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THE SEPTIC HEART
Current Understanding of Molecular Mechanisms and Clinical Implications

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Abstract

Septic cardiomyopathy is a key feature of sepsis-associated cardiovascular failure. Despite the lack of consistent diagnostic criteria, patients typically exhibit ventricular dilatation, reduced ventricular contractility and/or both right and left ventricular dysfunction with a reduced response to volume infusion. Although there is solid evidence that the presence of septic cardiomyopathy is a relevant contributor to organ dysfunction and an important factor in the already-complicated therapeutic management of septic patients, there are still several questions to be asked: Which factors/mechanisms cause a cardiac dysfunction associated with sepsis? How do we diagnose septic cardiomyopathy? How do we treat septic cardiomyopathy? How does septic cardiomyopathy influence the long-term outcome of the patient? Each of these questions is interrelated, and the answers require a profound understanding of the underlying pathophysiology that involves a complex mix of systemic factors and molecular, metabolic, and structural changes of the cardiomyocyte. The afterload-related cardiac performance, together with speckle-tracking echocardiography, could provide methods to improve the diagnostic accuracy and guide therapeutic strategies in patients with septic cardiomyopathy. As there are no specific/causal therapeutics for the treatment of septic cardiomyopathy, the current guidelines for the treatment of septic shock represent the cornerstone of septic cardiomyopathy therapy. This review provides an up-to-date overview of the current understanding of the pathophysiology, summarizes the evidence of currently available diagnostic tools and treatment options, and highlights the importance of further urgently needed studies aimed at improving diagnosis and investigating novel therapeutic targets for septic cardiomyopathy.

Introduction

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. Among the various organ systems that fail in sepsis, the heart is one of the most frequently affected organs, although the prevalence of septic cardiomyopathy varies depending on the definition used. In a recently published review, Beesley et al. summarized relevant studies that investigated the prevalence of myocardial dysfunction in septic patients[2]. In fact, the prevalence reported varies between 10% and 70%[2]. We think that the lack of a clear and consistent definition of

septic cardiomyopathy is indeed a major problem in the field and complicates not only the investigations of the prevalence of septic cardiomyopathy but also the investigations relating to the prognostic relevance of the presence of septic cardiomyopathy (see below). Thus, there is an urgent need for a stringent and evidence-based definition of septic cardiomyopathy.

We suggest defining septic cardiomyopathy broadly as a sepsis-associated acute syndrome of cardiac dysfunction unrelated to ischemia with (one or more) of the main characteristics: (i) left ventricular dilatation with normal- or low-filling pressure, (ii) reduced ventricular contractility, and (iii) right ventricular dysfunction or left ventricular (systolic or diastolic) dysfunction with a reduced response to volume infusion[2,3]. The presence of septic cardiomyopathy is a relevant contributor to organ dysfunction and an important factor in further complicating the therapeutic management of septic patients. Several mechanisms have been proposed to explain the pathophysiology of septic cardiomyopathy, including excessive formation of nitric oxide, reactive oxygen species or nitrogen radicals, and transcriptional and metabolic changes[4]. It is essential to realize, however, that alterations in any of the above (or other) signaling pathways can only induce a decrease in cardiac contractility by either affecting the transient rise in cytosolic calcium (Ca^{2+}) or myofilament function, which represents the final integrating step of a myriad of signaling pathways and which may cause the decrease in cardiac contractile force that defines septic cardiomyopathy.

Which factors/mechanisms cause a cardiac dysfunction associated with sepsis?

Pathogen Associated Molecular Patterns (PAMPs) and Toll-Like Receptors (TLRs)

The presence of a microorganism or pathogen is recognized in the host by pattern recognition receptors (PRRs), such as toll-like receptors (TLRs)[5]. TLRs are expressed in immune cells and other cells, including cardiomyocytes, and interact with different PAMPs, such as lipopolysaccharide (LPS), leading to the activation of NF-κB and the subsequent formation of pro-inflammatory cytokines[6]. Indeed, administration of endotoxin in healthy volunteers results in a reduction in left ventricle ejection fraction (LVEF) and an increase in left ventricular end diastolic volume (LVEDV), suggesting that endotoxin is a key driver of cardiovascular dysfunction in sepsis, a

response that has previously been linked to TLR4 activation[7]. In LPS models of sepsis, interfering with the TLR4 activation caused by LPS, e.g., by deletion of either TLR4 or its adapter protein MyD88, improved cardiovascular outcomes and decreased mortality[8]. In contrast, blockage of TLR4 activation with the MD2-TRL4 antagonist eritoran did not improve survival in patients with severe sepsis; however, no data on the impact of eritoran on cardiac function exist[9]. Another recent study also showed that the genetic deletion of TLR4, NLRP3 and caspase-1 did not improve cardiac function in a severe model of (colon ascendens stent peritonitis) sepsis, despite a reduction in the levels of pro-inflammatory cytokines[10]. In addition to LPS, further cell wall components of pathogenic microorganisms (e.g., lipoproteins) are released and recognized by pattern recognition receptors (e.g., 2, 5 and 9), resulting in cardiomyocyte inflammation and dysfunction[11,12]. In fact, these results indicate that sepsis-associated cardiac dysfunction is not only mediated by TLR4. Thus, the application of a TLR4 antagonist will be unable to improve the outcome of patients suffering from septic cardiomyopathy.

Danger-/damage-associated molecular patterns (DAMPs)

In general, sepsis-associated tissue injury and organ dysfunction (i.e., septic cardiomyopathy) develops secondary to an excessive host response to an infection. Although LPS is an important circulating myocardial depressant factor, myocardial dysfunction is not restricted to gram-negative bacterial sepsis[4]. During the last decades, endogenous ligands/mediators (DAMPs) have been described as causative agents of tissue injury and cell damage[13]. In contrast to PAMPs, the origin of DAMPs lies within the host. In this setting, secretion and activation of sheddases causes liberation of endothelial glycocalyx degradation products, such as heparan sulfates[13]. Heparanase remodels the endothelial glycocalyx by degradation of heparan sulfate fragments in various pathological processes, including inflammation, wound healing, and tumor angiogenesis and metastasis[14]. After cleavage of the 65-kDa heparanase to its active 50-kDa form by pro-inflammatory cytokines and reactive oxygen species, heparanase liberates heparan sulfate fragments, which act as highly potent DAMPs[14,15]. Indeed, heparan sulfate fragments in the serum of septic shock patients induce a pro-inflammatory response in cardiomyocytes, as well as cardiac mitochondrial dysfunction[15,16]. Notably, removal of the heparan sulfate fragments

from the serum of septic shock patients results in a significant reduction in inflammatory responses and restored mitochondrial function in cardiomyocytes[15,16]. In addition to heparan sulfate fragments, extracellular histone reduces mitochondrial membrane potential and the cellular ATP level by binding TLR2 and 4[4]. Alhamdi et al. measured increased histone levels in the serum of septic patients and showed a correlation of histone levels with cardiac troponin T, and more notably, with left ventricular dysfunction and arrhythmias[17]. This left ventricular dysfunction is mediated by complement (C5a)-dependent neutrophil activation, resulting in the formation of neutrophil extracellular traps (NETs)[18]. Furthermore, the high-mobility group protein B1 (HMGB1) is a DAMP released by cardiomyocytes (and other cells) in the presence of LPS. HMGB1-associated cardiac dysfunction is induced by the binding of HMGB1 to TLR4 and the associated increased level of intracellular reactive oxygen species (ROS). In addition, HMGB1 mediates calcium release from the sarcoplasmic reticulum (SR) through TLR4 and ROS, which leads to a decrease in calcium content in the SR and reduced contractility (see below)[19]. These data indicate that numerous mechanisms have been proposed, but therapies aimed at targeting a single mechanism (or pathway) have not been effective in improving outcome. However, we think that the investigation, and ultimately the identification, of the underlying molecular mechanisms is crucial for further evaluation of new therapeutics targeting *several* of these mechanisms in parallel. Notably, in a similar vein, a novel class of synthetic antimicrobial/host-defense peptides reduced septic cardiomyopathy by interacting with both PAMPs and DAMPs in rodent models of sepsis[20-22].

Cytokines

During the last few decades, Dr. Parrillo et al. showed that exposure of rat cardiomyocytes *ex vivo* to the serum of (acute-phase) sepsis patients reduced the extent of myocardial cell shortening and that this reversible depression is caused by a circulating myocardial depressant substance[23-25]. The authors suggested that TNF-α was responsible for the cardiovascular changes (including the myocardial dysfunction) associated with septic shock[26]. Indeed, a TNF-α challenge in rabbits (dose-dependent) depresses LV function, and Vincent et al. showed an improvement in ventricular function in septic shock patients treated with a murine anti-TNF antibody[27]. However, treatment with murine monoclonal anti-TNF-α was not enough

to improve survival[28]. Interleukin 1 (IL-1) is produced by neutrophils, macrophages and monocytes in response to TNF-α. Due to their short half-lives, TNF-α and IL-1 are only responsible for the early cardiac depression, while the prolonged effect of cardiac depression is attributed to excessive myocardial nitric oxide (NO) synthesis, which increases in response to TNF-α and IL-1[29] (Figure 1).

Nitric oxide (NO)

Nitric oxide synthase (NOS) generates NO through the oxidation of L-arginine, which forms L-citrulline (Figure 1). Three isoforms of NOS have been identified in myocardial cells: neuronal (nNOS), inducible (iNOS), and endothelial (eNOS). Unlike iNOS, both nNOS and eNOS continuously generate small amounts of NO. iNOS, on the other hand, is expressed in response to inflammation and generates large quantities of NO[30]. In 2010, Bougaki et al. suggested that activation of eNOS decreases inflammatory cytokine synthesis and prevents myocardial dysfunction in experimental (CAST) sepsis. Since then, however, it has also been suggested that NO formation by eNOS may contribute to the early myocardial dysfunction in sepsis[31]. The increased expression of iNOS plays a key role in the late cardiac dysfunction associated with sepsis. Many different mechanisms have been proposed by which an enhanced formation of NO by iNOS contributes to the cardiac dysfunction in sepsis. These include changes in both preload and afterload, downregulation of β-adrenergic receptors[32], a reduction in the response of cardiac myofilaments to Ca^{2+}[33] and a significant contribution to mitochondrial dysfunction[34] secondary to an increase in mitochondrial permeability that results from peroxynitrite production (from NO and superoxide anions)[35].

Mitochondrial dysfunction

Mitochondrial dysfunction is, in addition to a reduced blood supply, a potential cause of multiple organ failure, and, hence, a factor influencing the prognosis and outcomes in patients with sepsis. The mitochondrial dysfunction associated with septic cardiomyopathy is composed of the following: a change in mitochondrial architecture (swelling, internal vesicles formation and abnormalities in cristae), mitochondrial DNA damage[36], elevation in mitochondrial permeability transition and inhibition of the cytochrome C oxidase activity[37]. Downregulation of peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1alpha and beta (PGC-1α and PGC-

1β) causes impaired cardiac energy metabolism due to a reduced mitochondrial substrate flux. PPARγ induces PGC-1α and β and upregulates mitochondrial uncoupling protein 2 expression, which decreases production of mitochondrial ROS (mtROS). Moreover, PPARα regulates the mitochondrial oxidation of fatty acids, thereby controlling the production of mtROS (Figure 1).[38] Patients with sepsis show altered thyroid hormone levels (low T3 syndrome), which is known to both affect mitochondrial function and increase mortality in ICU patients[39]. Downregulation of mitochondrial protein gene transcription was observed in both healthy volunteers who received bacterial endotoxin and critically ill patients[40]. As a result of mitochondrial injury, ATP production is reduced, and if low ATP levels persist, the pathways leading to cell apoptosis are activated. However, cell death is not the main driver of the cardiac dysfunction that is associated with sepsis[41]. Cells may compensate any reduction in ATP generation by increasing glycolysis[42], but this alone is not sufficient to deliver the amounts of ATP that are generated by fully functional mitochondria. Under such circumstances, cells adapt by reducing their metabolic activity. This reduction may be a protective mechanism to prevent cell death, similar to the hibernation state of the heart triggered by brief episodes of ischemia[4,38].

Calcium handling

Septic cardiomyopathy develops as a result of myocardial Ca^{2+} dysregulation (Figure 1).[43] Under physiological conditions, Ca^{2+} enters the cardiomyocytes via L-type Ca^{2+}-channels (LTCC), which results in the release of Ca2+ from the sarcoplasmic reticulum (SR). Cytosolic Ca^{2+} binds to the inhibitory troponin, which removes its inhibitory effect on actin/myosin bonding, leading to their cross-linkage[44]. The amount of Ca^{2+} stored in the SR available for cytosolic release is regulated through the SR Ca^{2+}-ATPase (SERCA2), which represents the key Ca^{2+} regulatory protein in the heart[43]. The inhibition of SERCA2 leads to an impairment in diastolic relaxation, which is secondary to the blocked reuptake of Ca^{2+} into the SR[45]. Phospholamban (PLN) is the principal physiological inhibitor of SERCA2, and phosphorylation of PLN (pPLN) at serine[16] or threonine[17] residues enhances SERCA2 function by decreasing the efficacy of PLN-mediated inhibition[46]. The major phosphatase dephosphorylating PLN is protein phosphatase 1 (PP1), whose activity is controlled by its endogenous inhibitors, PP1 inhibitor-1 and 2. To date, there is very good evidence that the diastolic Ca^{2+} reuptake is reduced during endotoxemia[44]. SERCA2

inhibition after endotoxemia has already been described as early as 1976[47] and has been confirmed by a recent study that used a murine model of polymicrobial sepsis[20]. Notably, this SERCA was associated with a decline in ejection fraction and, hence, cardiac dysfunction[20].

How do we diagnose septic cardiomyopathy?

Key clinical features of septic cardiomyopathy

Septic cardiomyopathy is an acute syndrome of cardiac dysfunction on the basis of systemic infection and inflammation and lacks the ischemic component of coronary artery disease. Of note, as shown in a retrospective cohort analyses by Sato et al., a history of heart failure reveals an important risk factor for the development of septic cardiomyopathy (OR, 3.77; 95% CI, 1.37–10.40). Monitoring the parameters of cardiac performance is technically challenging, as they may deteriorate unnoticed over time. To make matters worse, the patient's baseline cardiac performance is frequently unknown. Moreover, patients present with a heterogeneous clinical picture, including the following: deteriorating hemodynamics under increasing inotropes; tachyarrhythmia; inadequate rise of blood pressure during a fluid challenge; indirect signs of inadequate perfusion, such as rising lactate; and decreased mixed venous oxygen saturation. While recognizing their technical limitation, the techniques presented in the following section provide a means of identifying cardiac dysfunction in septic cardiomyopathy.

Hemodynamic monitoring and ECG

Blood pressure derived from indwelling catheters remains crucial to both the diagnosis and monitoring of the compromised hemodynamic situation in septic patients. However, although frequently used to determine volume depletion, central venous pressure (CVP) has been shown to poorly correlate with left ventricular end-diastolic filling pressure (LVEDP)[48], which is considered to be a relevant target parameter during fluid resuscitation in patients with hypovolemic and septic shock[49]. In contrast, the Swan-Ganz catheter, or pulmonary artery catheter (PAC), allows for comprehensive hemodynamic monitoring. Along with cardiac output (CO), a PAC can provide readouts for pulmonary (PVR) and systemic (SVR) vascular resistance. In addition, PACs help to monitor systemic oxygen depletion by measuring mixed

venous oxygen saturation. Due to possible adverse events connected to its use[50], the PAC is not frequently used in the perioperative setting, with the exception of cardiothoracic patients[51]. However, the PAC may be particularly helpful in the setting of right ventricular failure, pulmonary hypertension, and major vascular or cardiac surgery[52]. Currently, there is no specific endorsement for the PAC in the setting of sepsis, although some authors consider a multimodal approach, including the use of a PAC in conjunction with echocardiography, in the setting of septic cardiomyopathy[53].

Pulse wave analysis (PWA) has been proposed as a potentially less invasive alternative for monitoring cardiac output. However, PWA is tremendously contingent on SVR. As SVR varies heavily during sepsis, in part due to continuous vasopressor therapy, the use of PWA for diagnosing septic cardiomyopathy is less than ideal[54].

In addition to all sophisticated monitoring available, one should still consider furnishing a simple 12-lead ECG as a standard procedure whenever cardiac dysfunction is assumed. ECG changes during septic cardiomyopathy, however, can be similar to a wide variety of other unspecific changes. Some of them may even make it appear as though the patient has acute coronary syndrome[55]. Of note, supraventricular arrhythmias, including atrial fibrillation, are frequent during septic shock. Although a recent small, single-center, prospective cohort study showed that a new onset of supraventricular arrhythmia is not related to myocardial dysfunction (defined by a LVEF <45 % or the need for an inotrope infusion in order to achieve an LVEF ≥45 %), but rather to acute renal failure. As such, further research is warranted to evaluate the causality between septic cardiomyopathy and atrial fibrillation.

Serum biomarkers

In addition to conventional markers of infection and inflammation, such as procalcitonin (PCT), C-reactive protein (CRP) or leukocyte count, some markers of heart failure, such as the N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) have been suggested to facilitate the diagnosis of septic cardiomyopathy[56] (AUC of 0.66, CI 0.46–0.86, p=0.14). A BNP plasma level > 190 ng/L could differentiate survivors from nonsurvivors, with a sensitivity of 70% (CI 55–85) and a specificity of 67% (CI 51–83). A recent investigation conducted in 900 patients revealed that NT-pro-BNP as well as high-sensitive cardiac troponin T (hs-cTNT) are substantially

correlated with the development of septic shock (with or without septic cardiomyopathy). In this investigation, NT-pro-BNP was superior to hs-cTNT in predicting 90-day mortality in patients with septic shock (OR 1.41 with a CI of 1.08–1.85, p=0.01 for NT-pro-BNP; OR 1.09 with a CI of 0.86–1.38, p=0.50 for hs-cTnT). Both NT-pro-BNP and hs-cTNT, however, failed to detect septic cardiomyopathy with a sufficient specificity in this investigation.[57] Thus, we think that these biomarkers are inadequate as diagnostic measures for septic cardiomyopathy. Hence, we decided not to include these biomarkers in our suggested definition of septic cardiomyopathy (see above).

Echocardiography

Estimating cardiac function during sepsis is particularly difficult without taking systemic hemodynamics, which can be significantly altered during the course of the infection, into account. No singular monitoring strategy can determine both cardiac and systemic hemodynamics at the same time[58]. Although an echocardiography in a hemodynamically unstable septic patient is widely considered indispensable, its significance in estimating the degree of septic cardiomyopathy is somewhat less clear. Echocardiographic parameters, such as the left ventricular ejection fraction (LVEF), depend for the most part on a complex system of pre- and afterload. More sophisticated procedures for estimating left and right ventricular contractility, such as the Myocardial Performance Index (MPI) or the Myocardial Velocity Index (MVI), depend on achieving certain angular alignments and appear to lack reproducibility. A novel echo-technique to determine cardiac function employs the measurement of the cardiac strain and strain rate using multiplanar tissue Doppler or speckle tracking. Speckle tracking can be performed retrospectively and is not dependent on certain angulations during measurements[59].

Speckle tracking was first described in 2004 and comprises a semiautomatic algorithm that detects discrete grayscale alterations (speckle patterns) caused by a diffuse reflection of the ultrasound beam within the examined tissue. These unique patterns are then used to identify, track, and thereby quantify two- and three-dimensional myocardial tissue deformation and motion. This technique allows for the detection of a complex tissue deformation in vital myocardium in opposition to measuring the simple displacement of a tissue segment that may also occur from scar

tissue. Hence, the strain measurements resulting from speckle tracking are considered to be better correlated with myocardial function than are traditional measurements. Compared to LVEF, speckle tracking is considerably less susceptible to changes in pre- or afterload or, indeed, myocardial compliance. This decrease in susceptibility is achieved by direct quantification of myocardial deformation[60]. Shahul et al. were able to demonstrate these properties by performing speckle tracking and acquiring longitudinal strains in 35 septic shock patients and 15 patients with sepsis, both with preserved ejection fraction. While global longitudinal strain worsened significantly in the septic shock patients during the first 24 hours, this was not true for patients with sepsis but without shock[61]. Further evidence for the potential diagnostic significance for the use of speckle tracking is provided by the more recent SPECKS trial. Ng et al. demonstrated that global and segmental longitudinal strains are significantly worse in septic shock patients than in patients with sepsis alone[60]. While these results suggest a potential role for speckle-tracking echocardiography in the diagnosis and treatment of patients with septic shock, large, randomized clinical trials that support this hypothesis have yet to be conducted. Thus, longitudinal strain may be a promising measure; however, there is not yet sufficient data to inform a diagnostic measure for septic cardiomyopathy.

Afterload-related cardiac performance (ACP)

While echocardiography has the potential for vastly improving the diagnosis of septic cardiomyopathy, it also carries the disadvantage of being a discontinuous measurement. Afterload-related cardiac performance (ACP) has been proposed as an option for a more relevant continuous monitoring of cardiac performance than is currently available.

$$ACP\ (\%) = \frac{100 \times CO}{560.68 \times \left((MAP - CVP) \times 80 \div CO\right)^{-0{,}645}}$$

Afterload-related cardiac performance (ACP). CO = cardiac output, MAP = mean arterial pressure, CVP = central venous pressure

Werdan et al. showed in 2011 that ACP remained below 60% in 63% of deceased patients in their study. Additionally, 75% of the survivors presented with an ACP

above 60%[62]. Although ACP still does not account for preload, a recent investigation conducted in 141 patients reveals its potential benefits for patients with septic cardiomyopathy. In that investigation, in contrast to cardiac output or cardiac power index, ACP correlated well with 30-day mortality when calculated on admission[63].

Taken together, it becomes clear that only a multimodal approach allows for an adequate diagnosis, classification and monitoring of septic cardiomyopathy. This approach must include a thorough physical examination and hemodynamic measurements (invasive and non-invasive). While sufficient data from studies investigating cardiac strain and strain rate, as well as ACP, MPI, and MVI are warranted, these parameters may help to optimally define, classify and monitor septic cardiomyopathy in the future.

How do we treat septic cardiomyopathy?

Initial fluid resuscitation in sepsis is a cornerstone to restoring hypovolemia. Crystalloids should be used and, if necessary, colloids may be added. The type of colloid that should be used for therapy has been a matter of debate for many years, and currently, human albumin and gelatin solutions are used. To prevent fluid overloading, fluid resuscitation should be guided by the usage of dynamic measures, e.g., stroke volume variation (SVV). The passive leg raise (PLR) is an easy-to-perform bedside test to estimate volume responsiveness of patients in the controlled ventilation mode[64,65]. If the MAP increases by more than 10% when the patient's legs are elevated to 45°, fluids should be added until the PLR test is negative (volume responsiveness below 10%). Although the measurement of MAP is inferior compared to CO or surrogate measurements, the MAP-based PLR test may be of worth in the first few hours until more sophisticated measures are established (see above). In line with our definition, an active recruiting sepsis trial defines fluid responsiveness as an increase of > 10% in MAP after PLR (ClinicalTrials.gov Identifier: NCT02715466).

Current guidelines recommend norepinephrine as a first-line drug intervention to improve blood pressure in septic shock patients suffering from hypotension despite adequate volume resuscitation[66]. Drugs with a combined alpha-adrenergic and beta-mimetic effect (lowest beta-mimetic effect: norepinephrine<dopamine<epinephrine)

have a theoretical advantage. The alpha-stimulating effect (resulting in increased afterload and decreased cardiac output) is accompanied by positive beta-mimetic effects on tissue perfusion and pulmonary vascular resistance[67]. Due to its ability to increase both myocardial oxygen consumption and the incidence of arrhythmias, epinephrine plays a minor role in the treatment of septic cardiomyopathy. Dopamine is inferior with respect to mortality and arrhythmias[68]. A multicenter randomized controlled trial (RCT) with approximately 1700 patients suffering from sepsis or septic shock showed a nearly statistically significant increased mortality in patients treated with dopamine compared to norepinephrine (50.2% vs. 45.9%; p=0.07)[69]. Moreover, a meta-analysis (11 randomized trials with n = 1,710 patients) confirms that the use of norepinephrine results in lower mortality (risk reduction 0.89; 95% CI 0.81–0.98) compared with dopamine[70]. Thus, the SCCM guidelines suggest the use of dopamine instead of norepinephrine only when a critically ill patient is at low risk of tachyarrhythmia and bradycardia[66]. Another vasopressor acting via V1-receptors is vasopressin[68]. Russel et al. conducted the VASST-study to evaluate vasopressin use in patients with septic shock. In this and other trials, vasopressin was proven to be an option in refractory septic shock but not as a first-line or single-use vasopressor[71]. Of note, vasopressin treatment in septic shock is associated with a significant reduction in heart rate but no change in CO or markers of hypoperfusion[72].

According to current guidelines, inotropic support with dobutamine is suggested when volume resuscitation and vasopressors alone cannot sufficiently restore persisting hypoperfusion[66,73]. While cardiovascular parameters are influenced positively, there is no definitive evidence that dobutamine may improve patient outcomes. The optimal dose of dobutamine in septic cardiomyopathy still has to be clarified in RCTs. Until then, doses of dobutamine up to 20μg/kg/min may be justified[66]. However, a combination of dobutamine and norepinephrine showed no effect on 28-day-mortality compared to epinephrine[74]. Similarly, as shown by a recent RCT with 516 patients, levosimendan, an inotrope and lusitrope calcium sensitizer, did not result in a lower mortality rate or less severe organ dysfunction among patients with septic shock[75].

The increased myocardial oxygen consumption caused by tachycardia is the theoretical background to controlling heart rate in patients with septic cardiomyopathy. Indeed, a phase-2 single-center-study demonstrated a 31.1%

reduction in 28-day mortality ($p<0.001$) when the heart rate was set between 80 and 94 bpm through esmolol titration[76]. To prove that this effect is not mediated by extracardiac mechanisms, ivabradine, a 'funny channel' current inhibitor, was planned to be investigated in sepsis. Although a case report of ivabradine treatment in three patients with sepsis was reported[77], the MODIfY study did not make it to the recruitment phase (clinicaltrials.gov; accessed on 02/04/2018). Pleiotropic effects of beta-blockade might increase (beta-2) or decrease (beta-1) inflammation[78]. Further experimental work showed that landiolol, a selective beta-1-blocker with a 4-minute half-life, might have detrimental effects on cerebral oxygenation when therapy is aimed only at attaining a certain heart rate[79]. RCTs are necessary to clarify the role of beta-blockers in septic cardiomyopathy therapy.

In summary, we suggest monitoring cardiac function by echocardiography and using an arterial thermodilution catheter to monitor cardiac output and SVR. As mentioned earlier, it is essential to keep in mind that cardiac output depends for the most part on a complex system of pre- and afterload and therefore has to be individually interpreted based on the patient's hemodynamic conditions. In our view, there is no need to treat LV-dysfunction, as defined by imaging techniques or low cardiac output, without signs of hypoperfusion. We suggest initiating volume resuscitation guided by PLR followed by norepinephrine to restore an adequate mean arterial pressure of at least 65mmHg, or 75mmHg in the case of preexisting hypertension. If a patient is diagnosed with septic cardiomyopathy (see above) and repeated measurements of decreased central venous oxygen saturation (ScVO2) and/or increased lactate in serum levels reflect tissue hypoperfusion, despite adequate volume resuscitation, we suggest adding dobutamine to the therapy. Notably, it is crucial for the patient's success to pursue predefined goals of circulation.

How does septic cardiomyopathy influence the long-term outcome of the patient?

Myocardial dysfunction in septic shock patients is common. It is seen in more than 50% of diagnosed cases regardless of whether or not the initial presentation pointed to cardiac dysfunction[61,80]. Even the influence of right heart dysfunction did not yield clear results with respect to the prognosis. According to a meta-analysis, RV function

was too varied to correlate with mortality[81], whereas others found out that an isolated RV dysfunction, especially when diagnosed with STE, may correlate with long-term survival in sepsis and septic shock[82,83]. A recently published retrospective study showed that although LV-dysfunction may persist in approximately one-third of patients with severe sepsis and septic shock in long-term follow-up, the survival rates did not differ[84]. Thus, long-term outcomes should be evaluated in trials with strict protocols regarding the echo-based diagnosis of RV and LV dysfunction in place to clarify the role of septic cardiomyopathy.

Conclusions

In summary, despite the lack of consistent diagnostic criteria for sepsis-associated myocardial dysfunction to date, septic cardiomyopathy is known to have three characteristics: (i) left ventricular dilatation with normal- or low-filling pressure, (ii) reduced ventricular contractility, and (iii) right ventricular dysfunction or left ventricular (systolic and/or diastolic) dysfunction with a reduced response to volume infusion. The afterload-related cardiac performance (ACP), together with speckle-tracking echocardiography, could provide methods of improving the diagnostic accuracy and guiding the therapeutic strategies in patients with septic cardiomyopathy. As there are no specific/causal therapeutics for the treatment of septic cardiomyopathy, the current guidelines for the treatment of septic shock therefore represent the cornerstone of septic cardiomyopathy therapy. Experimental and clinical investigations to improve the diagnosis and to identify new, innovative therapeutic approaches in septic cardiomyopathy are urgently needed.

Legends to figures

Figure 1. Pathophysiological mechanisms and factors that cause a cardiac dysfunction associated with sepsis and currently available diagnostic tools and treatment options. For further details, see main body of the text. ECG = electrocardiography; ATP = adenosine triphosphate; ADP = adenosine diphosphate; Pi = inorganic phosphate; mtDNA = mitochondrial deoxyribonucleic acid; β-OX = beta-oxidation; OXPHOS = oxidative phosphorylation; SERCA = sarcoplasmic reticulum Ca^{2+}-ATPase; PLN = phospholamban; pPLN = phosphorylated PLN; PGC-1 = peroxisome proliferator-activated receptor gamma coactivator 1; PPARγ = peroxisome proliferator-activated receptor gamma; mtROS = mitochondrial reactive oxygen species; NOS = nitric oxide synthase; NF-κB = nuclear factor kappa B; TNF-α = tumor necrosis factor alpha; IL-1 = interleukin 1; TLR = toll-like receptor; DAMP = danger-/damage-associated molecular patterns; and PAMP = pathogen-associated molecular patterns.

Tables

Table 1. Classification of afterload-related cardiac performance (ACP)

Cardiac function	ACP (%)
Normal	> 80
Slight impairment	60 – 80
Moderate impairment	40 – 60
Severe impairment	< 40

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