Induction and deduction in sepsis-induced cardiomyopathy: five typical categories

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Abstract
Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The heart is one of the most important oxygen delivery organs, and dysfunction significantly increases the mortality of the body. Hence, the heart has been studied in sepsis for over half a century. However, the definition of sepsis-induced cardiomyopathy is not unified yet, and the conventional conception seems outdated: left ventricular systolic dysfunction (LVSD) along with enlargement of the left ventricle, recovering in 7 to 10 days. With the application of echocardiography in intensive care units, not only LVSD but also left ventricular diastolic dysfunction, right ventricular dysfunction, and even diffuse ventricular dysfunction have been seen. The recognition of sepsis-induced cardiomyopathy is gradually becoming complete, although our understanding of it is not deep, which has made the diagnosis and treatment stagnate. In this review, we summarize the research on sepsis-induced cardiomyopathy. Women and young people with septic cardiomyopathy are more likely to have LVSD, which may have the same mechanism as stress cardiomyopathy. Elderly people with ischemic cardiomyopathy and hypertension tend to have left ventricular diastolic dysfunction. Patients with mechanical ventilation, acute respiratory distress syndrome or other complications of increased right ventricular afterload mostly have right ventricular dysfunction. Diffuse cardiac dysfunction has also been shown in some studies; patients with mixed or co-existing cardiac dysfunction are more common, theoretically. Thus, understanding the pathophysiology of sepsis-induced cardiomyopathy from the perspective of critical care echocardiography is essential.

Keywords: Sepsis; Sepsis-induced cardiomyopathy; Critical care echocardiography; Left ventricular systolic dysfunction; Left ventricular diastolic dysfunction; Right ventricular dysfunction

Introduction
There are no definitive epidemiologic data of sepsis all over the world at present, but according to reports from the Centers for Disease Control and Prevention, at least 1.7 million adults in the United States develop sepsis each year, and nearly 270,000 adults in the United States die as a result of sepsis. Injury of the cardiovascular system in sepsis has a strong influence on the death of patients; therefore, studying cardiac function becomes critically important. As long ago as the 19th century, Laennec found that the tone of the heart was weakened in acute febrile disease, and the cause of heart failure was attributed to fever then. In the mid-20th century, some scholars put forward the theory of cold shock and heat shock in sepsis. Monitoring cardiac output (CO) deepened the understanding of cardiac function in sepsis, but continuous advancements in methods have improved our understanding. Parker et al. used ventriculography to study cardiac function in the 1980s, which helped scholars form a traditional understanding of cardiac function in sepsis, that is, dilation of the left ventricle with systolic dysfunction and recovery in 7 to 10 days. In fact, the study also led scholars to explore the nature of cardiac function changes in sepsis, especially after critical care echocardiography, the visualization technology, is used extensively. More attention was then paid to the changes in left ventricular systole, left ventricular diastole and right ventricular function in sepsis. Now our understanding of the different cardiac functions in sepsis is rather complete. In the review of Martin et al in 2019, they proposed the main characteristics of sepsis-induced cardiomyopathy: left ventricular dilation with normal left ventricular filling pressure/low filling pressure, reduction of ventricular contractility, right ventricular dysfunction (RVD)/left ventricular (systolic/diastolic) dysfunction with decreased volume responsiveness. Geri et al. also proposed that cardiovascular clusters appear in sepsis. Though they stressed the importance of cardiac classification in sepsis in one way or another, their opinion focused only on the
phenomenon of cardiac function and hemodynamic changes in sepsis, and to some extent they emphasized the categorization with echocardiography, but the pathophysiologic mechanism was not clearly demonstrated. We will explain the possible pathophysiologic mechanism of the cardiac function changes in sepsis-induced cardiomyopathy from the perspective of the changes seen on critical care echocardiography [Figure 1].

**Left Ventricular Systolic Dysfunction vs. Takotsubo, One and the Same?**

**General knowledge and morbidity**

There are different scales of research on sepsis-induced cardiomyopathy, and the incidence of left ventricular systolic dysfunction (LVSD) varies. According to current incomplete statistical results, the morbidity of LVSD in sepsis patients is between 12% and 60%.[3,6-23] At the early stage, the study of cardiac function in sepsis patients was limited, with a focus on a single ventricle [Table 1].

**An explanation of left ventricular systolic dysfunction**

LVSD was the earliest focus of research on the heart in sepsis. What Parker et al.[10] found in 1984 was a milestone. Among the 20 sepsis patients they studied, 50% had decreased left ventricular systolic function. However, the reason for the decreased systolic function had no explanation at that time.

At present, the mechanism of LVSD in sepsis is based on the influence of load effects and LPS effects on left ventricular systolic function. The tension of the peripheral arteries and veins decrease in sepsis, and the stressed volume is converted into a non-stressed volume, which results in an insufficient effective circulation volume, that is, low preload and low afterload. At this time, the left ventricular systolic function can be significantly increased. But what makes the heart function collapse? Although the early goal-directed therapy program proposed by Rivers et al.[25] in 2001 was questioned by the ProCESS, ARISE, and ProMISE studies, fluid resuscitation is still indispensable in sepsis, the low preload condition can be corrected rapidly, and the afterload will directly impact myocardial contraction. Beyond a certain range, an increase in afterload will reduce myocardial contractility and CO. Repessé et al.[23] summarized the incidence of LVSD according to the time of evaluation in 2013. The study included four time points: 6, 12, 24, and 72 h. Over time, the proportion of LVSD gradually increased from 18% to 60%, reflecting the correlation between cardiac dysfunction and time in patients with sepsis treatment. They speculated that with time, sepsis is gradually controlled, followed by vasoplegia, and then the afterload is corrected. The LVSD is explained based on the theory of the coupling between left ventricular contractility and left ventricular afterload. The systolic function reduction is ascribed to the increase in afterload. While there are still some patients with sepsis who have fully adjusted preload and afterload, LVSD still exists, which may be explained by differential of gene expression, metabolic effects and endotoxin-induced structural and functional changes of the heart.[9,26]

**Left ventricular systolic dysfunction and stress**

Reviewing an article about left ventricular dysfunction in sepsis patients in 1985 by Ellrodt et al.,[27] we found that patients without basic cardiac diseases, female patients, and young patients are more likely to have systolic dysfunction, while those with basic heart diseases tend to have diastolic dysfunction, which may be related to the low blood supply to the heart. LVSD seems to have certain characteristics. We retrospectively analyzed the relevant articles about the factors that may influence LVSD in sepsis. Pulido et al.[11] found that the patients with moderate or severe systolic dysfunction were significantly younger than patients without systolic dysfunction, and the patients with systolic dysfunction were on average 59 years old, which is younger than the patients with diastolic dysfunction whose average age is 64 years. Young patients are more likely to suffer from systolic dysfunction in sepsis. It seems that systolic dysfunction patients in sepsis shares common characteristics with Takotsubo syndrome (TTS), proposed by a Japanese scholar.

Y-Hassan et al.[13] summarized commonalities of Takotsubo and systolic dysfunction in sepsis; sepsis was controlled as the only stress factor in the study; coronary occlusion was excluded by coronary angiography; systolic dysfunction and Takotsubo occurred. The average age of the patients in the study was 60 years, less than that of the patients with other stress factors. Thus, is it possible that the mechanism of systolic dysfunction in sepsis coincides with TTS? What we know about is that TTS is characterized by a temporary wall motion abnormality of the LV and shares common features with acute coronary syndrome.[28] Templin et al.[29] reported four types of TTS.

![Diagram of SIC classification](image-url)
Table 1: Relevant studies of left ventricular systolic dysfunction in patients with sepsis.

| Author et al (year) | LVSD (isolated) | Factors |
|--------------------|----------------|----------|
| Parker et al (1984) | 10/20, 50% (-)ERNA | – |
| J. Pochaert et al (1997) | 6/25, 24% (-)TEE | – |
| Bouhemad et al (2008) | 22/54, 40.7% (20.4%) TTE | – |
| Vieillard-Baron et al (2008) | 40/67, 60% (-) TTE | – |
| Weng et al (2012) | 16/61, 26.2% (-) TTE | – |
| Landesberg et al (2012) | 61/262, 23.3% (11.7%) TTE | – |
| Pulido et al (2012) | 29/106, 27.4% (8%) TTE | – |
| Endo et al (2013) | 23/93, 24.7% (-) TTE | – |
| Y-Hassan et al (2014) | Segmental 14 | Age |
| Orde et al (2014) | 20/60, 33% TTE 69% (-)STE | – |
| Prabhu et al (2015) | 18/66, 27.27% (-) TTE | – |
| Landesberg et al (2015) | 13/105, 12% (-) TTE | – |
| Dalla et al (2015) | 17/34, 50% (-) TTE | – |
| De Geer et al (2015) | 22/44, 50% (11.4%) TTE | – |
| Sato et al (2016) | 29/210, 13.8% (-) TTE | Age, HF |
| Boissier et al (2017) | 42/132, 31.8% (-) TTE/TEE | – |
| Vallabhajosyula (2017) | 22/58, 38% (29.3%) TTE | – |
| Clancy et al (2017) | 26/62, 40.3% (-) TTE | – |

The given figures represent the number/total number of systolic dysfunction studied and the percentage of systolic dysfunction (isolated left ventricular systolic dysfunction). LVSD (isolated): Left ventricular systolic dysfunction (isolated left ventricular systolic dysfunction); ERNA: Equilibrium radionuclide angiography; TTE: Trans-thoracic echocardiography; TEE: Trans-esophageal echocardiography; Meds: Medicines; HF: Heart failure; STE: Speckle tracking echocardiography; –: No data.

Prognosis

Y-Hassan et al[33] found that the mortality of LVSD in sepsis was 7%. Correcting for the bias, a meta-analysis performed by Huang et al[42] included more than 700 sepsis patients and found no relationship between LVSD and mortality in sepsis. The ventricular volume index was not related to mortality either. A systematic review by Sevilla Berrios et al[43] completed in 2014 also indicated that LVSD in sepsis patients is neither sensitive nor specific as an indicator of mortality.

Treatment

Normally, LVSD does not necessitate an adjustment of the treatment. This is done only if CO and central venous oxygen saturation decrease significantly. Even if sepsis is controlled, some patients still need cardiotonic therapy. In 2006, Rabuel and Mebazaa[44] concluded that approximately 15% of patients needed cardiotonic therapy to improve systemic circulation perfusion. As cardiotonic drugs, milrinone and levosimendan[45-47] are preferred. Catecholamines for sympathetic nerve excitation are not an option, which may have some connection with the stress explanation of LVSD in sepsis patients up to a point.

Left Ventricular Diastolic Dysfunction vs. Forgotten Backgrounds, More to Explore

General knowledge and morbidity

The morbidity of diastolic dysfunction is between 20% and 79%[7,10,11,22,23,48-52] in sepsis, higher than the prevalence in the community in Olmsted.[33] However,
the cause of left ventricular diastolic dysfunction (LVDD) in sepsis is still unknown [Table 2].

An explanation of right ventricular diastolic dysfunction

We searched articles in PubMed from 1960 to 2019, and several relevant studies on sepsis-induced cardiomyopathy by critical care echocardiography were found, in which patients with a past medical history of hypertension, diabetes, and ischemic cardiomyopathy are more likely to have diastolic dysfunction, as were older patients. An article also indicated that left atrial systolic dysfunction was closely related to left ventricular diastolic function.

Garvan and Kane published an article in JAMA claiming that age is a predictor of diastolic function deterioration in those who are 65 years or older and that persistent diastolic insufficiency is a risk factor for heart failure. Kuznetsova et al found that moderate to severe diastolic dysfunction increases the risk of symptomatic heart failure and mortality. Left ventricular diastolic function, as an important component of cardiac diastolic function, is clearly related to age, hypertension, diabetes, and left ventricular hypertrophy.

Jeong and Dudley also summarized the factors causing diastolic dysfunction. Besides the basic diseases mentioned above, they pointed out that the increase in wall stiffness in elderly patients, the increased ventricular hypertrophy caused by long-term afterload increases due to hypertension, and the relative decrease in coronary blood supply are of great importance. The increase in heart rate also reduces the diastolic time, which contributes the most to left ventricular diastolic function. An increase in heart rate is quite common in sepsis, which was proposed to be due to sympathetic hyperactivity in sepsis, also known as systemic inflammatory response syndrome. The animal study used esmolol to control the heart rate of rats to inhibit sympathetic activity, and the mortality of rats in the esmolol group was significantly lower than that in the control group. Recently, treatment with β-blocker to inhibit sympathetic activity was applied in sepsis patients, yielding good results.

Therefore, patients with LVDD tend to be elderly or to have a medical history of diabetes, ischemic cardiomyopathy, left ventricular hypertrophy, or heart rate increase in sepsis. More research still needs to be carried out to determine the difference in the morbidity of LVDD between sepsis and the general population.

In addition, in the paper of Ishizu published in 2018, weakness was also seen as an important factor causing diastolic dysfunction. Thus, the effects of sepsis which may induce the intensive care unit acquired weakness could be an important factor in diastolic function.

Prognosis

LVDD is closely related to mortality. Therefore, improvement of diastolic function may reduce the mortality of sepsis patients.

Treatment

Since 2016, the American Society of Echocardiography and the European Association of Cardiovascular Imaging updated the guideline for the diagnosis of LVDD, and the treatment of LVDD in sepsis has been paid more attention by critical care physicians. It is possible that the evaluation methods have become more applicable, especially in critical medicine. Critical care physicians can quickly distinguish the diastolic function of patients according to tricuspid regurgitation, left atrial volume index, e′ (the tissue Doppler velocity of mitral annulus which represents the diastolic function of left ventricle.) and average E/e′ (Be used as a parameter to estimate the left atrium pressure; E is the maximum pulse Doppler velocity on left ventricular diastolic period which represents the pressure of left atrium to some extend.) through critical care echocardiography. Left ventricular diastolic function can be monitored immediately and dynamically during the whole process of fluid resuscitation and symptom control in sepsis. Left atrial pressure estimated by Doppler can be controlled through the management of fluid, avoiding the occurrence of LVDD, which could cause an increase in pulmonary vein pressure and lead to RVD and low CO. The increase in heart rate is another significant clinical manifestation in

| Author (year) | LVDD (isolated) | Factors |
|---------------|-----------------|---------|
| Bouhemad et al (2008) |
| Landesberg et al (2012) |
| Pulido et al (2012) |
| Brown et al (2012) |
| Rolando et al (2015) |
| Sanfilippo et al (2015) |
| Lanspa et al (2016) |
| Gonzalez et al (2016) |
| Vallabarthosyula et al (2017) |
| Clancy et al (2017) |

The given figures represent the number/total number of diastolic dysfunctions in the study and the percentage of diastolic dysfunction (isolated left ventricular diastolic dysfunction percentage). LVDD (isolated): Left ventricular diastolic dysfunction (isolated left ventricular diastolic dysfunction); HTN: Hypertension; DM: Diabetes mellitus; IHD: Ischemic heart disease; CAD: Coronary artery disease; HR: Heart rate;–: No data.
sepsis, especially for patients with left ventricular hyper-trophy with declined compliance. Excluding other factors, such as low volume, fever, and anemia, β-blockers should be used to control heart rate and improve cardiac diastolic function. Arrhythmia that deteriorates the left ventricular diastolic function should also be taken seriously and corrected in sepsis.

**Right Ventricular Dysfunction vs. Loading, Sounded the Alarm**

**General knowledge and morbidity**

The incidence of RVD has shown a certain heterogeneity, ranging from 30% to 55%,[^62-66] which is no less than the incidence of LVDD.

**An explanation of right ventricular diastolic dysfunction**

As early as 1983, Hoffman et al[^63] found that RVD in sepsis often occurs after hypovolemia is corrected, and pulmonary vascular resistance increases at the same time. Kimchi et al[^63] pointed out that patients with right ventricular function recovery are more often those without pulmonary hypertension or respiratory distress among sepsis patients. Some scholars put forward the view of consistency of right heart and left heart function changes in patients with sepsis. Vallabhajosyula et al[^62] finished a historical cohort study in 2017, which included 338 patients with sepsis, 55% of whom had right heart dysfunction. The patients were divided into three groups: independent right heart dysfunction group, right heart and left heart dysfunction group, and without right heart dysfunction group. It was found that the mechanical ventilation rate was higher in patients with RVD. For sepsis patients, especially those who had septic shock, though the right heart is in the period without much tension under physiologic conditions, with positive fluid resuscitation, CO increases to some extent. At this time, after the load of the right heart is increased, the volume load is increased, as is the right heart tension. If there is a pulmonary infection, acute respiratory distress syndrome or even mechanical ventilation, which may increase the afterload of the right heart, will cause RVD. Some people even proposed reducing coronary perfusion, which needs further evidence.

**Prognosis**

Speckle tracking echocardiography (STE) is a new technique with high sensitivity for assessing cardiac function. In 2012, Furian et al[^67] studied the relationship between ventricular function and sepsis and concluded that RVD indicated poor prognosis. In 2014, Orde[^14] used this technology to find that patients with RVD in sepsis had higher mortality. A retrospective study of sepsis patients with RVD published by Winkelhorst et al[^68] in 2020 in the *Journal of Shock* found that the 1-year mortality rate of patients with severe RVD reached 57%. It seems that the incidence of RVD in this part of sepsis patients is related to the increase in right ventricular afterload, which highlights the vicious circle of the right heart function. However, the key link between mortality and the right ventricle still needs more study.

**Treatment**

The treatment of RVD has been paid more and more attention in clinical practice, especially after Wang et al[^69] published the Consensus on Right Ventricular Management in 2017, which emphasizes that RVD is easy to lead to auto-exaggerated vicious cycles. When right heart dysfunction happens due to the increase in afterload, it is easy to develop right heart high pressure and ventricular septum compression, which will affect the systolic and diastolic function of the left ventricle and cause CO to be significantly reduced. The treatment strategy mainly includes improving the perfusion of the right ventricle, reducing the preload and afterload of the right heart. Preload problems are solved more by clinical volume management, while afterload problems require related treatment to reducing pulmonary vascular resistance, such as reducing pulmonary vascular injury, treatment of pulmonary infection and acute respiratory distress syndrome, and weaning off of positive pressure ventilation as soon as possible. Coronary perfusion of the right heart itself is also an important factor affecting the function of the right heart during the adjustment of preload and the afterload.

**Diffuse Dysfunction, the Typical One**

With advancements in techniques, such as the development of STE, researchers have found that the incidence of insufficiency of the left or right heart is higher than that of traditional methods. Combining the current status of animal experiments, microscopic manifestations of cardiomyocytes in sepsis and the findings of a Chinese research team[^70], perhaps the diffuse inhibition of left and right heart is the classic clinical manifestation of sepsis.

**Co-existing Dysfunction, the Common One**

The proposal of this classification is mainly based on the description of comprehensive changes to cardiac function in sepsis mentioned above. The age, sex, basic disease, infection site and type of patient with sepsis are different, and the changes in cardiac function of patients with sepsis are multiple. We call this condition co-existing cardiac dysfunction in sepsis. This classification may help us to form a more complete understanding of the pathophysiologic mechanism of hemodynamics in clinical practice, which will help intensive care physicians improve their treatment.

**Conclusions**

In summary, sepsis-induced cardiomyopathic pathogenesis is quite complicated. According to our review, patients with sepsis and TTS may share the same pathophysiologic mechanism, that is, the pathophysiologic effect caused by stress. The LVDD may be explained by basic background factors, such as age, hypertension, and ischemic cardiomyopathy, to some extent. After removing the common factors that affect the heart rate, an increase in heart rate also affects left ventricular diastolic function. Mechanical ventilation or lung injury seems to play an important role in the development of RVD. However, the objective injury
of cardiomyocytes in sepsis patients may foreshadow diffuse dysfunction in sepsis. Our pace of research on the mechanism of cardiac function change in sepsis patients may influence by many factors, which is manifested as a mixed cardiac function change. A comprehensive analysis is needed to be done to guide the clinical diagnosis and treatment program.

Conflicts of interest
None.

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