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Management of Heart Failure Complications in Sepsis Patients

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ABSTRACT

Systemic infections such as sepsis are important clinical problems that cause heart decompensation or heart failure. Cardiac dysfunction caused by sepsis is caused by a functional decline in situations where energy needs are not met by energy production. This phenomenon is often encountered and is related to the severity of sepsis. Careful clinical assessment is needed to diagnose sepsis and heart failure, especially if the conditions overlap. Infections related to heart failure can occur in the community as well as during treatment at the hospital, where most are caused by pulmonary infections and urinary tract infections. Thus, in addition to specific biomarkers, clinical cardiologists have created new criteria for early detection and treatment of sepsis in heart failure patients. These criteria are based on clinical protocols, microbiological tests, and radiological tests. Increased levels of protein and procalcitonin can also point to infections as a cause of decompensated heart failure. This narrative review provides guidance for the management of heart failure complications in sepsis patients based on contemporary evidence and expert opinion.

Keywords: cardiovascular disease; heart failure; sepsis

INTRODUCTION

Heart failure and sepsis are serious public health problems. Heart failure affects over 5.7 million people in the United States each year, and sepsis affects 1.5 million.[1,2] Nearly half of heart failure patients die within five years of their initial diagnosis, and sepsis kills approximately 250,000 Americans each year. [1,3]

Systemic infections such as sepsis represent important clinical problems leading to cardiac decompensation or heart failure. The cardiovascular system plays an essential role in developing multiorgan dysfunction in sepsis. Although there has been a decreasein inpatient mortality due to sepsis since 2000, the mortality rate from sepsis remains high. Cardiovascular dysfunction significantly increases the sepsis mortality rate compared to sepsis cases without cardiac dysfunction. The infection itself can trigger cardiac decompensation and is a marker of mortality in heart failure patients. Sepsis is inflammation that is notregulated by the immune system in response to pathogenic organisms. The heart plays an essential role in the pathophysiology of septic shock, organ failure, and death (34). A study conducted by Cardoso et al. reported high rates of infection during hospitalization (45.8%) and mortality (21.5%) among heart failure patients.[5] Another study in mice showed that myocardial injury, abnormal electrical conduction, cardiac dysfunction, and increased cardiac apoptosis were the causes of cardiac instability in patients with severe infection. Several other studies have also found interactions between infectious agents, the immune system, and chemical mediators that have direct or indirect effects on the myocardium.[4,6]

Heart failure-associated infections can occur in the community or during hospitalization, where most are caused by pulmonary and urinary tract infections. Clinical cardiologists have developed new criteria for the early detection and management of sepsis in heart failure patients based on clinical protocols and microbiological and radiological tests in addition to the examination of specific biomarkers. Elevated levels of protein C (> 25 mg/dL) and procalcitonin may also help identify infection as the cause of decompensated heart failure.[7,8] This paper aims to examine the complete picture of sepsis in cardiac patients from diagnosis to management.

DEFINITION

Sepsis is the presence of at least 2 of the four criteria foran inflammatory response syndrome and evidence of ongoing infection. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Meanwhile, septic shock is a continuation of sepsis in the presence of circulatory and cellular/metabolic dysfunction. Sepsis and septic shock are serious health problems experienced by millions of people worldwide every year. Therefore, early identification and appropriate management of sepsis are needed.[11]

Heart failure is a complex collection of symptoms that a patient must present with: Symptoms of heart failure (typical shortness of breath at rest or during activities with/without fatigue); signs of fluid retention (pulmonary congestion or ankle oedema); There is objective evidence of structural or functional disturbance of the heart at rest.

Heart failure is a progressive health problem with high mortality and morbidity rates in both developed and developing countries, including Indonesia.[12]

EPIDEMIOLOGY

Recent epidemiological studies report an increasing trend in the incidence of sepsis and septicshock from 13 to 78 cases per 100,000 cases from 1998 to 2000.[13] In the late 1970s, it was estimated that there were 164,000 cases of sepsis annually in the United States. An observational cohort study by Stiermaier stated that 28-day mortality in septic patients was 29.5%and increased to 55.4% within three years of hospitalization. In addition, in elderly patients, having multiple comorbidities such as heart failure will increasethe risk of sepsis.[15]

The prevalence of heart failure (HF) increases sharply with age. Data from NHANES have shown that theproportion of adults with HF is 1.5% for men aged 40 to 59 years, 6.6% for men aged 60 to 79, and 10.6% for menaged 80. The proportions among women were 1.2%, 4.8%, and 13.5%, respectively. These data suggest that the prevalence of HF in women exceeds that of men among the elderly.[16] In the ADHERE study, the elderly were more likely to develop atrial fibrillation (AF), strokeor transient ischemic attack, and peripheral vascular disease than younger patients.[17] Renal failure is more common in elderly patients, and the prevalence varies according to the age limit used. Anemia also strongly affects this subgroup. For example, in the OPTIMIZE-HF survey, the proportion of anemia was 19.8% in the 75- year age group compared to 15.2% in the < 75-year age group.[18]

PATHOPHYSIOLOGY

OF PAMPs and DAMPs

When microorganisms invade a host, pathogen- *associated molecular patterns* (PAMPs) such as lipopolysaccharides (endotoxins) from gram-negative bacteria are recognized by immune cells. The binding of PAMPs to cell surface receptors activates the intracellular cascade. As a result, specific genes encoding various proteins, such as cytokines, receptors, and other inflammatory mediators, are up- or down-regulated.

[19] The spread from local infection to sepsis depends on the infection's severity and the inflammatory response's degree. In most severe cases, shock occurs due to decreased vascular tone, increased vascular permeability, and cardiomyopathy leading to sepsis, low stroke volume, low arterial blood pressure, and impairedorgan perfusion. Organ hypoperfusion is exacerbated by impaired microcirculation. If this condition isn't treated, it will lead to persistent shock, which can damage cells and make molecules like mitochondrial proteins, adenosine, or uric acid. [20]

Like PAMPs, DAMPs also have the potential to activate inflammation, causing a dangerous loop (Figure 1). If left untreated, it will reach the end point where the cell death pathway is activated, causing the host's death. This is influenced by host characteristics such as age, sex, comorbidities, and genetic background, as well as infectious properties such as the site of infection and virulence of the pathogen.[19] The final outcome of this process was predictable from the early stages of the disease resulting in 3 groups of patients, namely: (1) a group of patients who survived (survival group *)*, even without treatment; (2) a group of patients who did not survive (non-survival) where intensive care could only delay death and (3) a group of patients who would die if they did not receive therapy but could survive if they receivedproper treatment.[21]

DAMP damage-associated molecular pattern; MOF multiple organ failure; PAMP pathogen-associated molecular pattern; SIRS systemic inflammatory response syndrome.

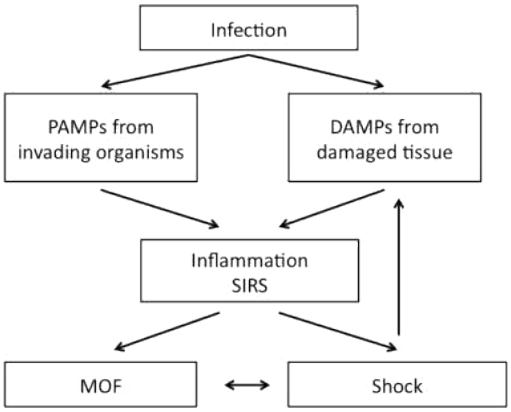

FIGURE 1: Inflammatory activation due to PAMP and DAMP.[19]

***Multiple organ dysfunction syndromes* (MODS)**

Sepsis affects the whole organism over a period of time. This syndrome can affect all organ systems, including the cardiovascular system, autonomic nervous system, endocrinesystem, metabolism, and bioenergetics. During septic shock, circulatory disturbances and mitochondrial damage decreaseATP production and put cells at risk for bio-energetic injury and cell death. To reduce the risk of cell death, adaptive changes can be activated. Decreased cellular function is likelyto limit energy use, creating a new balance between energy supply and consumption.[23] As a result, organs can survive in a non-functioning state similar to hibernation. Consequently, extensive tissue necrosis is not characteristic of sepsis- associated organ dysfunction. When the inflammatory process is over, the cells will make more energy, and the cell process will return to normal, allowing functional recovery.[19]

Septic-induced cardiomyopathy

Cardiac dysfunction is the most common organ manifestation during sepsis or septic shock. Cardiac involvement varies with the timing and severity of the sepsis syndrome. In the early stages of sepsis, echocardiographic findings showing a left-ventricular ejection fraction (LVEF) indicate sepsis. This is caused by an increase in cardiac contractility due to adrenergic stimulation. Importantly, despite a high LVEF, stroke volume at this stage is low because of insufficient cardiac preload caused by high vascular permeability and low vascular tone. During this early stage of sepsis, compensatory increases in heart rate are often not enough to keep cardiac output at a healthy level. This is shown by high lactate levels and low central venous oxygen saturation (ScvO2).[19]

Jarden et al. examined 90 patients with septic shock (28-day mortality rate of 62%) during the advanced phase of sepsis. The non-survival group had a higher severity score (SAPS 68 vs. 52) and received more fluid therapy (5.2 L/day vs. 4.1 L/day) than the survivor group, but had a lower end- diastolic volume, indicating persistent preload deficiency. After the administration of fluid loading, LVEF decreased significantly in all patient groups. However, by the time of transfer from the intensive care unit (ICU), the LVEF had returned to normal in the survivor group.

Cytosolic dysfunction in septic patients and the reversibility of the phenomenon in this group of survivors have been previously investigated by Parker et al. Recently, Vieillard-Baron et al. found that 40 of 67 septic shock patients had an LVEF of 45% within three days of hemodynamic support.

So, it can be concluded that left ventricular systolic dysfunction is common in septic patients and can potentially return to normal in the survivor group.[19]

Several studies have demonstrated the presence of systolic dysfunction during sepsis.[24,25] Landsberg et al. investigated 262 patients with severe sepsis and septic shock (30-day mortality of 30%) using echocardiography.[26] It is evident that there is a lower left ventricular end-diastolic volume and stroke volume in the non-survival group of patients. In addition, diastolic dysfunction is common and is associated with age, a previous history of hypertension and diabetes mellitus and is highly correlated with poor outcomes. Patients with systolic dysfunction (LVEF 50%) and/or diastolic dysfunction had a higher mortality rate.[26] So, it can be concluded that the severity of sepsis is related to the degree of organ involvement, especially in heart disorders. Other clinical aspects of sepsis-related cardiac dysfunction are tachyarrhythmias, right heart failure, elevated troponin levels, and type B natriuretic peptide.

Underlying

The mechanism by which sepsis causes cardiac dysfunction has been studied in depth. The early phase of sepsis is characterized by high levels of circulating catecholamines originating from the autonomic nervous system, lymphocytes, macrophages, and neutrophils. The primary mechanism of cardiac dysfunction due to sepsis is an adrenergic response at the cardiomyocyte level due to the regulation of the turn of adrenergic receptors and the depression of post-receptor signaling pathways. Cytokines and nitric oxide mediate these changes. Reducing this adrenergic response can be done through neuronal apoptosis in cardiovascular autonomic centers and by stopping catecholamines from working through reactive oxygen species (ROS).[19]

The high circulating levels of catecholamines due to endogenous and pharmacologic adrenergic stimulation explain the difference between normal in vivo cardiac contractility observed during a clinical examination and the significant decrease in contractility observed during a laboratory examination. However, adrenergic down-regulation leads to a decrease in cardiac reserve, which is seen in an improved response to dobutamine in septic shock patients. Preload optimization and catecholamine- induced tachycardia can lead to high cardiac output despite intrinsic myocardial depression. So, it can be concluded that myocardial depression can occur even in hyperdynamic conditions, as in the post-resuscitation condition of septic patients.[19]

Myocardial dysfunction induced by sepsis is characterized by disruption of the intracellular calcium pathway. In animal models of sepsis, the L-type calcium flow was slowed down, the number and activity of ryanodine receptors went down, and the calcium re- uptake into the sarcoplasmic reticulum changed.[27] At the myofibrillar level, sepsis can affect the calcium sensitivity of contractile proteins. These changes can impair both systolic and diastolic function.[19]

Severe infection causes myocardial cells to be genetically programmed. 527 genes whose transcription was significantly up or down within 6 hours of sepsis were identified using animal models of rats with fecal peritonitis who received fluid resuscitation. Dos Santos et al. reported the expression of genes that support contraction of the protein-associated fetal isoforms under iNOS- dependent conditions. These results show that genes are turned on and off early at the organ level during sepsis.[28]

More research needs to be done to find out how new interventions can change these mechanisms to make therapy work better. [19]

DIAGNOSIS

Careful clinical assessment is needed to determine the cause of heart failure. Although treatment for heart failure is generally the same for most patients, certain conditions require specific therapy. Most of the time, diagnostic tests are most accurate for people with heart failure who have a low ejection fraction. Diagnostic tests are often less sensitive. in heart failure patients with normal ejection fractions. Echocardiography is the most helpful method for evaluating systolic and diastolic dysfunction.[12]

An electrocardiogram should be performed in all patients with suspected heart failure. ECG abnormalities are common in heart failure. ECG abnormalities have little predictive value in diagnosing heart failure; if the ECG is normal, the likelihood of diagnosing heart failure, particularly with systolic dysfunction, is very low (10%). It is an essential component in the diagnosis of heart failure. A chest X-ray can detect cardiomegaly, pulmonary congestion, and pleural effusion, and it can detect lung disease or infection that causes or exacerbates shortness of breath. Cardiomegaly may be absent in acute and chronic heart failure. Routine laboratory examinations in patients suspected of heart failure are complete peripheral blood (hemoglobin, leukocytes, and platelets), electrolytes, creatinine, glomerular filtration rate (GFR), glucose, liver function tests, and urinalysis. Additional examinations are considered according to the clinical presentation. Significant hematological or electrolyte disturbances are rarely seen in patients with mild to moderate symptoms who have not been treated. However, mild anemia, hyponatremia, hyperkalemia, and decreased renal function are common, especially in patients treated with diuretics and/or ACEIs (Angiotensin Converting Enzyme Inhibitors). ARB (Angiotensin Receptor Blocker), or aldosterone antagonist.[12]

Evidence supports the use of natriuretic peptide plasma levels for diagnosis, making decisions to treat or discharge patients, and identifying patients at risk for decompensation. The normal concentration of natriuretic peptide before the patient was treated had a high negative predictive value and made the possibility of heart failure a very small cause of the patient's symptoms. Natriuretic peptide levels that remain high despite optimal therapy indicate a poor prognosis. Natriuretic peptide levels increase in response to increased ventricular wall pressure. Natriuretic peptides have a long half-life; a sudden decrease in ventricular wall pressure does not directly reduce natriuretic peptide levels. If the clinical picture is accompanied by the suspicion of acute coronary syndrome, a troponin examination is performed in patients with heart failure. Mild rises in cardiac troponin levels are common in patients with severe heart failure or decompensated heart failure who don't have myocardial ischemia.[12]

The term echocardiography is used for all cardiac ultrasound imaging techniques, including pulsed and continuous wave Doppler, color Doppler, and tissue Doppler imaging (TDI). Echocardiography is mandatory to confirm the diagnosis of heart failure and/or cardiac dysfunction and should be performed immediately in patients with suspected heart failure. The measurement of ventricular function to distinguish between patients with systolic dysfunction and patients with normal systolic function is the left ventricular ejection fraction (normal > 45 to 50%). [12]

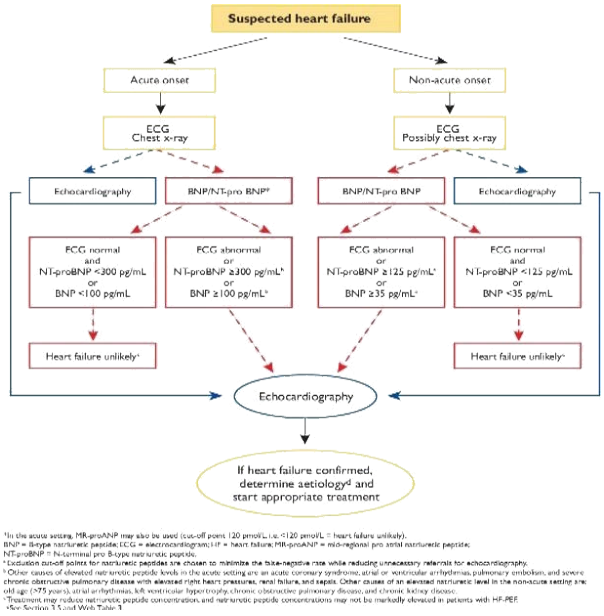

FIGURE 2: Algorithm for diagnosing heart failure.[29]

Sepsis itself may manifest through atypical electrocardiographic and echocardiographic changes. In some cases of sepsis, there is an increase in serum troponin or BNP concentrations. In addition, the ECG in sepsis can show ischemic patterns such as ST segment depression and specific T wave changes.[30]

Echocardiographic changes that are often seen in cases of sepsis include depression of left ventricular function that is seen through evaluation of the ejection fraction (EF%). However, in some cases, the EF value remains normal. This is due to peripheral blood vessels' low resistance to cover the hypokinetic or left ventricularwall. However, the most recommended echocardiographic examination approach in cases of myocardial dysfunction due to sepsis is to use a Doppler tissue pattern examination. The most crucial parameter in diagnosing myocardial dysfunction in sepsis is the peaksystolic velocity of the left ventricular mitral wall, which is associated with mortality in septic patients. Tissue Doppler systolic velocity can better demonstrate the actual ejection function of the left ventricular chamber interms of ejection fraction in patients who often appear normal, according to experimental studies.[30]

Circulating histones are essential mediators of cardiomyopathy-sepsis so that they can be used for prognostic and therapeutic purposes. Concentrations of histones play an important role in arrhythmias, LV dysfunction, and cardiac injury in patients with sepsis. Circulating histones are strongly associated with elevated cardiac troponin T (cTnT) levels in septic patients. In addition, there was also an association between circulating histones and SOFA scores, sepsis severity, and mortality. Cardiac dysfunction with elevated histone levels resulted in a worse prognosis, so treatment with anti-histone antibodies could reduce the consequences of cardiomyopathy and improve the prognosis of patients with sepsis.[35]

TREATMENT

Initial therapy

The main determinant in patients with septic shock is the time to shock resolution because the severity and duration of shock correlate with the degree of inflammation, organ dysfunction, and poor outcome. Application of the 6- hour protocol with predetermined hemodynamic goals significantly reduced the mortality rate from 57% to 42% in patients with severe sepsis and septic shock. 500 ml of crystalloid fluid is given every 30 minutes to achieve a central venous pressure of 8-12 mmHg.

Vasopressors or vasodilators are also given to maintain mean arterial blood pressure between 65-90 mmHg. If SvO2 remains <70%, oxygen transport can be increased using red blood cell transfusion until the hematocrit is 30%. If SvO2 is <70%, then dobutamine 2.5-20µg/kg BW/min is added to increase cardiac contractility. This procedure is added to the rapid diagnosis and treatment of the underlying infection and antibiotic therapy. This action is also recommended in the Surviving Sepsis Campaign guide.[19]

Fluids for preload

While adequate initial fluid therapy can be beneficial, excessive fluid administration can be dangerous.[31] The risk of developing pulmonary edema is increased mainly due to increased permeability of the pulmonary microcirculation and left ventricular systolic dysfunction. Pulmonary edema and concomitant hypoxic conditions can cause vasoconstriction and increased pulmonary vascular resistance (= right ventricular afterload), which can cause right ventricular deterioration with decreased stroke volume and cardiac output. Depending on the fluid used, additional disadvantages can arise, including electrolyte disturbances with normal saline administration, the risk of renal failure with colloid administration, and the high cost of albumin solution administration.[19]

Inotropic for contractility

During the early phase of sepsis, low ScVo2 values and hyperlactatemia indicate an imbalance between oxygen delivery and oxygen demand.[32] After optimization through oxygenation, volume status, and hematocrit, cardiac output can be increased using inotropes. The combination of norepinephrine and dobutamine may improve vascular modulation and cardiac effects compared to norepinephrine alone. However, a study involving 330 patients with septic shock showed no difference in ICU length of stay and mortality between the two strategies. Most importantly, catecholamines and phosphodiesterase inhibitors (which can also increase cAMP) have adverse effects on the heart (arrhythmias, increased oxygen demand) and other organs (hyperglycemia, muscle metabolism, stimulation of bacterial growth, immunosuppressants). Therefore, attempts to increase the cardiac index > 4.5 l/min/m^2 or increase fluid oxygen saturation by 70% with dobutamine administration during sepsis with organ failure are not beneficial and can even be dangerous. This underscores the importance of timing and dose in therapeutic intervention. Although initial administration of catecholamines can help correct shock and restore adequate organ perfusion, long-term administration, especially in high doses, can be dangerous.[19]

Milrinone and other phosphodiadterase III inhibitors have been used to stimulate the hearts of septic patients. This approach may be beneficial in patients receiving beta-blocker therapy because the adrenergic effects of milrione do not originate from beta-receptor stimulation but through decreased degradation of the second messenger cAMP. However, this group of agents can also decrease vascular tone, increasing the risk of arrhythmias and hypotension.

Acute cardiac complications include pneumococcal infection. Elevated cardiac troponin levels are linearly correlated with pneumococcal blood levels. Cardiac troponin (cTn) levels were significantly decreased with the administration of a suppressing agent, pneumolysin (PLY). [36]

Vasopressors for organ perfusion pressure

The most widely used vasopressor in the management of septic patients is norepinephrine at doses up to 1.0 g/kg/min.

Compared with dopamine, noradrenaline causes fewer arrhythmias and ischemia in the skin. Although catecholamines are effective in restoring hemodynamic instability, overuse can be dangerous. A retrospective analysis reported that maintaining mean arterial pressure >70mmHg was not associated with improved survival, whereas mortality could be increased in patients receiving increased doses of vasopressors to achieve this. Vasopressin or synthetic analogues, such as terlipressin, are not recommended as first-line therapy but can be categorized as adjunctive therapy. Vasopressin infusions of 0.01-0.04 U/min are safe to administer when norepinephrine is given at doses exceeding 0.5 g/kg/min.[19]

Metabolic interventions

Sepsis can cause metabolic changes and put vital organs at risk for damage. Several strategies have been proposed to reduce the cellular energy crisis. For example, pyruvate substitution has been evaluated as a provider of cellular ATP. Under aerobic conditions, pyruvate is metabolized in the Krebs cycle. Under anaerobic conditions, pyruvate is converted to lactate. Therapeutic administration of pyruvate can increase myocardial energy availability, thereby improving intracellular calcium metabolism.[19]

Sepsis can cause mitochondrial dysfunction, primarily affecting Complex I of the respiratory chain. Succinate acts as a substrate for complex II and has the potential to bypass complex I dysfunction to improve mitochondrial oxygen utilization and ATP production. The improvement of sepsis appears to require mitochondrial restoration through mitochondrial biogenesis. This process mainly relies on nitric oxide.[19] Elevated blood sugar levels are common in septic patients and represent an additional danger to cellular and mitochondrial integrity.[33] Thus, maintaining normoglycemia with insulin substitution may improve the therapeutic outcome of septic patients. Strategies that aim to maintain blood sugar levels of 4.5–10.0 mmol/L appear safer than tight controls because they prevent hypoglycemic episodes.[19]

SUMMARY

Systemic infections such as sepsis represent an important clinical problem leading to cardiac decompensation or heart failure. Cardiac dysfunction caused by sepsis is caused by functional impairment in situations where energy requirements do not meet energy production. This phenomenon is common and is related to the severity of sepsis. Careful clinical assessment is required to diagnose sepsis and heart failure, especially when these conditions overlap.

Sepsis can be manifested by abnormal electrocardiographic and echocardiographic changes. However, the most recommended echocardiographic examination approach in cases of myocardial dysfunction due to sepsis is to use a Doppler tissue pattern examination. The most important parameter in diagnosing myocardial dysfunction in sepsis is the peak systolic velocity of the left ventricular mitral wall, which is associated with mortality in septic patients.

The main determinant in patients with septic shock is the time of shock resolution because the severity and duration of shock correlate with the degree of inflammation, organ dysfunction, and poor outcome. Fluid therapy should be given with caution because it can cause various unwanted side effects. After optimization through oxygenation, volume status, and hematocrit, cardiac output can be increased using inotropes. Milrinone and other phosphodiadterase III inhibitors can also be used to stimulate the heart of septic patients.

The most widely used vasopressor in the management of septic patients is norepinephrine, where, compared to dopamine, noradrenaline causes fewer arrhythmias and skin ischemia.

Sepsis can cause metabolic changes and put vital organs at risk for damage. Several strategies have been proposed to reduce the cellular energy crisis. Therapeutic administration of pyruvate can increase myocardial energy availability, thereby improving intracellular calcium metabolism. Succinate acts as a substrate for complex II and has the potential to bypass complex I dysfunction to enhance oxygen utilization. Patients with septic shock often have high blood sugar levels. Maintaining normal blood sugar levels with insulin substitution can improve treatment outcomes.

LIST OF ABBREVIATIONS

ACEIs	: Angiotensin Converting Enzyme Inhibitors
ADHERE	: Acute Decompensated Heart Failure National Registry
HF	: Heart Failure
MODS	: Multiple organ Dysfunction Syndromes
EF	: Ejection Fraction (EF)
cTn	: Cardiac troponin
cTnT	: cardiac troponin T
ACEIs	: Angiotensin Converting Enzyme Inhibitors
ARB	: Angiotensin Receptor Blocker
PLY	: Pneumolysin
TDI	: Tissue Doppler Imaging
PAMPs	: Pathogen-*associated molecular patterns*
ScvO2	: Central venous oxygen saturation

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• Competing 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.

Authors' contributions

Abraham Dharmawan: Conceived the ideas, Writing-original draft. Feytie M. Mawey: Conceived the ideas, Writing-original draft.
Yunias Setiawati: Conceived the ideas, Supervision

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