Sepsis-induced cardiac dysfunction and pathogenetic mechanisms (Review)

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Abstract. Sepsis is a manifestation of the immune and inflammatory response to infection, which may lead to multi-organ failure. Health care advances have improved outcomes in critical illness, but it still remains the leading cause of death. Septic cardiomyopathy is heart dysfunction brought on by sepsis. Septic cardiomyopathy is a common consequence of sepsis and has a mortality rate of up to 70%. There is a lack of understanding of septic cardiomyopathy pathogenesis; knowledge of its pathogenesis and the identification of potential therapeutic targets may reduce the mortality rate of patients with sepsis and lead to clinical improvements. The present review aimed to summarize advances in the pathogenesis of cardiac dysfunction in sepsis, with a focus on mitochondrial dysfunction, metabolic changes and cell death modalities and pathways. The present review summarized diagnostic criteria and outlook for sepsis treatment, with the goal of identifying appropriate treatment methods for this disease.

Contents

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1. Introduction

Sepsis is a syndrome that occurs when microorganisms invade and cause systemic disease, which can be life-threatening (1,2). The third international consensus definition of septic shock and sepsis was published in 2016 and defined septic shock as organ dysfunction caused by systemic infection (3). The immune system is suppressed during sepsis, which leads to increased inflammatory response (4,5). The immune cells are triggered by bacteria, toxins and other factors that result in infection, releasing large quantities of inflammatory mediators (6,7). The release of inflammatory mediators without an appropriate anti-inflammatory response destroys the immune system, resulting in unrestrained inflammatory state and a decreased ability to neutralize pathogens (8-10).

Septic cardiomyopathy (SC), or septic shock, is a condition defined by cardiac dysfunction caused by sepsis. SC is clinically characterized by defective left ventricular systolic function and ventricular hypertrophy. According to statistics from the beginning of 2018, up to two-thirds of patients with septic shock experience SC, which has become one of the most common fatal diseases (11). Therefore, novel pathogenic mechanisms of SC must be researched. The present review aimed to summarize the pathophysiology of SC, focusing on mitochondrial dysfunction, metabolic alterations, signaling pathways and other mechanisms. These mechanisms of pathogenesis may be used to validate discovery of novel ways to treat sepsis contribute to decreased mortality in patients with SC.

2. Pathological findings and clinical symptoms

Before the onset of SC, pathogenic bacteria that infect the body and their endotoxins enter the bloodstream, stimulating the immune system and producing large amounts of inflammatory factors, leading to cytokine storm (12). Myocardial dysfunction may be caused by chronic inflammation with prolonged lasting effects. During sepsis, the inflammatory response contributes to an overproduction of catecholamines, which impairs myocardial function and myocardial contractility. Cardiac output is affected when tachycardia leads to reduced coronary perfusion and cardiac output (13). In addition, mitochondria in septic cardiomyocytes undergo structural changes, DNA damage, elevated permeability and activation of apoptotic pathways, which decrease metabolism, to accommodate

inadequate ATP production caused by mitochondrial dysfunction (14). SC can be characterized by elevated cardiac enzymes, characteristic changes in the electrocardiogram, hemodynamic changes, decreased left ventricular ejection fraction and systolic dysfunction (15). Clinical treatment is mainly divided into two aspects: Treatment of sepsis characteristics using antibiotics, vasoactive drugs, dopamine, glucocorticoids and antibacterial peptides. Traditional Chinese Medicine (TCM) treats septic cardiomyopathy through anti-inflammatory and anti-viral effects, and inhibition of apoptosis. Currently, TCM injections used clinically include Xuebijing injection and Shenfu injection.

3. Mitochondrial dysfunction

ATP is a compound synthesized in mitochondria and the cytosol during glycolysis. Mitochondria are abundant in the heart and are responsible for a significant amount of ATP production (16). The primary products following substrate oxidation, nicotinamide adenine dinucleotide and flavin adenine dinucleotide, provide electrons for complexes I and II. Under physiological conditions, electrons move from complex I to complex II, then from complex III to complex IV by oxidative phosphorylation (OXPHOS) (17). Complexes I-IV are involved in transferring electrons from the tricarboxylic acid cycle to mitochondria (18). During this process, a proton can be transferred from the mitochondrial matrix to the inner mitochondrial membrane (IMM) and O_2 is reduced to H_2O in the mitochondria (19). Between the IMM space and the mitochondrial matrix, protons accumulate, causing a proton motive force ($\Delta\Psi$). ATP regeneration via F_0F_1-ATPase (ATP synthase) is activated by $\Delta\Psi$, which transfers the proton from the mitochondrial matrix to the IMM (20-22). Therefore, F_0F_1-ATPase activity is associated with respiratory chain activity and ATP formation.

In addition, increased superoxide (O^{2-}) and nitric oxide (NO) production can cause direct oxidative or nitrosative damage and inhibition of OXPHOS complexes, leading to decreased O_2 consumption and mitochondrial membrane potential. Finally, $\Delta\Psi$ decreases due to increased uncoupling protein-mediated proton leak and Ca^{2+}-induced mitochondrial permeability transition pore (mPTP) opening and direct oxidative damage of the IMM. The mechanism of mitochondrial dysfunction and adaptive response to mitochondrial dysfunction is shown in Fig. 1.

Mitochondrial dysfunction is a key component of sepsis (23). The most commonly used models of sepsis are lipopolysaccharide (LPS) or cecal ligation and puncture (CLP) (24). In an LPS-induced rat model, the expression of the peroxisome proliferator-activated receptor (PPAR) γ coactivator 1α (PGC1α) gene, as well as mitochondrial membrane potential, is significantly decreased (25). Mitochondrial respiratory chain complexes I and II function less efficiently in a CLP-induced rat model (26,27).

Reactive oxygen species (ROS) and nitric oxide (NO). Under physiological conditions, mitochondria reduce monovalent O_2 by generating O^{2-} During substrate oxidation, a small amount of O_2 is reduced by Mn superoxide dismutase to H_2O_2. However, a steady state concentration of ROS causes reversible or irreversible modifications to biomolecules, such as protein carbonylation or lipid peroxidation (28,29). In addition, mitochondrial enzymes function normally and mitochondrial DNA is particularly susceptible to damage caused by ROS, leading to incomplete reduction of oxygen and superoxide formation, which leads to ROS production (30). Decreased production of ROS prevents mitochondrial dysfunction in LPS-induced animal models (31,32). In LPS-induced rat models, increased ROS causes mitochondrial respiratory dysfunction, which leads to septic cardiac disease and performance (33,34). In addition, ROS production is decreased by increasing the activity of complex enzymes in mitochondria in CLP-induced mouse models (35,36).

Mitochondria also produce NO via the activity of mitochondrial NO synthase (mtNOS), which physiologically regulates mitochondrial respiration by inhibition of cytochrome C oxidase (37,38). Under physiological conditions, abundant O^{2-} and NO react to form peroxynitrite ($ONOO^-$), which acts as a strong oxidizing agent. The enhanced expression of mtNOS is induced in CLP-induced mouse models, which contributes to increased mitochondrial $ONOO^-$ levels (39,40). The critical causative factors responsible for mitochondrial dysfunction include inducible NOS (iNOS) synthase and mtNOS. It has been reported that mitochondrial dysfunction is not observed in the iNOS knockout mouse model (41). Pharmacological inhibition or genetic deletion of iNOS improves heart function in mouse models (41,42). Moreover, studies have found that the activities of complexes I and IV on the IMM are decreased by significantly boosting NO for a long time (43). Therefore, mitochondrial disorders attributed to NO may be primarily caused by abnormal iNOS expression. At present, most of the aforementioned studies have been conducted on iNOS-induced NO production, which may have some limitations, such as focus only on iNOS induced NO production, with a lack of mtNOS studies. However, NO is produced by multiple NOS isoforms (not only mitochondria) in different intracellular locations and cell types. In summary, one of the major causes of mitochondrial dysfunction involves ROS and NO, which may be key mechanisms of action in sepsis (Table I).

Calcium transport. Mitochondrial membrane permeability occurs within the mitochondrial membrane via the Ca^{2+} transport channel mPTP (44), the primary components of which are ATP synthase dimers and mitochondrial phosphate transporters (45). The three key processes involved in calcium transport are as follows: Firstly, cyclophilin D activates the pores in response to changes in mitochondrial calcium levels (46). Secondly, mPTP activation facilitates release of calcium from the mitochondria into the cytosol, where it activates calcium-dependent pathways (47,48). Ca^{2+} overload triggers the mPTP to open and release cytochrome C into the cytoplasm and the cytoplasm is released (45). In addition, the Ca^{2+}-dependent state of the mPTP is influenced by the calcium concentration within the cell (49). Generally, calcium transport causes mitochondrial swelling and dysfunction as a result of calcium transport. A study has shown mitochondrial vacuolation and damaged mitochondrial cristae in cardiomyocytes of septic rats with increased cytochrome C in the cytoplasm (50). At the same time, the amount of Ca^{2+} able to enter the cytoplasm is determined by

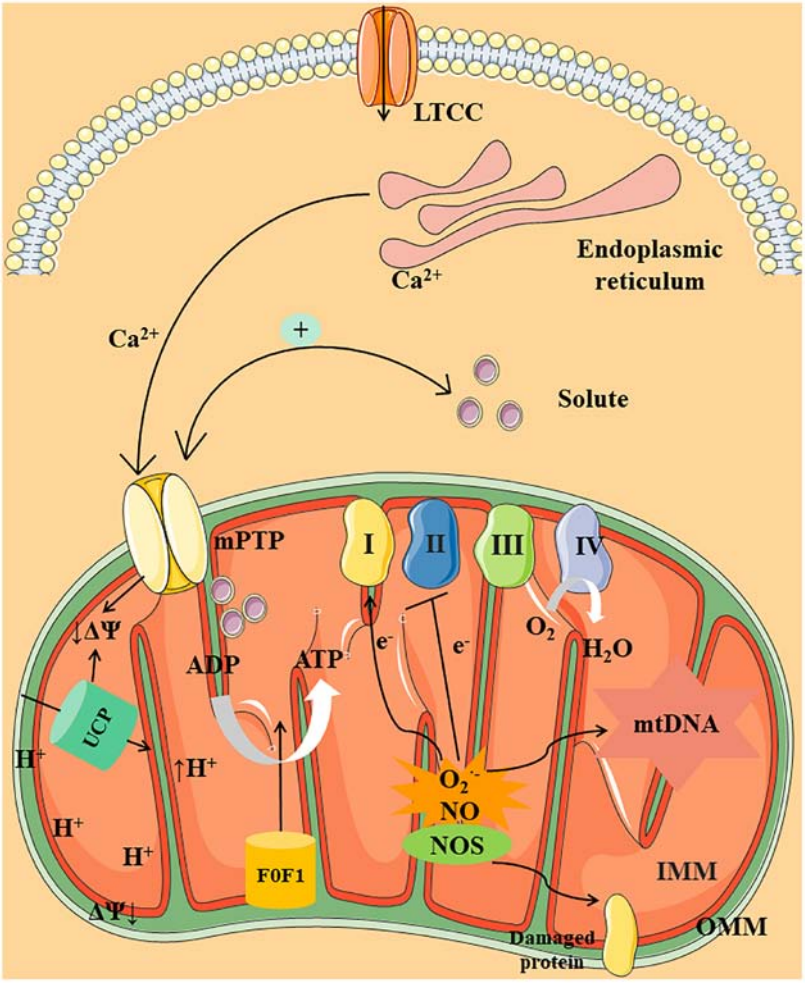

Figure 1. Mitochondrial mechanisms in septic cardiomyopathy. Increased superoxide (O^{2-}) and NO production can cause direct oxidative or nitrosative damage and inhibition of OXPHOS complexes, lead to decreased O_2 consumption and decreased Δψ. In addition, Δψ may drop due to increased (UCP)-mediated proton leak, increased Ca^{2+}-induced mPTP opening and direct oxidative damage of the inner mitochondrial membrane. In addition, Ca^{2+} homeostasis was changed due to endoplasmic reticulum stress and LTCC damage. NO, nitric oxide; OXPHOS, oxidative phosphorylation; Δψ, proton motive force; UCP, uncoupling protein; mPTP, mitochondrial permeability transition pore; LTCC, L-type calcium channels; mtDNA, Mitochondrial DNA; F0F1, ATP synthase.

the number of membrane L-type calcium channels and the amount of Ca^{2+} stored in the sarcoplasmic reticulum (51). Additionally, dantrolene prevents mitochondrial Ca^{2+} overload, which improves mitochondrial dysfunction, by inhibiting sarcoplasmic reticulum Ca^{2+} leaks (52). Taken together, these conditions may result in cytoplasmic calcium overload, leading to mitochondrial deterioration and contractile dysfunction due to mPTP opening.

Drugs for treating mitochondrial dysfunction. Triphenylphosphonium (TPP), covalent quinone (MitoQ) and vitamin E have been prescribed as medications for treating SC. A powerful antioxidant targeting mitochondria, MitoQ binds coenzyme Q10 via triphenylphosphine, used for improving mitochondrial function in SC (53). In a rat model of sepsis, treatment with vitamin E conjugated to TPP decreased ROS-related damage (54). Additionally, as an antioxidant, lipoic acid might improve mitochondrial performance and alleviate septic shock (55). To determine whether the treatment modality used to treat mitochondrial dysfunction could be a viable therapeutic option in the future, researchers need to use drugs to prevent or reverse specific mitochondrial functions.

4. Metabolic changes in SC

There is evidence that metabolic dysregulation occurs in SC, suggesting that targeting metabolic pathways may offer notable benefits in SC treatment (56). During sepsis, hypermetabolism is characterized by a catabolic state that depletes carbohydrate, lipid and protein stores (57). The primary metabolic processes during sepsis involve lipid, ketone, glucose and amino acid metabolism (Fig. 2). The physiological indices of lipid metabolism, such as fatty acid oxidation, are reduced during sepsis and the expression of both cardiac fatty acids and lipid metabolizing enzymes is reduced. When glucose is metabolized, glucose oxidation, insulin resistance and cardiac glucose uptake are decreased. Additionally, there is a reduction in the absorption of ketone bodies and amino acids during ketone and amino acid metabolism (58).

Lipid metabolism in SC. During sepsis, there is a significant demand for energy, which is met by lipid mobilization (59). To make up for energy loss, adipose tissue undergoes increased lipolysis to release fatty acid and glycerol into the bloodstream (60). Sepsis is characterized by notable deregulation of

Table I. Summary of mitochondrial dysfunction caused by ROS and NO.

Condition	Model	Inducer	Effect	First author, year	(Refs.)
ROS	Wistar male rat	LPS	Decreased expression of ROS and increased MMP	Hu *et al*, 2022	(31)
	C57BL/6J mouse	LPS	Decreased expression of ROS and improved mitochondrial respiratory function	Ji *et al*, 2022	(33)
		CLP	Increased activity of complex enzymes in mitochondria	Liu *et al*, 2022	(35)
NO	Wistar male rat	LPS	Decreased expression of mtNOS and increased $ONOO^-$ levels	Boveris *et al*, 2002	(39)
	Knockout iNOS mouse	CLP	Lack of inducible NOS and mtNOS does not induce mitochondrial dysfunction	Escames *et al*, 2007	(40)
	C57BL/6J mouse	CLP	Genetic deletion of iNOS improves cardiac dysfunction caused by sepsis	van de Sandt *et al* 2013	(41)

ROS, reactive oxygen species; mtNOS, mitochondrial nitric oxygen synthase; LPS, lipopolysaccharide; MMP, mitochondrial membrane potential; i, inducible.

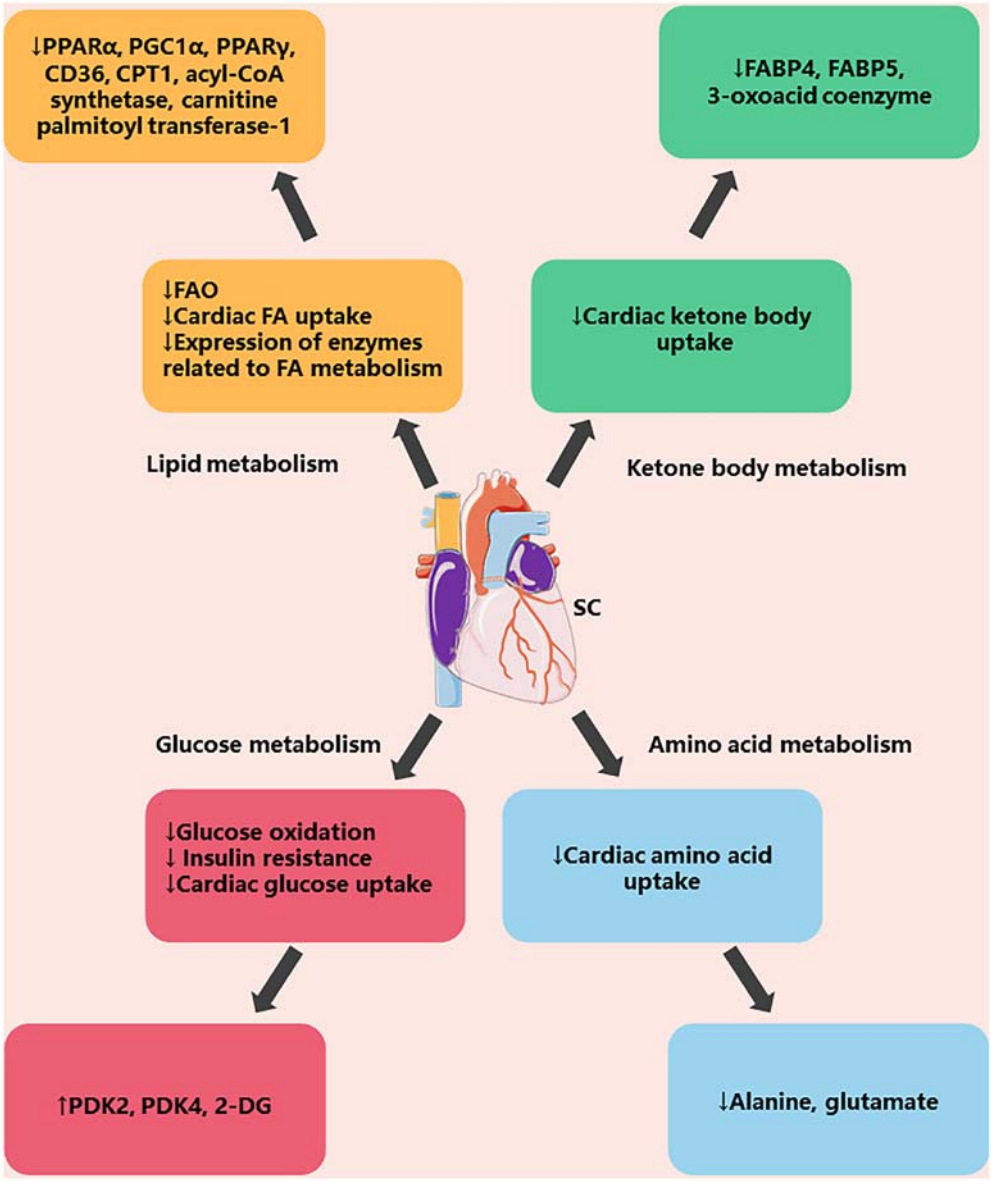

Figure 2. Metabolic changes in septic cardiomyopathy. FA, fatty acids; FAO, fatty acid oxidation; KB, ketone bodies.

Table II. Metabolic changes in septic cardiomyopathy.

Metabolism	Model	Inducer	Effect	First author, year	(Refs.)
Lipid	C57BL/6J mouse	LPS	Decreased expression of PPARα and PGC1α and activation of PPARγ	Drosatos *et al*, 2011 and 2013	(61,63)
	Zucker lean rat	LPS	CD36 and CPT1 lead to inefficient lipid metabolism in transit	Sharma *et al*, 2004	(64)
	Male Syrian hamster	LPS	Decreased expression of acyl-CoA synthetase	Memon *et al*, 1998	(65)
	C57BL/6J mouse	LPS	Decreased expression of CPT1	Feingold *et al*, 2004	(66)
	Human	Septic shock	Imbalance of FA demand and supply between cytoplasm and mitochondria may cause lipid accumulation	Rossi *et al*, 2007	(67)
Ketone	Double knock out FABP4 and FABP5 mouse	LPS	Decreased expression of genes associated with 3-oxoacid coenzyme	Umbarawan *et al*, 2017	(72)
Glucose	Female pig	CLP	Decreased myocardial glucose levels	Chew *et al*, 2013	(75)
	C57BL/6J mouse	CLP	PDK2 and PDK4 protein inhibit glucose oxidation	Standage *et al,* 2017	(77)
	C57BL/6J mouse	CLP	2-DG improves cardiac function and survival outcomes	Zheng *et al*, 2017	(78)
Amino acid	Sprague-Dawley rat	CLP	Decreased amino acid uptake by the heart	Warner *et al*, 1989	(82)
	Sprague-Dawley rat	CLP	Alanine and glutamate lead to altered metabolism in septic heart disease	Hotchkiss *et al*, 1991	(74)

LPS, lipopolysaccharide; PPAR, peroxisome proliferator-activated receptor; PGC, Primordial Germ Cell; CPT1, carnitine palmitoyltransferase1; FA, fatty acids; PDK, phosphoinositide-dependent protein kinase; 2-DG, 2-deoxy-D-glucose.

genes typically involved in lipid metabolism due to the inflammatory response, such as PPARα, PGC1α and PPARγ. At the same time, FA metabolism stops when carnitine palmitoyltransferase 1, acyl coenzyme a synthetase and carnitine palmitoyltransferase-1 expression is impaired. Studies have shown that LPS reduces PPARα and PGC1α expression in LPS-induced rats, thereby regulating the β-oxidation pathway (61,62). The inhibition of PPARγ activation protects mice from sepsis-related cardiac dysfunction (63). In addition, studies have found that defects in the enzymes carnitine palmitoyl transferase 1 and CD36 cause inefficient fatty acid transport, which contributes to fatty acid oxidation (64). Finally, studies have found that LPS reduces enzymes activity related to FA metabolism, such as acyl-CoA synthetase and carnitine palmitoyl transferase-1 (65,66). Imbalance of FA demand and supply between the cytoplasm and mitochondria may cause lipid accumulation in the cytoplasm (67). Moreover, patients with sepsis exhibit fat buildup in cardiac muscle, kidney and liver (68). Taken together, lipid metabolism and associated enzyme transport are notable energy providers in sepsis (Table II).

Ketone metabolism in SC. Sepsis may lead to a high metabolic state throughout the body, which increases ketone body production and lipid breakdown (69). During prolonged fasting, hypoglycemia occurs, resulting in promotion of ketogenesis in hepatocyte mitochondria. The ketogenic effect may serve a valuable role in biodefense as ketone bodies confer resistance to ROS (70). Ketone body metabolism may increase ATP production or contribute to systemic hypercatabolism associated with calorie restriction (71,72). Ketone metabolism is a method to maintain cardiac energy homeostasis. Studies have found that LPS injection in mice lacking fatty acid binding protein 4 (FABP4) and FABP5 inhibits hepatic and cardiac ketogenesis, as FABP4 serves an active role in FA transport (73,74). At the same time, gene expression associated with 3-oxoacid coenzyme was significantly reduced in both DoubleClick and wild-type mice (73,74).

The aforementioned studies suggest that ketone bodies may represent a pathogenic mechanism in sepsis (Table II).

Glucose metabolism in SC. During SC, glucose oxidation does not increase to compensate for the decrease in FAO caused by insulin resistance and glucose metabolism inhibition (75,76). In mice models of endotoxic shock, there is a rapid drop in myocardial glucose levels compared with hemorrhagic shock (77,78) Increased levels of pyruvate dehydrogenase kinase 2 (PDK2) and PDK4 protein inhibit glucose oxidation (79). Moreover, 2-deoxy-D-glucose (2-DG) also improves cardiac function and survival outcomes in a mouse model of sepsis (80). The aforementioned findings indicate that increased glycolytic metabolism contributes to cardiac dysfunction in sepsis and that modulating metabolism following sepsis would be an appropriate strategy (Table II).

Amino acid metabolism in SC. Amino acids play crucial roles in both the synthesis and breakdown of proteins, which is vital

Table III. Mechanisms of sepsis pathogenesis caused by PPAR and NF-κB signaling pathways.

Pathway	Model	Inducer	Effects	First author, year	(Refs.)
PPAR	C57BL/6 J mouse	CLP	Decreased phosphorylation and activation of NF-κB p65	Xia *et al*, 2020	(94)
	C57BL/6 J mouse	LPS	Decreased total protein concentration and neutrophil and macrophage expression	Chen *et al*, 2021	(95)
	C57BL/6 J mouse	CLP	Decreased endothelial cell hyperpermeability and phosphorylation of p38	Chen *et al*, 2022	(97)
NF-κB	THP-1 macrophage	LPS	Increased phosphorylation of p65 and IκB	Cao *et al*, 2022	(104)
	C57BL/6 J mouse	CLP	Decreased expression of inflammatory factors and neutrophils	Wang *et al*, 2022	(105)
	RAW 264.7 cell	LPS	Decreased TNFα and IL-6 levels	Ruan *et al*, 2022	(107)

PPAR, peroxisome proliferator-activated receptor; CLP, cecal ligation-peferation; LPS, lipopolysaccharide.

for maintaining cellular homeostasis. Sepsis activates proteolysis, which splits proteins into smaller polypeptides and amino acids, allowing them to rebuild energy-rich molecules (81-83). It is reported that amino acid uptake by the heart is 90% lower compared with other organs in CLP-induced mouse models (84,85). Moreover, studies have demonstrated that decreases in alanine and glutamate lead to changes in cardiac metabolism in rats (86,87). Collectively, amino acids may be required for the liver to maintain protein hydrolysis in sepsis (Table II).

5. Signaling pathway of SC

PPAR pathway. Nuclear receptor transcription factors regulate metabolic homeostasis, inflammatory response and cell death through nuclear receptors (76,77). Studies have found that PPARα is present in the liver, PPARβ is highly active in skeletal muscle and PPARγ is associated with the control of the inflammatory reaction, apoptosis and sepsis (88,89). PPARγ suppresses expression of pro-inflammatory genes, mainly by scavenging transcription factors and their cofactors, thus preventing binding to their cognate binding sites in the promoters of target genes (90,91). In addition, immune cells can produce large amounts of pro-inflammatory mediators in the early stages of sepsis, and PPARγ regulates sepsis by promoting apoptosis (92,93). In a mouse model of CLP-induced inflammation, inhibition of NF-κB p65 phosphorylation and activation via upregulation of PPARγ attenuates inflammation (94). Studies have found that total protein concentration, neutrophils and macrophages are reduced in LPS-induced mice (95,96) Decreased inflammatory factor release is attributed to the conversion of macrophages from type M1 to M2. Moreover, the M1 macrophage increases chemokine ligand production in a CLP-induced mouse model by increasing endothelial cell hyperpermeability and phosphorylation of p38 by inhibiting PPARγ (97). In conclusion, activation of PPARγ may contribute to reduction of pro-inflammatory properties during SC (Table III).

NF-κB pathway. The predominant form of NF-κB is a heterodimer of p50 and p65 proteins (98). The protein is normally sequestered in the cytosol by a class of inhibitory proteins known as IκBs. These comprise seven members, including IκBα, IκBβ and IκBγ (99). Under physiological conditions, NF-κB forms a complex with IκBα to undergo cytoplasmic sequestration. When stimulated by activating signals, NF-κB undergoes phosphorylation, ubiquitination and degradation, which leads to an activated NF-κB form that travels to the nucleus to induce gene transcription (100). NF-κB attenuates sepsis-induced systemic inflammation and myocardial injury by inhibiting NF-κB signaling (101). Additionally, studies have demonstrated that suppressing NF-κB activation decreases systemic hypotension, improves septic myocardial dysfunction and vascular abnormality, inhibits expression of numerous pro-inflammatory genes, decreases intravascular coagulation and neutrophil infiltration and prevents endothelial leakage (102,103).

When the NF-κB signaling pathway is engaged, phosphorylation of NF-κB pathway factors such as p65 and inhibitor κBα occurs (104,105). Moreover, studies have shown that decreasing TNF-α and IL-6 secretion, cytokines that promote inflammation in a LPS-induced rat model, stimulates the NF-κB signaling pathway (106,107). In summary, NF-κB suppresses inflammatory factors and proinflammatory genes that might be involved in sepsis symptoms (Table III).

6. Association between cell death and SC

Association between ferroptosis and SC. Ferroptosis pathways are iron-dependent, non-apoptotic and characterized by specific biochemical and morphological changes (108). The majority of iron in the body is bound to hemoglobin and myoglobin, with the rest primarily bound to ferritin and transferrin (109). In some cases, the cellular defense mechanism limits the cell iron export system, leading to an overload of cellular iron. Peroxylated lipids are produced as a result of the Fenton reaction, resulting in the damage of organelles (110). The bloodstream contains tetrapyrrole hemoglobin containing iron during SC. Under the action of heme oxygenase 1 (HO-1) enzyme, stable heme is degraded to biliverdin, carbon monoxide and iron *in vivo* (111,112). Additionally, HO-1 induces immunosuppression during sepsis, promotes helper

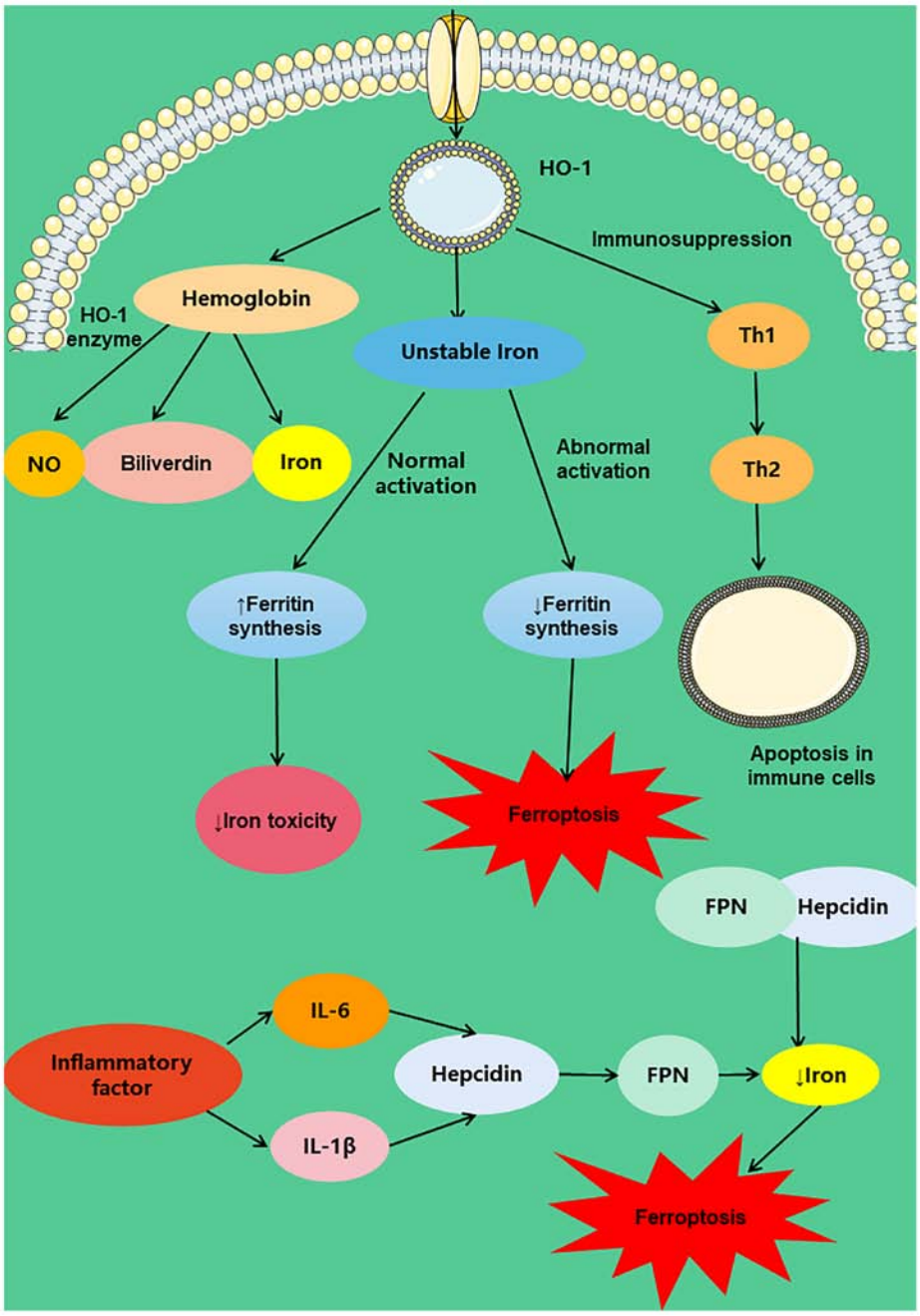

Figure 3. Summary of HO-1 and Hepcidin action mechanism in septic cardiomyopathy. HO-1, heme oxygenase 1; Th1, T helper cell 1; Th2, T helper cell 2; FPN, Hepcidin ubiquitinates ferroportin.

T cell 1(Th1) to Th2 cytokine transfer and induces apoptosis in immune cells (113). The product of the HO-1 reaction is unstable iron, which promotes synthesis of ferritin and reduces the toxic effects of iron. The abnormal activation of HO-1 may result in the loss of the antioxidant action, increase levels of the labile iron pool (LIP) and eventually cause iron deficiency (114). In a mouse model of sepsis, the expression of HO-1 leads to altered iron metabolism protein levels and ferroptosis (115). Taken together, HO-1 causes ferroptosis by degrading heme and elevating LIP to release ferritin into the body.

Hepcidin, a liver-derived peptide hormone, maintains iron homeostasis in the body. Studies have shown that hepcidin ubiquitinates ferroportin (FPN) and reduces its activity, thus lowering iron concentrations (116,117) Patients with sepsis have significantly higher concentrations of hepcidin. Expression of hepcidin is induced by IL-6 and IL-1β when inflammation takes place (118). The serum iron levels are effectively regulated by hepcidin in a mouse model induced by LPS (119). Furthermore, studies have shown that high hepcidin expression decreases FPN activity, which decreases iron levels in plasma (120,121) Hence, hepcidin protein expression inhibits iron transport, causing an imbalance in iron homeostasis, which results in death from iron deficiency (Fig. 3).

Association between pyroptosis and SC. Under physiological conditions, pyroptosis is mediated by inflammasome-activated caspases and gasdermin D (GSDMD), final effectors

of the GSDM protein family, leading to pore formation in the plasma membrane and leakage of inflammatory mediators (122,123). Under pathogenic conditions, LPS from Gram-negative bacteria directly activates caspase 4/5/11, in the inflammasome pathway, without the need for the inflammasome or caspase-1. GSDMD can be cleaved to produce N-GSDMD by activated caspase 4/5/11. N-GSDMD indirectly promotes NLRP3 inflammasome assembly via K^+ efflux, which aggravates pyroptosis (124,125). Studies have found that doxorubicin upregulates NADPH oxidase 1 and NADPH oxidase 4 expression, thereby activating dynamin-related protein-1and promoting mitochondrial fission, leading to excessive accumulation of ROS in mitochondria and activation of the NLRP3 inflammasome and caspase-1dependent apoptosis (126,127) Certain studies have found that GSDMD knockout significantly decreases NLRP3 and caspase-1 expression, increases survival and improves cardiac dysfunction in mice (128,129). Moreover, LPS directly affects nuclear localization of sting and interferon regulatory factor-3-activated sting then activates NLRP3, leading to cardiac dysfunction as well as pyroptosis (130). Collectively, pyroptosis is induced in most forms of cardiomyopathy and blocking pyroptosis by direct or indirect approaches that target the pyroptotic machinery or upstream regulators may exert a protective effect.

7. Conclusion and future research prospects

Myocardial dysfunction caused by sepsis is one of the main reasons for the high mortality rate of sepsis and it is crucial to investigate the pathogenesis of sepsis-induced cardiac dysfunction and find treatment methods. The present study summarized the primary factors that contribute to the pathogenesis of SC, such as mitochondrial dysfunction, metabolic changes, cell death and signaling pathways. Mitochondrial dysfunction, primarily due to increased ROS and no steady-state concentrations inside mitochondria, increases various reversible and irreversible toxic modifications on biomolecules, such as protein carbonylation and lipid peroxidation (28,131). Meanwhile, excessive ROS and NO damage the mitochondrial respiratory chain structure and aggravate the biosynthesis of ROS (132,133). Metabolism in sepsis requires the adjustment of immune function via metabolism of fat, the metabolism of amino acids, metabolism of glucose and the absorption of a large amount of energy from cell's own metabolism (134,135). In addition, ferroptosis and pyroptosis contribute to pathogenesis of SC. Iron molecules contribute to the aggregation of ferritin at the cell membrane through the HO-1 reaction; however, activation of iron molecules by ferritin leads to an increase in iron output, leading to iron enrichment (136,137). By regulating the key molecule GSDMD, pyroptosis activates NLRP 3 inflammatory bodies and caspase 1-dependent apoptosis, leading to myocardial dysfunction in sepsis (138,139).

According to previous treatment methods, the relevant methods for the treatment of sepsis were divided into two main categories, the first category was the basic treatment methods for the characteristics of sepsis. Antibiotics decrease the release of inflammatory factors and mediators by regulating pathogenic microorganisms and the immune system to improve shock relieve clinical symptoms and signs of sepsis (140,141). Dopamine, a vasoactive drug, maintains a steady state of cardiac function by regulating the mean arterial tone (142,143). Glucocorticoids are effective in decreasing the duration of vasopressor use and maintaining haemodynamic balance and improve the clinical symptoms of patients with sepsis within a short period of time (144,145). The second type of treatment is herbal injections, whose mechanism of action is to attenuate the release of inflammatory factors and increase body immunity. Xuebijing injection inhibits release of high mobility group protein B1 in the serum of patients and decreases release of inflammatory factor mediators, thus treating sepsis (146). Effective interventions to control the way sepsis develops are necessary to translate basic research into clinical practice. Knowledge of sepsis and heart failure may lead to better treatment of myocardial infarction in future.

To the best of our knowledge, the metabolism of cells has not been investigated in SC. Secondly, although metabolic changes during sepsis have been reported, there is a lack of information on specific mechanism of action studies. Lastly, it is unclear how ferroptosis and pyroptosis occur during SC. Therefore, researchers should investigate the pathogenesis of SC using new methods and tools, such as network pharmacology, proteomics, metabolomics and gut microbiota analysis.

The present study reviewed the pathogenesis of SC with the goal of providing new ideas for the prevention and treatment of SC. In conclusion, this review summarizes the mitochondrial dysfunction (including reactive oxygen species, nitric oxide and calcium ion transport), metabolic changes (including lipid metabolism, ketone body metabolism, glucose metabolism and amino acid metabolism) and cell death modes (including iron death and cellular pyroptosis) associated with septic cardiomyopathy during sepsis. SC was not caused by all pathogenic mechanisms, but only a few that were relatively important were discussed in the review.

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Availability of data and materials

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Authors' contributions

JS and XF conceived the subject of the review, performed the investigation, and wrote and edited the original draft. KZ, HB and LL wrote, reviewed, and edited the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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