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Perspective

Sepsis-related cardiomyopathy: Not an easy task for ICU physicians

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ABSTRACT

Sepsis-induced myocardial dysfunction is common. In addition to acute coronary syndrome, at least two types of left ventricular dysfunction can occur in septic patients: typical septic cardiomyopathy (SC) and sepsis-related takotsubo cardiomyopathy (ST). Although the definition of septic cardiomyopathy is based on left ventricular (LV) systolic dysfunction, both ventricles can be affected. In this context, it has been increasingly recognized that right ventricular (RV) systolic dysfunction is associated with long-term prognosis in septic patients. Unlike typical SC, ST patients usually displayed LV apical and circumferential mid-ventricular hypokinesia and basal hypercontractility. Timely and precise evaluation of heart dysfunction in sepsis patients is not easy but obviously mandatory. Further studies are still warranted regarding the mechanism, evaluation, and management of septic cardiomyopathy.

Sepsis is a major health problem that affects millions of people around the world each year. Myocardial dysfunction is common in patients with sepsis and can affect both ventricles.[1,2] The traditional definition of septic cardiomyopathy was based on left ventricular (LV) dysfunction.[3] However, there are at least two types of LV dysfunction that can occur in patients with sepsis: typical septic cardiomyopathy (SC) and sepsis-related takotsubo cardiomyopathy (ST).[4]

Septic Cardiomyopathy (SC)

In patients with sepsis, the diagnosis of SC is usually based on a decrease in LV ejection fraction (LVEF) and the presence of global LV systolic dysfunction.[3,5,6] As LVEF is not a load independent parameter, the presence of LV systolic dysfunction can be unmasked by the administration of norepinephrine infusion.[3] Therefore, the blood pressure should be taken into consideration during evaluation of LV systolic function.

There is currently no consensus on the mechanism of SC, and several potential mechanisms have been discussed. First, as disruption of the microcirculation has been proposed to be a common phenomenon in patients with sepsis, some researchers speculate that alterations in the coronary microcirculation may contribute to the occurrence of SC.[7] However, other researchers have argued that the blood flow in the coronary microcirculation increases instead of decreasing.[8,9] Second, the release of cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 during endotoxemia can give rise to myocardial depression either directly or through the release of nitrogen monoxide. A previous study found that catecholamine infusions can increase levels of IL-6, which may be blocked by β blockers. The authors, therefore, hypothesized that measures to decrease the dose of catecholamines may help down regulate the myocardial cytokine load.[10] Third, in an animal model of endotoxic shock, researchers found that reduced calcium sensitivity of the myocardium contributed to myocardial depression.[11]; this may explain why levosimendan can improve myocardial contractility. Fourth, mitochondrial dysfunction may also contribute to myocardial depression in sepsis. An animal study found that targeting mitochondrial dysfunction can improve heart function and lower mortality.[12,13]

Although the definition of SC is based on LV systolic dysfunction, both ventricles can be affected.[2,3] In this context, it has been increasingly recognized that right ventricular (RV) systolic dysfunction is associated with long-term prognosis in septic patients.[14,15] The RV is anatomically and functionally different from the LV and is more prone to be compromised by alterations in the afterload.[16] Besides a decrease in intrinsic RV contractile function in sepsis and septic shock, an increase in RV afterload is common and results from complications including acute respira-

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tory distress syndrome (ARDS), concomitant LV dysfunction, or positive pressure ventilation.[17–19] In a previous study, we found that RV pulmonary arterial coupling, represented by the ratio of tricuspid annular plane systolic excursion/pulmonary arterial systolic pressure, is associated with 1-year all-cause mortality in septic patients.[20] Thus, although the definition of SC is based on LV systolic dysfunction, physicians should be more cognizant of RV dysfunction. In addition, apart from source control and the administration of appropriate antibiotics, the integrated treatment of SC should aim to improve the hemodynamic state rather than merely reverse decreases in LV or RV systolic function by administering inotropic agents.

Characteristics of Sepsis-Related Takotsubo Cardiomyopathy

The LV motion characteristic of typical SC represents a global compromise in LV systolic function. The presence of regional wall motion abnormality indicates that acute coronary syndrome (ACS) or ST should be considered. ACS is beyond the scope of this review; therefore, we have restricted the discussion to ST, which is a reversible stress-induced cardiac dysfunction.[21,22] Interestingly, ST is not rare in septic patients. Some cases of takotsubo cardiomyopathy have been reported in septic patients.[23,24] Park et al.[25] concluded that takotsubo cardiomyopathy is a frequent phenomenon in critically ill patients admitted for non-cardiac disease. They noted that 62% of the patients with takotsubo cardiomyopathy in their cohort had sepsis.

Takotsubo cardiomyopathy is generally characterized by reversible systolic dysfunction of the apical and/or mid segments of the LV, with a presentation mimicking myocardial infarction; however, it occurs in the absence of coronary artery disease.[26] Coronary angiography is usually requested for the diagnosis of takotsubo cardiomyopathy to exclude coronary artery disease.[27] In intensive care unit (ICU) settings, the following signs indicate the presence of takotsubo cardiomyopathy rather than ACS.[4]: severe acute LV dysfunction without significant serum troponin and creatine kinase-MB elevation, symmetrical mid and apical regional wall motion abnormalities on echocardiography, and repeated echocardiography in a few days to weeks confirming complete recovery of LV function.

The mechanism and pathophysiology of takotsubo cardiomyopathy have not been clearly elucidated. The role of transient catecholamine toxicity, coronary vasospasm, and microcirculatory alterations are among the proposed hypotheses.[28,29] Similar to ACS, takotsubo cardiomyopathy can present with T-wave and ST-segment abnormalities on electrocardiography, minor elevations in cardiac biomarkers, and LV regional wall-motion abnormalities extending beyond the area of distribution of a single epicardial artery, in the absence of obstructive coronary disease. In the ICU, cardiac catheterization often poses a challenge in critically ill patients. Thus, timely echocardiographic examination emerges as a prerequisite to identify whether the regional wall motion abnormality is localized to any specific coronary distribution. A prior study showed that in-hospital mortality rates of takotsubo cardiomyopathy range from 0% to 8%.[30] Most of the patients survive the acute episode and recover normal LV function within 1–4 weeks.[21] Older patients with takotsubo cardiomyopathy are more likely to develop heart failure. Madhavan et al..[31] found the following two variables to be risk factors for acute heart failure in patients with takotsubo cardiomyopathy: age >70 years and LVEF <40%.

Unlike typical SC, ST usually displays LV apical and midventricular circumferential hypokinesia and basal hypercontractility.[32] Most patients with ST who are admitted to the ICU are intubated; therefore, the diagnosis is more likely to be missed in the ICU than in the cardiac care unit or emergency department, where patients were admitted based on complaints of chest pain and/or dyspnea.[33,34] Routine echocardiography may help physicians to identify patients with ST. In this context, a normal or hypercontractile LV basal segment can lead to LV outflow tract obstruction (LVOTO) in takotsubo patients. El Mahmoud et al.[35] reported that LVOTO occurs in 25% of all patients with takotsubo cardiomyopathy. Patients with takotsubo cardiomyopathy who are in a state of shock can usually be categorized into two types depending on the presence of LVOTO. Those with no signs of LVOTO who are in shock due to pump dysfunction can be treated cautiously with inotropes. However, it should be noted that patients with LVOTO should not be treated with inotropic agents, because these agents can worsen the degree of obstruction.[36] Only a small proportion of patients with ST display LVOTO; however, the diagnosis is worth considering, as inotrope administration in such patients could result in dire consequences. Therefore, we believe that echocardiographic examination for distinguishing between ST and SC is justified, as it helps to differentiate between various types of LV systolic dysfunction and identifies the occurrence of LVOTO.

To date, no studies have reported on whether patients with ST tend to have poorer LV function than those with SC. LV systolic function is compromised in both patients with SC and ST; this can result in a decrease of cardiac output. Previous studies have reported that elevated levels of circulating catecholamines could cause takotsubo cardiomyopathy.[28,37] Although the extent to which catecholamine use contributes to the occurrence of ST remains unclear, the identification of patients with ST can guide physicians regarding the use of non-catecholamine drugs or maintenance of catecholamine infusions at the minimum possible rate.

In a previous study on patients with takotsubo cardiomyopathy, RV involvement was observed in 28.8% of patients with major adverse events and in only 9.5% of those without any major adverse events.[38] It is essential that a volume responsiveness assessment is performed in patients with ST who have normal RV. In combination with compromised LV systolic function, i.e., isolated LV systolic dysfunction, normal RV function has been deemed to be an important contributor to pulmonary edema.[39] In this context, we have previously found that respiratory variations in the diameter of the inferior vena cava are less likely to reflect volume responsiveness in patients with isolated LV systolic dysfunction.[40]

In summary, sepsis-related cardiomyopathy is complicated and can compromise LV, RV, or both. The underlying mechanisms of the various types of sepsis-related cardiomyopathy may differ, resulting in differences on electrocardiography and echocardiography; clinically observed heart function may also differ. Timely and precise evaluation of heart dysfunction in patients with sepsis is not easy, but obviously mandatory. Further studies are warranted for evaluating the mechanisms of SC and its management.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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