Function During Treatments (Figs. 21.14, 21.15, and 21.16)

21.2.5 Comments

This is a typical case of fulminant myocarditis with the main clinical features of stormy malignant arrhythmias, cardiac arrest, and refractory cardiogenic shock at the beginning of the disease. The successful rescue of this case left three deep impressions of the author:

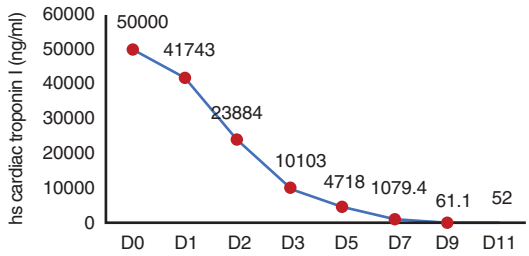


Fig. 21.14 Trend chart of troponin I changes after admission

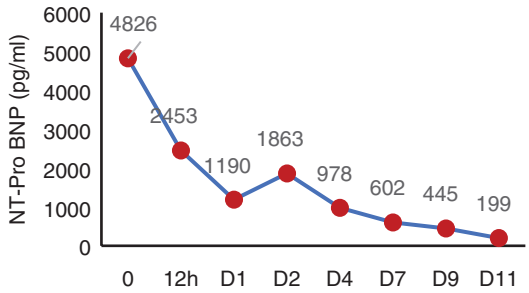


Fig. 21.15 Trend chart of NT-pro BNP of troponin after admission

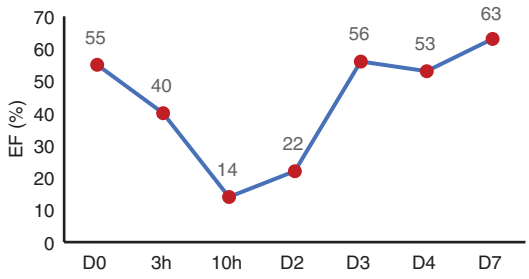


Fig. 21.16 Trend chart of troponin changes after admission

1. Timely referral by community hospitals creates conditions for patient survival.

   Many fulminant myocarditis patients have malignant arrhythmia and refractory cardiogenic shock as the main manifestations. This condition rapidly leads to multiple irreversible systemic organ failure or even sudden death. The primary hospitals for the first diagnosis of such patients are mostly grassroots units. If the basic hospitals do not have a good understanding of the disease, misdiagnosis or missed diagnosis will occur, leading to patient death. **Patients can only survive the malignant cardiogenic shock and arrhythmias with the assistance of circulatory support devices**. However, due to lack of equipment or technical strength, the treatment capacity of grassroots hospitals is relatively weak, so timely referral is primordial to save the lives of patients. Fortunately, the patient was transferred to a superior unit with treatment conditions for the first time after receiving treatment at a grassroots hospital.
2. The disease progresses and changes rapidly.

   The LVEF values obtained at the time of admission was 55%, but only 3 h later, it fell to 40%, and then to 14% 10 h after admission. The ventricular wall motion diffusely decreased severely, with peristaltic pulses. This rapidly changing nature of the heart gives us important warning signs: when we suspect patients with early stage fulminant myocarditis, their heart color shows cardiac function in patients with normal levels, but we must be highly alert to the potential for a precipitated decline in cardiac function, and thus must have foresight and should not wait for patients' circulation to collapse after treatment as this might lead to disease progression and patient death.
3. The diagnosis and treatment of fulminant myocarditis requires comprehensive treatment

   A well-trained cardiac critical care team is extremely important for the diagnosis and treatment of fulminant myocarditis. The team

has to successfully complete the use of all types of life-assistance devices, including IABP and ECMO, temporary cardiac pacing, coronary angiography, and other examinations and treatments in a very short period, because early treatment of fulminant myocarditis is lifesaving. Mechanical life support can temporarily stabilize circulation and is a palliative strategy. Therefore, it is necessary to supplement immunomodulation therapy to treat myocardial inflammation, especially the timely and adequate use of glucocorticoids. The patient's cardiac function improved significantly after one day of treatment, largely due to the timely, adequate, and prolonged use of immunomodulatory drugs. Therefore, the treatment of fulminant myocarditis is a combination of strategies based on mechanical life support and immunomodulatory therapy, combined with infection prevention and injury treatment with water-soluble and fat-soluble vitamins.

21.3 Typical Case 3

The patient was a 34-year-old woman.

21.3.1 Clinical Features

21.3.1.1 Chief Complaint

The chief complaints of the patient were dizziness and fatigue for 3 days with six convulsions.

21.3.1.2 Present Medical History

After catching a cold at noon on August 13, 2019, the patient developed persistent dizziness, accompanied by general fatigue, muscle aches, poor appetite, and lethargy. In addition, she complained of fever although she had not measured her body temperature. She had no nasal congestion, runny nose, chills, nausea, vomiting, abdominal pain, diarrhea. On August 14, the patient experienced aggravated dizziness and fatigue in the evening. On the morning of August 15, the patient developed convulsions on her way to the local clinic. Furthermore, she lost consciousness, which lasted for a few minutes. Her electrocardiogram (ECG) showed sinus rhythm and ST changes. Her troponin I, myoglobin, and fibrinogen levels were 11.83 ng/mL, 92.9 ng/mL, and 344 mg/dL, respectively. The creatine kinase isozyme, alanine aminotransferase, and lactate dehydrogenase activities were 36, 500, and 707 U/L, respectively. Prothrombin time was 13.30 s with an activity of 84%. The international standardized ratio was 1.12. She was administered aspirin and ticagrelor. Moreover, she was given acid inhibition, gastric protection, and liver protection treatments. She experienced five convulsions during the period; each convulsion was preceded by palpitations and loss of consciousness, which could be alleviated after several seconds. The patient visited our hospital and complained of palpitation, convulsions, loss of consciousness, and urinary incontinence. An emergency ECG showed ventricular fibrillation and emergency non-synchronous electrical defibrillation. In addition, coronary angiography and intra-aortic balloon counterpulsation were performed after cardioversion, which indicated no significant stenosis of the LM, LAD, LCX, and RCA. After coronary angiography, she was admitted to our department diagnosed as fulminant myocarditis.

21.3.1.3 Past Medical History

The patient denied a history of hypertension, diabetes, and coronary heart disease.

21.3.1.4 Physical Examination

Her temperature was 36 °C, pulse 77 beats per minute (bpm), respiration 20 beats/min, and blood pressure 96/64 mmHg. The breath sounds of both lungs were rough, rales could be heard, and there was no wheezing. Her heart rate was 77 bpm, with a small cardiac boundary, uniform rhythm, and no murmurs in the auscultation area of each valve. The abdomen was flat and soft, without tenderness, and the liver and spleen were not palpable under the ribs. Physiological reflexes were present, and the pathological signs were negative.

21.3.1.5 Examination and Laboratory Tests

The ECG obtained at the local hospital (Fig. 21.17) showed sinus rhythm, ST changes (possible acute anterior inter wall myocardial infarction). The results of laboratory test are mentioned above.

21.3.2 Diagnosis

The patient was diagnosed with fulminant myocarditis.

21.3.3 Treatment

21.3.3.1 Day 1

Immediately after admission, coronary angiography was performed that showed no significant stenosis of the LM, LAD, LCX, and RCA. Because the patient started suffering from frequent ventricular tachycardia in the catheterization room, the possibility of fulminant myocarditis was considered and intra-aortic balloon pump (IABP) implantation was immediately performed. The working mode of IABP was set as ECG-triggered. The counterpulsation ratio was 1:1, and the counterpulsation pressure was measured at 70 mmHg (Fig. 21.18).

Although IABP was performed, the patient had unstable circulation and frequent arrhythmias, such as ventricular tachycardia and ventricular premature rhythm. Bedside venoarterial extracorporeal membrane oxygenation (VA ECMO) implantation was performed 5 h later using a vascular approach, in which the right femoral artery and femoral vein were punctured. The initial speed was set at 3500 rpm and the flow rate was 3.5 L/min. Her blood pressure gradually returned to 100/64 mmHg. Afterward, bedside continuous venovenous hemofiltration (CVVH) treatment was performed, followed by ECMO without heparin anticoagulation. The ultrafiltration volume was 1.0 L. The patient complained of chest tightness and chest pain. We gradually lowered the pacing frequency of the temporary pacemaker to 60 bpm and the rotational speed of ECMO to 2080 rpm. The concentrated red blood cells were transfused intermittently.

21.3.3.2 Bedside Echocardiography

Bedside echocardiography showed that the atrial and ventricular chambers were small. The interventricular septum and cardiac wall were thin,

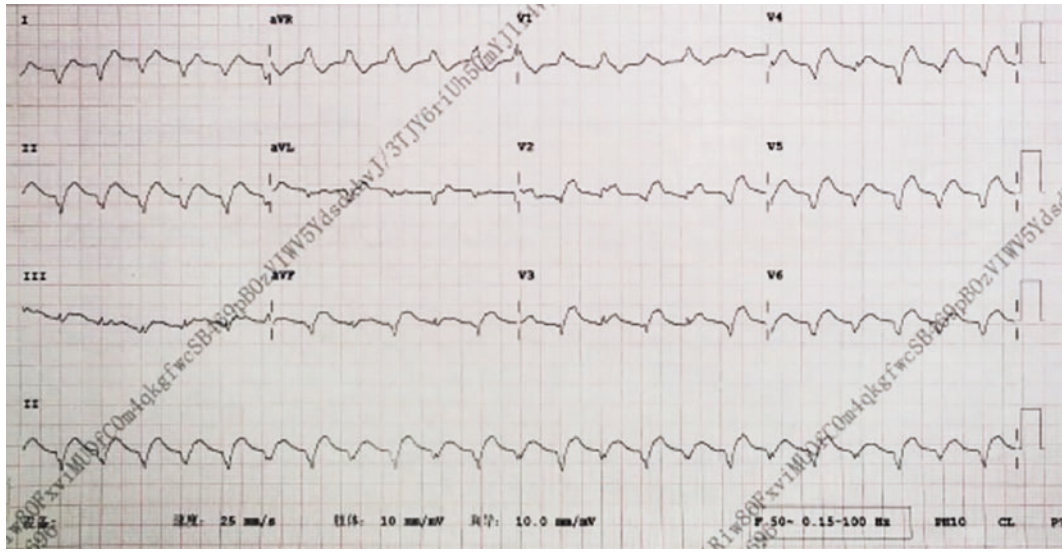


Fig. 21.17 Emergency ECG: ventricular tachycardia with low voltage. ECG, electrocardiogram

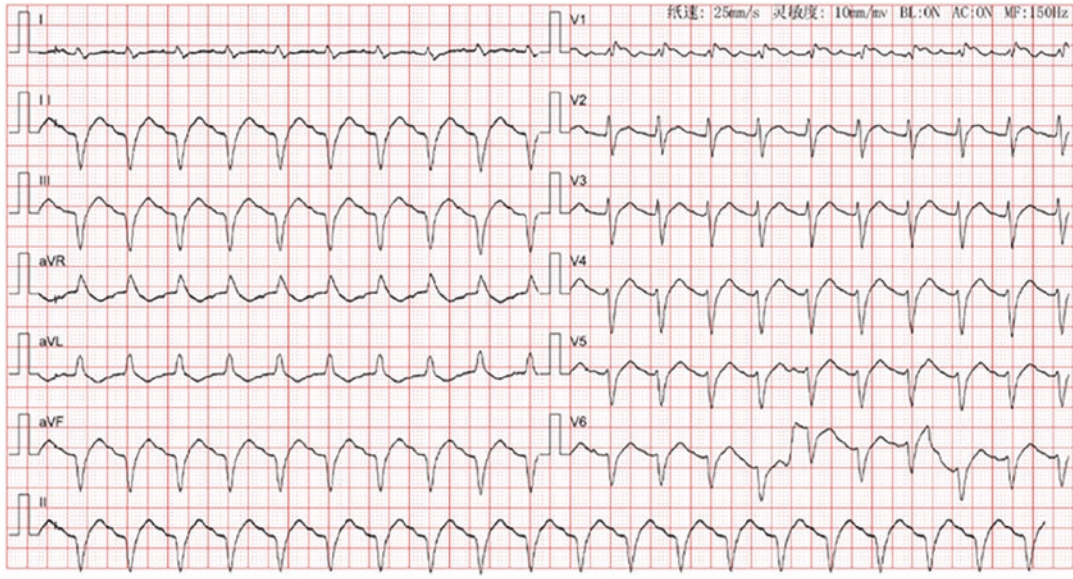


Fig. 21.18 ECG immediately after admission: sinus rhythm, QS type of lower wall lead, and poor R wave increase of front wall lead, similar to the ECG of large area myocardial infarction. *ECG* electrocardiogram

with reduced left ventricular diffuse compartment wall motion. Her left ventricular ejection fraction (LVEF) was 30% (Fig. 21.19).

21.3.3.3 2 Days After Admission

Two days after admission, life support therapy and IABP were continued, and ECMO parameters were adjusted. The flow rate was maintained at 2.5–3.5 L/min. The fraction of inspired oxygen (FiO_2) was about 40%. The patient's right upper extremity finger pulse oxygen saturation fluctuated between 93% and 100%. The patient was conscious and still reported chest tightness, shortness of breath, and discomfort, which showed a significant improvement than a day ago. ECG revealed a ventricular rate of approximately 70–80 bpm, with frequent premature ventricular contractions (PVCs, and monitoring shows no pulmonary vein atrial tachycardia, and occasional pacemaker rhythm (minimum pacemaker frequency, 70 bpm). Non-invasive ventilation was continued.

Echocardiography showed that the LVEF was reduced to 16%, indicating that the systolic function of the left ventricle was extremely low, the whole heart movement was diffusely weakened, and the left ventricle presented peristaltic pulsation.

21.3.3.4 Days 3–5

The patient complained of chest tightness and shortness of breath. The bilevel positive airway pressure (BiPAP) ventilator was stopped on the second day. The patient reported no shortness of breath or discomfort during full spontaneous breathing. Troponin levels, although significantly lower than the day before, remained high. In addition, the ECG showed that the ventricular rate fluctuated between 75 and 90 bpm. On the fourth day after admission, her blood pressure remained stable, and the intensity of VA ECMO assistance was gradually reduced. The patient's blood oxygen saturation fluctuated between 95 and 100%. Therefore, VA ECMO was removed on the fourth day after admission, and bedside femoral artery incision and suture were performed by the vascular surgery department, followed by local aseptic treatment and bandaging. The glucocorticoid dosage was gradually decreased 3 days after the admission. The nutritional support was continued. After the removal of ECMO on admission, the patient's blood pres-

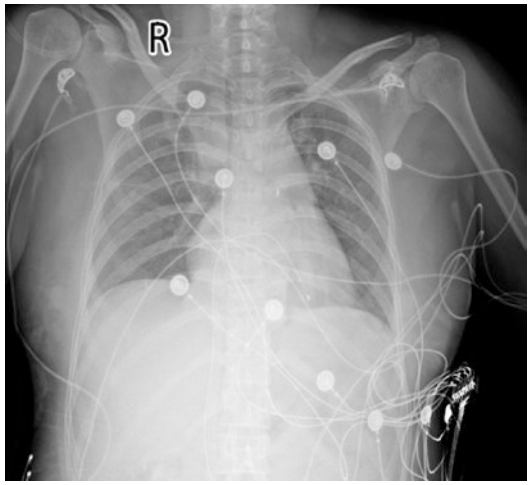


Fig. 21.19 After implantation of IABP and temporary cardiac pacemaker, bedside chest radiograph suggested the thickening of lung texture and signs of pulmonary congestion. X-ray shows IABP catheter and temporary pacemaker electrode. *IABP* intra-aortic balloon pump

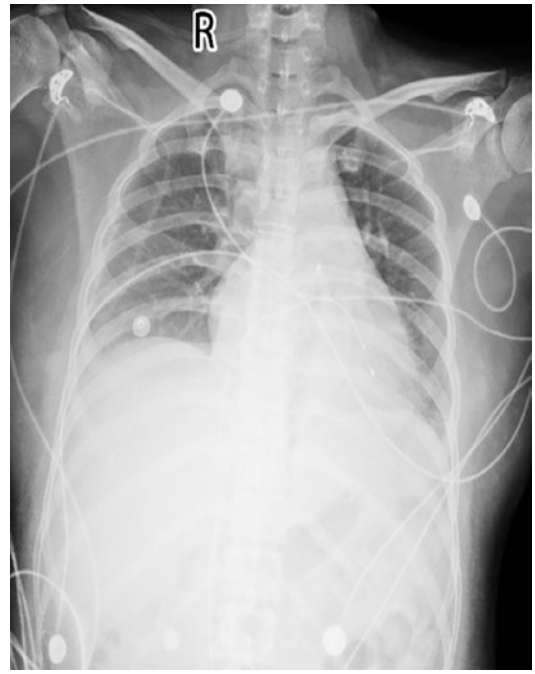


Fig. 21.20 Chest X-ray on the fourth day of admission: the patient's lung bruises were better than the previous blood report, and the IABP catheter and temporary cardiac pacemaker electrodes were still retained

sure varied from 100–140 to 60–85 mmHg, and anti-myocardial remodeling therapy was initiated (perindopril was started at 2 mg qd, and gradually increased to 4 mg qd before discharge until follow-up after discharge). Echocardiography revealed an LVEF of 19%.

From day 5, temporary cardiac pacing therapy was discontinued according to the following ambulatory ECG results: sinus rhythm + pacemaker rhythm (VVI), with a minimum ventricular rate of 68 bpm at 08:06. The maximum ventricular rate was 103 bpm at 14:35. The mean ventricular rate was 77 bpm with occasional pacing beats. Frequent premature ventricular beats of 4005 times per the whole course were observed (Fig. 21.20).

21.3.3.5 6 Days After Admission: Before Discharge

The patient's symptoms gradually disappeared, with no chest tightness, shortness of breath, and discomfort. ECG revealed occasional premature beats, and the ventricular rate fluctuated between 80 and 90 bpm. On the 6th day after admission, a β-blocker was added, with the initial dose of 23.75 mg qd of metoprolol sustained-release tablets. After the addition, the patient's blood pressure fluctuated between 100–120 and 60–75 mmHg and resting ventricular rate between 70 and 80 bpm. The patient's blood pressure and heart rate were continually observed. The dose of metoprolol was gradually increased to 47.5 mg qd before discharge and was maintained until the first follow-up after discharge. Her LVEF increased to 58%, as measured by echocardiography (Fig. 21.21).

Check date, 21:13, August 26, 2019

Check items. Magnetic resonance perfusion-weighted imaging (PWI) + multidirectional delayed enhancement (indicating the examination site)

During the examination, the patient's heart rate was 76 bpm. The left ventricle end-diastolic diameter was 4.4 cm, the end-diastolic diameter was 2.6 cm, and the shortening rate was 40.9%. The left atrium size was 2.5 cm, the myocardial thickness of each segment of the left ventricle at the end of diastole was normal, i.e., 8.0 mm, and the lower wall was 6.0 mm.

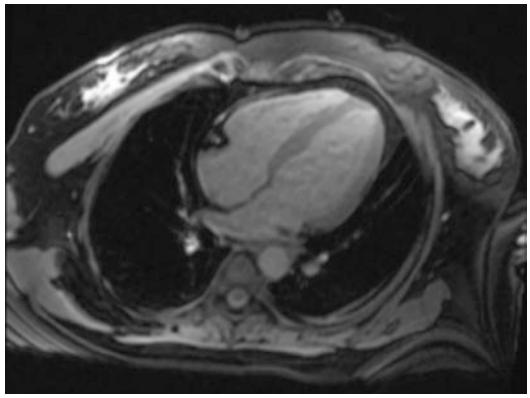


Fig. 21.21 On the 10th day of admission, cardiac magnetic resonance examination revealed diffuse myocardial edema in the left ventricle, representing typical myocarditis

The right ventricle was not dilated. The transverse diameter of the right atrium was 3.8 cm, with the overall positive contractile movement of the right ventricle. No regurgitation signal was observed in the tricuspid valve. Double and Triple T2 increased the myocardial signals in the upper left ventricle. The pericardium was not thick.

No fluid signal was observed in the pericardium and chest cavity.

Her LVEF was 53%, CO was 4.2 L/min, and end-diastolic volume (EDV) was 52 mL/m.

Cardiac perfusion. We did not observe any signal of an abnormal filling defect in the first perfusion myocardium and no abnormal enhancement in delayed enhancement.

Diagnosis:

Diffuse myocardial edema was observed in the left ventricle. Considering the history of acute myocarditis, a follow-up of 13 months was recommended.

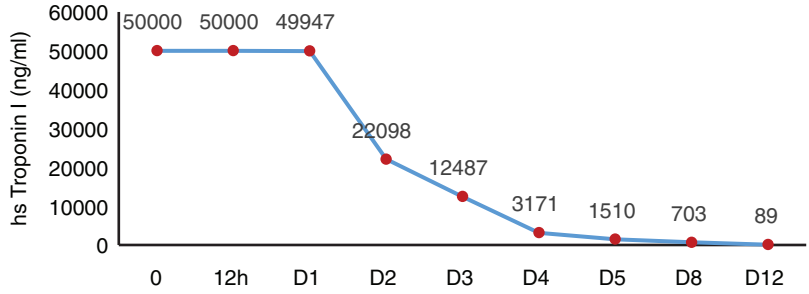
Left ventricular systolic function was slightly reduced.

Thirteen days after admission, the patient was discharged without complaints of palpitation, chest tightness, chest pain, and other discomforts. Her vital signs were stable and she was discharged with the following medical advice: sustained-release trimetazidine tablets 35 mg, oral, twice a day; coenzyme Q10 tablets 10 mg, oral 3 mg/day; perindopril tert-butylamine tablets 4 mg, oral, once a day; prednisone acetate tablets (prednisone) 20 mg, oral, once a day; and metoprolol 47.5 mg oral, once a day.

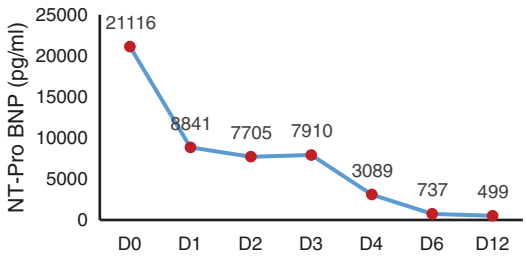
Summary of medical advice for treatment after admission:

1. ***Continuous IABP application, 6 days***
2. ***Temporary cardiac pacing therapy, 5 days***
3. ***VA-ECMO assistance, 4 days***
4. ***CRRT treatment, 3 days***
5. ***Non-invasive ventilation (BiPAP), 2 days***
6. ***Immunomodulation treatment: methylprednisolone 200 mg/day × 3 days + 80 mg/day × 3 days + 40 mg/day × 2 days; IVIG 10 g/day × 4 days***
7. ***Neuraminidase inhibitor: oseltamivir capsule 150 mg/day × 7 days, oral + penciclovir 0.5 g/day × 5 days, intravenous (i.v.) drop***
8. ***Prevention of infection: cefoperazone sodium and sulbactam sodium 6 g/day × 3 days***

21.3.4 Variation Trend of Primary Indicators During Admission



Changes in highly sensitive cardiac troponin, a marker of myocardial injury, in patients after admission



Change in the trend of NT-PRO BNP, a serum marker of heart failure in patients after admission. NT-PRO BNP, N-terminal (NT)-pro hormone B-type natriuretic peptide

21.3.5 Comments

According to the primary clinical manifestations, the patient was diagnosed with fulminant myocarditis. Patients with fulminant myocarditis can be roughly divided into three types: (1) Those with cardiogenic shock, which is characterized by refractory cardiogenic shock, and severe left heart failure. The primary clinical manifestations are hypotension, chest tightness, shortness of breath, dyspnea, and oliguria. (2) Arrhythmia type whose primary clinical feature is malignant arrhythmia, including palpitation, amaurosis, syncope, or sudden death. (3) Mixed type, which is characterized by simultaneous cardiogenic shock and malignant arrhythmia, with mixed manifestations such as hypotension and syncope.

In this case, the patient had a typical onset process, with prologue manifestations of the upper respiratory tract infection, primarily characterized by severe malignant arrhythmias. Her ECG showed ventricular tachycardia and other ventricular arrhythmias. Fortunately, she was successfully resuscitated and received a proper diagnosis and treatment. Her early hemodynamic disorder was insignificant.

Because the patient had malignant arrhythmias as the primary clinical presentation, her ECG suggested extensive inferior and anterior wall myocardial infarction. Therefore, coronary angiography was performed in the emergency department through the green channel that ruled out acute myocardial infarction. Based on her clinical characteristics, a clinical diagnosis of fulminant myocarditis was rapidly established, and a comprehensive treatment plan based on life support was provided. IABP therapy and temporary cardiac pacemaker implantation were immediately implemented in the catheter room to provide left ventricular assistance and cardiac rhythm support.

We emphasize that IABP implantation should be a priority in life support treatment strategies for fulminant myocarditis. IABP is the most commonly used left ventricular assist device in the clinic that can significantly reduce left ventricular afterload. Therefore, IABP implantation was prioritized for treating this patient. However,

IABP implantation largely depends on the patient's remaining heart function. IABP is ineffective in patients with recurrent severe arrhythmias or refractory shock. After the patient was transferred to the Coronary Care Unit (CCU), VA ECMO was implanted for sequential life support, including renal support and respiratory support, due to recurrent ventricular tachycardia.

In the case of the use of life support to increase the chances of survival of patients, immunomodulation therapy can improve the prognosis of patients. In our case, a large dose of glucocorticoid was administered immediately upon admission, which was gradually reduced until the inflammatory storm disappeared. Therefore, the treatment of fulminant myocarditis involves a combination of therapies and a comprehensive treatment regimen, in which every element is indispensable.

21.4 Typical Case 4

A 33-year-old female patient was transferred to our hospital on October 27, 2021 due to persistent cough and fever. Seven days ago, she had a cough, fatigue, and fever; and went to a local hospital. She was treated for having a cold. However, the symptoms had not improved and 5 days later, she suddenly experienced chest pain, chest tightness, and shortness of breath, with dizziness and weakness. Coronary angiography showed normal coronary arteries. Computed tomography (CT) excluded aortic dissection and pulmonary thromboembolism. At this time, the patient had a blood pressure of 80/60 mmHg and a heart rate of 120 beats/min. Bedside echocardiography showed a left ventricular diastolic function (LVEF) of 50%. The blood volume replenishing products and vasoactive drugs (dopamine) were administered but did not improve the patient's condition. She then progressed to having a low blood pressure and became unconscious. Thus, she was transferred to our hospital where immediate endotracheal intubation and mechanical ventilation were done.

Upon admission to the ICU at 3 AM October 28th, the patient's vital signs were unstable, temperature of 36.0 °C, pulse rate of 120/min, respiratory rate of 18 breaths/min, and blood pressure of 55/23 mmHg. She had rough and heavy breathing, weak heart sounds, and tachycardia at 120 beats/min.

Her laboratory test results were shown as follows (Table 21.1, column A). Cytokine levels were in disorder, especially soluble ST2 level of >200 pg/mL (ref. <30 pg/mL). Urine routine test showed red blood cell of 3+, urine protein of 2+, and urine glucose of 2+. Based on bedside echocardiography, the heart wall was thickened, and LVEF of 40%. The patient was diagnosed with myocarditis and shock. Her treatments included: (1) posterior pituitary injection 30 U in 50 mL solution by microinjection pump, 5 mL/h, (2) cedilanid 0.2 mg intravenous injection, (3) norepinephrine 10 mg by microinjection pump, 2 mL/h, (4) methylprednisolone 80 mg intravenous drip, and (5) blood volume replenishing as anti-shock therapy.

After 10 h of treatment, this patient's situation worsened. She slipped into a complete coma. Her pulse rate was of 149/min, blood pressure of 95/62 mmHg under injection of vasopressin and norepinephrine pump maintaining (30 U, 20 mL/h and 20 mg 20 mL/h, respectively). She was forced transferred to our CCU. Laboratory test results were shown as follows (Table 21.1, column B), and echocardiography showed LVEF decreased to 19%, with pericardial effusion. The patient was immediately diagnosed with the highly suspected fulminant myocarditis (FM).

Her laboratory tests indicated indicating disseminated intravascular coagulation (DIC) (Table 21.1, column B). Blood lactic acid level is >15.50 mmol/L, and blood gas analysis showed severe metabolic acidosis (pH 7.101, and HCO_3^- 12.1 (ref. 22–26)). In the same time the cytokine detection showed massive increasing: IL-6 1287.0 pg/mL (ref. <7.0), IL-8 of 330.0 pg/mL (ref. <62), IL-10 621.0 pg/mL (ref. <9.1). These data confirmed the diagnosis of fulminant myocarditis with cardiogenic shock. Immediately after transfer to CCU, we initiated treatments: (1) Intra-aortic balloon pump (IABP) and vein-artery extracorporeal membrane oxygenation (VA-ECMO) to rest her heart; (2) large doses of steroids (methyl-

Table 21.1 Laboratory test results of the patient before and after admission to CCU

	Before admission	On admission (CCU)	8 h after CCU	15 h after CCU	39 h after CCU	Reference ranges
Blood Cell counting						
WBC ($\times 10^9$/L)	13.88	14.58	16.39	16.95	14.68	3.50–9.50
Neutrophils ($\times 10^9$/L) (%)	10.53 (75.9)	12.26 (84.2)	13.97 (85.2)	15.52 (91.5)	14.20 (96.8)	1.80–6.30 (40.0–75.0)
Platelet ($\times 10^9$/L)	171	65.0	70.0	91.0	68.0	125.0–350.0
Blood coagulation						
PT (s)	14.6	55.6	35.5	38.8	47.9	11.5–14.5
PTA (%)	79	12	20	18.0	14	75.0–125.0
INR	1.15	6.58	3.65	4.11	5.41	0.80–1.20
Fibrinogen (g/L)	1.72	0.60	0.60	1.64	1.51	2.00–4.00
APTT (s)	35.5	>180.0	76.4	81.9	87.1	29.0–42.0
Thrombin time (s)	19.7	56.0	20.5	24.5	23.5	14.0–19.0
D-dimer (μg/mL FEU)	2.17	5.39	8.59	14.85	>21.0	<0.5
FDP (μg/mL)	6	–	34.2	58.2	128.6	<5.0
Sera biochemistry assay						
ALT (U/L)	62	1037	3897	6200	5126	<34
AST (U/L)	49	1096	5552	>7000	>7000	<33
Total protein (g/L)	51.5	30.2	43.44	56.3	51.8	64–83
Albumin (g/L)	29.6	15.5	22.4	36.2	30.1	29.6
LDH (g/L)	300	>1867	>1867	>1867	>1867	135–214
CRP (mg/L)	2.8	0.6	–	8.5	–	<1
eGFR (mL/min/1.73 m^2)	77.8	40.8	48.3	44.9	42.2	>90
Creatinine (μmol/L)	85	145	126	134	141	45–84
Glucose (mmol/L)	17.66		9.90	–	–	3.90–6.10
Lactic acid (mmol/L)	12.63	>15.50	–	>15.50	>15.50	0.50–2.20
Cardiac biomarkers						
NT-pro BNP (pg/mL)	27,101	>35,000	29,243	35,911	–	<116
cTnI (pg/mL)	2100.1	3671.1	10,079.3	18,695.1	–	<15.7

Notes: *eGFR* estimated glomerular filtration rate, *WBC* weight blood cells, *PT* prothrombin time, *PTA* prothrombin activity, *APTT* activated partial thromboplastic time, *INR* international normalized ration, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *FDP* fibrin degradation products, *LDH* lactate dehydrogenase, *CRP* C-reactive protein, *NT-pro-BNP* N-terminal pro-brain natriuretic peptide, *cTnI* cardio troponin I

prednisolone 400 mg, intravenous drip) and IVIG (20 g, once a day); (3) oral oseltamivir 75 mg, twice a day, and trimetazidine 35 mg, twice a day via stomach tube, (4) Cryoprecipitated antihemophilic factors, fresh frozen plasma, and albumin was used to correct the DIC, and (5) sodium bicarbonate while in continuous veno-venous hemofiltration (CVVH) therapy was also applied to her against the acidosis to address her renal problems. Her blood pressure increased to 86/64 mmHg, and pH recovered to 7.292.

After the next 8 h of treatment, the patient's blood pressure was maintained at 80/50 mmHg with high doses of posterior pituitary, dopamine, and norepinephrine injection pump, and heart rate at 130/min. She developed anisocoria (left pupil 6 mm, right pupil 7 mm), and slow pupil reflection of light and clammy limbs. Her laboratory test result was also shown as follows (Table 21.1, column C). Her echocardiography showed LVEF of 14%. We added human fibrinogen 2.0 g intravenous drip, albumin, and vitamin

K1 against DIC, and L-glutathione reduced and magnesium isoglycyrrhizinate to save her liver.

Another 7 h later, her DIC cannot be corrected. Her liver failure worsened quickly (Table 21.1, column D). In the next 24 h, the patient was still in coma. Her blood pressure was at 84/34 mmHg. She had equal pupils. Her laboratory test results indicated neither the DIC situation nor the liver failure improved (Table 21.1, column D). Ultrasonic examination showed LVEF 14%, bilateral pleural effusion, and pericardial effusion. The patient suddenly developed atrial fibrillation with fast ventricular rate. The atrial fibrillation continued for the remaining course of disease as it cannot be converted.

After 2-day treatments, the patient was still in a coma, blood pressure was at 82/54 mmHg, pulse rate of 137/min. She had equal pupils, slow pupillary light reflex, rough breathing sounds on both lung fields, weak heart sounds, and bilateral swelling on all extremities. Her laboratory test result indicated severe DIC, liver and renal failure (Table 21.1, column E). Echocardiography showed ventricular septal thickening (1.2 cm), left ventricular posterior wall thickening and edema (1.3 cm), diffusely decreased motion of the left ventricular wall, LVEF of 17%, and pericardial effusion. The patient had no response to these treatments and died. The final diagnosis: fulminant myocarditis with cardiogenic shock, multiple organ failure, DIC, and capillary leakage syndrome.

21.4.1 Comments

1. This patient presented with cold-like symptoms, but quickly developed chest pain, chest tightness, and shortness of breath, accompanying dizziness and weakness. Fulminant myocarditis can rapidly progress to an extent that it is diagnosed and treated too lately. Unfortunately for this patient, our doctors were not able to make the correct diagnosis and treat it in time.
2. The patient had developed coma, before being transferred to our hospital. Due to hypotension, the ICU used a large dose of vasoactive drugs, especially posterior pituitary, and norepinephrine, with cardiotonic drug like cedilanid. These treatments will only increase the load on the heart but would not bring any benefit to patients with fulminant myocarditis. Furthermore, large dose use of posterior pituitary and norepinephrine induced multiple organ damage including hepatocyte necrosis and refractory DIC. Correct therapy should be applied based on the "life support-based comprehensive treatment regimen" without any delay.
3. Fulminant myocarditis can easily lead to refractory shock. In this case, the patient quickly developed DIC, acute liver failure, and renal failure in several hours. The treatment of FM should follow a pithy formula, the "four extremely early", summarized from FM patients' treatment and prognosis, which is "extremely early identification, extremely early diagnosis, extremely early prediction, and extremely early treatment". The "extremely early prediction" indicates that once the FM diagnosis is made, an expectation of the patient's situation will turn south in a very short time should be foreseen. This would mean immediately giving correct treatments even before signs of disease worsening. In this case, even if we applied almost every right therapy for FM after the patient's transferring to the CCU, it was too late to save her young life.

21.5 Typical Case 5

Patient, female, 33 years old.

21.5.1 The Clinical Features

21.5.1.1 Chief Complaint

Chest tightness with fever for 2 days after intermittent activity

21.5.1.2 Present Medical History

The patient presented with chest distress and discomfort, accompanied by neck pain after taking

part in an activity 2 days before. Chest distress was reported in the left chest, lasting from a few minutes to more than ten minutes, and chest tightness and fatigue were experienced. Her body temperature was 37.8 °C at night rest, and she self-administered Tylenol. In the morning, her body temperature rose to 38.8 °C again, and she received Tamiflu and ibuprofen antipyretic antiviral therapy. After getting up in the morning, her chest tightness and fatigue had not alleviated. She then went to hospital, where an electrocardiography (ECG) examination indicated myocardial ischemia.

21.5.1.3 Past Medical History

A history of hypertension, diabetes, chronic gastritis, asthma, chronic bronchitis, and other diseases were all denied. Furthermore, there was no history of infectious diseases or allergies.

21.5.1.4 Physical Examination

T 36.5 °C, pulse 110/min, respiration 20/min, blood pressure 132/73 mmHg. She manifested with a conscious and alert step into the room There were no obvious dry or wet rales in the lower lung. Her heart rate was 110 beats/min, and her heart rhythm was regular.

21.5.1.5 Examination (Fig. 21.22)

21.5.2 Diagnosis

Acute myocarditis?

Coronary heart disease?

21.5.3 Treatment

21.5.3.1 Day 1 After Admission

Laboratory tests after admission (cardiac troponin I (cTnI), myoglobin (myo), creatine kinase-MB (CK-MB)) indicated that cTnI was 6317.4 pg/mL, CK-MB 6.0 ng/mL, N-terminal pro-brain-natriuretic peptide (NT-proBNP) 848 pg/mL, as well hypersensitive C-reactive protein (hs-CRP) 25.8 mg/L were all significantly elevated.

Bedside Echocardiography

The heart chambers were not enlarged. The wall thickness of the ventricle was maintained. The wall motion of the basal segment of the inferior wall of the left ventricle had decreased slightly. LVEF was 60%.

After admission, her body temperature fluctuated between 37.8 and 38.4 °C. Troponin I, BNP,

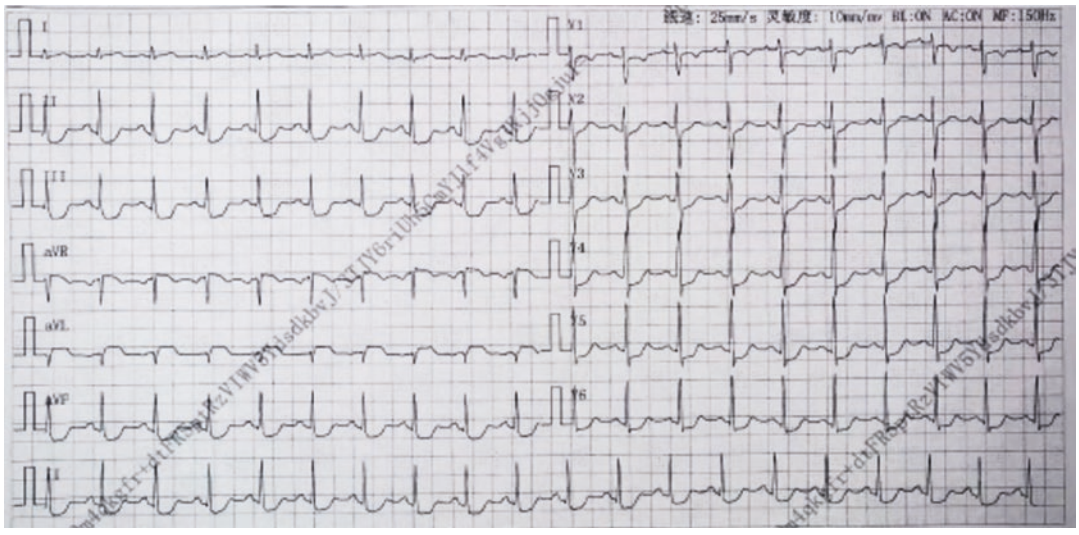


Fig. 21.22 Outpatient ECG: Sinus tachycardia, extensive ST segment descent, T wave low level

lactic acid etc., were all checked. Immunomodulatory therapy was started immediately with methylprednisolone 80 mg Qd. Trimetazidine and coenzyme Q10 were administered to improve myocardial metabolism, and fat-soluble vitamins, and proton pump inhibitors were dispensed for symptomatic treatment. The following morning, a cardiac MRI examination revealed reduced ventricular septal movement, extensive myocardial edema changes, and highly suspicious myocarditis (Fig. 21.23).

The patient complained of chest distress and discomfort. Combined with the MRI results, the patient's myocarditis was considered to have progressed. The glucocorticoid dose (methylperone 80 mg bid) was increased, while intravenous immunoglobin (IVIG) (10 g qd) was added, and the neuraminidase inhibitor oseltamivir (75 mg bid) was increased (Fig. 21.24).

21.5.3.2 On the Second Day of Hospital

Hs-cTnI was 23603.9 pg/mL and NT-pro BNP was significantly higher than before, 1580 pg/mL↑. A reexamination by heart color ultrasound suggested that the ventricular wall motion continued to decrease, motion was weakened, and her health had declined sharply (Fig. 21.25)

Ambulatory ECG

Sinus rhythm, with a minimum heart rate of 66 beats/min, occurred at 22:46. The maximum heart rate was 141 beats/min at 16:26. The average heart rate was 87 beats/min. Occasional atrial and ventricular premature beats and trail tachycardia were evident; complete right bundle branch block, ST segment of lower wall and anterior wall were significantly lowered during the whole process, and ST segment of avR lead was elevated, which was consistent with ECG changes associated with the main disease.

Due to the aggravation of her condition, she was immediately transferred to the Critical Care Unit (CCU) for further treatment. The patient complained of chest tightness accompanied by fatigue and panting after activity. Physical examination: BP 94/62 mmHg, P 107 bpm, R 20 times/min, SpO_2 100%, T 36.4 °C, hs-cTnI 49,648.3 pg/mL, and NT-proBNP 3252 pg/mL, suggested that markers of myocardial injury and heart failure had increased significantly. Considering the continuous aggravation of myocardial inflammation, the dosage of methylperone was increased to 200 mg to 400 mg/day. IABP treatment was initiated immediately with blood pressure fluctuations of 80–95/45–65 mmHg.

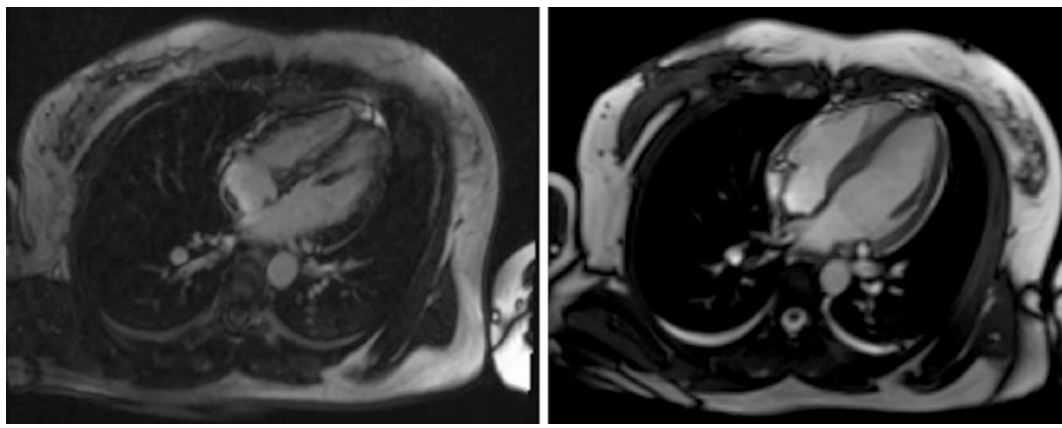


Fig. 21.23 On the second day after admission, an MRI examination of the heart showed reduced ventricular septal movement, myocardial edema and necrosis in the ventricular septum and the anterior and inferior wall of the left ventricle

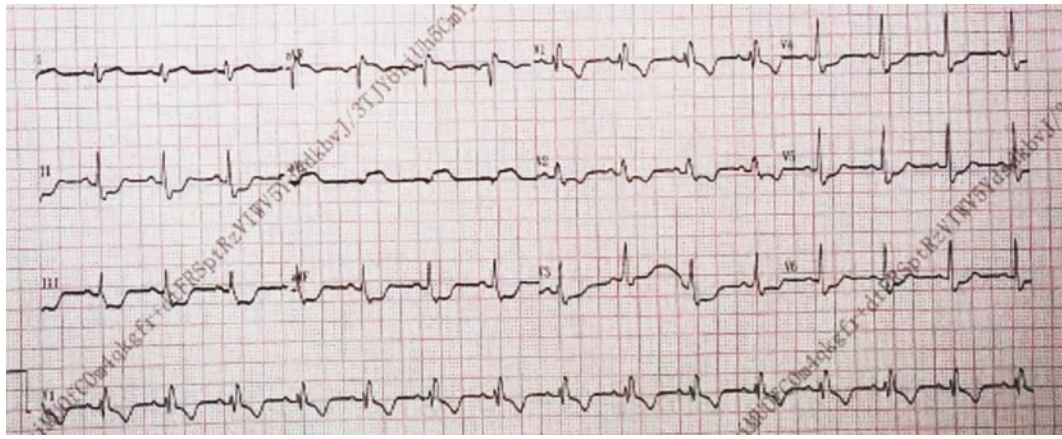


Fig. 21.24 ECG on the first day after admission: Sinus tachycardia, complete right bundle branch block

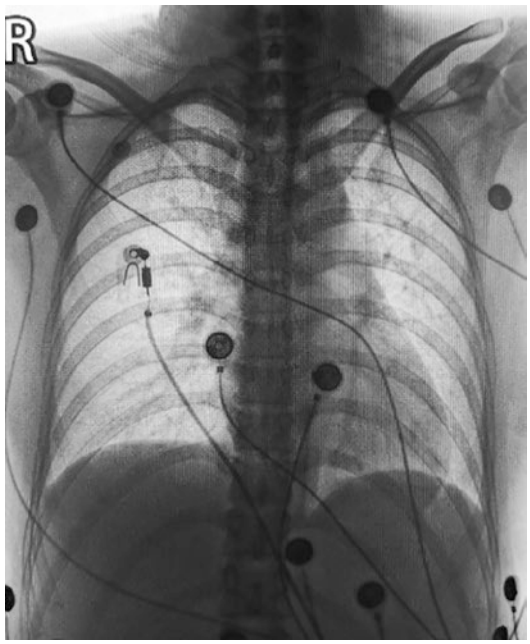


Fig. 21.25 Chest radiograph on the first day after admission: enhanced lung texture

21.5.3.3 The Third Day of Admission

At 9:48 in the morning, the patient's blood pressure suddenly dropped to 52/34 mmHg. The patient's consciousness was blurred, and her spirit was dim. Physical examination: HR, 104 times/min continuous application of IABP resulted in an anti-surge pressure of 57 mm Hg. Dopamine was continuously pumped intravenously at 20–40 mg/kg/min. There was no significant increase in blood pressure.

At 9:56, ECG monitoring was carried out, and ventricular tachycardia, a blood pressure of 112/70 mmHg, and heart rate of 180 bpm were evident. A BiPAP ventilator was immediately used to assist respiration, amiodarone 300 mg was pumped intravenously at 10 mL/h, sodium bicarb 60 mL was intravenously injected, and 200 J synchronous electro-cardioversion was administered twice, but these did not work, and according to ECG monitoring, she was still enduring a ventricular tachycardia. ECMO implantation was performed immediately at a rotational speed of 3500 rpm, with a flow rate of 3.5 L/min. The patient's blood pressure gradually increased to 106/68 mmHg. Continuous renal replacement therapy (CRRT) was performed for 12 h. About 5 h later, the cardiac rhythm recovered to sinus (Fig. 21.26).

Cardiac injury biomarkers were measured again. Myo 227.7 ng/mL, creatine kinase MB-type isoenzyme 43.0 ng/mL. The patient was conscious and still had chest tightness and fatigue. Physical examination showed clear breath sounds in both lungs, no dry or wet rales were heard, no pulsation was observed in the precardiac area, no vibration was touched, her heart boundary was not large, heart sounds were clear, as were those of her pacemaker heart rate, and no pathological murmur was heard in each valve area. The abdomen was flat and soft, with no ten-

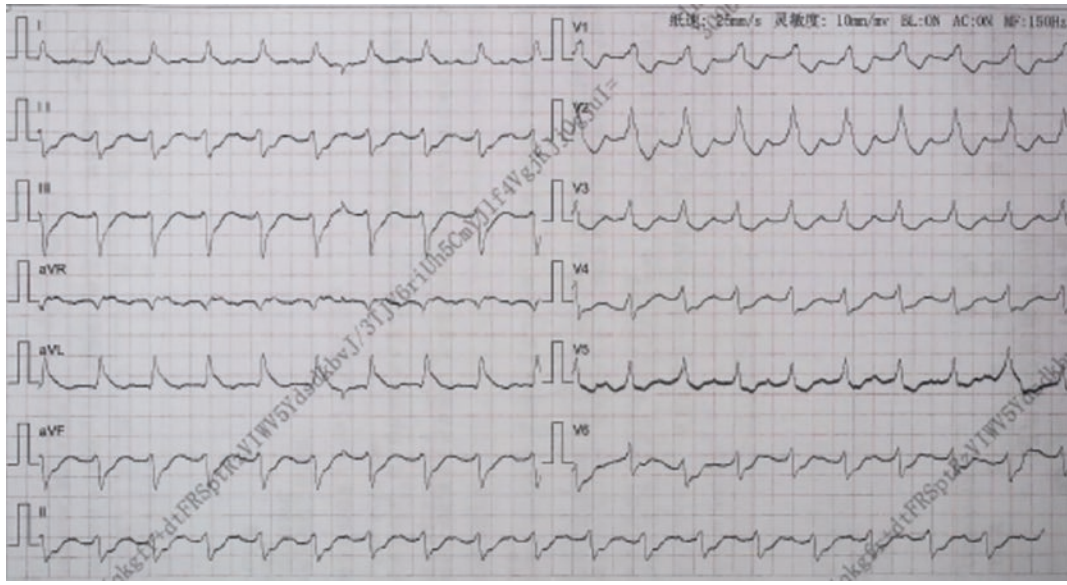


Fig. 21.26 ECG showed ventricular tachycardia

derness or bouncing pain, the liver and spleen were not reached under the ribs, there was no percussion pain in the kidney area, no mobile dullness, and no edema in both lower limbs.

Echocardiography revealed a left ventricular segmental wall movement abnormality, decreased left ventricular systolic function, and left ventricular apex abnormal echo mass shadow (thrombus suspect?) Ventricular septum thickening and small pericardial effusion.

21.5.3.4 Day 4–7 of Admission

The patient's general condition improved slightly. Her mental state was fair, and she complained of chest tightness and fatigue. Physical examination revealed clear breath sounds in both lungs. No dry or wet rales were heard, no pulsation was observed in the precardiac area, no tremor was felt, her heart boundary was not large and her heart sounds and pacemaker heart rate were clear. CVVH treatment was continued with ECMO, there was no heparin anticoagulation and ultrafiltration: 2.7 L, QB: 160 mL/min, lasted 24 h. A review was carried out of her hs-cTnI, revealing 25,146.3 pg/mL. We maintained the examination of hypersensitive cardiac troponin I and NT-Pro BNP once a day, and they manifested a gradual decrease. One week later, cTnI 6039.9 pg/mL, and NT-proBNP levels of 1888 pg/mL had both reduced significantly.

Echocardiography showed an LVEF of 22%, left ventricular hypertrophy, reduced left ventricular systolic function, reduced left ventricular wall motion in the middle segment of the lower left ventricular wall, and a small amount of pericardial effusion.

21.5.3.5 Day 8 of Admission

Echocardiography showed that the LVEF had significantly increased from 22% to 50% from the echocardiography result 1 week after admission. The left ventricle diameter was 4.8 cm, the left atrium was normal, and the interventricular septum and posterior wall of the left ventricle were 1.0 cm thick, but the wall motion of the left ventricle decreased diffusely, especially in the middle segment of the lower wall. LVEF was 40%. Pericardium visceral parietal separation, the maximum liquid dark area left in the ventricular posterior wall was 0.2, 0.5 cm in the left ventricular lateral wall, and 1.1 cm in the right ventricular lateral wall, indicating a small amount of pericardial effusion.

21.5.3.6 Echocardiography Diagnosis After 1 Week: Reduced Left Ventricular Systolic Function

The patient's general condition improved, but she still complained of fatigue. Her chest tightness improved significantly. Physical examination showed clear breath sounds in both lungs, no dry or wet rales were heard, no pulsation or flutter was observed in the precardiac area, the heart boundary was not large, the heart sounds were clear, no pathological murmur was heard in the valve areas, the abdomen was flat and soft, no tenderness or rebound pain was detected, no percussion pain was reached under the liver and spleen ribs, no percussion pain in the kidney area, no mobile turbid sound was observed, and no edema in the lower limbs. Cardiac echocardiography showed 46% EF, decreased left ventricular systolic function, and decreased ventricular wall movement in the middle segment of the lower left ventricular wall and lower side wall, and a small amount of pericardial effusion. The patient showed significant improvement in cardiac function, stable hemodynamics, and significant improvement in symptoms. Therefore, ECMO was removed, and incision and suturing were performed at the bedside femoral artery puncture site (Fig. 21.27).

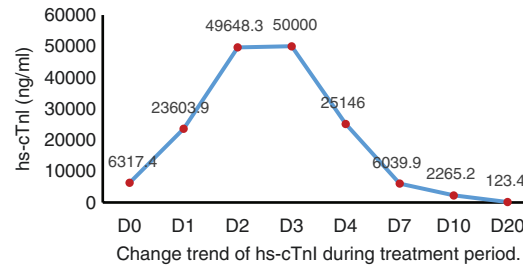
21.5.3.7 The Ninth Day of Admission

Echocardiography showed that the LVEF was 50%, decreased left ventricular systolic function, slightly decreased left ventricular wall motion in the basal segment of the lower left ventricular wall, and a small amount of pericardial effusion. The patient's condition improved, and the vitamins and amino acids were discontinued.

21.5.3.8 On the Tenth Day of Admission

IABP was removed, furosemide diuretic was administered to relieve cardiac load, invasive blood pressure monitoring was stopped, and antibiotic use was gradually reduced. Intravenous methylprednisolone and γ-globulin were discontinued. She was administered oral prednisone 40 mg, and metoprolol sustained-release tablets 23.75 mg qd were added to improve myocardial remodeling. The pacemaker was stopped 2 weeks after admission. She was transferred to the general ward for further treatment until the 20th day of discharge.

21.5.4 Variation Trend of Main Indicators During Admission



Change trend of hs-cTnI during treatment period

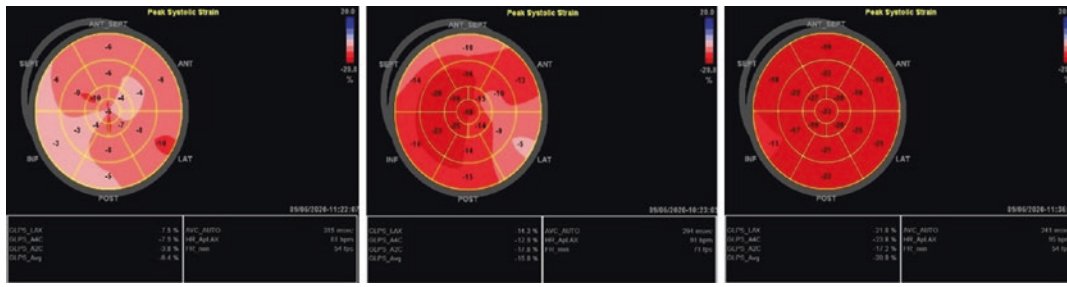
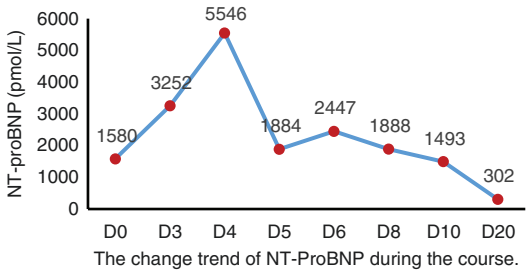
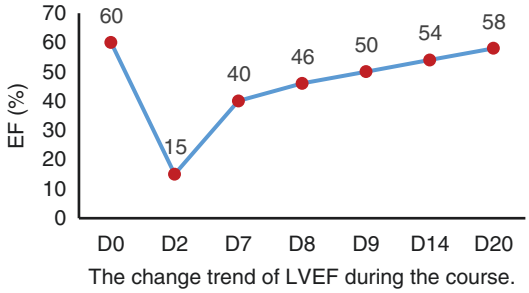


Fig. 21.27 "Bull's eye pattern" of ventricular wall movement by cardiac ultrasound spot tracer on days 1, 4, and 7 after admission. The lighter the red color is, the weaker the chamber wall movement, and the darker the red color, the stronger the chamber wall movement. As seen in these dynamic bovine eye images of the heart, the patient presented diffuse diminished ventricular wall movement, but local movement was weaker



The change trend of NT-ProBNP during the course



The change trend of LVEF during the course

21.5.5 Comments

A 35-year-old woman developed cardiogenic shock and malignant arrhythmia with chest tightness as the primary complaint. The characteristics of this case were that after the diagnosis of myocarditis, the patient immediately received immunomodulation therapy and gradually increased the dosage of glucocorticoids, but the patient's cardiac function continued to decline and the hypotension progressively worsened. The whole process of diagnosis and treatment of the case was correct, but the patient's condition still appeared aggravated, which showed that the characteristics of fulminant myocarditis had changed quickly. Therefore, the doctor's anticipation of fulminant myocarditis was particularly important. Based on anticipation, and on a "life-support based comprehensive treatment regimen" as the guiding principle, close observation conditions and timely adjustment of the treatment plan reduced the mortality of the patient's fulminant myocarditis.

21.6 Typical Case 6

The patient was a 55-year-old man who was transferred to our hospital on November 7, 2021. The patient was a 55-year-old man who was transferred to our hospital on November 7, 2021, because he was experiencing chills for five days, which was followed by several episodes of fainting, 2 days after the onset of chills. The chills were accompanied by dry cough, with episodes lasting for approximately 30 min. In the clinic, paracetamol (Tylenol) and roxithromycin were administered orally, which provided no relief. The patient continued to develop chills and was noted to have fatigue every night. On November 5, the patient developed palpitations and chest tightness while at work. This was followed by five episodes of syncope with an unknown duration. The patient was then sent to the local hospital for treatment, during which syncope occurred repeatedly. Both cardiac troponin I (cTnI) and N-terminal pro-brain-natriuretic peptide (NT-proBNP) levels were elevated at 8556 pg/mL (ref. 0–15 pg/mL) and 6351 pg/mL (ref. <161 pg/mL), respectively.

In the local hospital, the electrocardiogram (ECG) showed a complete right bundle branch block and slight ST-segment elevations in leads V3-V6. Coronary angiography was performed to exclude acute myocardial infarction and the results were unremarkable. While the patient was undergoing chest X-ray examination, he experienced sudden cardiac arrest with a third-degree atrioventricular block (AVB) on the cardiac monitor. The heartbeat was recovered after transthoracic heart compression and temporary pacemaker implantation. The patient was then transferred to our hospital and was diagnosed with "fulminant myocarditis" base on the quick progression of disease, elevated cardiac injury biomarkers and negative coronary angiography results. Prior to the onset of symptoms, the patient was always in good health and denied any chronic or infectious history. He suffered from a liver abscess in 2001 and improved after antibiotic treatment (no information about exact antibiotics). The patient was a physical worker. He was a smoker for more than

20 years (one pack of cigarette every day) and did not quit before disease onset. His mother and sister had a history of coronary heart disease.

On the day of admission in our hospital, which was day 5 of illness onset, the patient was conscious. Vital signs showed a blood pressure of 113/82 mmHg, heart rate of 83 beats/min (bpm), respiration of 20 cycles/min, and temperature of 36.3 °C. The patient's heart sound was very low and dull, but with regular rhythm. No cardiac murmur was heard in each valvular area of auscultation and no bilateral leg edema was observed.

The results of examination after admission on November 7 are shown as follow: high sensitivity cardiac troponin I (hs-cTnI) of 4266.2 pg/mL, D-dimer of 20.89 μg/mL, hypersensitive C-reactive protein (CRP) of 5.8 mg/L, interleukin-2 receptor (IL-2R) of 718 U/mL (ref. 223–710 U/mL), interleukin-6 of 68.19 pg/mL, tumor necrosis factor-α (TNF-α) of 8.6 pg/mL (ref. <8.1 pg/mL), sST2 >200 ng/mL, triglyceride of 1.86 mmol/L, glutamic pyruvic transaminase of 65 U/L, and glutamic oxaloacetic transaminase of 79 U/L. The ESR; blood coagulation studies; and procalcitonin, serum creatinine, and blood glucose levels were all normal. Bedside ECG and color doppler ultrasound were performed immediately after admission. The ECG showed sinus rhythm, first-degree AVB, right bundle branch block, and left anterior branch block (Fig. 21.28). Bedside echocardiography showed left atrial enlargement (3.7 cm), interventricular septal thickening (1.1 cm), diffusely decreased left ventricular wall motion, and left ventricular ejection fraction (LVEF) of 28%.

On admission, the patient was diagnosed with fulminant myocarditis. This was based on the history of cough, chills, sudden onset, fatal arrhythmia, hemodynamic instability, and significantly increased serum cTnI and NT-ProBNP levels with coronary angiography showing no coronary stenosis and combined ECG and color Doppler echocardiography showing diffuse wall motion disorder with significantly decreased LVEF.

His blood pressure decreased to 86/60 mmHg after admission, and the patient was given immediate treatment as follows: (1) an insertion of 40 mL intra-aortic balloon counter-pulsation (IABP); (2) methylprednisolone (400 mg intravenous drip for the first day, which was then reduced to 200 mg once a day on the following day); (3) intravenous immunoglobulin (IVIG) (20 g drip, once a day); and (4) oseltamivir phos-

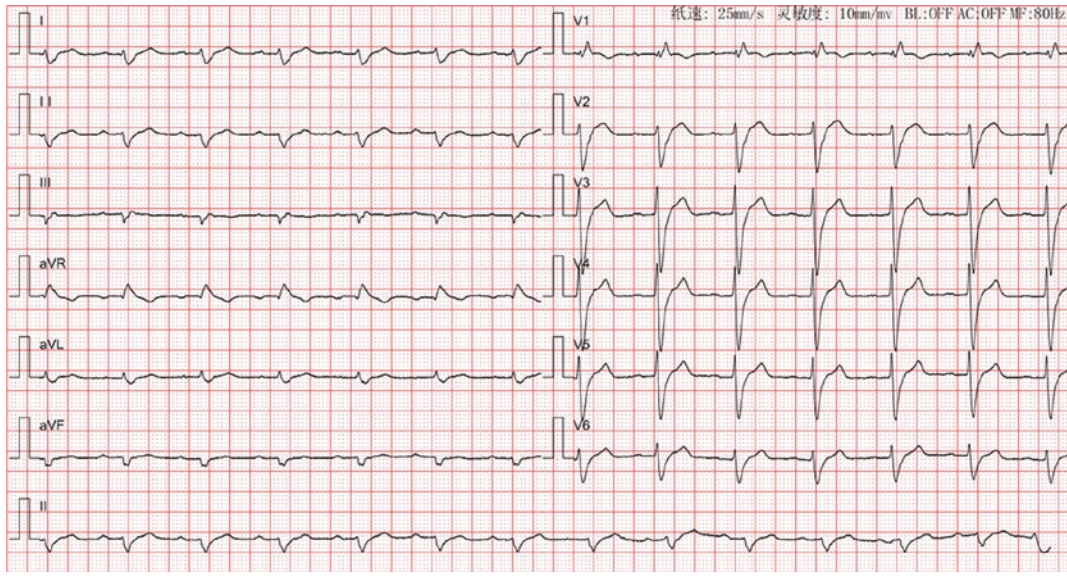


Fig. 21.28 ECG on admission shows sinus rhythm, first-degree atrioventricular block, right bundle branch block, and left anterior branch block. In addition, it shows low voltage and broadening of QRS wave duration

phate capsule (75 mg, twice a day). The patient's blood pressure increased and was maintained at 110/60 mmHg and his heart rate reduced to 70 bpm immediately after IABP. After these treatments, the patient felt relief from his symptoms. Laboratory tests showed no increase in antiviral IgM for pathogen examination, but more importantly, serum cytokine levels were significantly increased: IL-2R, 718 U/mL; IL-6, 8.19 pg/mL (ref. <7.0 pg/mL); TNF-α, 8.6 pg/mL; and soluble ST2, >200 pg/mL (ref. <30 pg/mL). On the third day of hospital admission, cTnI was 576.8 pg/mL with ECG showing sinus rhythm, right bundle branch block, and Q-wave in lead III. IVIG and methylprednisolone doses were reduced to 5 g intravenous drip once daily and 80 mg per day, respectively. On the fifth day, bedside ultrasound showed an LVEF of 45% with significantly improved left ventricular wall motion, blood pressure of 124/80 mmHg, and heart rate of 75 bpm. Thus, IABP and temporary pacemaker treatments were discontinued. Percutaneous endomyocardial biopsy was performed on the sixth day of hospital stay. The pathological analysis showed that the local myocardial fiber tissue was slightly atrophied and the small foci of myocardial cell necrosis was infiltrated with many inflammatory cells (dominated by lymphocytes) and macrophages, which suggested myocarditis (Fig. 21.29). Immunohistochemistry showed infiltrating inflammatory cells CD3 (+), CD4 (+), CD8 (+), CD20 (partly+), positive control (+), CD19 (partly+), and CD68 (tissue cells) (Fig. 21.30). Desmin (myocardium) special staining showed Masson scattered collagen fibers (+), positive control (+) (Fig. 21.31). On the sev-

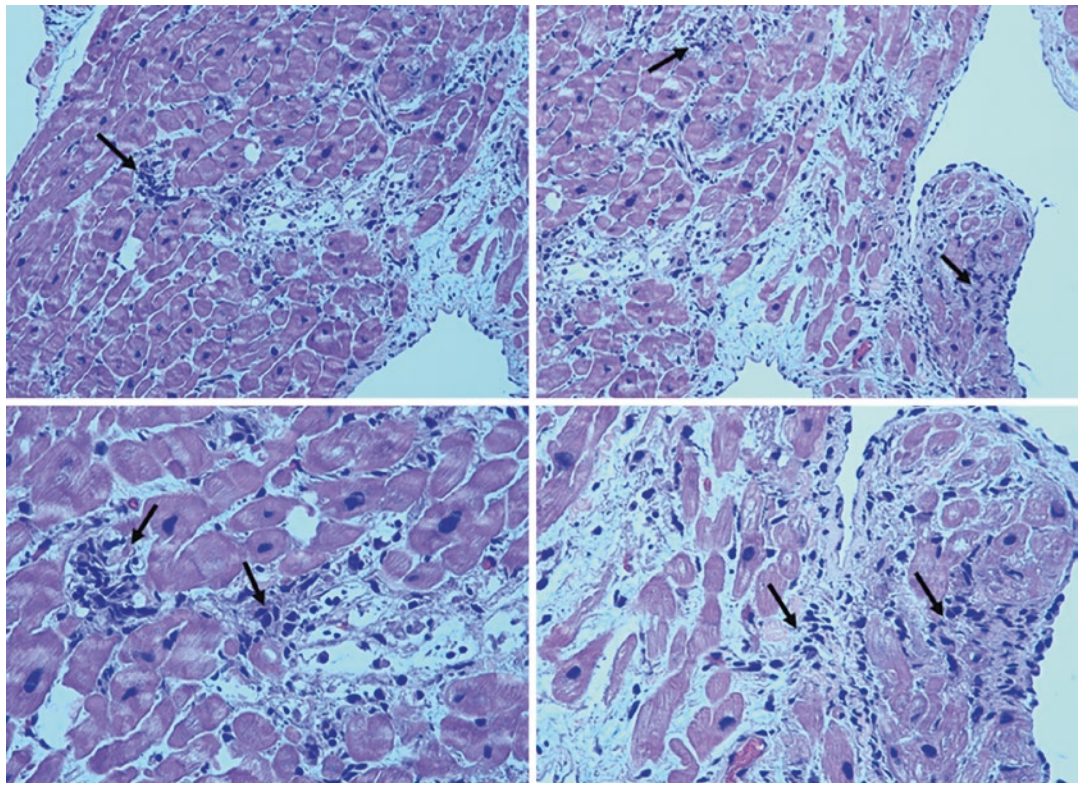


Fig. 21.29 Pathology of myocardial biopsy on the fifth day after admission. Diagnosis hints: (ventricular muscle biopsy) all samples taken from the tissue were submitted for examination. The local myocardial fiber tissue was slightly atrophied and the small foci of myocardial cell necrosis with infiltration of inflammatory cells (dominated by lymphocytes) and macrophages was noted. The results are consistent with the changes in myocarditis. Inflammatory cells group are shown by black arrows

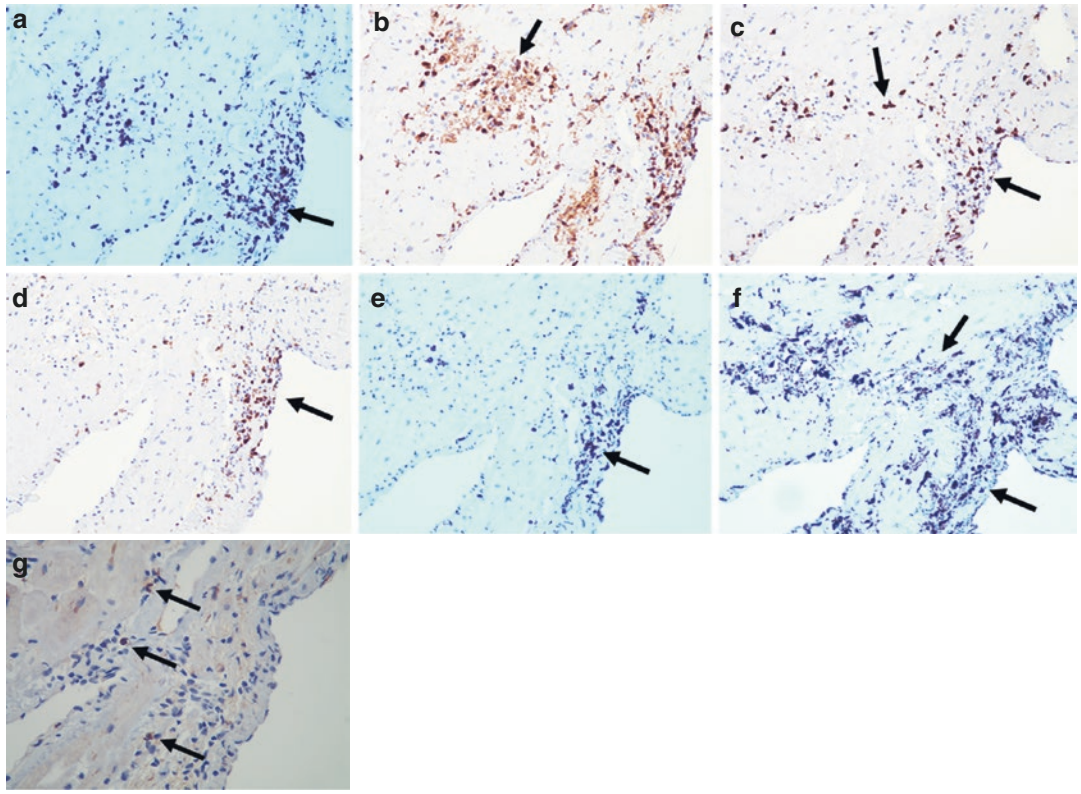


Fig. 21.30 Immunohistochemistry shows infiltrative inflammatory cells. (**a**) CD3 (+), (**b**) CD4 (+), (**c**) CD8 (+), (**d**) CD20 (partly+), (**e**) CD19 (partly+), (**f**) CD68 (tissue cells); (**g**) MPO (neutrophil); positive control (+). Positive staining cell groups are shown by black arrows

enth day of hospital stay, cTnI was reduced to 219.8 pg/mL. A 24-h ambulatory electrocardiogram monitoring showed normal sinus rhythm and a heart rate of 42–77 bpm, with occasional atrial premature beats (322 beats over 24 h) and 58 occasional ventricular premature beats over 24 h. The ST-segment of the inferior wall and anterior walls was elevated, and the T-wave was slightly inverted during the monitoring period. Delayed-enhancement magnetic resonance perfusion imaging was performed, which revealed abnormal enhancement in the inferior wall of the apical segment of the left ventricle; elevated signal intensity in the lateral wall, inferior wall, and middle to apical segment of the superior basal segment of DOUBLE and TRIPLE; and left ventricular function LVEF of 54% (Fig. 21.32). Bedside heart ultrasound indicated an LVEF of 50%. On the 10th day of hospital stay, cTnI decreased to the normal range (32.8 pg/mL). The patient was

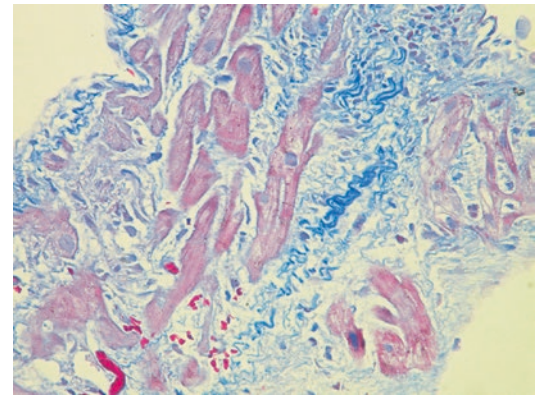


Fig. 21.31 Desmin (myocardium) special staining shows Masson scattered collagen fibers (+), positive control (+). Collagen is marked by blue staining, and muscle fibers are marked by red staining

permitted to be discharged on the 12th day with take-home medications of oral prednisone acetate tablets 40 mg per day; trimetazidine hydro-

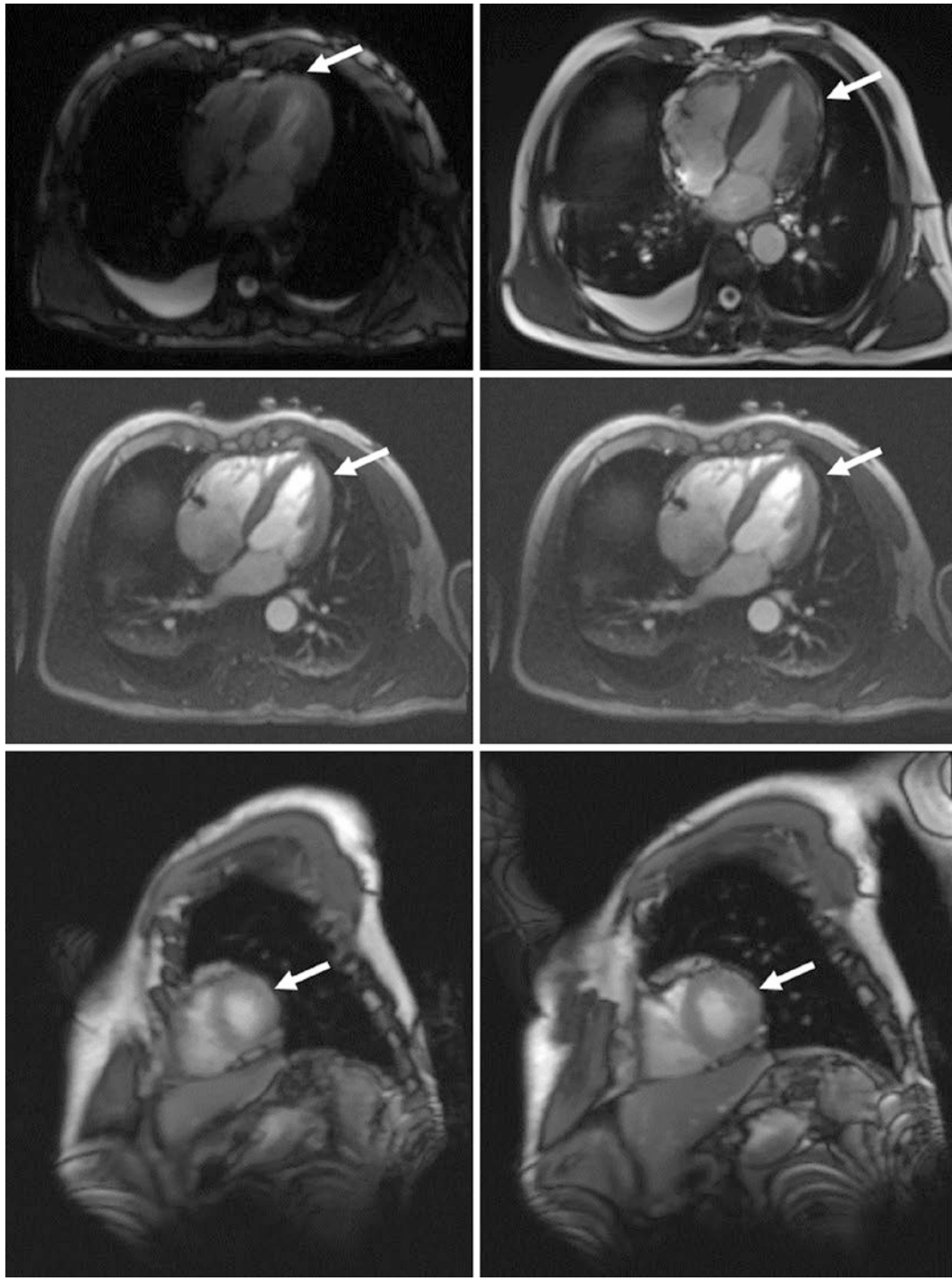


Fig. 21.32 Magnetic resonance imaging-perfusion imaging-multi-directional delayed enhancement on the eighth day of hospital stay. Diagnostic hints: basal segment lateral wall, inferior wall and middle segment to apical segment myocardial edema, and apical segment inferior wall necrosis. Combined with medical history, the possibility of myocarditis and bilateral pleural effusion can be considered. The epicardium myocardial injury and edema are shown by white arrows

chloride sustained-release tablets 35 mg, twice a day; coenzyme Q10 20 mg, three times a day; perindopril tert-butylamine tablets 4 mg, once a day; and beta blocker (metoprolol) 23.75 mg per day with a gradually increasing dose.

21.6.1 Comments

1. This patient had cold-like symptoms but soon developed severe hemodynamic instability, such as hypotension, cardiogenic shock, and fatal arrhythmias.
2. The patient developed palpitations, fatigue, and chest tightness while at work, syncope after chills, and the myocardial biomarkers cTnI and NT-proBNP were elevated. Thus, coronary artery angiography was performed and acute myocardial infarction was excluded. This test is very important and must be the first consideration according to the Chinese expert consensus statement when cases of fulminant myocarditis are encountered. Sequential echocardiography showed global motion decline of the left ventricular wall and marked elevation in serum inflammatory factor levels, especially SST2 levels, all of which supported the diagnosis of fulminant myocarditis. Based on our experience, "extremely early identification, extremely early diagnosis, extremely early prediction, and extremely early treatment," are vitally important.
3. Do not wait; immediately start treatment according to the "life support-based comprehensive treatment regimen": circulatory support with IABP and immunomodulation therapy using sufficient doses of both glucocorticoid and IVIG. In this case, the blood pressure increased from 86/60 to 110/60 mmHg. After a few days of therapy, the patient's condition improved quickly. Certainly, if the hemodynamics are not stable after IABP, veno-arterial extracorporeal membrane oxygenation (ECMO) should be provided. In this case, the patient did not need ECMO, similar to most patients encountered, since IABP support was initiated very early.
4. Endomyocardial biopsy was performed and the results showed lymphatic fulminant myocarditis. In the many years of treating fulminant myocarditis, it has been noted that patients with abrupt onset are most likely to have lymphatic type of fulminant myocarditis, or occasionally eosinophilic type of fulminant myocarditis due to acute allergy.
5. After discharge, the patient still needs to take steroids (prednisolone), ACE inhibitors (captopril), beta blockers (metoprolol), and trimetazidine, because residual inflammation remains an obstacle to a complete recovery.

Appendix A: Chinese Expert Consensus Statement on the Nursing Strategies of Adult Fulminant Myocarditis

Abstract **Objective**: To establish an expert consensus report on the nursing strategy of fulminant myocarditis in adults in order to standardize clinical nursing practice.

Methods: Based on a literature review and qualitative interviews, an expert consensus draft on the nursing strategy of fulminant myocarditis in adults was developed according to the disease characteristics. A two-round Delphi study and expert meetings were conducted to modify and refine the draft with the aid of objective evidence and expert suggestions, and a final expert consensus report was formed.

Results: The expert consensus report consisted of six parts: early assessment and dynamic monitoring; intravenous therapy and medication nursing; mechanical life support therapy and nursing; prevention and nursing care of common complications; rehabilitation nursing; and professional team management.

Conclusion: Expert consensus plays a guiding role in standardizing clinical practice for fulminant myocarditis in adults, which will ultimately improve the treatment effect and clinical nursing quality.

Keywords Fulminant myocarditis; Illness assessment; Intravenous therapy; Medication nursing; Life support therapy; Rehabilitation nursing; Nursing strategy; Expert consensus

Myocarditis refers to inflammatory injuries caused by various pathogens that can result in heart dysfunction, such as decreased systolic or diastolic function, or arrhythmias [1]. Fulminant myocarditis is the most severe and specific type of myocarditis. Its mortality rate is 40–80% after treatment with drugs and mechanical support [2].

In 2017, the Section of Precision Medicine Group of the Chinese Society of Cardiology issued a "Chinese Expert Consensus Statement on the Diagnosis and Treatment of Fulminant Myocarditis" [3]. The panel proposed a new treatment regimen termed "life support-based comprehensive treatment regimen." The core content of this treatment regimen includes (1) mechanical life support (applications of mechanical respirators and circulatory support systems, including intra-aortic balloon pump and extracorporeal membrane oxygenation); (2) immunological modulation using sufficient doses of glucocorticoid and immunoglobulin; and (3) antiviral reagents using neuraminidase inhibitors combined with other symptomatic treatments (e.g., acute left heart failure therapy, anti-shock therapy, anti-arrhythmia therapy, and real-time monitoring). Fulminant myocarditis is characterized by rapid progress and multiple potential complications that require professional nursing. However, there are no clinical practice norms for reference. Therefore, the Committee of Chinese Cardiopulmonary Rehabilitation Nursing Alliance and Cardiovascular Committee of Wuhan Nursing Association organized experts and formulated the "Expert Consensus on Nursing Strategy of

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Fulminant Myocarditis in Adults" based on the characteristics of the disease, the latest nursing research progress, and evidence-based nursing. The consensus aims to standardize clinical nursing practice for fulminant myocarditis and guide clinical nursing decisions scientifically, in order to improve early identification, nursing professional ability, treatment effect, and clinical nursing quality.

Consensus

Formulation

The consensus was initiated by the nursing team of Tongji Hospital, which is affiliated with Tongji Medical College, Huazhong University of Science and Technology. The Committee of Chinese Cardiopulmonary Rehabilitation Nursing Alliance and Cardiovascular Committee of Wuhan Nursing Association organized a panel of experts, including 5 medical experts, 36 nursing experts, and 1 rehabilitation therapist from 18 hospitals across China. According to the characteristics of fulminant myocarditis, the expert panel generated a preliminary consensus based on a literature review and qualitative interviews. The consensus was finally formed through a two-round Delphi process and expert panel meetings.

Application Scope

The scope of applications includes (1) formulating clinical nursing practice plans; (2) guiding clinical care pathways; (3) formulating nursing practice evaluation standards; (4) standardizing nursing technical operations; and (5) providing reference for clinical nursing training. In addition, it was determined to be better to combine the consensus with the "Chinese Expert Consensus Statement on the Diagnosis and Treatment of Fulminant Myocarditis" [3] to comprehensively understand the clinical characteristics, treatment, and nursing of fulminant myocarditis.

Clinical Evaluation and Treatments

Definition

Myocarditis is an inflammatory injury caused by various pathogens that can ultimately result in heart dysfunction. There are usually three clinical stages of myocarditis: acute, subacute, and chronic phases. The acute phase lasts for 3–5 days, during which active viral replication and invasion severely damages the myocardium. Immunological reactions play a major role in the subacute phase, and few patients eventually enter the chronic phase. In this phase, patients may suffer from chronic, persistent, but sudden aggravated inflammatory reactions, as well as decreased contractility, myocardial fibrosis, and cardiomegaly. Fulminant myocarditis is usually defined as a myocardial inflammatory disease with a rapid outbreak complicated by severe hemodynamic dysfunction. Therefore, it is more likely to be clinically diagnosed. Compared with common myocarditis, there are no characteristic differences in histology and pathology.

Etiology

Common causes can be classified into three classes: infection, autoimmune disease, and poisoning or toxic drug effects. Infections cause the majority of myocarditis cases, with the most common pathogens being viruses, including enteroviruses (especially Coxsackie B virus), adenovirus, cytomegalovirus, Epstein-Barr virus (EBV), and influenza virus. The mechanisms leading to myocardial injury include direct injury and immunogenic injury. Abnormal activation of the immune system, excessive macrophage polarization, and accumulation in tissues or organs can cause indirect injury, which is an important pathophysiological mechanism of rapid progression [3].

Symptoms

Fulminant myocarditis can attack people at any age, especially healthy young adults, and has a higher incidence rate during winter and spring. Fulminant myocarditis is characterized by rapid

progress, hemodynamic dysfunction (such as pump failure and circulation failure), and severe arrhythmia, which could be accompanied by respiratory, liver, and kidney failure in some patients. Hemodynamic dysfunction and abnormal cardiac function are the most significant manifestations and indicators of disease severity. The main symptoms include the following. (1) Premonitory symptoms of viral infection: patients may have fever, weakness, reduced appetite, nasal obstruction, pharyngalgia, cough, and diarrhea. It must be noted that individual symptoms vary greatly. (2) Symptoms of cardiac injury: panting, dyspnea, chest distress or pain, palpitation, dizziness, extreme weakness, and obvious loss of appetite. (3) Hemodynamic dysfunction: some patients may rapidly develop acute left heart failure or cardiac shock and have symptoms of passive pulmonary congestion and shock. A few patients experience fainting episodes, syncope, or sudden death. (4) Symptoms of injury to other organs: fulminant myocarditis can also involve other organs, causing dysfunction or even failure. This includes liver dysfunction, kidney injury, blood coagulation disorders, and respiratory injury, which may lead to rapid deterioration of the patient's condition.

The main signs include (1) a rise in body temperature; (2) frequent hypotension—patients with particularly severe disease may have undetectable blood pressure; (3) tachypnea; (4) a mismatch between increased heart rate and body temperature; (5) occurrence of various arrhythmias, which can be life-threatening; (6) the usually normal heart border could be weakened or absent and heart sounds could be blunt; (7) signs of shock, hypoperfusion, and other organ dysfunction [3].

Treatments

Symptomatic and Supportive Treatment

Symptomatic and supportive treatments include bed rest, oxygen supply, infection prevention, myocardial metabolism improvement, anti-shock and acute left heart failure prevention, antiarrhythmia, and water-soluble and lipid-soluble vitamin supplementation [3].

Anti-viral and Immunomodulating Therapy

Therapy for fulminant myocarditis patients comprises administration of immunomodulating therapy by using a large dosage of glucocorticoids and intravenous immunoglobulin as well as antiviral therapy using neuraminidase inhibitors, which serve as the core drug therapy for patients with fulminant myocarditis [3].

Mechanical Circulatory Support

As the myocardium is diffusely and severely injured, the heart's pump function is dramatically decreased in patients with fulminant myocarditis. Pulmonary congestion and pulmonary inflammatory injury further exacerbate this condition. As a result, blood and oxygen supply to tissues cannot meet the body's demand and consumption. Mechanical circulatory support treatment, including circulation support, respiration support, and continuous renal replacement, can give the heart enough rest, allowing it to regain normal function under systematic treatment. Therefore, life support treatment should be at the center of all treatment plans [3].

Contents of the Consensus

Early Assessment and Dynamic Monitoring

The patients' consciousness, heart rate/rhythm, body temperature, pulse, respiration, blood pressure, and oxygen saturation should be assessed and monitored to recognize early symptoms. Since fulminant myocarditis has a sudden onset, premonitory symptoms of viral infection and myocardial damage rapidly progress to severe hemodynamic dysfunction [3]. Therefore, patients should be transferred to hospitals with cardiac care units (CCUs) to receive proper respiratory and circulatory monitoring and life support. Nurses should dynamically monitor invasive

Table A.1 Dynamic monitoring of patients with fulminant myocarditis

Monitoring	Suggestion
Consciousness	All fulminant myocarditis patients should be monitored closely.
Hemodynamics	Heart rate/rhythm, blood pressure (i.e., invasive artery blood pressure, mean arterial pressure) and central venous pressure should be monitored closely.
Respiration	Respiratory rate and blood oxygen saturation should be monitored closely. Arterial blood gas analysis should be monitored every 4–6 h in the early stage.
Cardiac biomarker	cTnI, BNP or NT-proBNP, ECG and echocardiography should be monitored according to the condition of patients.
Body temperature	Axillary and rectal temperature, skin temperature and color changes of extremities should be monitored every 4 h.
Management of fluids	Intake (e.g., intravenous infusion, blood transfusion and intestinal intake) and output (e.g., urine, drainage, diaphoresis, and vomiting volume) should be recorded every hour.
Psychology and sleep	Nurses should evaluate psychological and sleep status and provide targeted psychological intervention to ensure patients obtain sufficient sleep.

hemodynamics, cardiac biomarker (cTnI and BNP or NT-proBNP) levels, and arterial blood gas analysis. The nurse should assist in bedside ECG, echocardiogram, chest X-ray, and other auxiliary examinations. If chest tightness and pain occur, acute myocardial infarction should be excluded, and preparations for emergency coronary angiography should be completed as soon as possible. The dynamic monitoring of patients with fulminant myocarditis is summarized in Table A.1.

Intravenous Treatment and Medication Nursing

Intravenous Treatment

1. A central venous catheter should be inserted before systemic heparinization, and more than two venous channels should be established to ensure subsequent venous treatment.
2. Nursing staff should reasonably arrange the administration sequence and give priority to drugs, such as glucocorticoids, immunoglobulins, and neuraminidase inhibitors.
3. The infusion speed should be controlled according to the hemodynamics and cardiac function to avoid heart overload, inadequate circulation volume, and blood pressure drop.
4. Vasoactive drugs are recommended for micropump infusion, and their use is different from that of other drugs. Venous access and maintenance of mean arterial pressure (MAP) ≥65 mmHg.
5. A micropump is used to inject vasoactive drugs intravenously. Different venous channels are used to maintain a mean arterial pressure (MAP) above 65 mmHg.

Medication Nursing

Neuraminidase inhibitors can inhibit the neuraminidase of influenza virus, thus inhibiting the release of newly synthesized viruses from infected cells and the replication and transmission of viruses in the human body. Adverse reactions to neuraminidase inhibitors include nausea, vomiting, and dizziness, which can be relieved after discontinuation of the drug. During high-dose glucocorticoid treatment, attention should be paid to the symptoms of gastrointestinal adverse reactions and gradually reduce the dose to avoid rebound effects. When using immunoglobulin, the infusion rate should be gradually increased to observe allergic reactions. Due to the large doses of glucocorticoids and immunoglobulins, nurses should explain the purpose of medication to patients and their families to gain understanding and cooperation. Life-support treatment is the first choice of treatment during anti-shock therapy. When life support is insufficient to maintain circulation, vasoactive drugs should be used. If it is impossible to use the central venous catheter, nurses should use a peripheral intravenous catheter and pay attention to infusion phlebitis [4].

Life Support Nursing

One of the cores of "life support-based comprehensive treatment regimen" is mechanical life-support treatment. Mechanical life-support

Table A.2 Nursing of VA-ECMO

	Suggestion
Effective operation	The nurse should assess the external loop each hour, including correct catheter connection, catheter shake, component, and reasonable alarm setting [12]
Key parameter management	(1) Rotational speed and flow rate
	Nurses should adjust the rotational speed following the doctor's advice, which should be between 1500 and 4000 r min^{-1}. During the treatment, the flow rate should be closely observed in accordance with the rotational speed and the perfusion flow should be adjusted timely according to the venous oxygen saturation, mean arterial pressure, blood lactic acid level, and urine volume.
	(2) Air flow and oxygen concentration
	Nurses should monitor blood gas analysis (residual alkali, blood lactic acid) every 2 h and every 4–6 h after stabilization, and dynamically adjust air flow and oxygen concentration following the doctor's advice [13].
	(3) Pressure
	Nurses should monitor the pressure at the inlet and outlet of the oxygenator. It indicates that the arterial intubation end of the patient is blocked after the oxygenator when the two-point pressure increases. It indicates the formation of the oxygenator thrombosis when the pressure difference between the two points increases.
	(4) Temperature
	Patients' body temperature should be maintained close to 37 °C and the temperature of the water tank should be set at 36–37 °C. Temperatures that are too low will lead to the disorder of hemodynamics and blood coagulation mechanism. However, temperatures that are too high will increase the oxygen consumption of the body [14].

treatment, including circulation, respiration support, and CRRT, can provide the heart with sufficient rest, allowing it to regain its normal function under systematic treatment [5].

Application Time

All fulminant myocarditis patients should receive life support treatment as soon as possible to reduce cardiac load, improve cardiac function, and reduce mortality [6]. Life support treatments are as follows: (1) circulation support: the nurse should assist in IABP placement once the systolic blood pressure is less than 90 mmHg, LVEF is less than 40%, blood lactic acid is over 2 mmol L^{-1}, or cardiac index is less than 2 L min^{-1} m^{-1} [7]. ECMO should be added once if IABP is unable to sufficiently improve circulation [8]; (2) respiratory support: patients with respiratory dysfunction (respiratory distress or hypoxemia) should receive respirator-assisted ventilation. Therefore, non-invasive positive-pressure ventilation is recommended. If it is ineffective or not tolerated by the patient, a tracheal cannula should be used [9]; (3) continuous renal replacement therapy: CRRT can continuously filter out toxins and cytokines, reduce cardiac load, maintain water-electrolyte and acid-base balance, and recover vessel response to vasoactive drugs [10]. All patients with fulminant myocarditis should receive CRRT as early as possible.

Circulatory Support Nursing

Nurses should closely observe the operation of circulatory support equipment and regularly feedback the treatment effect to the doctor. Nurses should ensure the effectiveness of the IABP and observe the effect of counterpulsation treatment [11]. The care for VA-ECMO is shown in Table A.2.

Respiratory Support Care

Respiratory support care has two strategies: (1) Lung ventilation protective strategy [15], which aims to set appropriate ventilator parameters and prevent barotrauma and volutrauma. Experts recommend that ventilator parameters should be set as follows: tidal volume 3–5 mL/kg, respiration frequency <8 times/min, positive end expiratory pressure (PEEP) 5–15 cmH_2O, plateau pressure <25 cmH_2O, and FiO_2 30–40%. (2) A sedation and analgesia strategy [16], which aims for all sedation strategies to start with real-time assessment and ensure adequate control of sedative medicine, preventing medication overdose. The

Table A.3 Nursing strategy of patients with fulminant myocarditis receiving CRRT

Step	Recommendation
Vascular access	Blood purification tube connect the ECMO loop [17]. An independent and temporary hemodialysis catheter could be established for patients without ECMO support.
Commencing treatment	Initial flow speed: 30–50 mL/min, the speed is adjusted to 100 mL/min for 3–5 min after the blood was drained, blood pump was adjusted to 150–200 mL/min for 30 min when there is no adverse cardiac events.
Volume management	Three-level management [18]: monitoring of central venous pressure (CVP), invasive arterial blood pressure, ultrafiltration rate
Weaning indication	No manifestations of volume overload; water-salt and acid-base are balanced; the dose of vasoactive drugs is not large; no serious infection; daily urine output is more than 500 mL
Step-by-step blood autotransfusion	Blood flow rate decrease to 180 mL/min for 15 min; blood flow decrease to 150 mL/min, while replacement volume and control the ultrafiltration fraction decrease by 20% for 15 min; ultrafiltration should be turned off with blood flow speed decreasing to 100 mL/min for 15 min; blood flow speed decrease to 50 mL/min and start blood autotransfusion [19].

Richmond Agitation Sedation Scale is recommended as a tool to conduct daily neurological function assessment for patients. RASS during daytime should be maintained between –2 and 0, while nighttime is set between –3 and –1.

Continuous Renal Replacement Therapy (CRRT) Care

The procedure is demonstrated in Table A.3.

Catheter Management

All catheters connected to life support devices must be closely monitored. Nurses managing catheters should secure IABP and ECMO catheters and prevent occlusion, damage, rupture, or breakage [20]. The external catheters of life support devices are positioned parallel to patients' axis and secured at the end of the bed without tension. Subcutaneous sutures are used to secure V-A catheters and adhesive anchors, and additional large transparent film dressings cover the insertion site. The connections between catheters need to be resecured using hemostatic forceps. Nurses must examine all connections of the catheter every 1 h to prevent distortion, displacement, or prolapse. The length of the external catheter should be measured at the nurse shift handover and recorded on the medical system [21]. Patients must remain on bedrest with the head of the bed raised no more than 30° and should not flex the affected leg at the hip. Daily assessment of patients' cardiopulmonary function provides evidence for doctors to assist in the weaning of life support devices.

Anticoagulation Management

Nurses managing ECMO should assess the external loop each hour, including correct catheter connection, reasonable alarm setting, clotting formation in external ECOM catheters, and membrane lung through light flush. The clotting formation in external ECMO catheters and membrane lung is defined as a dark visual color settling on the catheters and membrane lung, and does not flow with blood. The activated coagulation time (ACT) or activated partial thromboplastin time (APTT) were measured at intervals of 2–3 h and shifted to the interval of 6 h after patient stabilization. The range of ACT and APTT is recommended to be maintained: (1) keep ACT 150–180 s and APTT 50–70 s for patients with IABP; (2) keep ACT 180–210 s [22] and APTT 50–70 s for patients with ECMO, ACT is suggested to be maintained at 150–170 s under active hemorrhage, ACT is suggested to be maintained at 200–210 s under a decrease in assisted circulation flow; (3) patients receiving ECMO and IABP would follow the ECMO anticoagulation principle; (4) patients receiving CRRT and ECMO/IABP would follow the ECMO or IABP anticoagulation principle.

Common Complications Prevention and Care

Arrhythmia

Hemodynamic disorders would exacerbate if patients with fulminant myocarditis had adverse arrhythmias, which could threaten a patient's life.

Patients with arrhythmia presented with sinus bradycardia, an ECG showed a wide QRS wave, echocardiography indicated worse left ventricular function, and laboratory tests demonstrated continuous rise and fluctuation in cardiac troponin (cTnI). Unsustained VT occurs when continuous hypoperfusion occurs. Therefore, preventions and immediate life support treatment should be the main approach to prevent arrhythmia. In volume management, nurses should monitor patients' dynamic electrolytes to prevent arrhythmia caused by electrolyte disorders. In addition, anti-arrhythmic drugs should be administered to patients with ventricular tachycardia, ventricular fibrillation, and other adverse cardiac events. Cardiopulmonary resuscitation and defibrillation with direct current should be administered to patients, if necessary. When patients present with bradycardia and high atrioventricular block, temporary pacemaker implantation is the preferred choice, and cardiotonic drugs are encouraged to be administered. Most patients with fulminant myocarditis can recover from arrhythmia when they are in the acute stage, and permanent pacemaker implantation is not recommended in the acute stage [3].

Hemorrhage and Thrombosis Care

Fulminant myocarditis receiving life support devices require appropriate anticoagulation therapy to reduce the risk of hemorrhage and thrombosis caused by catheter insertion or mobilization limitation. Hemorrhage and thrombosis are common complications related to circulation support treatment [23], and studies have shown that there is a 20% incidence of thrombosis among patients receiving ECMO [24]. For prevention, the following steps should be taken: (1) close observation at the insertion site, including observation of the color of drainage fluid, hemorrhage in urine and stool, clot in the catheters, skin temperature, limb swelling, pain, and other symptoms related to pulmonary embolism. Laboratory test results for patients should be traced, including the D-dimer and ACT. Thrombosis in catheters should be suspected if there is poorly triggered, low counterpulsation pressure; (2) anticoagulation therapy should be dynamically adjusted to maintain the APTT and ACT at the target range; (3) invasive procedures should be conducted before heparin therapy and decrease the frequency of subcutaneous injection, intramuscular injection, intravenous/intraarterial punction. The time for compressing the insertion site should be extended to patients undergoing anticoagulation therapy; (4) instruct and assist patients to perform active or passive mobilization training using a pressure device to prevent venous thrombosis of the lower limbs. For treatment, once bleeding occurs, report to the doctor immediately, identifying the bleeding site, and take hemostasis measures according to the amount of bleeding. After thrombosis of the lower limbs, blood vessel color ultrasound should be performed in time to clarify the position, avoid massage, and thrombolytic therapy should be performed if necessary.

Infection

There are 9–65% nosocomial infections in patients receiving ECMO, mainly caused by severe disease, intestinal flora migration, catheter microbial colonization, and immune system damage [25]. For prevention, patient's temperature and insertion site require regular observation. Nurses should monitor laboratory test results and physical examination results to identify the infection. For patients receiving ECMO, one nurse and one doctor should be appointed to care for the patient and implement bedside isolation, including aseptic operation and hand hygiene. Nurses should change bed units such as bed sheets, quilt cases, and patient uniforms. A nurse assistant should disinfect medical devices with 75% ethanol or disinfectant wipes twice a day. Nurses should take measures to prevent catheter-related blood flow infection, catheter-related urinary tract infection, and ventilator-associated pneumonia. Antibiotics are administered to prevent infection. With respect to treatment, reporting to the doctor and medicine therapy are priorities for infectious patients. Nurses should perform expectoration machines on patients with pulmonary infections to improve sputum drainage.

Hemolysis

Patients may manifest hemolysis, present an increase in free hemoglobin, hemoglobinuria,

and secondary damage to multiple organs because the ECMO device could damage red blood cells. Researchers have reported that the incidence of hemolysis among patients receiving ECMO was 25.8% [26]. During ECMO, nurses should pay attention to indicators such as pump pressure, speed, and flow rate, and avoid running at high speed for a long time after reaching the target flow rate. With respect to treatment, several indicators should be observed, including jaundice, hyperbilirubinemia, hemoglobinuria, and other manifestations. If a patient experiences hemolysis, the medical team should investigate the cause and take immediate action, such as alkalization of urine and reduction of negative pressure at the venous end of ECMO (<30 mmHg). If necessary, the corresponding consumable materials (e.g., oxygenators) or plasmapheresis should be replaced when necessary.

Lower Extremity Arterial Ischemia

Lower extremity arterial ischemia occurs during lower-extremity arterial catheterization. Studies have shown that the incidence of lower extremity arterial ischemia is 6.4% among patients with IABP [27], while patients with ECMO had a higher risk of lower extremity arterial ischemia. For prevention, the appropriate size of the arterial sheath should be selected according to the height of the patient. The circulation of both lower limbs should be closely evaluated, and the pulse of the dorsal foot artery, local skin temperature, color, muscle tension, leg circumference, capillary reflux, and other conditions should be observed on the intubated side, and compared with the healthy side. Nurses should keep limbs warm and maintain their joints at functional positions. Physical exercise should be performed for target patients under the guidance of the medical staff. With respect to treatment, if the pulse of the lateral dorsalis pedis artery is weakened or disappeared, the local skin is pale or cyanosis, the temperature drops, and limbs are numb, the doctor should be informed and immediate action should be taken. If necessary, nurses should assist doctors in supplying blood to the distal lower limbs with an appropriate perfusion tube to establish distal perfusion [25].

Brain Injury

The main cause of brain injury is hypoperfusion. For prevention, nurses should closely observe patients' status, including consciousness, emotion, and headache, to perform an in-time neurological assessment. CT of the brain is necessary for those who are suspected to have brain injury. Ice cap or dehydration therapy should be used for patients with brain injuries. Mild hypothermia is recommended for patients who undergo CPR or receive sedation treatment to maintain a central temperature of 32–34 °C for 24 h [28]. With regards to treatment, immediately informing doctors that brain injury occurs in patients is necessary. The medical team should apply an ice cap to patients, mild hypothermia, and a dehydrating agent, and hormone should be administered to the patient.

Rehabilitation Strategy

The core of rehabilitation strategy is exercise training, with improvements in nutrition, psychology, and family centered care. The cardiac rehabilitation team should conduct cardiopulmonary function assessment before exercise training and implement an individual cardiac rehabilitation plan. The content of the rehabilitation strategy is demonstrated as follows:

Exercise Rehabilitation

ECG and blood pressure monitoring should be performed on patients [29], and rehabilitation exercises should be carried out step by step according to the patient's condition. (1) In the acute phase, absolute bed rest and good posture management by the nurse to complete basic care. After the vital signs are stable, body position changes and limb movements can be monitored. (2) Unconsciousness by the nurse to assist the physical therapist limbs and distal small joint passive movement through ventilator-assisted breathing training and lung physical therapy techniques to maintain the normal function of the patient's lungs. Nurses should urge sober patients for active movements. For patients who cannot tolerate upright position, posture adaptability

training should be carried out in the order of high decubitus, long sitting, bedside sitting, and standing position. Exercise intensity should increase the heart rate by no more than 20 times/min, and exercise time should be 10–15 min each time, 3 times a day [30]. The out-of-bed rule is followed. (3) For patients who can leave the bed, rehabilitation training should be based on walking. Symptom-restricted exercise intensity was used, and the appropriate score was 11–13 points (a little exertion), and the heart rate was maintained at 65–80% of the maximum heart rate in the 6 min walking test. The exercise time was 30–45 min each time, 5 times a week, and the walking distance gradually increased from 25 to 800 m. The latter part of walking training can guide vertical movements, such as up and down stairs. (4) A 6 min walking test is feasible before discharge to guide further exercise rehabilitation, and aerobic exercise is recommended to be the main exercise, 30–45 min each time, 5 times a week, with the exercise intensity ranging from low to moderate [31]. (5) After discharge, it is recommended to go to the cardiac rehabilitation center for standardized cardiac rehabilitation.

Nutrition Rehabilitation

Nurses should assess the patient's nutritional status and preference, and develop individual nutrition. In the acute phase, patients are recommended to consume low-fat, low-salt fluid food to decrease gastrointestinal adverse reactions from hormone therapy and myocardial oxygen consumption. For fast patients, parental nutrition should be established via intravenous access. Enteral nutrition should be started as soon as possible, and patients should be encouraged to eat orally and eat less and more frequently. The food schedule should be easy to digest and rich in vitamins. Nurses should control the input and output of the patients and prevent constipation. If necessary, laxatives are instructed to forcibly avoid defecating.

Psychological Rehabilitation

Patients' psychological problems should be evaluated. Nurses should implement the target plan based on these results. If the patient continues to experience stress, anxiety, or fear, a psychologist should be called for to provide professional advice.

Health Instruction and Follow-Up

Health instruction and follow up should comprise the following: (1) Instructing smokers to quit smoking, and all patients should be instructed to avoid second-hand smoke [32]. Nurses should encourage patients to develop good living habits. (2) Patients should keep warm when they feel cold and avoid crowded places, especially if they suffer from chronic respiratory or cardiovascular diseases. Vaccination with influenza and pneumococcal vaccines is recommended [33]. (3) For patients with fulminant myocarditis, nurses should establish follow-up files after obtaining the consent of the patients to guide the patients to adopt a healthy lifestyle. To evaluate cardiac function among patients discharged from the hospital after 1 month, 3 months, 6 months, and 12 months, the main indicators should include electrocardiogram, echocardiography, BNP/BNP-PRO, liver and kidney function, cardiac magnetic resonance examination, and follow-up health management to improve long-term prognosis [34].

Professional Team Management

Patients with fulminant myocarditis should receive systematic and standardized professional team management as soon as possible. The team should be led by a cardiovascular specialist/critical care physician, and the head nurse/nursing expert of the critical care unit should serve as the coordinator. It should include core members such as a multidisciplinary medical treatment team, critical care specialists, and blood purification nurses [35]. The nurses in this team must have at least 5 years of experience in the intensive care unit, master disease-related knowledge, and life-support therapy devices. Team members should arrive at the ward within 30 min after receiving the notice [36], and initiate a nurse-patient ratio of 2:1 or 1:1 intensive care mode. The patient should be provided 24-h continuous bedside care,

multidisciplinary cooperation, and all-out treatment, which could help the patient successfully navigate the acute phase and improve the success rate of treatment.

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Appendix B: Actively Promote and Apply the China's Regimen for Treatments of Fulminant Myocarditis to Save More Lives

Dao Wen Wang and Rutai Hui

Abstract Fulminant myocarditis is a sudden diffuse inflammation of the heart, with abrupt onset and rapid progression and features of hypotension/cardiogenic shock and sudden cardiac death. Pathologically, there were lymphocytic, eosinophilic, and giant cell types. The vast majority of cells are lymphocytic type, mainly manifested by lymphocyte and monocyte/macrophage infiltration. Its pathophysiological basis is excessive immune activation and formation of cell/inflammatory factor storms caused by pathogens entering the human body through pattern recognition receptors. The life support-based comprehensive treatment regimen recommended in the Chinese Expert Consensus on Fulminant Myocarditis in Adults, which includes mechanical circulatory support, use of adequate doses of both glucocorticoids, and immune globulin immunomodulation, can effectively treat patients and reduce the fatality rate to approximately 5%. The regimen particularly emphasizes early identification, early diagnosis, early prediction, and early treatment as well as the need to strengthen basic research to improve the understanding of its pathogenesis and efficacy and long-term prognosis.

Keywords Myocarditis; Excessive immune activation; Inflammatory storm; Immunomodulation; Mechanical circulatory support

Fulminant myocarditis is defined as a sudden and severe disseminated cardiac inflammation with abrupt onset, extremely rapid progression, and rapidly developed hemodynamic disturbances (hypotension and cardiogenic shock), leading to fatal ventricular arrhythmia or multiorgan/multisystem failure with extremely high mortality [1]. Timely and appropriate treatment can effectively save patients' lives. The main treatment measures include maintaining rapid circulatory stability using adequate [2] doses of glucocorticoids and immunoglobulins for immune regulation, continuous circulatory support, and heart transplantation [1, 3–6].

Features of fulminant myocarditis and its specific pathophysiology are currently poorly understood, which is a major challenge in its management. To summarize new experiences and findings in a timely manner, promote advancements in this field in the country, improve treatments, and save more lives, the Precision Medicine Group of the Chinese Society of Cardiology recommended the country's experts to formulate and publish the Chinese Expert Consensus on the Diagnosis and Treatment of Fulminant Myocarditis in Adults in China and proposed an effective treatment regimen (hereinafter referred to as the Chinese regimen) [7]. This

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regimen is simple, feasible, and has a high cost-effectiveness ratio [8–10]. Here is a brief introduction of the important related issues.

Diagnosis and Treatment Status at Home and Abroad

Fulminant myocarditis is sporadic and has been reported worldwide. The disease is rare, but by no means uncommon, and precise data on its incidence are currently lacking owing to diagnostic limitations. Approximately 40–50 patients with fulminant myocarditis are admitted to the Coronary Care Unit of Wuhan Tongji Hospital every year, and other hospitals such as Fuwai Central China Cardiovascular Hospital in Henan Province and Dongguan Kanghua Hospital in Guangzhou receive similar number of patients.

There are approximately 30,000–50,000 adult fulminant myocarditis cases in China every year, and the number of cases double when children are included. Because of hemodynamic disturbances in patients, vasoactive drugs (especially norepinephrine and pituitary hormone) and cardiotonic drugs (including levosimendan) were routinely used in the past, and the mortality rate reported abroad was as high as 50–70% [11, 12]. With the application of mechanical circulation technology, the treatment effect has significantly improved, but the fatality rate remains as high as 40% [13]. Western countries place special emphasis on timely endomyocardial biopsy, and routine use of cytotoxic drugs owing to a large number of inflammatory cell infiltrations in myocardial biopsy has not improved clinical outcomes. The treatment situation in China is similar. On the one hand, diagnosis is delayed in primary hospitals. Even if the diagnosis is clear, most patients are not correctly treated. Therefore, the mortality rate in primary hospitals is high. This is similar to the situation in Western countries, with a mortality rate of 50–60% [14].

Since the publication of the Chinese regimen for the treatment of fulminant myocarditis in 2017 [6, 9], some large medical/cardiac centers have actively practiced this regimen, reducing the risk of in-hospital mortality from 50% with traditional treatment to 3.7% [9, 14]. On this basis, Wang et al. hosted 30 special study classes nationwide and delivered more than 100 lectures at the conference, achieving good results. The articles in the issue of "Fulminant Myocarditis" in *Chin J Cardiol* (2022;50(3)) reflect the results of the application of the Chinese regimen in different hospitals. However, to make this new concept widely accepted across the country, publicity and education must be strengthened.

Core Content of the Chinese Regimen

The Chinese regimen, also known as the life support-based comprehensive treatment regimen, has the following basic principles: (1) unloading the cardiac burden and resting the extremely failing heart instead of using cardiotonic and vasoactive drugs, especially norepinephrine; (2) using reasonable immune regulation instead of cytotoxic drugs for immunosuppression; and (3) using neuraminidase inhibitors in combination [8]. According to the actual situation in China, two core treatment measures need to be adhered to and strengthened: (1) Mechanical circulatory support should be started as soon as possible, with special emphasis on intra-aortic balloon pump (IABP) first. If IABP is not sufficient to correct shock, ECMO is added as a strategy to treat the symptoms. (2) Immunomodulatory therapy, including the use of both adequate doses of glucocorticoids and immunoglobulins, is a strategy for treating fulminant myocarditis. As an example, methylprednisolone 200–500 mg/day is administered according to the early stage of the disease and gradually tapered after 3–5 days on the basis of the improvement of cardiac function and 20 g of intravenous immunoglobulin is administered daily for 3–5 days. This combination has a significant immunomodulatory effect, emphasizing "immunomodulation" rather than "immune-suppression". (3) Use of neuraminidase inhibitors,

such as oral oseltamivir 75 mg twice a day or intravenous peramivir 300 mg, helps reduce myocardial damage by inhibiting neuraminidase [15].

The basis of the Chinese regimen is the pathogenesis hypothesis put forward by Wang et al.: different pathogens (viruses and bacteria, chemicals, drugs, or toxins) act on the pattern recognition receptors of cardiomyocytes and immune cells, resulting in increased inflammatory cell infiltration and activation, and together with cardiac cells, they secrete a large number of cytokines and inflammatory factors, producing an inflammatory storm; simultaneously, damage-related molecules released by the destruction of tissue cells also act on the corresponding pattern recognition receptors, as well as the subsequent acquired immune response, which synergistically inhibit myocardial function and endothelial injury, leading to myocardial edema, cardiogenic shock, and arrhythmias [16, 17].

This regimen has been promoted in many hospitals in China and has achieved remarkable results, with survival rate of >95% of patients with fulminant myocarditis [10, 14]. A 1-year follow-up of 56 patients with fulminant myocarditis in Wuhan Tongji Hospital treated with the Chinese regimen showed that although 20–25% of cases had recurrence, arrhythmia, or dilated heart, only 1 died [18], which is in marked contrast to the 60-day mortality rate of 28% and the 1-year mortality rate of 39.6% in Western countries [2]. At the Fuwai Central China Cardiovascular Hospital in Zhengzhou, traditional cardiotonic and vasoactive drugs were used to treat patients with fulminant myocarditis. Most of these patients did not survive; however, among the 37 patients treated with the Chinese regimen, 34 were clinically cured and discharged [19]. Of 88 patients with fulminant myocarditis treated at Kanghua Hospital in Dongguan, Guangdong, the mortality rate was 56.7% in those treated with the traditional treatment regimen, 30% in those treated with intermediate regimen treatment [hormones + gamma globulin or mechanical circulatory support only (IABP + ECMO)], and 7.9% in those treated with the Chinese regimen [20]. These suggest that complete implementation of the Chinese protocol is essential for the good therapeutic effect.

Features of the Chinese Regimen

1. Emphasize vigilance in the treatment of fulminant myocarditis: The emphasis of this regimen is "early identification, early diagnosis, early prediction, and early treatment." It is necessary to make full use of the current routine clinical diagnosis and examination methods, make judgments as soon as possible, and provide prompt circulatory support and immunomodulatory treatment. This can save patients' life without the need for complex laboratory tests. Many patients with fulminant myocarditis have clinical symptoms similar to those of the common cold at onset, with significant differences [1]. Statistics from Wuhan Tongji Hospital suggest that approximately 90% of patients with fulminant myocarditis seek medical attention or referrals due to dyspnea, weakness and not diet, and the remaining 10% due to syncope or requirement of CPR. In addition, notable features are fatigue and lack of appetite [8, 9, 14]. Physicians should be highly sensitive and vigilant of this symptom and conduct a comprehensive emergency examination of suspected patients, including clinical manifestations, routine physical examination, and detection of signs of fulminant myocarditis, such as low and dull heart sounds (rapid changes). Especially, attention should be paid to monitoring rapid changes in hemodynamics, such as a sudden drop in blood pressure, and the need for mechanical circulatory assist devices or vasopressors; electrocardiograms suggesting rapid heart rate, low voltage, and QRS widening changes; routine blood and comprehensive blood biochemical tests showing markedly elevated cardiac troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP), and echo-

cardiogram with markedly reduced ventricular motion. Repeated examinations show that these clinical indices change rapidly, and the left ventricular ejection fraction decreases sharply. Usually, emergency coronary angiography should be performed to exclude acute myocardial infarction. Based on these findings, a diagnosis can be made quickly.

2. Pay attention to signs of circulatory failure and arrhythmia: During routine physical examination, physicians should pay attention to signs of heart failure and hemodynamic failure, including decreased blood pressure, rapid heartbeat, markedly dull heart sounds, and a galloping rhythm. Attention should also be paid to early signs of circulatory failure, including low arterial pressure, sinus tachycardia, clammy limbs, and elevated lactate level. In patients with fulminant myocarditis, cardiac systolic function is abnormal, the ability of the acutely affected heart to increase stroke volume is limited, and cardiac output is significantly dependent on a compensatory increase in heart rate, such as sinus tachycardia. At this time, drugs that decrease heart rate and have negative inotropic effects should be avoided, including beta-blocker, diltiazem, and verapamil, so as not to destroy the body's compensatory mechanism that can lead to circulatory disorders, resulting in circulatory failure.
3. Make full use of laboratory test results: Routine blood tests show high white blood cell counts and high neutrophil or lymphocyte counts, which do not necessarily indicate bacterial infection, but suggest an innate immune response. Urgent tests for arterial blood gas, blood lactate, whole blood routine, blood electrolytes, basal metabolism, bilirubin, alanine aminotransferase, and aspartate aminotransferase are required.
   (a) Repeated ECG examinations: QRS low voltage, interval widening, and myocardial injury (ST segment elevation) caused by myocardial injury and edema in patients with fulminant myocarditis are mostly inconsistent with coronary artery distribution, but some also show lead selection. If ST-T changes are found, emergency coronary angiography should be promptly performed to identify and exclude myocardial infarction. ECG leads show that the injury is generally characterized by non-vascular distribution and may also show segmental distribution of coronary arteries, with ST segment elevation in adjacent leads, similar to coronary artery occlusion. In such cases, coronary angiography should be performed promptly. Patients may also present with evidence of pericarditis with PR-segment depression and various arrhythmias, including frequent ectopic beats, ventricular arrhythmias, and conduction abnormalities. Heart rate is usually increased, but ECG arrhythmias or sinus bradycardia, left bundle branch block, decreased QRS amplitude, premature ventricular contractions, and ventricular tachycardia may also occur due to myocardial edema. The above conditions suggest that disease progression and should be promptly treated [21, 22].
   (b) Biomarker monitoring of myocardial injury: Serum troponin (T or I) level is elevated in patients with fulminant myocarditis, which requires emergency coronary angiography to exclude acute coronary syndrome. In a registry study of 386 patients with fulminant myocarditis, although the left ventricular ejection fraction did not decrease, serum troponin level was elevated in 100% of patients, and erythrocyte sedimentation rate and C-reactive protein level were elevated in 99% (385/386) of patients [23]. The European Society of Cardiology and other cardiology societies recommend serum cardiac troponin, NT-proBNP, erythrocyte sedimentation rate, and C-reactive protein tests. Abnormalities in these indicators suggest myocardial injury and cardiac dysfunction; however, normal results do not rule out acute myocarditis. Elevated atrial peptide levels are associated with poor prognosis [3–5, 24].

China's experience has shown that both troponin-I and NT-proBNP levels are markedly increased in patients with fulminant myocarditis, which is often significantly higher than that in patients with general acute myocardial infarction.

(c) Routine viral serological examination is not recommended, and the sensitivity and specificity of serum virological examination are not high compared with those of endomyocardial biopsy viral genome examination (RT-PCR/PCR). Even negative viral serology results do not rule out viral infection [25, 26]. Second-generation sequencing, including metagenomic sequencing, may provide pathogenic results [1, 25, 26]. Serological tests are less sensitive to in situ hybridization of endomyocardial biopsy samples, with only 4% seropositive evidence confirmed by endomyocardial biopsy [26]. The Chinese expert consensus does not emphasize complex and lengthy etiological diagnoses in the first-aid phase. Our attempted viral serological tests were almost always negative; therefore, no recommendations were made.

(d) Cardiac imaging and functional monitoring: Invasive blood pressure monitoring, electronic blood pressure monitoring, and echocardiography are important. The echocardiography of patients with fulminant myocarditis is very distinctive, and the overall motion of the ventricle is significantly reduced, and on this basis, segmental motion differences may also occur; the left ventricular ejection fraction decreases and changes very rapidly in the early stage, showing a sharp decline; left ventricular myocardial hypertrophy of usually 12–13 mm, and rarely >20 mm in thickness, is caused by myocardial edema, which can be rapidly improved by the Chinese regimen. Cardiac magnetic resonance imaging and two-dimensional speckle tracking echocardiography were used to evaluate the main indicators of left ventricular systolic function, including global cardiac longitudinal strain, global myocardial radial strain, and global myocardial circumferential strain [27]. Echocardiography is non-invasive, simple, and easy to perform and should be performed at least once a day in the early stage. Cardiac magnetic resonance examination showed early changes in the adventitia and middle layer in myocardial edema, which were different from those in the intima and middle layer in myocardial infarction, which was helpful for the diagnosis of myocarditis. However, the patient's condition is unstable, and cardiac magnetic resonance examination requires appropriate techniques, expertise, and equipment. Not every prefecture-level hospital meets these conditions, and the Chinese regimen does not recommend it as an examination method for acute treatment. After the acute stage, hemodynamics is stable and cardiac magnetic resonance examination can be performed.

(e) Emergency rescue cannot be bound by endocardial biopsy results: histopathological diagnosis of endocardial biopsy is generally considered the gold standard for the diagnosis of myocarditis, but it has many limitations, and inflammatory infiltration is not always parallel to clinical manifestations. The pathological and viral genomic results of biopsy samples can guide treatment and determine prognosis [4, 28], but the detection threshold of copy number related to the diagnosis of various viruses has not yet been determined, and the virus is not found in most patients. The current Chinese regimen does not emphasize the gold standard status of endomyocardial biopsy for the diagnosis of myocarditis for the following reasons: (1) Endocardial biopsy is an invasive test, which is not widely acceptable by the Chinese population, and obtaining informed consent requires a lot of time; (2) in some prefecture-level tertiary hospitals in China, endocardial

biopsy may not be available. Even if it can be implemented, it will take 2–3 days to obtain the result and 7–10 days for complex cases. However, to study the pathological types and pathogenesis, the Wuhan Tongji Hospital has routinely performed endocardial biopsy. At present, 90% of fulminant myocarditis cases in the Chinese population are lymphocytic type, very few are eosinophilic type, and no giant cell type is found. Even in developed Western countries, the number of patients diagnosed using endomyocardial biopsy is limited in clinical practice. The U.S. Fulminant Myocarditis Registry has shown that the rate of endomyocardial biopsy is <5% [29]; in Europe, the rate is relatively high, reaching 20–50%.

4. The Chinese regimen focuses on key life-saving measures for fulminant myocarditis [9]:
   (a) Timely and adequate circulatory support: Currently, the commonly used clinical mechanical circulatory support devices include IABP, ECMO, cardiac hemodynamic assist device, the axial flow pump Impella, and the adult ventricle assistive device TandemHeart/external biventricular assist device (paracorporeal LVAD, Levitronix pump GmbH) [8]. Circulatory support equipment is generally expensive and requires specialized technical personnel to install and maintain. Therefore, IABP is the first choice for the Chinese regimen, which can be implemented in general tertiary hospitals. IABP can significantly reduce left ventricular afterload, reduce intra-aortic diastolic pressure by 5–30%, increase cardiac output and stroke volume by 20%, reduce left ventricular afterload, and increase coronary blood flow and cerebral and renal blood perfusion [10, 30]. The experience at our center has proven that IABP can increase the systolic blood pressure of patients by 20–25 mmHg and slow down the increased heart rate by more than 10 times, which can stabilize circulation in most patients with early fulminant myocarditis. However, owing to the small size of the IABP, the pump function is relatively low and can provide only 15–20% additional circulation support. If circulatory stability of IABP is difficult, venous–arterial ECMO should be added. Venous–arterial ECMO can regulate blood flow between 0.50 and 4.75 L/min, and a flow rate of 3–4 L/min can provide more powerful circulatory support and meet the basic needs of body circulation [31]. ECMO increases the left ventricular afterload, which creates a hedging effect on the opening of the aortic valve, resulting in left ventricular dilatation and an increased risk of heart failure. Therefore, the Chinese regimen recommends the combined use of venous–arterial ECMO and IABP as an excellent match for the treatment of fulminant myocarditis and can be used as the first-line treatment for refractory cardiogenic shock [10].

   ECMO has its advantages and can reduce cardiac preload by 40–60% and is increasingly used in the treatment of fulminant myocarditis; however, the Chinese regimen still prefers IABP or IABP plus ECMO, mainly because ECMO is expensive as well as has many adverse consequences for long-term use; A series of recent case studies have found that ECMO leads to left ventricular distention and increases the risk of heart failure; long-term use of ECMO increases the need for two ventricular support; the oxygenated blood provided by the ECMO pump directly enters the descending aorta from the femoral artery, contrary to the natural blood flow direction, and the turbulent flow increases the afterload on the left ventricle, which can cause endothelial damage, and prolonged application may cause thrombosis, coagulation abnormalities, and increase the risk of stroke; ECMO increases the risk of infection; and high flow of venous–arterial ECMO increases left ventricular afterload, mechanical stress activates the car-

diac mechano-transduction network, activates cardiac fibroblasts, and promotes inflammatory responses [31–33], and cardiac remodeling occurs over time [34]. On the other hand, IABP can be very effective in reducing cardiac afterload; therefore, the combination of IABP and ECMO can overcome some of the adverse effects of the latter [10, 35].

The Chinese regimen draws on the clinical experience of Wang et al. and multiple centers across the country; that is, IABP can increase stroke volume by 15–25%, which is sufficient to provide circulatory support for most patients with fulminant myocarditis. Among more than 100 patients with fulminant myocarditis treated by Wang et al., 75% could maintain circulatory stability only with IABP, and the remaining patients could be treated with IABP plus ECMO to maintain circulatory stability [14].

(b) Immunomodulation therapy: It includes the use of both adequate doses of glucocorticoids and adequate doses of immunoglobulin. Glucocorticoid is a drug used for immunomodulation. The Chinese regimen uses hormone therapy as one of key rescue measures. Glucocorticoids are most widely used for lymphocytic myocarditis; if immunomodulatory fulminant myocarditis is suspected, 1 g intravenous succinyl prednisolone should be administered immediately before endomyocardial biopsy or other further diagnostic workups for 1–4 days. Treatment with steroids does not affect diagnosis. If giant cell myocarditis is diagnosed, additional immunosuppressive agents are required. There is currently insufficient evidence for antiviral drugs, which are not recommended by guidelines [1, 4, 7, 9].

Glucocorticoids for lymphocytic myocarditis can improve left ventricular ejection fraction, but there is no evidence that they reduce mortality [1, 8]. The 2016 American Heart Association (AHA) guidelines state that the empirical use of immunomodulatory agents is generally not recommended prior to the diagnosis of myocarditis [4]. The efficacy of glucocorticoids in the treatment of fulminant myocarditis remains controversial. It is generally accepted that glucocorticoids should be used with caution during the viremia phase. However, according to Wang et al., the vast majority of patients with fulminant myocarditis already are suffering cytokine storms at admission to the hospital. Excessive immune activation and inflammatory storm are the main pathophysiology. In most cases, viremia is not a major concern. When complicated with cardiogenic shock, patients' immunity is extremely poor. Glucocorticoids can significantly improve immune function by anti-shock and metabolic regulation and play an urgent role in immunomodulatory therapy. The goal of the early use of glucocorticoids is mainly to control cytokine storm, myocardial edema and shock, but that the use of glucocorticoids will accelerate the virus spread is a concern harbored by many clinicians. Experimental research and clinical observations by Wang et al. suggested that early and sufficient glucocorticoid administration can stimulate the secretion of interferons, reduce the virus titer, and reduce the mortality rate of patients with fulminant myocarditis to <5% [14, 36]. Therefore, glucocorticoids showed beneficial effects regardless of the virus-positive or virus-negative state.

Laboratory evidence and clinical practice support the urgent need to correct immune dysfunction. Endocardial biopsies suggest that there are many different types of inflammatory cell infiltration in the myocardial tissue of patients with myocarditis [5]. Wang et al. analyzed the expression profiles of 122 cytokines in the peripheral blood of four patients with fulminant myocarditis and found that, compared with healthy controls, patients with fulminant myocarditis had an early cytokine storm,

the expression of a series of inflammation-related factors was upregulated, and the expression of some cytokines was downregulated [8]. Intracellular components released from pathogenic molecules and the damaged myocardium act on cellular receptors, such as toll-like receptors, to stimulate the innate immune response system, activate downstream signaling cascades, and cause further cellular responses, including cytokine expression, which repeats and gradually increases. Cytokine storms directly affect myocardial contraction and electrical conduction. Even without myocardial necrosis, contractile and conduction functions of the myocardium are impaired, leading to circulatory disturbances and cardiogenic shock. Inflammation and cytokine storm can also lead to extensive myocardial edema, necrosis, and a hypodynamic ventricular wall [36]. It is generally believed that cardiomyocytes are terminally undifferentiated cells and that the body cannot produce an effective number of new cardiomyocytes to replace the necrotic myocardium.

Glucocorticoids and high-dose gamma-globulin can regulate immunity and correct early immune disorders. Wang et al. found that the upregulated cytokines in the early cytokine storm in patients with fulminant myocarditis can be restored to normal levels after glucocorticoid + immunoglobulin treatment and adequate circulatory support therapy [14]. Simultaneously, immunoglobulins, which can bind to the Fc receptors of macrophages, inhibit excessive activation of macrophages, thereby significantly inhibiting excessive inflammatory responses and playing an important role in immune regulation [37, 38]. Monitoring the serum levels of these factors can help determine whether a patient is at the peak of a cytokine storm or in recovery. During the 1-year follow-up of patients, approximately 20% of patients with fulminant myocarditis developed heart failure, arrhythmia, or cardiomegaly, and the recurrence rate of myocarditis was approximately 10% [8]. Evidence suggests that cytokine storms affect the process of cardiac remodeling and timely correction of immune disorders caused by cytokine storms can improve prognosis.

(c) The Chinese protocol recommends immunomodulators rather than immunosuppressants: immunosuppressive treatment regimens and drugs include glucocorticoid/cyclosporine regimens, tacrolimus/cyclophosphamide-based regimens, tacrolimus/mycophenolate mofetil (Xiaoxing)-based regimens, cyclophosphamide/azathioprine-based regimens, azathioprine, moromona-CD3 antibody, and mycophenolate mofetil. Immunomodulators include glucocorticoids and antithymocyte globulin [39, 40]. The internationally accepted view is that only the following types of myocarditis are recommended for immunosuppressive therapy, which may improve clinical outcomes: giant cell myocarditis, eosinophilic myocarditis, and autoimmune disease combined with myocarditis, such as cardiac sarcoidosis [40–42]. Immunosuppressive therapy should be considered only in patients with lymphocytic myocarditis in the absence of evidence of acute infection and in response to standard therapy [4]. However, our observations suggest that most of these diseases do not manifest as fulminant myocarditis. The Chinese regimen does not advocate the use of cytotoxic immunosuppressants but recommends the use of immunomodulators [42]. More than 50 cytokines are upregulated and more than 10 are downregulated in the acute-phase plasma of patients with fulminant myocarditis, which is the so-called cytokine storm. Serum interleukin-33 (IL-33) soluble fragment sST2 was significantly elevated in a patient on admission. After the patient recovered, the levels gradually

returned to normal. Treatment of normal mice with sST2 inhibited their cardiac function and induced myocarditis, whereas treatment with anti-sST2 antibody in fulminant myocarditis mice improved their cardiac function and survival. The survival rate was 70% in the anti-sST2 antibody-treated group and only 36% in the group not administered anti-sST2 antibody [8, 9]. According to the regulatory effect of cytokine storms on the pathogenesis of fulminant myocarditis, Wang et al. proposed a comprehensive treatment plan for mechanical life (circulation) support for fulminant myocarditis and implemented it in clinical practice [14]. From the acute stage of admission, glucocorticoids (methylprednisolone 200–400 mg/day) should be administered for 3–5 days, and then the hormones should be gradually reduced to maintenance dosage. Intravenous immunoglobulin should be used simultaneously, but cytotoxic drugs such as cyclosporine and azathioprine are not recommended. Clinical trials have demonstrated that cytotoxic drugs do not improve survival or reduce long-term mortality in patients with fulminant myocarditis [43, 44].

(d) Antiviral therapy: The Chinese regimen proposes a new concept of neuraminidase inhibitors for the treatment of fulminant myocarditis. Recent studies suggest that the release of neuraminidase increases during myocardial injury, and neuraminidase digests neuraminic acid at the outer membrane glycoprotein terminals of myocardial cells, which is harmful to the heart. Neuraminidase is released from the heart in inflammatory and damaged states, exacerbating heart damage [45]. Clinical trials have confirmed that oseltamivir (Tamiflu) can inhibit neuraminidase release to protect the heart in the treatment of fulminant myocarditis [14, 45]. If a virus such as a parvovirus is detected, antiviral drugs such as ganciclovir can be used.

In summary, the Chinese regimen for fulminant myocarditis proposes a comprehensive treatment plan based on life support, emphasizing mechanical circulatory support and immunomodulatory therapy (hormones and immunoglobulin), with special emphasis on "early identification, early diagnosis, early prevention, and early treatment." This regimen can reduce the mortality rate to <5% and is worthy of promotion. It is necessary to strengthen the resources (talent and equipment) and technical training required for the rescue of fulminant myocarditis in county-level hospitals, strengthen publicity and education, and raise the vigilance of fulminant myocarditis. In the future, the content of sub-phenotyping in the Chinese regimen should be improved and precise treatment should be implemented according to pathological typing.

Conflicts of Interest All authors declare no conflict of interest.

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