14 Novel Conceptions in Treatments of Fulminant Myocarditis

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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

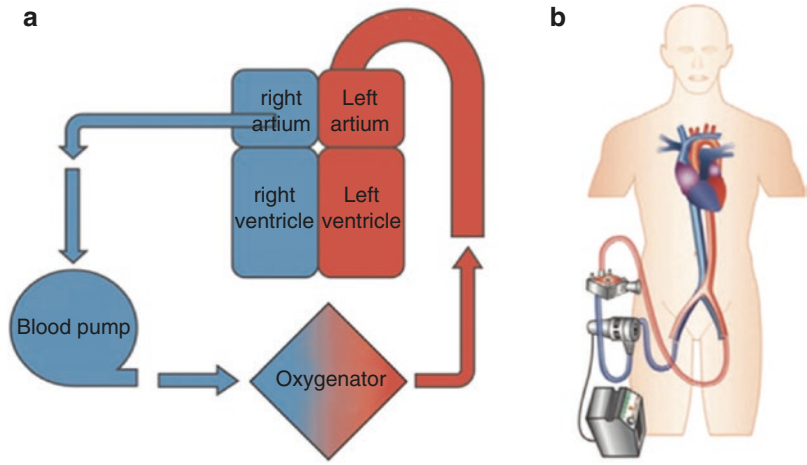

Fig. 14.1 V-A ECMO schematic diagram. Femoral vein-femoral artery cannulation V-A ECMO. (**a**) cited from Maya Guglin, Mark J Zucker, Vanessa M Bazan, et al. Venoarterial ECMO for Adults: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2019 Feb 19;73(6):698–716. https://doi.org/10.1016/j.jacc.2018.11.038. (**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

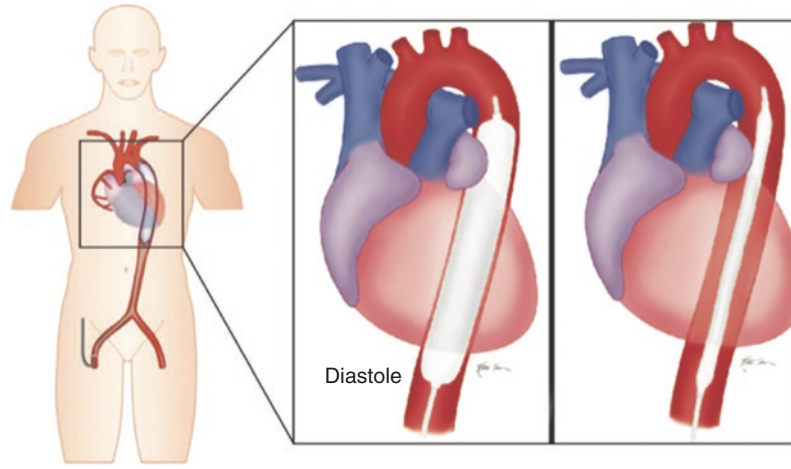

Fig. 14.2 IABP schematic diagram

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.

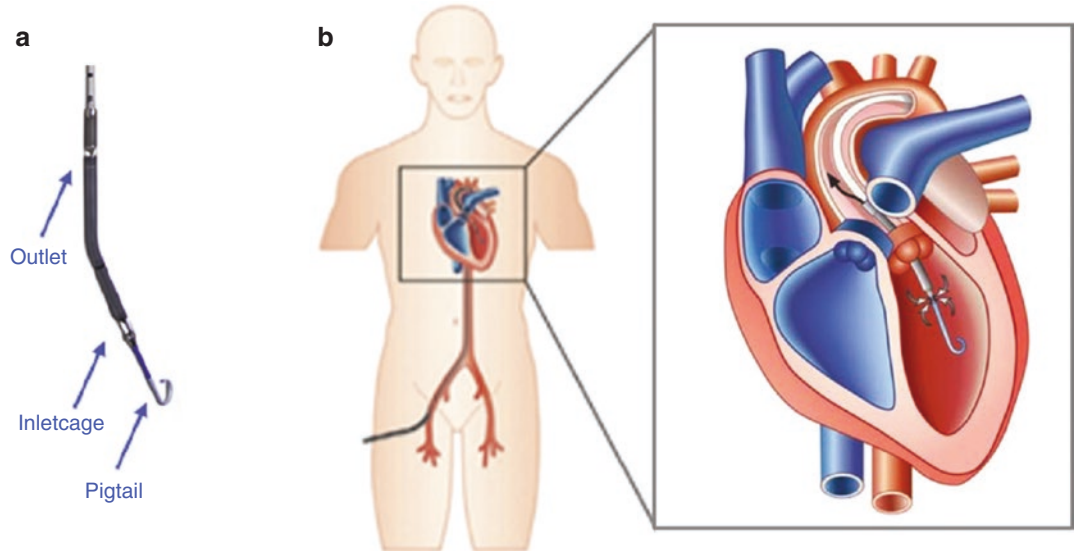

Fig. 14.3 Impella left ventricular assist device. (**a**) Impella installation schematic diagram. (**a**) modified from Balthazar T, Vandenbriele C, Verbrugge H, et al. Managing Patients With Short-Term Mechanical Circulatory Support JACC Review Topic of the Week. *J Am Coll Cardiol.* 2021 Mar 9;77(9):1243–1256. 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

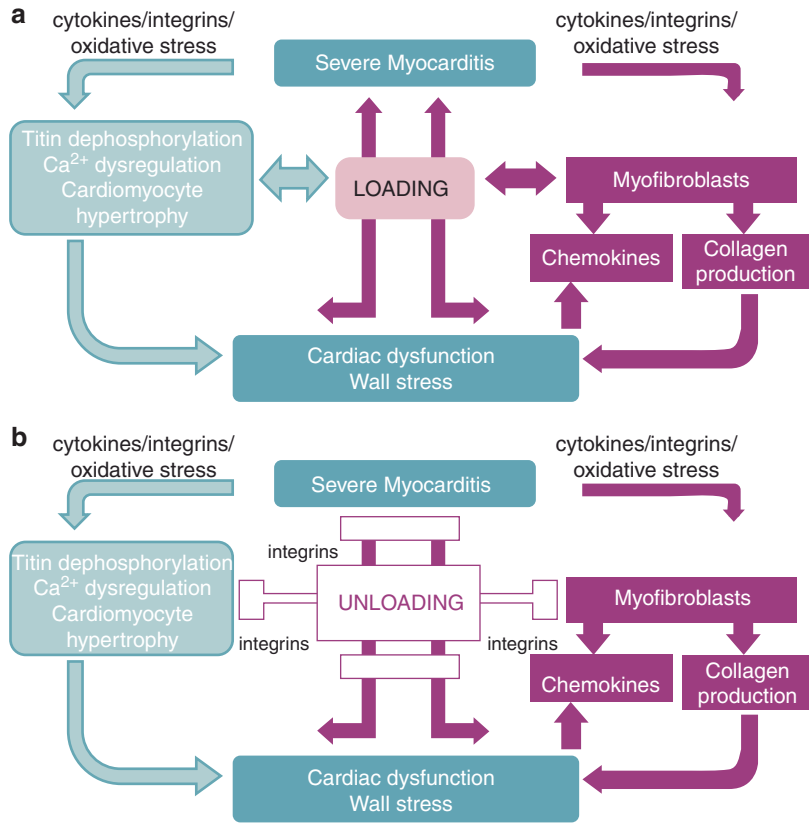

Fig. 14.4 The influence of cardiac load on the pathophysiological process of severe myocarditis. Cited from Spillmann F, Van Linthout S, Schmidt G, et al. Mode-of-action of the PROPELLA concept in fulminant myocarditis. Eur Heart J. 2019;40(26):2164–2169. https://doi.org/10.1093/eurheartj/ehz124

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.

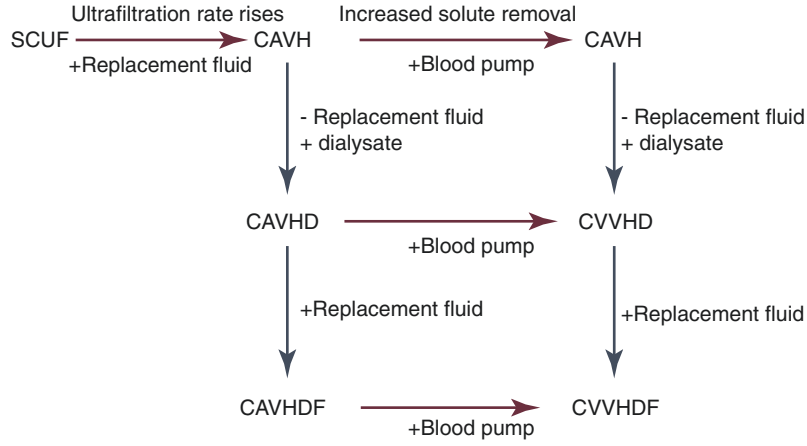

Fig. 14.5 F(ab′)2-and Fc-dependent pathways of IVIG activity. Cited from Schwab I. Nimmerjahn F. Intravenous immunoglobulin therapy: how does IgG modulate the immune system? *Nat Rev Immunol.* 2013;13(3):176–189. https://doi.org/10.1038/nri3401

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

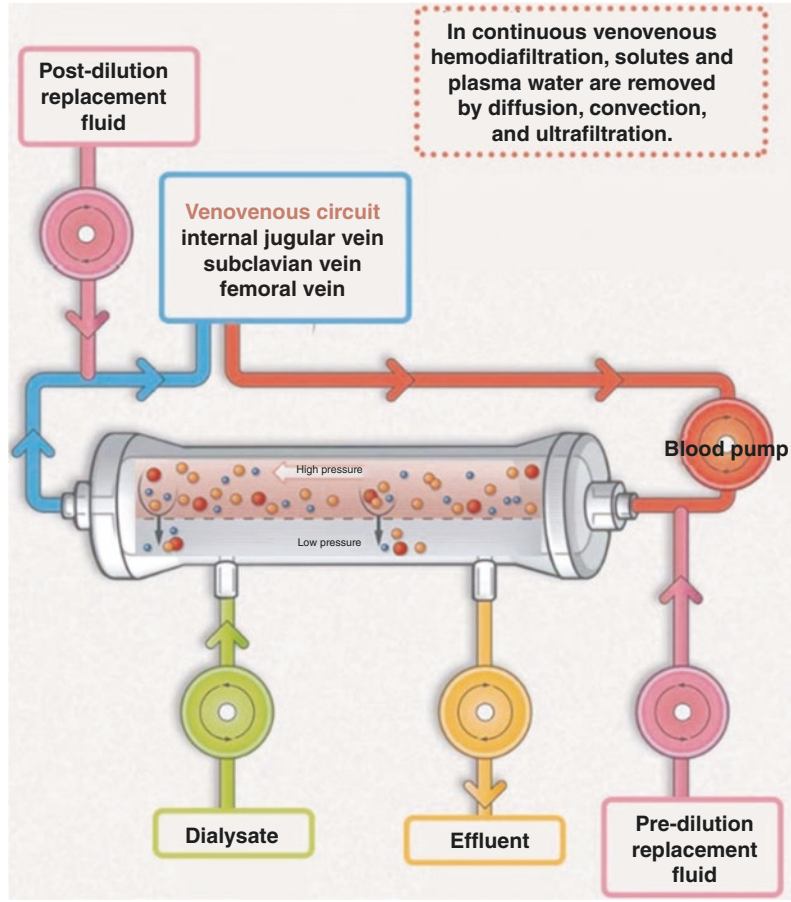

Fig. 14.6 IVIG's regulation of the immune system. Cited from Durandy A, Kaveri SV, Kuijpers TW, et al. Intravenous immunoglobulins—understanding properties and mechanisms. *Clin Exp Immunol.* 2009;158 Suppl 1(Suppl 1):2–13. https://doi.org/10.1111/j.1365--2249.2009.04022.x

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].

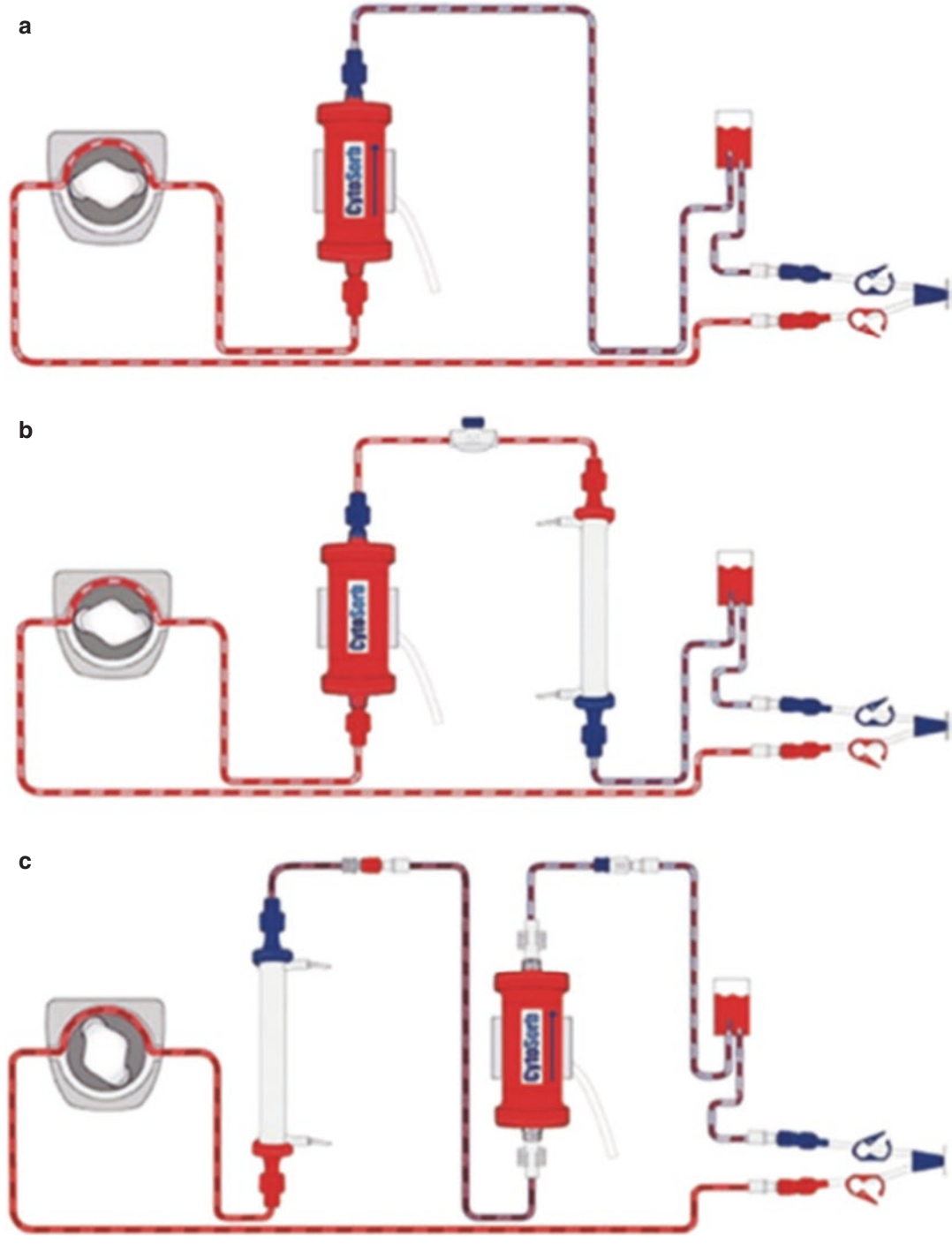

Fig. 14.7 Genomic and nongenomic immunoregulation by glucocorticoids. Cited from Löwenberg M, Verhaar AP, van den Brink GR, Hommes DW. Glucocorticoid signaling: a nongenomic mechanism for T-cell immunosuppression. *Trends Mol Med.* 2007;13(4):158–163. https://doi.org/10.1016/j.molmed.2007.02.001

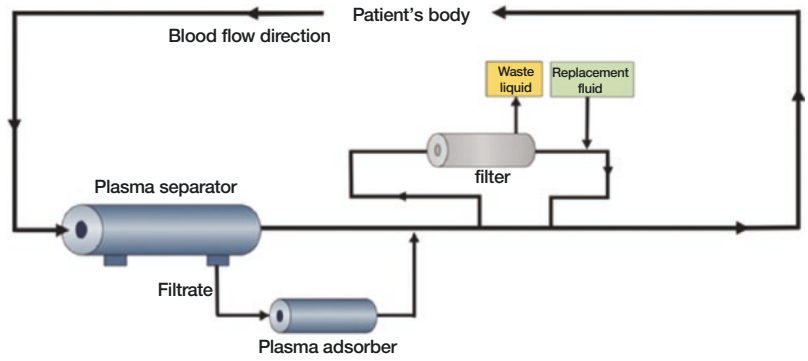

Fig. 14.8 Regulation of glucocorticoids on immune cells and non-immune cells

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

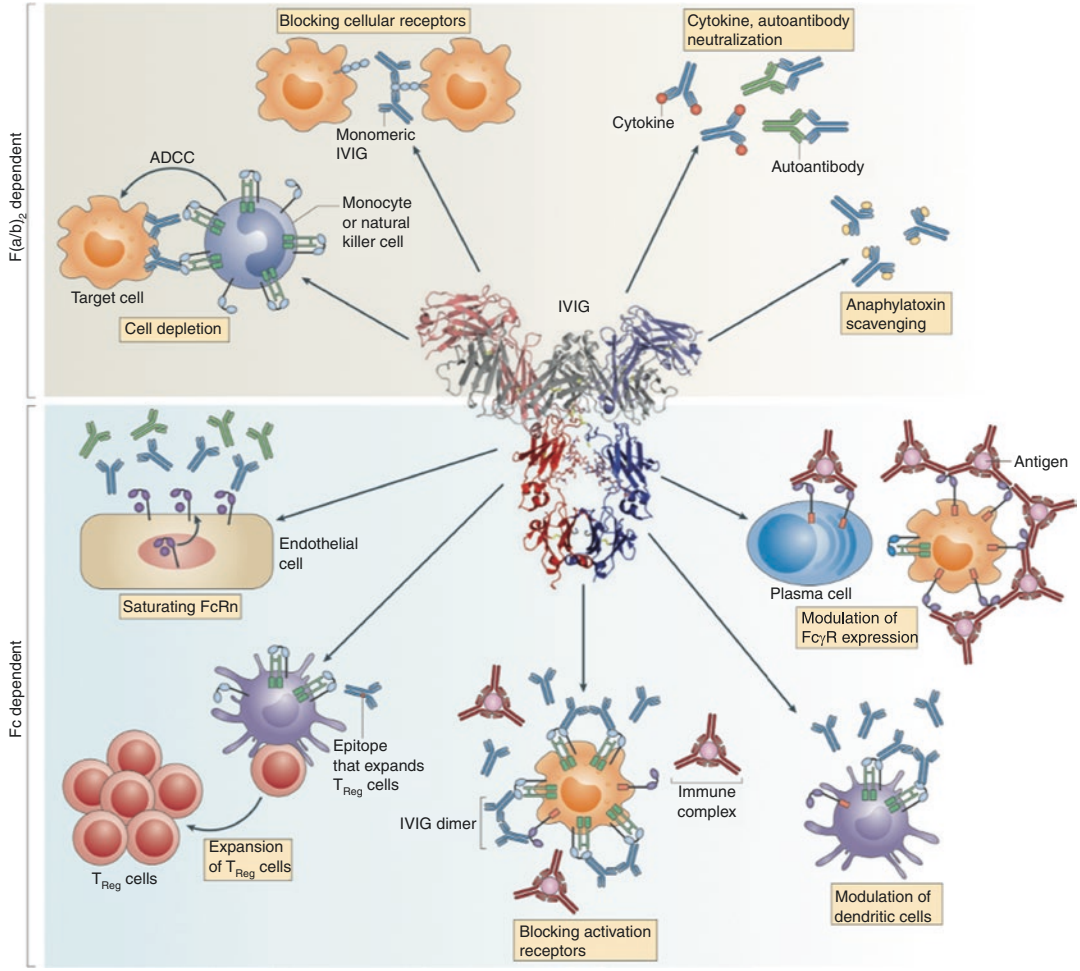

Fig. 14.9 Common CRRT mode and its conversion

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

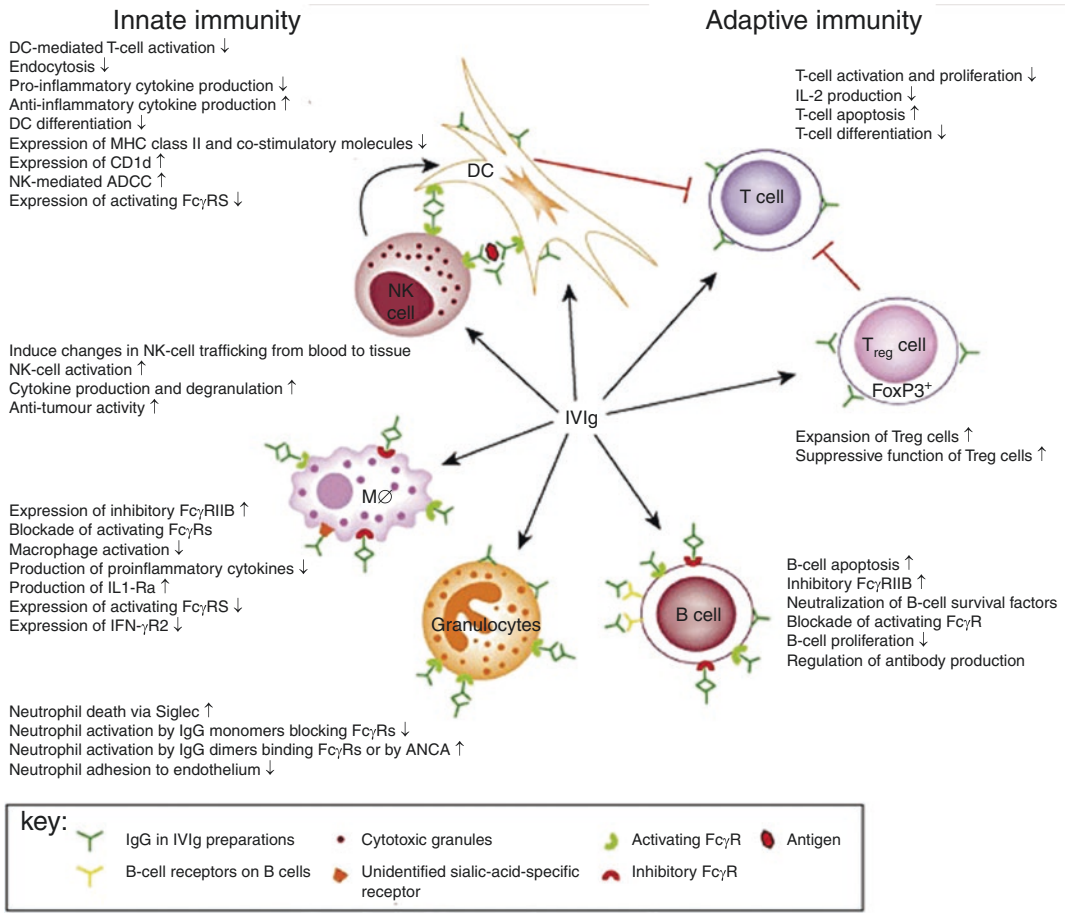

Fig. 14.10 The main component of the CRRT loop

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.

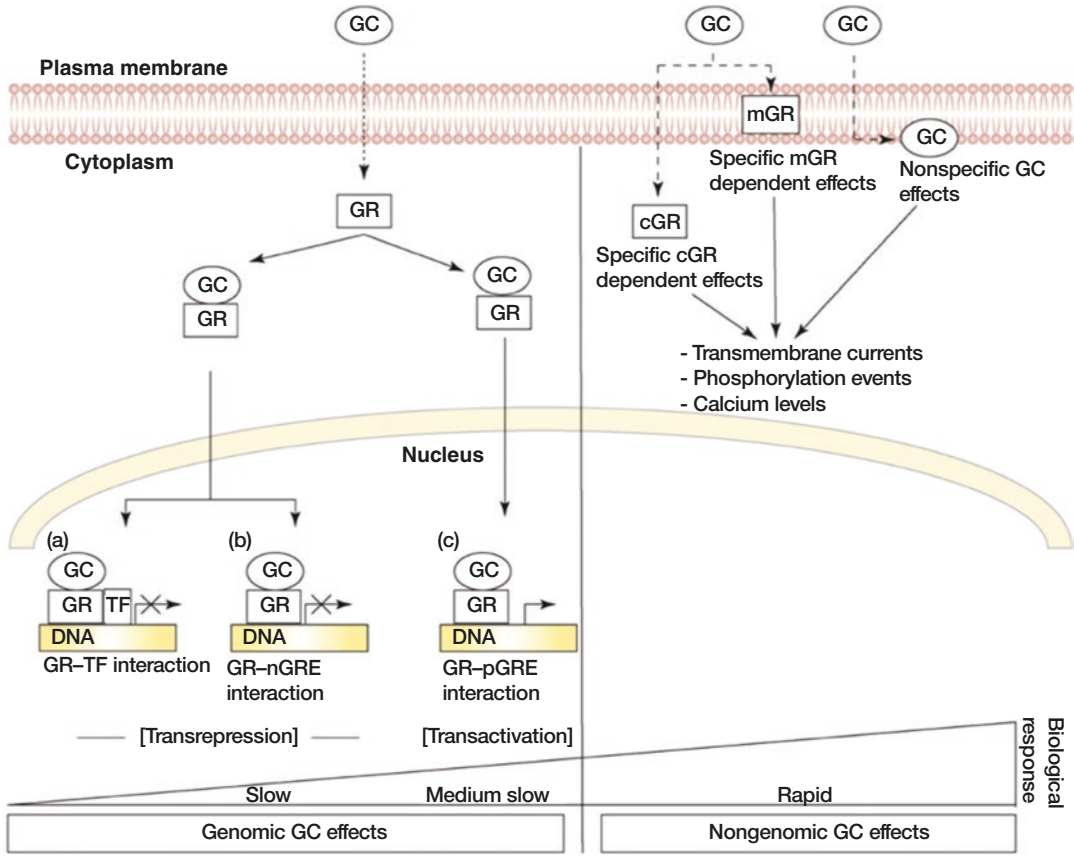

Fig. 14.11 CytoSorb loop. CytoSorb Independent treatment (**a**); Pre-dialyzer mode (**b**); Post-dialyzer mode (**c**)

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).

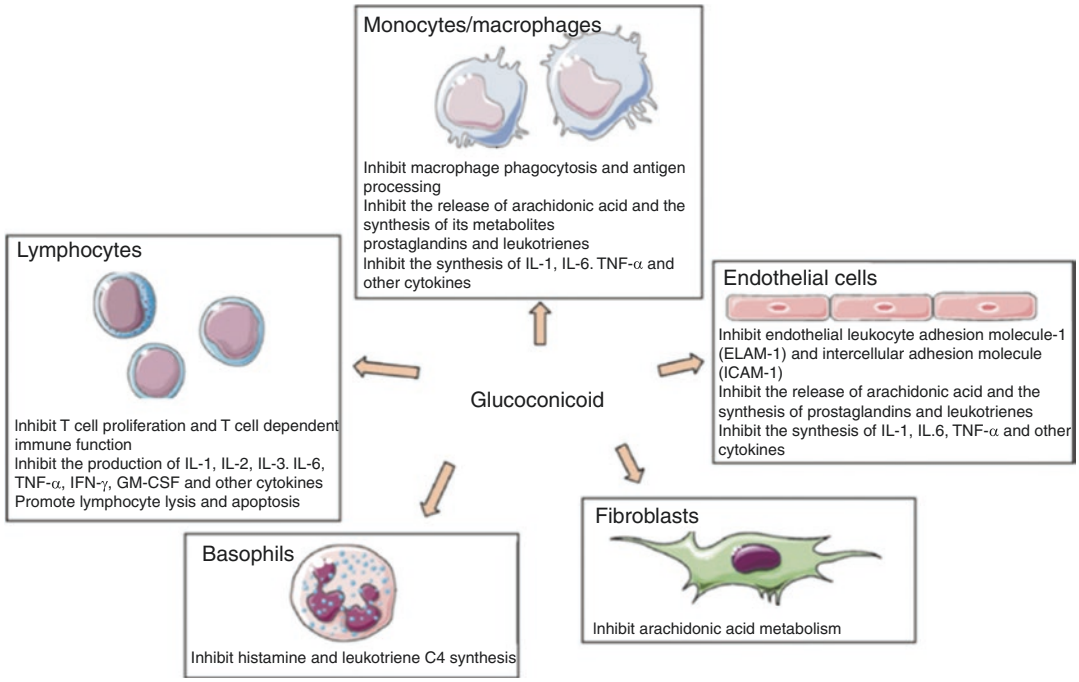

Fig. 14.12 CPFA schematic diagram

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

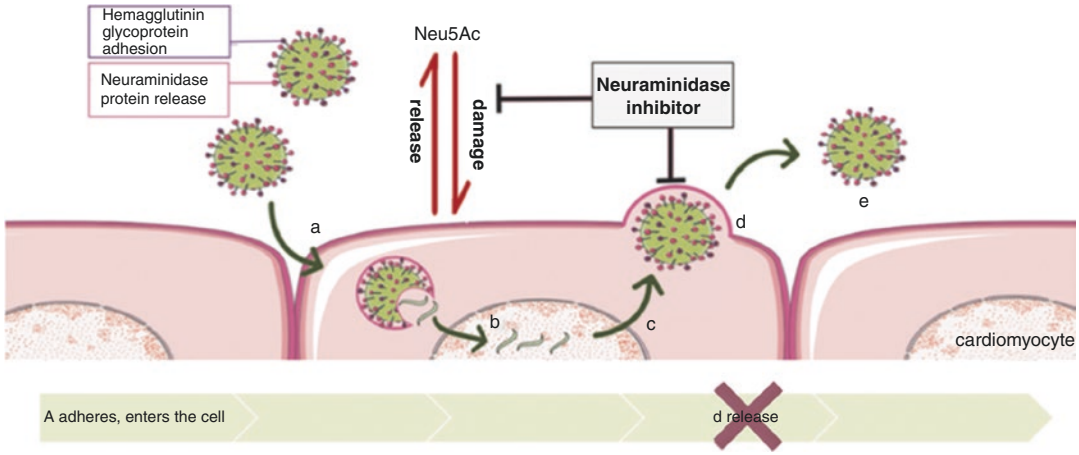

Fig. 14.13 Underlying mechanism of neuraminidase inhibitors

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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