

# Progress in the Clinical Assessment and Treatment of Myocardial Depression in Critically Ill Patient with Sepsis

Xu-Dong Shen<sup>1</sup>, Hua-Sheng Zhang<sup>1</sup>, Rui Zhang<sup>1</sup>, Jun Li<sup>1</sup>, Zhi-Gang Zhou<sup>1</sup>, Zhi-Xian Jin<sup>2</sup>, Yin-Jia Wang<sup>1</sup>

<sup>1</sup>Department of Critical Care Medicine, Calmette Hospital Affiliated to Kunming Medical University, Kunming, 650011, People's Republic of China;

<sup>2</sup>Department of Respiratory Medicine, Calmette Hospital Affiliated to Kunming Medical University, Kunming, 650011, People's Republic of China

Correspondence: Yin-Jia Wang, Department of Critical Care Medicine, Calmette Hospital Affiliated to Kunming Medical University, No. 1228 of Beijing Road, Panlong District, Kunming, 650011, People's Republic of China, Tel +86 15877990372, Fax +86 10 66666666; +871-67390508, Email wangyinjia@outlook.com

**Abstract:** Myocardial inhibition is the main cause of death in patients with sepsis. In recent years, methodological differences in the diagnosis, assessment, and treatment of septic myocardial depression have been observed, and how to objectively and accurately evaluate the degree of myocardial depression and the timing of treatment strategies have generally been the focus of this area of research. Based on the relevant research at home and abroad, the current review summarizes the clinical characteristics, methodological diagnosis, and symptomatic treatment of septic myocardial depression. The aim of doing so is to provide a reference for the early identification and treatment of patients with sepsis and myocardial depression.

**Keywords:** sepsis, myocardial depression, left ventricular systolic function, fluid resuscitation

## Introduction

Sepsis is a systemic inflammatory reaction caused by infection,<sup>1,2</sup> and its continued progression may lead to severe sepsis, septic shock, and even death. Cardiovascular failure caused by myocardial depression is the main cause of death in patients with sepsis.<sup>3,4</sup> Myocardial depression occurs in approximately 50% of patients with sepsis; compared with patients with normal cardiac function, the mortality of those with myocardial depression increases by 20%. Its risk factors of SIMD include younger age, a history of diabetes mellitus or heart failure, elevated NT pro-BNP, and positive result of blood culture, and a reduced EF < 30%.<sup>5</sup> Its pathophysiology is on the basis of myocardial contractile dysfunction. The myocardial contractile dysfunction is caused by microcirculatory dysfunction and autonomic dysregulation, like secretion of inflammatory cytokines and metabolism of nitric oxide.<sup>6</sup>

Although there's no approved guidelines, myocardial depression in patients with sepsis must be detected in time and active treatment measures must be implemented to reduce the mortality caused by sepsis and improve patient prognosis. Several treatments of sepsis, such as transfusion, anti-inflammatory drugs like corticosteroid, vasopressors, can relieve the symptoms of SIMD to some extent.<sup>6</sup>

This review summarizes the process of diagnosing and treating myocardial depression in the presence of sepsis.

## The Characteristics of Septic Myocardial Depression Systolic Dysfunction

Approximately 50% of patients with septic shock have a significantly lower left ventricular ejection fraction (LVEF). Most patients who survive the treatment have significant left ventricular enlargement, accompanied by an increased ventricular volume at the end of diastolic and systolic phases, a normal stroke volume, low peripheral vascular resistance,

and a high cardiac index. Patients who subsequently died had lower peripheral vascular resistance, a normal or high LVEF, a higher cardiac index, and normal ventricular and stroke volume, respectively.<sup>7</sup>

Myocardial depression can occur in the very early stages of sepsis. In most patients, it occurs in the first three days following the onset of sepsis, and cardiac function essentially recovers in 7–10 days.

The structure and function of the heart's right ventricle are similar to that of the left. Surviving patients may have a significant decrease in right ventricular ejection fraction (RVEF) and acute right ventricular dilatation in the early stage before gradually recovering. In patients who subsequently die, the RVEF and right ventricular end-diastolic volume may not change.<sup>8</sup>

## Diastolic Dysfunction

In addition to systolic dysfunction, in patients with sepsis-induced myocardial dysfunction (SIMD), an abnormal diastolic function may also be observed. The advent of echocardiography has enabled convenient conditions for better study of the cardiac system's diastolic phase. One study revealed that approximately 1/5 patients with SIMD experienced diastolic dysfunction and another 1/5 had both systolic and diastolic dysfunction.<sup>9</sup> In a prospective study conducted by Mariana et al,<sup>10</sup> echocardiographic investigation found that 20–60% of SIMD patients experienced a transient and reversible decline in ventricular diastolic function accompanied by systolic dysfunction and ventricular dilatation. The onset time of diastolic function impairment may be much earlier compared with systolic function impairment, and the recovery time is also longer compared with the latter. A meta-analysis revealed that the incidence of diastolic dysfunction in SIMD patients was higher compared with systolic dysfunction, and there was a significant relationship between diastolic dysfunction and mortality.<sup>11</sup>

## Diagnosis of Septic Myocardial Depression

### Echocardiography

In the 1990s, two-dimensional echocardiography was first used in the evaluation and study of SIMD. To date, echocardiography remains the “gold standard” for the evaluation of SIMD.<sup>12</sup> The technique can obtain the anatomical structure, hemodynamics, and functional characteristics of the heart to review myocardial depression; additionally, an LVEF <50% is one of the criteria for SIMD.<sup>13</sup> Furthermore, critical patients have a poor response to volume resuscitation, and echocardiography can monitor blood volume and response to volume resuscitation in real-time.<sup>14</sup> Patients with severe sepsis may also experience warm shock, with high output and low resistance, or cold shock with low output and high resistance/low output and low resistance.<sup>15</sup>

Cold shock is the most common form of septic shock in children. Bedside dynamic echocardiography can help to identify abnormal circulatory functioning, evaluate the patient's condition, guide medication, and ensure the rescue of critical patients in time. However, this technique is significantly impacted by the expertise of the echocardiographic operator, and the LVEF is affected by the left ventricular preload and afterload. In addition, repeated measurements are not equivalent to continuous monitoring.

### Electrocardiography

An electrocardiogram (ECG) is not a good index for evaluating SIMD in a clinical setting. Although ST-segment elevation/depression, Q-wave, left bundle branch block, QT-wave interval prolongation, a high sharp T-wave, and a J-wave can be detected on the ECG of a SIMD patient, these changes are not specific.<sup>16</sup>

### Hemodynamic Detection

The Swan–Ganz technique: Cardiac output is measured by placing a floating catheter in the pulmonary artery to assist in the diagnosis of SIMD, to determine the time of drug administration, and to monitor the efficacy.<sup>17</sup> The parameters measured by the Swan–Ganz technique include right atrial pressure, pulmonary artery pressure, central venous pressure, pulmonary circulation resistance, and stroke work. However, the Swan–Ganz technique is highly traumatic, complicated to execute, can cause several complications, and has high requirements for instrument use and personnel, which limits its

clinical application.<sup>18</sup> Also, systemic arterial stiffness has also been reported in the diagnosis of sepsis-induced hemodynamic changes.<sup>18</sup> The greater the value, the more severe the degree of arteriosclerosis, the higher the risk of cardiovascular and cerebrovascular disease. So this is a convenient and simple diagnosis method.<sup>18</sup>

## Pulse-Indicated Continuous Cardiac Output Monitoring

The pulse-indicated continuous cardiac output (PiCCO) technique combines a pulmonary thermal dilution and an arterial pulse contour analysis technique to reflect the whole-heart blood flow force parameters by measuring the changes in temperature in large arteries over time.<sup>19</sup> This technique is different from the traditional thermodilution method, in which the right heart index is measured to represent the whole-heart index. The parameters monitored by PiCCO include cardiac output, cardiac function index, whole heart end-diastolic volume, intrathoracic blood volume, extravascular lung water, stroke volume variation, and the left ventricular contractility index.<sup>20</sup> The PiCCO technique is simple to operate and also applicable to children. However, because it is a traumatic procedure, it presents the risk of infection and thrombosis; it is also costly to perform. In addition, some studies have noted that the PiCCO technique may underestimate the continuous cardiac output of SIMD patients and is thus not as reliable as the traditional transpulmonary thermodilution method.

## Noninvasive Cardiac Output Monitoring

This technique measures cardiac output through bioelectrical impedance technology. Its most significant technical feature is that it is non-invasive; the monitoring indicators include stroke volume, heart rate, blood pressure, peripheral resistance, and total intrathoracic volume.<sup>21</sup> One study showed a good correlation between the cardiac output measured by a noninvasive cardiac output monitoring method and by pulmonary thermal dilution; additionally, the monitoring error was smaller, the accuracy was higher, the response to hemodynamic changes was faster, and the sensitivity and specificity values were higher.<sup>22</sup>

## Cardiac Output Ultrasonic Monitoring

The left and right cardiac function parameters are monitored by continuous Doppler ultrasound to determine the hemodynamic characteristics of patients. Through comparison, it was found that a high correlation existed between the results of cardiac output and the stroke volume detected by ultrasonic cardiac output monitoring, pulmonary artery catheterization, and other methods.<sup>23</sup> Horster et al<sup>24</sup> compared the results of ultrasonic cardiac output monitoring and PiCCO monitoring in terms of cardiac output in patients with sepsis and found no significant difference between the two methods. This technique can display the waveform of blood flow velocity with good repeatability, can be used for the dynamic bedside monitoring of critical patients, and is suitable for use in the intensive care unit (ICU); additionally, its non-invasive nature is appropriate for children and other patients who cannot undergo invasive testing.

## Circulating Biological Markers

Changes in specific biomarker levels in SIMD patients have a suggestive effect on the diagnosis of myocardial depression. Patients who are suspected of having myocardial depression should be further diagnosed by echocardiography.

Troponin I is a structural protein in striated muscle with a small molecular weight; it is expressed only in the myocardium, is a specific myocardium antigen, and has high sensitivity and specificity for the diagnosis of SIMD.<sup>25</sup> Following myocardial cell damage, troponin I, which moves freely in cytoplasm, is rapidly released into the blood from the cytoplasm through cell membranes. Sustained myocardial injury activates proteolytic enzymes, which causes the release of bound troponin I.<sup>26</sup> Troponin I increases at 5–8 h after septic myocardial damage, peaks at 12–24 h, and continues to be released for 1–2 weeks; as such, it can be used as a retrospective detection index. However, the long maintenance time involved is not conducive for detecting recent myocardial re-injury. Using echocardiography, Innocenti et al<sup>27</sup> found that an increase in troponin I was closely related to left ventricular dysfunction in patients with severe sepsis.

A natural hormone with biological activity, B-type natriuretic peptide (BNP) is primarily synthesized by myocardial cells and can also be expressed in brain tissue. The main mechanism for the release of BNP in SIMD patients is ventricular pressure overload, volume overload, and ventricular wall dilatation. The causes also include lipopolysaccharides, interleukin-1, tumor necrosis factor alpha, and other cytokines that stimulate messenger ribonucleic acid expression and renal dysfunction.<sup>28</sup> B-type natriuretic peptide increases most significantly on the fifth day after SIMD injury, particularly in SIMD patients with a decreased LVEF.<sup>29</sup> Furthermore, BNP is typically expressed as a precursor that comprises 108 amino acids. After stimulation, it is cleaved into inactive linear and active cyclic polypeptides under the action of activated enzymes. The inactive linear N-terminal polypeptide is relatively stable *in vitro*, which is conducive to detection, with 1163 pg/mL as the cut-off point; the sensitivity and specificity for diagnosing SIMD are 76% and 74%, respectively.<sup>30</sup>

Myocardial enzyme creatinine kinase MB isoenzyme (CK-MB) is a creatine kinase isoenzyme that mainly acts on the myocardium. It has a small molecular weight, and the level at which it is present in the body rises within 4–6 h after the onset of SIMD, reaches a peak within 24 h, and recovers after 2–3 days; as such, it can reflect the early onset of SIMD. However, in addition to the myocardium, CK-MB also exists in skeletal muscle; accordingly, its sensitivity and specificity are relatively insufficient.<sup>31</sup>

Myoglobin is specific to rhabdomyocytes, and its presence in normal human serum is very low. It can be detected immediately when myocardial depression occurs in the presence of sepsis. Myoglobin has a small molecular weight and a short half-life. It will be released from myocardial cells soon after the onset of SIMD and will quickly be eliminated from the kidneys. Myoglobin has a short detection window and high sensitivity, but it will increase in the presence of primary heart disease or any other disease that can lead to myocardial injury. As such, it has poor specificity. Similar to myocardial enzymes, it must be combined with other indicators and is better suited for making a diagnosis that excludes SIMD.<sup>32</sup>

Cardiac fatty acid-binding protein (cFABP) is a soluble cytoplasmic protein that is broadly present in the cytoplasm of myocardial cells. It has strong tissue specificity and is a newly discovered marker of myocardial injury. When myocardial cells suffer irreversible damage, such as ischemia and hypoxia, fatty acids mobilize the oxidation function, rapidly increase the level of cFABP, and release it into the peripheral blood.<sup>33</sup> Additionally, cFABP can be detected at 1.5 h after myocardial injury, reach a peak at 6 h, and return to a normal level at 24 h. It is highly sensitive for diagnosing initial SIMD.<sup>34</sup> Erenler et al found cFABP to be an independent factor for predicting organ dysfunction and mortality in patients with SIMD; the areas under the receiver operating characteristic curve were 0.755 and 0.784, respectively, making it useful for evaluating the prognosis and risk stratification of patients. Furthermore, cFABP not only increases rapidly following myocardial injury but can also be rapidly removed from the kidneys; combined with its simple operation, it thus indicates value for use as a potential SIMD index.

## The Treatment of Septic Myocardial Depression

Sepsis-induced myocardial dysfunction is a common complication that causes death in patients with severe sepsis. The mortality of patients with sepsis alongside SIMD is as high as 70%, and the degree of cardiac function depression is significantly correlated with the mortality rate. The early detection of myocardial depression in patients with sepsis and its effective treatment is important for reducing the mortality of patients with severe sepsis.

### Anti-Infection

Following a definitive diagnosis of sepsis, empirical broad-spectrum antibiotic treatment should immediately be completed while controlling the source of the infection to maximally inhibit pathogenic bacteria; aerobic and anaerobic cultures should also be performed to guide the follow-up treatment.<sup>35</sup> However, in recent years, the situation of multidrug-resistant bacteria in the ICUs of medical institutions has become more serious, setting new challenges for infection control. Antibacterial peptide is an amphiphilic cationic peptide with a broad antibacterial spectrum that can neutralize lipopolysaccharides and teichoic acid in bacterial cell walls, and improve patients' innate or acquired immunity.<sup>36</sup>

### Fluid Resuscitation

Fluid resuscitation is an important treatment approach for SIMD. In patients with SIMD, the increase of capillary osmotic pressure and dilation of the venous system can lead to a decrease in the effective circulating blood volume and

ventricular preload, while the diastolic pressure-volume curve remains smooth. The initial dose of fluid resuscitation can have a significant impact on patients' cardiac function.<sup>37</sup> According to relevant international guidelines, patients experiencing septic shock should undergo fluid replacement immediately in the early stages of resuscitation. The dose of fluid replacement within the initial 3 h should be at least 30 mL/kg/h; however, excessive fluid replacement at the initial stage may increase the risk of death. Clinically, the fluid replacement process is guided according to central venous pressure, blood oxygen saturation, urine volume, and lactate levels, combined with a passive leg-lifting test and a rapid fluid replacement test.<sup>38</sup> The mortality of patients with a central venous pressure >12 mmHg will be increased; to ensure adequate oxygen supply, maintaining the central venous pressure below 8 mmHg is conducive to reducing mortality.<sup>39</sup> Vitamin B1 and C supplementation are beneficial for improving vascular permeability and the lactate clearance rate; used in combination with fluid resuscitation, it may also help patients obtain greater clinical benefits.<sup>40</sup>

## Improving Myocardial Function

Dobutamine is a positive inotropic drug that can improve myocardial contractility and afterload and capillary wedge pressure, as well as reduce the levels of troponin I and cFABP in peripheral circulation.<sup>41</sup> Dobutamine is recommended as the first-choice treatment for improving cardiac function. However, Leeanne et al<sup>41</sup> found that although the drug could improve myocardial contractility, it could also increase cardiac oxygen consumption, which may lead to arrhythmia and increase the risk of malignant cardiovascular events. Gelinas et al<sup>42</sup> showed that although dobutamine could improve heart rate, left ventricular ejection index, and the cardiac index of patients with SIMD, it had no significant effect on microcirculation and peripheral perfusion, nor could it improve the prognosis of patients, and even increased their 90-day mortality risk. However, the research results lack experimental support and require additional verification.

Levosimendan is an intramuscular calcium sensitizer that can improve the stability of the complex formed by troponin C and calcium ions and open adenosine 5-triphosphate (ATP)-dependent potassium channels, inhibit coronary artery and systemic vascular dilatation, protect myocardial cells from damage, and, accordingly, protect patients with SIMD.<sup>43</sup> Levosimendan also had anti-inflammatory and antioxidant effects, promoted the expression of nitric oxide, inhibited the expression of hypoxia inducible factor 1, and no serious adverse reactions were observed.<sup>44</sup> However, a meta-analysis revealed that levosimendan had no improvement effect on organ dysfunction in patients with SIMD and no significant effect on the 28-day mortality rate.<sup>45</sup> Therefore, the therapeutic effect of levosimendan is controversial, and the clinical benefit and timing of its use require further investigation.

Trimetazidine can inhibit the enzymes in the beta-oxidation pathway in myocardial cells, render glucose the main energy source of myocardial cells to help improve the energy supply in cases of myocardial ischemia, inhibit the activity of sodium-potassium-ATPase, and increases the ATP concentration of myocardial cells. The drug is commonly used in the treatment of heart diseases. Chen et al<sup>46</sup> showed that trimetazidine could alleviate the impairment of cardiac function caused by lipopolysaccharides, reduce inflammatory reaction and damage, inhibit apoptosis, and improve the survival rate of mice with SIMD. Another study confirmed that trimetazidine could reduce the level of serum malondialdehyde in rats with sepsis, and improve the stability of cell membranes and tissue antioxidant capacity.<sup>47</sup> However, trimetazidine is rarely used in the treatment of SIMD in clinical practice, and there is a lack of evidence-based medical evidence in this regard. Its mechanism in the treatment of SIMD thus requires additional research.

An initial heart rate in SIMD patients <106 beats/min indicates a good prognosis. An existing study revealed that the early application of beta-receptor blockers could play anti-inflammatory and cardioprotective roles in patients with SIMD and reduce their mortality rate. Relevant mechanisms may include the following: improving the sensitivity to catecholamine and inhibiting the cardiac toxicity mediated by catecholamine; slowing down the heart rate, reducing myocardial oxygen consumption, and increasing diastolic filling time.<sup>48</sup>

## Organ Function Support

At present, there is no specific treatment for SIMD. However, a study concluded that myocardial depression was reversible; accordingly, actively providing organ function support during the course of the disease can help create good treatment conditions and improve patient prognosis.<sup>49</sup>



Continuous renal replacement therapy can remove inflammatory factors, reduce inflammatory injury to myocardial cells, improve cardiac function and stabilize hemodynamics, and provide sufficient liquid “space” for the discharge of excess water and electrolytes in the body, which is conducive to the implementation of other treatment schemes. The survival rate of patients with sepsis receiving continuous renal replacement therapy within 48 h following admission is significantly higher than among those receiving treatment after 48 h.<sup>50</sup> Ulinastatin can reduce the levels of inflammatory factors and oxygen free radicals; combined with continuous renal replacement therapy, it can reduce the acute and chronic scores of sepsis and have a good therapeutic effect.<sup>51</sup>

Arteriovenous extracorporeal membrane oxygenation is a parallel circuit of pulmonary circulation, the perfusion volume of which can reach 75% of cardiac output, and is a process that can promote blood circulation and maintain oxygenation. Wada et al<sup>52</sup> showed that, although arteriovenous extracorporeal membrane oxygenation increased myocardial afterload and reduced stroke output, it could provide sufficient blood perfusion and buy time for the recovery of myocardial depression and achieved good results in clinical practice.<sup>52</sup> Research also revealed that 70% of patients with SIMD recovered and were discharged after receiving this treatment. Brechot et al<sup>53</sup> showed that arteriovenous extracorporeal membrane oxygenation could improve the prognosis of patients with SIMD with refractory hypoxemia. Aortic balloon counterpulsation helped increase coronary artery blood flow perfusion, improved the myocardial cell oxygen supply, reduced afterload, and maintained hemodynamic stability in patients with SIMD. It is suitable for patients with poor cardiac function and no significant reduction in peripheral vascular resistance.<sup>54</sup> An existing study showed that, following aortic balloon counterpulsation, the average arterial pressure could be increased by 30% in 60% of patients with SIMD.<sup>55</sup>

## Conclusion

Sepsis-induced myocardial dysfunction is common in cases of severe sepsis and septic shock. Its mechanism is complex, its progress is rapid, and its mortality rate is high; therefore, the early diagnosis of SIMD is particularly important. Active anti-infection, effective fluid resuscitation and organ function support, maintaining hemodynamic stability, and myocardial function recovery are the main methods for treating the condition; however, these approaches also have inherent disadvantages. Although currently there’s no approved guidelines, its treatment can be anti-infection, fluid resuscitation, improving myocardial function and organ function support. New therapeutic methods, such as gene therapy and immunotherapy have also emerged, but more research is needed to verify their large-scale clinical application. The continuous development of diagnosis and treatment technology is thus of great significance for improving the diagnosis and treatment effect, reducing the mortality rate, and improving the prognosis of patients with SIMD.

## Disclosure

The authors report no conflicts of interest in this work.

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