Management of Myocardial Dysfunction in Severe Sepsis

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Abstract and Introduction

Abstract

Sepsis-induced cardiac dysfunction is a frequent and severe complication of septic shock. The mechanisms responsible for its development are complex and intricate. Echocardiography is the best method to make the diagnosis of cardiac dysfunction. Biomarkers (B-type natriuretic peptides and cardiac troponins) can alert clinicians of the possibility of cardiac dysfunction. Low plasma levels can serve to rule out a severe cardiac dysfunction. By contrast, high levels should prompt the performance of an echocardiographic examination. The transpulmonary thermodilution monitor and the pulmonary artery catheter can also be used to alert clinicians or to monitor the effects of inotropic therapy. Dobutamine is the first-line therapy. Its administration remains a matter of debate and should be carefully monitored in terms of efficacy and tolerance.

Introduction

Septic shock is one of the main causes of admission and death in critically ill patients. Septic shock is a combination of hypovolemia, peripheral vascular dysfunction resulting in hypotension and abnormalities in the local/regional distribution of blood flow, cardiac failure, and cell dysfunction.

Importantly, the hemodynamic profile differs from patient to patient, at least regarding the macrocirculatory disturbances. Some septic patients experience a high degree of hypovolemia, whereas others experience a high degree of impairment of vascular tone, and still others experience severe cardiac failure. A variety of combinations can thus exist.

Using transesophageal echocardiography (TEE), Vieillard-Baron et al recently showed that global left ventricular (LV) hypokinesia, defined by LV ejection fraction (LVEF) <45%, was observed in 60% of patients during the first 3 days of treatment of septic shock. In 39% of patients, LV hypokinesia was present at admission (primary hypokinesia), and in 21% of patients, LVEF was normal at admission and LV hypokinesia appeared after norepinephrine infusion (secondary hypokinesia). Interestingly, this myocardial depression was reversible in all patients.

Characteristics of Sepsis-induced Cardiac Dysfunction

Left Ventricular Dysfunction

Myocardial depression in patients with septic shock was initially described as biventricular dilatation associated with a depressed LVEF, which was transient and reversible with a gradual return toward a normal ventricular volume and normal ejection fraction in 7 to 10 days after onset of sepsis in the survivors. In a pivotal study using radionuclide cineangiography, Parker et al found that survivors had lower initial LVEF (mean value: 32%) than nonsurvivors (always > 40%).

There is still some controversy on the presence of acute LV dilatation in septic shock. Some recent echocardiographic studies reported an LV dilatation associated with LV systolic impairment in animals and humans with septic shock, whereas the left ventricle was not dilated in other studies. Importantly, inability of the heart to adapt through dilatation seems to be a pejorative factor and to be associated with worse outcome, in both animals and humans.

Two prospective human studies using TEE reported the presence of a transient and reversible diastolic dysfunction, isolated or associated with systolic dysfunction with or without dilatation, in 20 to 60% of patients with septic shock.

Right Ventricular Dysfunction

Using radionuclide angiography, Parker et al reported similar patterns of change in right ventricular (RV) and LV function with a decreased ejection fraction, and increased end-diastolic volume. Using echocardiography, RV dysfunction was observed in 30% of patients. It may be related to intrinsic myocardial depression and to increased pulmonary vascular resistance, which is a common characteristic of sepsis and results in increased RV afterload.
Mechanisms of Sepsis-induced Cardiac Dysfunction

Numerous mechanisms have been suspected to be responsible for the sepsis-induced cardiac dysfunction. Because they are well detailed elsewhere,[13,14] this article only briefly reviews the role of the major mechanisms.

Extramyocardial Mechanisms

Role of Coronary Blood Flow It is now admitted that ischemic phenomena do not play a major role in sepsis-induced cardiac dysfunction. Coronary blood flow was shown to be preserved in patients with septic shock.[15,16] Nevertheless, if diastolic arterial pressure is very low because of a marked decrease in vascular tone, myocardial ischemia could ensue because diastolic blood pressure is the driving pressure for the LV coronary blood flow.[17]

Role of Circulating Myocardial Depressant Factors The concept of a circulating myocardial depressant factor in sepsis was first proposed in the 1970s[18] and then confirmed by Parrillo et al.[19] Indeed, serum obtained from patients during the acute phase of septic shock was able to decrease the extent and the velocity of rat cardiomyocytes shortening measured in vitro, whereas serum obtained from nonseptic patients immediately restored the contractile force.[19] Importantly, this phenomenon no longer persisted in the recovery phase.[19]

Cytokines such as interleukin 1 (IL-1) and tumor necrosis factor alpha (TNFα) are thought to be the circulating myocardial depressant factors.[20] However, although cytokines might account for myocardial depression at the initial phase of sepsis, they cannot exert a prolonged effect because IL-1 and TNFα plasma levels return to normal values within 48 hours after the sepsis onset.[21]

Moreover, studies using isolated cardiomyocytes harvested from endotoxin-induced septic animals and studied ex vivo, reported contractile depression similar to in vivo measurements in spite of the absence of a direct contact with plasma.[22,23] This suggests that intramyocardial mechanisms can be involved in the sepsis-induced cardiac dysfunction irrespective of the presence of circulating depressing substances.

Intramyocardial Mechanisms

Role of β1-Adrenergic Receptor Hyporesponsiveness The physiological pathway of β1-receptor agonists leads to the formation of cyclic adenosine monophosphate (cAMP) through adenylate cyclase. This triggers intracellular transduction signals, which lead to the release of calcium ions from the sarcoplasmic reticulum into the cytosol and eventually to the contraction of myocardial cells. During septic shock, a decrease in the number of β1-receptors and in the adenylate cyclase activity was reported.[24] In patients with septic shock, Silverman et al showed that dobutamine did not increase cardiac output and that isoproterenol did not increase cAMP, whereas these effects were not observed in septic patients without shock.[25] These modifications seem to evolve over time.[22] Indeed, an enhancement of the β1-agonist inotropic effects is likely to occur in the first 12 hours,[22] probably as the consequence of externalization of β1-receptors at the myocardial cell surface.[26] After the first 36 hours, the inotropic effects are altered,[22] probably due to internalization of β1-receptors.[26]

Role of Reduced Sensitivity of Myofilament to Calcium Cardiac contraction requires that calcium ions combine with the troponin complex, especially with the troponin C. Interaction of calcium ion with the troponin C leads to a spatial conformation change of troponin I, which releases actin, allows formation of actin and myosin bridges and in fine cardiac contraction. Tavernier et al showed that myofilament calcium sensitivity is decreased during sepsis.[23] Protein phosphorylation of troponin I, at the site where the calcium ion normally combines to the troponin complex, may be involved in this reduced ability of calcium to activate the myofilament.[23]

Role of Nitric Oxide and Peroxynitrite Pathways Septic cardiomyopathy induced by cytokines is at least mediated by intracellular nitric oxide (NO) increase.[27] This enhanced production of NO is due to calcium-dependant constitutive or inducible NO synthase (NOS) activation in cardiac myocytes, especially NOS 2, and NO directly induces production of cyclic guanosine monophosphate, which is a phosphodiesterase activator. However, the use of NOS inhibitors could not restore myocardial contractility in endotoxin shock.[28] It is now thought that NO rather plays an indirect role via the production of free radicals, especially cytotoxic peroxynitrite. In this regard, adding peroxynitrite neutralizers improved endotoxin-induced myocardial dysfunction.[29]

Role of Apoptosis Apoptosis can be either due to direct cytotoxicity of NO and peroxynitrite[30] or due to caspase activation by
cytokines. Inhibitors of caspases can completely prevent endotoxin-induced myocardial dysfunction in animals. Caspase-induced cardiac dysfunction can be explained by both destruction of myofilaments and calcium homeostasis deregulation. However, the reversible nature of the sepsis-induced cardiac dysfunction suggests that apoptosis plays a minor role.

**Detection of Sepsis-induced Cardiac Dysfunction**

**Echocardiography**

Echocardiography is the reference method with which to evidence sepsis-induced cardiac dysfunction. Using the Simpson method, echocardiography allows measuring the LVEF, which is the key variable for diagnosing myocardial depression (Fig. 1). It must be stressed that LVEF also depends on the LV afterload and thus on the level of systolic arterial pressure. For example, an LVEF value of 40% indicates a mild depression of LV contractility in case of normal systolic arterial pressure, but a marked myocardial depression in case of low systolic arterial pressure. Echocardiography also allows assessing the degree of sepsis-induced diastolic impairment through analysis of transmitral flow and Doppler tissue imaging. The RV function can be assessed by measuring the RV/LV end-diastolic area ratio in the four-chamber view.

![Diagram of Echocardiography Process](http://www.medscape.com/viewarticle/749209_print)
Echocardiography has two important limitations. First, it is an operator-dependent technique, which requires a long training period to acquire the skill needed to obtain reliable measurements. Second, although it allows repetitive measurements, it cannot be considered as a continuous monitoring method.

**Pulmonary Artery Catheter**

Pulmonary artery catheterization (PAC) is a traditional hemodynamic monitoring method in patients with septic shock. It can help to detect sepsis-induced cardiac dysfunction by showing low cardiac output and elevated cardiac filling pressures.\(^1\) However, this definition is questionable. First, during sepsis, cardiac output can be normal or even high in spite of the presence of cardiac dysfunction. Second, measurements of cardiac filling pressures are subject to numerous pitfalls. Difficulties in measurements and interpretation of PAC data due to insufficient physician knowledge are probably one of the reasons for the decline in PAC use in addition to its high invasiveness.

In the setting of sepsis, PAC would be more helpful for making the decision to infuse inotropic drugs and monitoring their effects than for diagnosing the sepsis-induced cardiac dysfunction (Fig. 1). In this context, continuous monitoring of mixed venous blood oxygen saturation (SvO\(_2\)) can be particularly useful. A low value of SvO\(_2\) (< 65 to 70%) can serve as a trigger for deciding to initiate inotropic therapy in the context of low cardiac output and high pulmonary artery occlusion pressure (PAOP) or even better in the context of low echocardiographic LVEF (Fig. 1).

**PiCCO System**

PiCCO technology (Pulsion Medical Systems AG, Munich, Germany) has emerged as an advanced hemodynamic monitoring technology aimed at being an alternative to the PAC. Using transpulmonary thermodilution, it can provide important variables such as cardiac output, global end-diastolic volume (a marker of cardiac preload), and extravascular lung water (a marker of pulmonary edema). It can also measure the cardiac function index (CFI), which is a marker of the systolic function of the heart.\(^{34,35}\) In patients with septic shock, a good correlation between CFI and LVEF measured using echocardiography was reported.\(^{35}\) Importantly, a value of CFI <3.2 minutes\(^{-1}\) allowed suspicion of an LVEF <35% with good accuracy. This suggests...
that a low value of CFI can alert clinicians and incite them to (re)perform an echocardiographic examination to confirm that the systolic function is actually impaired and to explore the underlying mechanisms responsible for this cardiac dysfunction. Importantly, changes in CFI were found to correlate with changes in LVEF. This suggests that repetitive CFI measurements can be performed to follow the direct impact of inotropic therapy during sepsis-induced cardiac dysfunction.

Using the pulse contour analysis principle, the PiCCO system (Pulsion) also allows real-time monitoring of cardiac output and of pulse pressure/stroke volume variation.

**B-type Natriuretic Peptides**

The prohormone B-type natriuretic peptide (BNP) is synthesized by the ventricular myocytes in response to an increased myocardial stretch. In the circulation, the biologically active BNP hormone is separated from the N-terminal portion of the prohormone, named NT-proBNP. Both systolic and diastolic dysfunction of the left ventricle can result in high circulating BNP and NT-proBNP levels.

Some studies show that septic patients with myocardial depression have higher plasma BNP and/or NT-proBNP levels. Others show that plasma BNP levels could be elevated during sepsis in spite of normal LVEF. In fact, in addition to myocardial stretch, other factors can contribute to elevate natriuretic peptides during sepsis. First, lipopolysaccharide and cytokines, especially TNFα and IL-1β, have been shown to stimulate the BNP messenger RNA (mRNA) expression and the BNP secretion dose-dependently in cultured rat myocytes. Second, the activity of neutral endopeptidase 24.11, which is the enzyme responsible for the plasmatic degradation of BNP, has been shown to be decreased in patients with septic shock. Third, renal dysfunction can reduce the clearance of natriuretic peptides and increase their plasma level even in the absence of a marked increase in proBNP production secondary to increased myocardial stretch.

In summary, it seems reasonable to state that low BNP levels rule out a severe cardiac dysfunction. Nevertheless, presence of high plasma BNP/NT-proBNP levels either on admission or during the course of the disease should rapidly prompt echocardiographic examination to check whether cardiac dysfunction has developed.

**Cardiac Troponins**

Myocardial cell injury results in the release of cardiac troponins. In patients with septic shock, elevated troponin I and troponin T levels have been observed in 50% and in 60 to 100% of cases, respectively. Several studies in severe sepsis patients found a relationship between elevated troponin levels and (1) LV dysfunction assessed by echocardiography, and (2) short-term outcome.

The mechanisms contributing to elevated troponin levels during sepsis are numerous. As mentioned earlier, coronary blood flow is generally maintained or even increased during sepsis. However, in patients with prior coronary disease, high troponin levels due to myocardial ischemia may occur in relation to an increase in myocardial oxygen demand (tachycardia) and/or to a decrease in oxygen supply (anemia, hypoxemia, low diastolic arterial pressure). Microthrombosis in the myocardium may also occur because severe sepsis is a procoagulant state. Myocardial injury related to catecholamine toxicity has been proposed as another mechanism contributing to increased troponin release.

In summary, during sepsis, cardiac troponin release indicates the presence of cardiomyocyte damage and thus provides structural information. It seems reasonable to recommend monitoring cardiac troponins during severe sepsis to increase alertness to the presence of cardiac dysfunction in individual patients.

**Treatment of Sepsis-induced Cardiac Dysfunction**

**Which Patients Need to be Treated?**

Treating sepsis-induced cardiac dysfunction is a matter of debate. It must be remembered that therapeutic strategies aimed at systematically targeting supranormal cardiac output values using fluid and inotropes failed to improve outcome and could even be deleterious. The most recent guidelines of the Surviving Sepsis Campaign recommend giving inotropic drugs if a value of central venous oxygen saturation (ScvO2) ≥70% is not achieved after adequate fluid resuscitation (guided with central venous pressure), vasopressor drug infusion, and correction of anemia.

However, one may be cautious about these recommendations. First, ensuring that volume status is adequate before starting...
Inotrope therapy is a difficult challenge when the central venous pressure alone is taken for guiding fluid resuscitation. More reliable tests (dynamic volume responsiveness indices) would indisputably be preferred. Second, the threshold ScvO₂ (70%) has been arbitrarily fixed, probably in relation to the protocol proposed by Rivers et al. Finally, it is regrettable that the presence of a proven cardiac dysfunction (using echocardiography) was not mentioned as a prerequisite for the decision of inotropic therapy in these guidelines.

Because inotropic agents are not devoid of serious side effects (to be discussed), it seems to us more reasonable to carefully assess the patient's cardiac function—at best by echocardiography—before deciding to treat sepsis-induced myocardial depression.

When systolic cardiac dysfunction is diagnosed with certainty (e.g., LVEF <45% in the presence of restored mean arterial pressure) while the patient is no longer fluid responsive and anemic, the decision to give inotropic therapy should take into account the SvO₂/ScvO₂ value (Fig. 1):

- In case of low SvO₂/ScvO₂ value (e.g., <70%), it seems reasonable to give inotropes.
- In case of high SvO₂/ScvO₂ value (e.g., > 80%), it seems preferable not to give inotropes.
- In case of intermediate SvO₂/ScvO₂ values (e.g., between 70% and 80%), the decision is not straightforward. One should pay attention to other indicators such as veno-arterial PCO₂ difference. In difficult cases, efficacy and tolerance of the inotropic drug can be tested during a brief period before making a definitive therapeutic decision (see later discussion).

In any case, the value of arterial oxygen saturation must be taken into consideration when the SvO₂/ScvO₂ is interpreted. It is estimated that only 10 to 20% of patients who have sepsis-induced cardiac dysfunction really need to receive inotropic drugs.

**Treatment Options**

The ideal inotrope is the drug that would improve myocardial contractility without (1) provoking tachycardia and/or arrhythmias, (2) producing arterial hypotension, and (3) impairing microcirculation.

*Dobutamine* remains the first-line therapy of sepsis-induced cardiac dysfunction. It activates the β₁-adrenergic pathway after its binding to the β₁-receptor (Fig. 2). However, β₁-agonist agents can be less effective in case of septic shock. In this regard, Kumar et al showed that dobutamine infusion increased the LVEF by more than 10% in only 35% of patients with septic shock. When dobutamine therapy is considered, it is important to test its short-term effects in terms of efficacy and in terms of tolerance before any prolonged administration.
Criteria of efficacy should be predefined and generally include increases in stroke volume and myocardial function indices [echocardiography, PICCO (Pulsion)], increase in SvO$_2$/ScvO$_2$, and reduction of blood lactate level (Fig. 1). Note that in case of profound tissue hypoxia, an increase in oxygen consumption should follow the increase in cardiac output such that SvO$_2$/ScvO$_2$ does not increase significantly until a critical level of cardiac output is achieved. In other words, the absence of a large increase of SvO$_2$/ScvO$_2$ during the initial period of resuscitation with dobutamine is not an indicator of inefficacy of the drug and should not discourage the clinician to continue this therapeutic strategy.

Regarding tolerance of dobutamine therapy, monitoring echocardiography is mandatory because this drug is able to induce tachycardia or arrhythmias. Blood pressure monitoring is also important to perform given that dobutamine can induce additional hypotension due to a specific vasodilation (through β$_2$-adrenergic receptors activation).

Levosimendan is a calcium sensitizer, which acts directly on myofilaments by improving their calcium sensitivity. Its mode of action is thus completely independent of the β$_1$-adrenergic pathway (Fig. 2), and it might represent an alternative to dobutamine. In septic animals, levosimendan improves both systolic and diastolic cardiac function.$^{[52]}$ In a prospective, randomized study, Morelli et al showed in 28 patients with refractory septic shock (ie, persisting LV dysfunction after 48 hours of conventional treatment including dobutamine 5 µg/kg/min), that levosimendan (0.2 µg/kg/min) but not dobutamine, increased cardiac index and LVEF while decreasing PAOP.$^{[53]}$ Moreover, levosimendan increased gastric mucosal flow and creatinine clearance while it decreased blood lactate level.$^{[53]}$ Finally, levosimendan can improve RV performance by decreasing RV afterload through pulmonary vasodilator effect.$^{[54]}$ Owing to its vasodilatory effects, levosimendan should not be used in
absence of a concomitant administration of vasoconstrictor agents in the setting of septic shock. More studies are required to conclude definitively about the utility of levosimendan in septic shock with myocardial depression. Nevertheless, because the place of levosimendan is unclear in cases of acute heart failure, the commercialization of this drug has been impeded in many countries over the World.

Norepinephrine is used as a first-line vasopressor in septic shock owing to its α-agonist properties. As a β₁-agonist, it can also increase cardiac contractility and cardiac output. Because these effects are moderate, norepinephrine is not considered as the drug of choice in case of patent sepsis-induced cardiac dysfunction.

Epinephrine is a potent inotropic agent owing to its β₁-agonist properties. Although, it was shown to be as effective as the combination of norepinephrine plus dobutamine, it is not recommended as a first-line therapy to treat sepsis-induced cardiac dysfunction. Indeed, epinephrine can induce lactic acidosis and impair splanchnic microcirculation and gastric mucosal perfusion.

Milrinone, as well as all other phosphodiesterase inhibitors, exerts an inotropic effect by increasing the cAMP concentration in the cardiomyocyte cytosol. Because of their vasodilatory effects and the lack of strong positive data, these drugs are not recommended for the management of sepsis-induced cardiac dysfunction.

Antiinflammatory therapies, such as transforming growth factor β₁ and inflammation pathway inhibitors, could block the development of sepsis-induced cardiac dysfunction, although these agents have no inotropic effect. They represent a potential new therapeutic approach of sepsis-induced cardiac dysfunction.

Conclusion

Sepsis-induced cardiac dysfunction is frequent and occurs early in the course of septic shock. It affects both the left and the right ventricle. It is reversible, and the degree of its severity is variable from patient to patient. The mechanisms responsible for its development are extramyocardial and intramyocardial.

Several tools can be used to diagnose sepsis-induced cardiac dysfunction, but echocardiography is the cornerstone for the diagnosis.

Treatment of sepsis-induced cardiac dysfunction should not be systematic and should be initiated in function of the real impact of this abnormality on tissue oxygenation. Measuring SvO₂/ScvO₂ can be helpful for the decision-making process. The treatment is based on the inotrope administration, especially dobutamine. In any case, it is important to test short-term effects of inotropic drugs in terms of efficacy as well as in terms of tolerance before any prolonged administration.

References

