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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.[1] 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.[2] 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.[3,4] In a pivotal study using radionuclide cineangiography, Parker et al found that survivors had lower initial LVEF (mean value: 32%) than nonsurvivors (always > 40%).[3]

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[5] and humans[6] with septic shock, whereas the left ventricle was not dilated in other studies.[7,8] 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.[3,5]

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.[9,10]

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.[11] Using echocardiography, RV dysfunction was observed in 30% of patients.[12] 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 β_1-Adrenergic Receptor Hyporesponsiveness The physiological pathway of β_1-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 β_1-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 isoprotenerol 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 β_1-agonist inotropic effects is likely to occur in the first 12 hours,[22] probably as the consequence of externalization of β_1-receptors at the myocardial cell surface.[26] After the first 36 hours, the inotropic effects are altered,[22] probably due to internalization of β_1- 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]

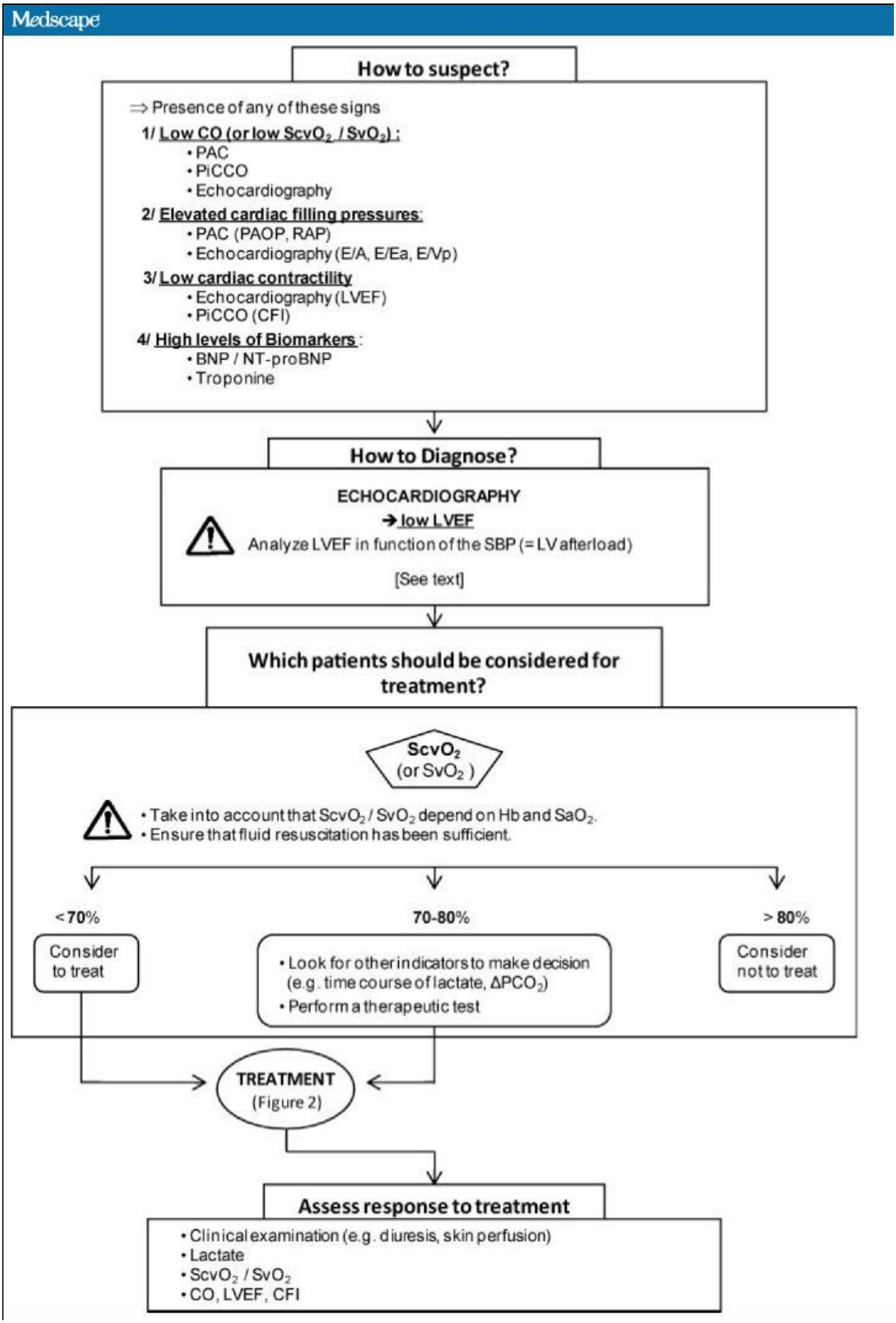
Role of Nitric Oxide and Peroxynitrite Pathways Septic cardiomyopathy induced by cytokines is at least mediated by intracellular nitric oxide (NO) increase.[27] This enhanced production of NO is due to calcium-dependant constitutive or inducible NO synthase (NOS) activation in cardiac myocytes, especially 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 endotoxinic 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.[31] Inhibitors of caspases can completely prevent endotoxin-induced myocardial dysfunction in animals.[32] 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.[9,10] The RV function can be assessed by measuring the RV/LV end-diastolic area ratio in the four-chamber view.[33]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How to suspect?
⇒ Presence of any of these signs
1/ Low CO (or low ScvO2 / SvO2) :
• PAC
• PiCCO
• Echocardiography
2/ Elevated cardiac filling pressures:
• PAC (PAOP, RAP)
• Echocardiography (E/A, E/Ea, E/Vp)
3/ Low cardiac contractility
• Echocardiography (LVEF)
• PiCCO (CFI)
4/ High levels of Biomarkers :
• BNP / NT-proBNP
• Troponine
How to Diagnose?
ECHOCARDIOGRAPHY
→ low LVEF
Analyze LVEF in function of the SBP (= LV afterload)
[See text]
Which patients should be considered for treatment?
ScvO2 (or SvO2)
• Take into account that ScvO2 / SvO2 depend on Hb and SaO2.
• Ensure that fluid resuscitation has been sufficient.
< 70%
70-80%
> 80%
Consider to treat
• Look for other indicators to make decision (e.g. time course of lactate, ΔPCO2)
• Perform a therapeutic test
Consider not to treat
TREATMENT (Figure 2)
Assess response to treatment
• Clinical examination (e.g. diuresis, skin perfusion)
• Lactate
• ScvO2 / SvO2
• CO, LVEF, CFI

Figure 1. Proposal of protocol for managing sepsis-induced cardiac dysfunction. CO, cardiac output; $ScvO_2$, central venous oxygen saturation; SvO_2, mixed venous oxygen saturation; PAC, pulmonary artery catheter; PAOP, pulmonary artery occlusion pressure; RAP, right atrial pressure; LVEF, left ventricular ejection fraction; CFI, cardiac function index; SBP, systolic blood pressure; LV, left ventricle; Hb, plasma hemoglobin concentration; SaO_2, arterial oxygen saturation; ΔPCO_2, veno-arterial difference in PCO_2.

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.[35] 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.[36,37] Others show that plasma BNP levels could be elevated during sepsis in spite of normal LVEF.[38] 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.[39] 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.[40] 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%[41] and in 60 to 100% of cases,[42] respectively. Several studies in severe sepsis patients found a relationship between elevated troponin levels and (1) LV dysfunction assessed by echocardiography,[41] and (2) short-term outcome.[43]

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.[15,16] 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.[44]

In summary, during sepsis, cardiac troponin release indicates the presence of cardiomyocyte damage and thus provides structural information.[45] 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.[46] The most recent guidelines of the Surviving Sepsis Campaign recommend giving inotropic drugs if a value of central venous oxygen saturation ($ScvO_2$) ≥70% is not achieved after adequate fluid resuscitation (guided with central venous pressure), vasopressive drug infusion, and correction of anemia.[1]

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 resucitation.[47] More reliable tests (dynamic volume responsiveness indices) would indisputably be preferred.[48] Second, the threshold $ScvO_2$ (70%) has been arbitrarily fixed, probably in relation to the protocol proposed by Rivers et al.[49] 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 (eg, 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 $SvO_2/ScvO_2$ value (Fig. 1):

- In case of low $SvO_2/ScvO_2$ value (eg, <70%), it seems reasonable to give inotropes.

- In case of high $SvO_2/ScvO_2$ value (eg, > 80%), it seems preferable not to give inotropes.

- In case of intermediate $SvO_2/ScvO_2$ values (eg, between 70% and 80%), the decision is not straightforward. One should pay attention to other indicators such as veno-arterial PCO_2 difference.[50] 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 $SvO_2/ScvO_2$ is interpreted. It is estimated that only 10 to 20% of patients who have sepsis-induced cardiac dysfunction really need to receive inotropic drugs.[13]

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.[1] It activates the β_1-adrenergic pathway after its binding to the β_1-receptor (Fig. 2). However, β_1-agonist agents can be less effective in case of septic shock.[25] 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.[51] 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.

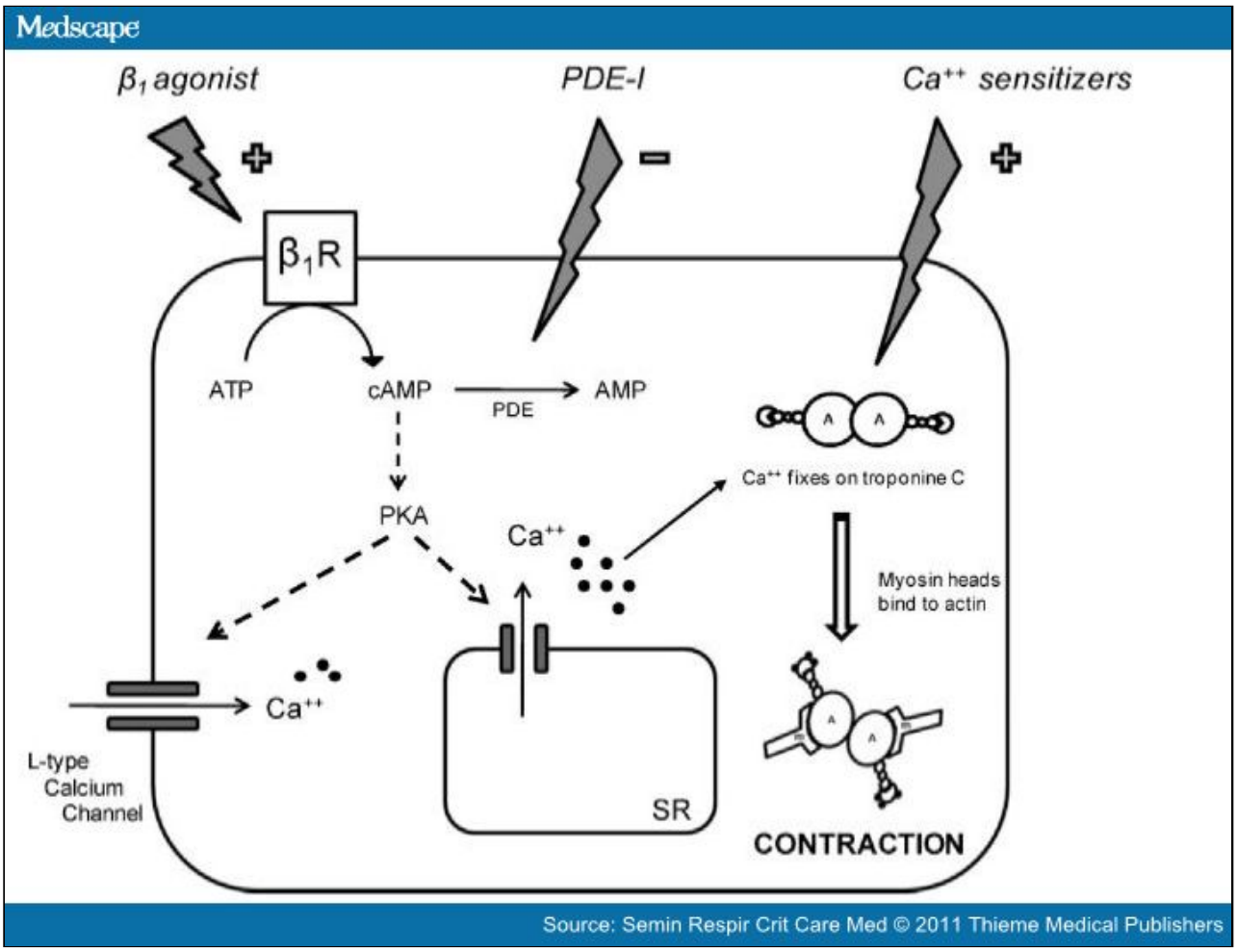

Figure 2. Different classes of inotropes with different mechanisms of action. β_1R, β_1-receptor; PDE, phosphodiesterase; PKA, protein kinase A; SR, sarcoplasmic reticulum; ATP, adenosine triphosphate; AMP, adenosine monophosphate; cAMP, cyclic adenosine monophosphate; PDE-I, phosphodiesterase inhibitor; A, actin filament; m, myosin filament.

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 vasodilatator 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 β_1-agonist, it can also increase cardiac contractility and cardiac output.[55] 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 β_1-agonist properties. Although, it was shown to be as effective as the combination of norepinephrine plus dobutamine,[56] it is not recommended as a first-line therapy to treat sepsis-induced cardiac dysfunction.[1] Indeed, epinephrine can induce lactic acidosis[57,58] and impair splanchnic microcirculation and gastric mucosal perfusion.[57,59]

Milrinone, as well as all other phosphodiesterase inhibitors, exerts an inotropic effect by increasing the cAMP concentration in the cardiomyocyte cytosol (Fig. 2). 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 β_1 and inflammation pathway inhibitors, could block the development of sepsis-induced cardiac dysfunction, although these agents have no inotropic effect.[20,60] 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 SvO_2/$ScvO_2$ 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

1. Dellinger RP, Levy MM, Carlet JM, et al; International Surviving Sepsis Campaign Guidelines Committee; American Association of Critical-Care Nurses; American College of Chest Physicians; American College of Emergency Physicians; Canadian Critical Care Society; European Society of Clinical Microbiology and Infectious Diseases; European Society of Intensive Care Medicine; European Respiratory Society; International Sepsis Forum; Japanese Association for Acute Medicine; Japanese Society of Intensive Care Medicine; Society of Critical Care Medicine; Society of Hospital Medicine; Surgical Infection Society; World Federation of Societies of Intensive and Critical Care Medicine. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36(1):296–327
2. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, Jardin F. Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 2008;36(6):1701–1706
3. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984;100(4):483–490
4. Parrillo JE. Pathogenetic mechanisms of septic shock. N Engl J Med 1993;328(20):1471–1477
5. Zanotti Cavazzoni SL, Guglielmi M, Parrillo JE, Walker T, Dellinger RP, Hollenberg SM. Ventricular dilation is associated with improved cardiovascular performance and survival in sepsis. Chest 2010;138(4):848–855
6. Bouhemad B, Nicolas-Robin A, Arbelot C, ArthaudM, Féger F, Rouby JJ. Acute left ventricular dilatation and shockinduced myocardial dysfunction. Crit Care Med 2009;37(2):441–447
7. Jardin F, Fourme T, Page B, et al. Persistent preload defect in severe sepsis despite fluid loading: a longitudinal echocardiographic study in patients with septic shock. Chest 1999;116(5):1354–1359
8. Poelaert J, Declerck C, Vogelaers D, Colardyn F, Visser CA. Left ventricular systolic and diastolic function in septic shock. Intensive Care Med 1997;23(5):553–560
9. Bouhemad B, Nicolas-Robin A, Arbelot C, Arthaud M, Féger F, Rouby JJ. Isolated and reversible impairment of ventricular relaxation in patients with septic shock. Crit Care Med 2008;36(3):766–774

10. Etchecopar-Chevreuil C, François B, Clavel M, Pichon N, Gastinne H, Vignon P. Cardiac morphological and functional changes during early septic shock: a transesophageal echocardiographic study. Intensive Care Med 2008;34(2):250–256
11. Parker MM, McCarthy KE, Ognibene FP, Parrillo JE. Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression of septic shock in humans. Chest 1990;97(1):126–131
12. Vieillard Baron A, Schmitt JM, Beauchet A, et al. Early preload adaptation in septic shock? A transesophageal echocardiographic study. Anesthesiology 2001;94(3):400–406
13. Rabuel C, Mebazaa A. Septic shock: a heart story since the 1960s. Intensive Care Med 2006;32(6):799–807
14. Hunter JD, Doddi M. Sepsis and the heart. Br J Anaesth 2010;104(1):3–11
15. Cunnion RE, Schaer GL, Parker MM, Natanson C, Parrillo JE. The coronary circulation in human septic shock. Circulation 1986;73(4):637–644
16. Dhainaut JF, Huyghebaert MF, Monsallier JF, et al. Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. Circulation 1987;75(3):533–541
17. Lamia B, Chemla D, Richard C, Teboul JL. Clinical review: interpretation of arterial pressure wave in shock states. Crit Care 2005;9(6):601–606
18. Lefer AM. Role of a myocardial depressant factor in the pathogenesis of circulatory shock. Fed Proc 1970;29(6):1836–1847
19. Parrillo JE, Burch C, Shelhamer JH, Parker MM, Natanson C, Schuette W. A circulating myocardial depressant substance in humans with septic shock: septic shock patients with a reduced ejection fraction have a circulating factor that depresses in vitro myocardial cell performance. J Clin Invest 1985;76(4):1539–1553
20. Kumar A, Kumar A, Paladugu B, Mensing J, Parrillo JE. Transforming growth factor-beta1 blocks in vitro cardiac myocyte depression induced by tumor necrosis factor-alpha, interleukin-1beta, and human septic shock serum. Crit Care Med 2007;35(2):358–364
21. Chensue SW, Terebuh PD, Remick DG, Scales WE, Kunkel SL. In vivo biologic and immunohistochemical analysis of interleukin-1 alpha, beta and tumor necrosis factor during experimental endotoxemia: kinetics, Kupffer cell expression, and glucocorticoid effects. Am J Pathol 1991;138(2):395–402
22. Abi-Gerges N, Tavernier B, Mebazaa A, et al. Sequential changes in autonomic regulation of cardiac myocytes after in vivo endotoxin injection in rat. Am J Respir Crit Care Med 1999;160(4):1196–1204
23. Tavernier B, Li JM, El-Omar MM, et al. Cardiac contractile impairment associated with increased phosphorylation of troponin I in endotoxemic rats. FASEB J 2001;15(2):294–296
24. Reithmann C, Hallström S, Pilz G, Kapsner T, Schlag G, Werdan K. Desensitization of rat cardiomyocyte adenylyl cyclase stimulation by plasma of noradrenaline-treated patients with septic shock. Circ Shock 1993;41(1):48–59
25. Silverman HJ, Penaranda R, Orens JB, Lee NH. Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: association with myocardial hyporesponsiveness to catecholamines. Crit Care Med 1993;21(1):31–39
26. Tang C, Liu MS. Initial externalization followed by internalization of beta-adrenergic receptors in rat heart during sepsis. Am J Physiol 1996;270(1 Pt 2):R254–R263
27. Kumar A, Paladugu B, Mensing J, Kumar A, Parrillo JE. Nitric oxide-dependent and -independent mechanisms are involved in TNF-alpha -induced depression of cardiac myocyte contractility. Am J Physiol Regul Integr Comp Physiol 2007;292(5):R1900–R1906
28. Vona-Davis L, Wearden P, Hill J, Hill R. Cardiac response to nitric oxide synthase inhibition using aminoguanidine in a rat model of endotoxemia. Shock 2002;17(5):404–410
29. Lancel S, Tissier S, Mordon S, et al. Peroxynitrite decomposition catalysts prevent myocardial dysfunction and inflammation in endotoxemic rats. J Am Coll Cardiol 2004;43(12):2348–2358
30. Ahmad R, Rasheed Z, Ahsan H. Biochemical and cellular toxicology of peroxynitrite: implications in cell death and autoimmune phenomenon. Immunopharmacol mmunotoxicol 2009;31(3):388–396
31. Carlson DL, Willis MS, White DJ, Horton JW, Giroir BP. Tumor necrosis factor-alpha-induced caspase activation mediates endotoxin-related cardiac dysfunction. Crit Care Med 2005;33(5):1021–1028
32. Nevie`re R, Fauvel H, Chopin C, Formstecher P, Marchetti P. Caspase inhibition prevents cardiac dysfunction and heart apoptosis in a rat model of sepsis. Am J Respir Crit Care Med 2001;163(1):218–225
33. Vieillard-Baron A. Assessment of right ventricular function. Curr Opin Crit Care 2009;15(3):254–260
34. Combes A, Berneau JB, Luyt CE, Trouillet JL. Estimation of left ventricular systolic function by single transpulmonary thermodilution. Intensive Care Med 2004;30(7):1377–1383
35. Jabot J, Monnet X, Bouchra L, Chemla D, Richard C, Teboul JL. Cardiac function index provided by transpulmonary thermodilution behaves as an indicator of left ventricular systolic function. Crit Care Med 2009;37(11):2913–2918
36. Charpentier J, Luyt CE, Fulla Y, et al. Brain natriuretic peptide: a marker of myocardial dysfunction and prognosis during severe sepsis. Crit Care Med 2004;32(3):660–665
37. Brueckmann M, Huhle G, Lang S, et al. Prognostic value of plasma N-terminal pro-brain natriuretic peptide in patients with severe sepsis. Circulation 2005;112(4):527–534

38. Maeder M, Fehr T, Rickli H, Ammann P. Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. Chest 2006;129(5):1349–1366
39. Ma KK, Ogawa T, de Bold AJ. Selective upregulation of cardiac brain natriuretic peptide at the transcriptional and translational levels by pro-inflammatory cytokines and by conditioned medium derived from mixed lymphocyte reactions via p38 MAP kinase. J Mol Cell Cardiol 2004;36(4):505–513
40. Pirracchio R, Deye N, Lukaszewicz AC, et al. Impaired plasma B-type natriuretic peptide clearance in human septic shock. Crit Care Med 2008;36(9):2542–2546
41. Fernandes CJ Jr, Akamine N, Knobel E. Cardiac troponin: a new serum marker of myocardial injury in sepsis. Intensive Care Med 1999;25(10):1165–1168
42. Røsjø H, Varpula M, Hagve TA, et al; The FINNSEPSIS Study Group. Circulating high sensitivity troponin T in severe sepsis and septic shock: distribution, associated factors, and relation to outcome. Intensive Care Med 2011;37(1):77–85
43. Ammann P, Maggiorini M, Bertel O, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. J Am Coll Cardiol 2003;41(11):2004–2009
44. Turner A, Tsamitros M, Bellomo R. Myocardial cell injury in septic shock. Crit Care Med 1999;27(9):1775–1780
45. Merx MW, Weber C. Sepsis and the heart. Circulation 2007;116(7):793–802
46. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl JMed 1994;330(24):1717–1722
47. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39(2):259–265
48. Monnet X, Teboul JL. Volume responsiveness. Curr Opin Crit Care 2007;13(5):549–553
49. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl JMed 2001;345(19):1368–1377
50. Teboul JL, Mercat A, Lenique F, Berton C, Richard C. Value of the venous-arterial PCO2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. Crit Care Med 1998;26(6):1007–1010
51. Kumar A, Schupp E, Bunnell E, Ali A, Milcarek B, Parrillo JE. Cardiovascular response to dobutamine stress predicts outcome in severe sepsis and septic shock. Crit Care 2008;12(2):R35
52. Barraud D, Faivre V, Damy T, et al. Levosimendan restores both systolic and diastolic cardiac performance in lipopolysaccharide-treated rabbits: comparison with dobutamine and milrinone. Crit Care Med 2007;35(5):1376–1382
53. Morelli A, De Castro S, Teboul JL, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med 2005;31(5):638–644
54. Morelli A, Teboul JL, Maggiore SM, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. Crit Care Med 2006;34(9):2287–2293
55. Hamzaoui O, Georger JF, Monnet X, et al. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. Crit Care 2010;14(4):R142
56. Annane D, Vignon P, Renault A, et al; CATS Study Group. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet 2007;370(9588):676–684
57. Levy B, Bollaert PE, Charpentier C, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Med 1997;23(3):282–287
58. Levy B, Mansart A, Bollaert PE, Franck P, Mallie JP. Effects of epinephrine and norepinephrine on hemodynamics, oxidative metabolism, and organ energetics in endotoxemic rats. Intensive Care Med 2003;29(2):292–300
59. Duranteau J, Sitbon P, Teboul JL, et al. Effects of epinephrine, norepinephrine, or the combination of norepinephrine and dobutamine on gastric mucosa in septic shock. Crit Care Med 1999;27(5):893–900
60. Creagh-Brown BC, Quinlan GJ, Evans TW, Burke-Gaffney A. The RAGE axis in systemic inflammation, acute lung injury and myocardial dysfunction: an important therapeutic target? Intensive Care Med 2010;36(10):1644–1656

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