Sepsis-associated myocardial dysfunction: from bedside to bench

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Abstract

Although the hemodynamic profile of sepsis is characterized by a high cardiac output state, there is clear evidence of myocardial dysfunction in patients with severe sepsis and septic shock. Cardiac abnormalities in sepsis include various degrees of left ventricular systolic dysfunction, left ventricular diastolic dysfunction, and right ventricular dysfunction. Possible underlying mechanisms include direct negative inotropic effects of circulating depressant substances, altered G-protein coupling, myocardial β1-receptor desensitization, and cytopathic hypoxia due to microcirculatory and metabolic abnormalities of the cardiomyocytes. We discuss herein the conflicting findings of the heterogeneous studies conducted in this field and, based on clinical data and findings from experimental work, hypothesize on the underlying pathophysiology and the mechanisms of established and innovative therapies.

Key words: Sepsis, shock, myocardial depression, microcirculation, cytopathic hypoxia

Introduction

Severe sepsis and septic shock are common (1) and, despite advances in therapy, they are still associated with a very high mortality (1). The majority of patients with sepsis die of refractory hypotension and cardiovascular collapse. Although the hemodynamic profile of septic shock after adequate fluid resuscitation is typically characterized by a high cardiac output state, myocardial dysfunction is a common and well-recognized feature (2). However, despite intensive research over the last few decades, there are many unanswered questions regarding the clinical picture and underlying mechanisms of sepsis and septic shock. The aim of this review is to provide clinicians with a critical summary of the data in this controversial field. First, we describe the different observations of myocardial dysfunction at the bedside and discuss the findings critically. Second, we hypothesize on the underlying pathophysiology. Finally, findings from intervention studies in sepsis are discussed in the light of the concept of myocardial depression.

Definitions

Sepsis is defined as the presence of the systemic inflammatory response syndrome (SIRS) in the setting of a documented or presumed infection. SIRS requires the presence of two of the following: increased or decreased body temperature or leukocyte count; tachycardia; and tachypnea. The severity of sepsis is graded according to the associated organ dysfunction and hemodynamic compromise (Table I) (3,4). It is important to recognize that the original definitions of severe sepsis and septic shock relied only on the degree of vasodilatation, whereas in both the modification by the International Sepsis Definition Conference (3) and a recent review by specialists in the field (4), myocardial depression, defined as low cardiac index or echocardiographic evidence of cardiac dysfunction, has been included in the definition of severe sepsis.

Current hemodynamic concept

Current understanding of hemodynamic disturbances in sepsis has recently been extensively
summarized (5). In brief, the evolution from sepsis to septic shock is a dynamic process resulting from infection, host-pathogen interaction, and the balance between pro- and anti-inflammatory mediators. Inability of the circulation to meet the tissue oxygen demands results in global tissue hypoxia and shock. Patients may present with various hemodynamic patterns, as shown in Fig. 1 (5,6). In patients with early, unresuscitated ('hypodynamic') septic shock, the increased oxygen demand leads to a compensatory increase in oxygen extraction, which is clinically reflected by low mixed venous (SvO2) or central venous (ScvO2) oxygen saturations, indicating an inappropriately low cardiac index (CI) during this ‘delivery-dependent’ phase. If the physiologic compensatory mechanisms (tachycardia, tachypnea) for increasing oxygen delivery are exhausted, rising lactate levels indicate anaerobic metabolism (and an altered pyruvate/lactate balance mediated by catecholamine regulation of glycolysis). Lactate levels >4 mmol/l have been found to be important markers of severe tissue hypoperfusion, in particular when encountered in the context of clinical features of peripheral hypoperfusion. Aggressive fluid administration most often results in the typical hyperdynamic profile of sepsis, i.e. the combination of a high CI with a low systemic vascular resistance (SVR). In a compensated situation, where oxygen utilization is not significantly impaired, lactate levels may be normal, and SvO2 is normal to high (6). However, in severe disease, oxygen utilization is disturbed due to impaired microcirculation (microthrombi preventing gas exchange, functional shunting) and metabolic disturbances (especially mitochondrial dysfunction), a condition referred to as “microcirculatory and mitochondrial distress syndrome” by some authors (7). These abnormalities, together with subsequent tissue hypoxia despite appropriately increased oxygen-carrying capacity (‘cytopathic hypoxia’), are currently seen as the “motor of sepsis” (7). In patients with such a pattern, both lactate and SvO2 levels are high, reflecting cellular hypoxia due to failure of the tissues to extract oxygen despite abundant availability (5,6). In contrast, a shock pattern comprising a high lactate level and low SvO2 despite appropriate fluid resuscitation suggests an insufficient oxygen transport capacity, which is typical of cardiogenic shock, thus indicating overt myocardial depression in sepsis (6). Such a pattern has been reported to occur in 10–15% of volume-resuscitated patients (8). However, as discussed in the following, changes in cardiac performance are much more frequent in patients with severe sepsis and septic shock, and in many patients with septic shock there may be a ‘cardiogenic’ contribution to the shock state.

### Cardiac dysfunction in sepsis: clinical findings

#### Left ventricular systolic function

In several studies (2), clear evidence of intrinsic depressed left ventricular performance was revealed in a considerable percentage of patients with septic shock. The phenomenon of ‘myocardial depression’ was first described > 20 years ago by Parker et al. (9). They performed serial radionuclide ventriculograms...
(RNVs) in 20 patients with appropriately volume-
resuscitated septic shock, all of whom exhibited a
typical pattern of hyperdynamic shock, i.e. a com-
bination of high CI and low SVR. In 10 of them, a
transiently depressed left ventricular ejection fraction
(LVEF) of <40% was observed. Interestingly, this
phenomenon was observed only in those who
survived. Overall, survivors (n = 13) had substan-
tially increased left ventricular end-diastolic and
end-systolic volumes, and thus preserved stroke
volumes despite impaired LVEF (32% ± 4%), which
remained low for 4 days and returned to normal
within 7–10 days. In contrast, non-survivors had
normal ventricular dimensions and normal LVEF
(55% ± 5%), which did not show any changes until
death (9). Mean stroke volume indices did not differ
between the groups (Fig. 2). Of note, the population
of this frequently cited key study in the field
consisted of 16 patients with cancer, and the
remaining four patients had mediastinitis following
coronary artery bypass grafting (n = 3) or infection
in the presence of a history of hypertrophic cardio-
myopathy (n = 1). Thus, these patients may not have

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**Fig. 1.** Hemodynamic patterns of early severe sepsis and septic shock. Lactate and SvO₂ levels provide information on CI and oxygen utilization during the (A) delivery-dependent phase and (B) delivery-independent phase. Redrawn from Otero et al. (6) with permission from the American College of Chest Physicians.

**Fig. 2.** Time course of LVEF in the whole study group (left panel) and analyzed separately for survivors and non-survivors (right panel). Data are given as mean ± SD. Reprinted from Parker et al. (9) with permission from the American College of Physicians.
been representative of those in more contemporary trials, and it cannot be discounted that mortality was influenced by factors other than sepsis, e.g. tumor compression, bypass closure.

Non-survivors had a lower mean SVR index than survivors, which led the authors to postulate that all patients with septic shock may develop myocardial depression, but that in non-survivors the lower afterload would result in a normal LVEF despite impaired myocardial contractility (9). Indeed, another study by the same group (10) identified an SVR index 24 h after the onset of shock of \( \frac{82}{1529} \) dyn s/cm\(^2\) m\(^2\) as a favorable prognostic predictor.

A comparison of patients with normotensive sepsis (\(n = 62\)) and a control group of patients with trauma (\(n = 18\)) and similar CI, SVR index, and mean arterial pressure (MAP) revealed that septic patients had a lower LVEF and a higher left ventricular end-diastolic volume index (LVEDVI) and left ventricular end-systolic volume index compared to trauma patients (2). Thus, this study provided evidence that changes in left ventricular function were already present in patients with normotensive sepsis, and not only in those with septic shock.

In a combined pulmonary artery catheter and RNV study (11), patients with septic shock and even those with normotensive sepsis were found to have a markedly abnormal response of the left ventricular stroke work index (LVSWI), a measure of external left ventricular work, to volume infusion, indicating that an impairment of intrinsic myocardial performance was present in patients with sepsis. The slope of the relationship between the increase in LVEDVI and the increase in LVSWI (i.e. the Frank–Starling relationship) was steepest in patients without sepsis, flattest in those with septic shock, and intermediate in those with normotensive sepsis.

In accordance with the study of Parker et al. (9), an impairment of left ventricular systolic function expressed as an LVEF [transthoracic echocardiography (TTE)] or a left ventricular fractional area contraction ([LVFAC]; transesophageal echocardiography (TEE)] <50% was found in echocardiographic studies (12,13) in \(\approx 50\)% of patients with severe sepsis and septic shock. However, the typical pattern of left ventricular dilation in combination with impaired LVEF has only rarely been reported in echocardiography studies (13). Regional wall motion abnormalities in patients with sepsis and other causes of critical illness have also been reported in some RNV and echocardiography studies (14,15).

In summary, many authors agree that septic shock and even severe sepsis without shock are associated with various degrees of impairment of left ventricular systolic function, whereas its combination with left ventricular dilation could not be reproduced in all studies.

Several factors may account for the discrepancies among the studies. First, the timing of the studies plays a critical role. Only serial studies including the very early phase of sepsis can provide sufficient information on the highly dynamic process of sepsis-associated myocardial depression, and such studies have only been performed using RNV and not echocardiography. Second, imaging modalities may have influenced the findings. RNV was used in initial studies to determine left ventricular function...

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Fig. 3. Overview of possible mechanisms involved in the pathogenesis of sepsis-associated myocardial dysfunction.
and dimensions, whereas in more recent studies echocardiography was performed. RNV has the advantage of being less operator-dependent compared to echocardiography, but valvular and other pathologies may be missed. Today, RNV has been completely replaced by echocardiography in the intensive care unit (ICU) setting. However, one should consider that TTE images in ventilator-dependent ICU patients are often of poor quality, and that foreshortening of the left ventricle in the apical four-chamber view and poor visualization of the endocardial border often preclude a comprehensive and accurate determination of ventricular dimensions and LVEF from multiple views, as would be required for scientific purposes. Contrast application may overcome this problem in ICU patients, but has rarely been used in the studies under discussion. TEE provides high-quality pictures, and left ventricular function can be reliably assessed by means of the transgastric view. However, TEE is semi-invasive, requires a high degree of training, and is not broadly available in the ICU setting. Therefore, apart from a few exceptions (16), it is not routinely used in critically ill patients.

Although the phenomenon of sepsis-associated impairment of left ventricular systolic dysfunction was described decades ago, several issues have not yet been addressed. In particular, data from experimental studies are controversial concerning the presence of macroscopic changes of the left ventricular wall, i.e. whether there is an inflammatory infiltration and/or edema of the myocardium with thickening of the left ventricular wall, similar to the findings observed in myocarditis (17), or whether inflammation and macroscopic changes play no major role (apart from in apoptosis and hibernation, as discussed later) (18,19). Surprisingly, serial data on left ventricular dimensions (12), left ventricular wall thickness, and left ventricular muscle mass have rarely been reported in patients with sepsis-associated myocardial depression. This might be due to the fact that an appropriate parasternal (long- or short-axis) view, the typical view for obtaining these measurements, can often not be obtained in critically ill, sedated, and ventilated patients. Unfortunately, this information cannot be obtained from RNV studies either. A study using serial MRI examinations might be very interesting in terms of better description of the functional changes of the left ventricle as well as the underlying pathophysiology. Conventional and late-enhancement imaging might provide information about the presence of myocardial edema and scarring, and a diffuse or localized process, and might differentiate ischemic from non-ischemic changes. However, from a practical and ethical point of view such a study is hardly ever performed.

Left ventricular diastolic function

Left ventricular diastolic function is determined by both active relaxation and passive stiffness. The former is an energy-dependent process, and it is easy to imagine that impaired left ventricular systolic dysfunction induced by any mechanism is also accompanied by impaired left ventricular relaxation, and that left ventricular diastolic dysfunction may precede systolic dysfunction in many cases.

Data from clinical studies on this issue are very sparse, however. In the first study in the field (20), lower ratios of early peak flow velocity (E) to atrial peak flow velocity (A) were reported in patients with septic shock and patients with sepsis without shock as compared to controls. In a small study (21) among patients with severe sepsis undergoing TTE, non-survivors were found to have a more abnormal pattern of left ventricular relaxation, i.e. a lower E indexed for the mitral time–velocity integral and a longer deceleration time as compared to non-survivors. Although non-survivors tended to be older than survivors, which in part could explain the findings, deceleration time (but not age) turned out to be the only independent predictor of mortality. In a combined pulmonary artery catheter and TTE study (22), patients were subdivided into three subsets based on analysis of transmitial inflow and pulmonary vein flow patterns: (i) normal systolic left ventricular function (defined as LVFAC > 40%), E/A ratio > 1 and systolic to diastolic pulmonary vein flow velocity ratio (S/D) > 1, i.e. normal systolic and diastolic left ventricular function; (ii) normal LVFAC ( > 40%), E/A > 1 and S/D < 1, i.e. normal systolic but impaired diastolic left ventricular function; and (iii) LVFAC < 40%, E/A < 1 and S/D < 1, i.e. both systolic and diastolic left ventricular dysfunction. There was no significant difference in SVR or LVSWI between the groups. However, patients in the third group were significantly older and had a higher mortality rate than those in the other two groups. The study was limited by the small number of patients and the fact that the groups differed with respect to their baseline characteristics. Interestingly, however, it revealed that patients with lower LVFAC have worse outcome, and that patients with preserved LVFAC have better outcome regardless of diastolic dysfunction, which is contrary to the findings of the key study of Parker et al. (9).

All of those studies have several limitations, however. First, diastolic function was assessed only once during the process of illness, and it is unknown whether it was pre-existing or not. This issue seems
Survival could be predicted by the initial right thermodilution techniques (26), it was found that survivors but not in those who died in the ICU (RNV studies). In contrast, in another study using transsystolic dysfunction. Very similar to the pattern for and dilatation often accompany left ventricular tance, and that intrinsic right ventricular dysfunction occurs independently of pulmonary vascular resistance, and that intrinsic right ventricular dysfunction and dilatation often accompany left ventricular systolic dysfunction. Very similar to the pattern for the left ventricle, Parker et al. (25) observed transient right ventricular dilation and dysfunction in survivors but not in those who died in the ICU (RNV studies). In contrast, in another study using thermodilution techniques (26), it was found that survival could be predicted by the initial right ventricular ejection fraction in patients with sepsis and septic shock. Accordingly, similar to the changes in left ventricular function, there is clear evidence of sepsis-associated right ventricular dysfunction. The prognostic impact of this finding is less clear. Owing to the complex shape of the right ventricle, assessment of right ventricular volumes and function is challenging, and many of the techniques employed to assess right ventricular dysfunction in sepsis must be regarded as imperfect.

Pathomechanisms

Although myocardial depression in septic shock has been described in several studies, the underlying pathophysiology is still not completely understood. An in-depth discussion of possible molecular mechanisms involved in myocardial dysfunction in sepsis is beyond the scope of this clinically oriented paper and can be found elsewhere (27). However, a review of some key concepts is warranted to aid the understanding of several forms of therapy.

Depressant substances

Based on the observation that serum from patients with septic shock and impaired LVEF induced significant depression of rat cardiomyocyte contraction, whereas administration of serum from non-septic patients did not, the concept of a circulating ‘depressant’ factor was developed (28). Attempts to definitely identify this substance have not yet been successful but among a list of possible candidates several cytokines, including tumor-necrosis factor-α, interleukin (IL)-1β, and IL-6, may play a central role (27). Synergism between several cytokines rather than the effect of a single mediator is likely to be responsible for the effects of myocardial depression. Of note, administration of cytokine antagonists (e.g. anti-TNF-α) did not result in a survival benefit in clinical studies. The exact mechanism of how these depressant substances induce myocardial dysfunction is not clear but direct negative inotropic effects, altered G-protein coupling, and decreased β1-receptor density may contribute to the phenomenon. In the cellular process, nitric oxide- and non-nitric oxide-dependent mechanisms may play a role.

Myocardial perfusion

An early hypothesis to explain sepsis-associated myocardial depression was global myocardial ischemia, as this was observed in some canine models of sepsis (2). However, this hypothesis was rejected years ago based on the findings of a study (29) in which coronary blood flow was assessed by means of...
coronary sinus thermodilution catheters in patients with septic shock. This small study \( n = 7 \) revealed that coronary blood flow did not differ between patients with septic shock and normal subjects as long as heart rate was below 100 beats/min, and that coronary blood flow was even higher in patients with septic shock as compared to normal subjects if the heart rate exceeded 100 beats/min. There was no significant difference in coronary blood flow between patients with septic shock who developed myocardial depression \( n = 4 \) and those who did not \( n = 3 \), and in no patient was net myocardial lactate production demonstrated \( 29 \). However, this study also clearly demonstrated that patients with septic shock had higher coronary sinus oxygen saturations and thus lower oxygen extraction rates compared to normal subjects. Although not all patients developed myocardial depression, and coronary oxygen saturation and oxygen extraction did not differ among those who developed myocardial depression and those who did not, these data indicate that the concept of preserved flow and oxygen availability but decreased oxygen extraction in appropriately volume-resuscitated patients with septic shock also applies to the myocardium itself. Accordingly, a 'microcirculatory and mitochondrial distress syndrome', with impaired oxygen utilization due to shunting and anaerobic metabolism, seems to be present not only in other tissue but also in the heart. Obviously, this does not result in a reduced LVEF in all patients, indicating that other factors may play a role in the development of myocardial dysfunction with depressed LVEF.

This concept is supported by the findings of a recent observational experimental study \( 30 \) suggesting that myocardial dysfunction in sepsis might be due to myocardial hibernation. Using MRI, positron emission tomography (PET), and single-photon emission tomography imaging, mice with experimentally induced sepsis (cecal ligation and double puncture) were found to have impaired myocardial function in the presence of changes previously observed in myocardial hibernation: in septic mice, myocardial 18-fluorodeoxyglucose density was increased, the myocardial-specific glucose transporter GLUT4 was upregulated, and myocardial glycogen deposition was increased as compared to baseline and sham-operated mice. Of note, these changes, which are very similar to those observed in myocardial hibernation due to chronic ischemia, were found to occur despite preserved myocardial perfusion \( 30 \). Based on these findings, it has been proposed that 'cytopathic hypoxia' may also underlie cardiac dysfunction in sepsis. Of note, other authors had previously shown profound organ dysfunction but little cell death in a variety of organs in patients with septic shock.

One of the arguments against the myocardial 'cytopathic hypoxia' hypothesis has been that the adenosine triphosphate (ATP) content in the dysfunctional septic heart is well preserved. However, during hibernation cardiomyocytes remain viable due to downregulation of oxygen consumption, energy requirements, and ATP demands. Interestingly, sepsis-associated inhibition of cytochrome oxidase, the terminal oxidase of the electron-transport chain, has been demonstrated in a previous study \( 31 \).

Similar PET and MRI studies have not been performed in humans, mainly for practical reasons. However, the recent observation \( 32 \) of the apical ballooning syndrome in patients with sepsis might be seen as a possible clinical link between myocardial hibernation or stunning and sepsis-associated myocardial dysfunction. The apical ballooning syndrome is a reversible pattern of severe hypokinesis of the apex and normal or enhanced contraction of the base, which has previously been observed \( 33 \) in patients suffering from emotional stress and presenting with a clinical picture hard to distinguish from acute myocardial infarction. Typical features include chest pain, electrocardiography (ECG) changes, and troponin release, all of which are reversible in most cases. This syndrome is known to occur in the absence of significant coronary artery disease and any inflammatory or ischemic signs during MRI \( 34 \), and myocardial stunning due to catecholamine spillover has been suggested as the underlying mechanism \( 33 \). Several variants of the originally reported syndrome have been described, e.g. a reverse pattern with akinesia of the base and a hypercontractile apex \( 35 \). Similar features have been observed in patients with subarachnoid hemorrhage \( 36 \), which has also been attributed to catecholamine toxicity. Interestingly, patients with apical balloononing, subarachnoid hemorrhage, and other forms of critical illness, including sepsis \( 15 \), exhibit very similar ECG changes, so-called global T-wave inversion \( 33,37 \), which is also observed in myocardial ischemia due to coronary artery disease \( 38 \). In fact, there is also evidence of microcirculatory changes in patients with the apical ballooning syndrome \( 39 \).

**New hypotheses arising from biomarker studies**

The introduction of biomarkers has shed new light on the phenomenon of myocardial dysfunction in sepsis. The concept of myocyte hypoxia despite preserved coronary flow is supported by the observation of elevated cardiac troponin levels in patients
with severe sepsis and septic shock, even those in whom flow-limiting coronary artery disease was excluded by stress echocardiography, coronary angiography, or autopsy (40). Several authors reported a relationship between elevated levels of cardiac troponin I (cTnI) and cardiac troponin T (cTnT), highly sensitive and specific biomarkers of myocardial damage, and left ventricular dysfunction in patients with severe sepsis and septic shock. In addition, the duration of hypotension and the maximal vasopressor doses administered were found to be correlated with cardiac troponin levels. Finally, elevated troponin levels have been shown (41) to be related to the severity of the disease, as expressed by global scores such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score or the Simplified Acute Physiology Score II, as well as short-term prognosis. However, as left ventricular function has previously been shown to normalize after an episode of sepsis-induced myocardial dysfunction (9), it is still a matter of debate whether troponin release in patients with sepsis really reflects myocardial necrosis, and thus irreversible myocardial damage, or a type of reversible myocardial injury. It has been hypothesized (42) that troponin leakage due to ischemia or other stimuli is possible even if myocardial necrosis does not occur. Interestingly, Piper et al. (43) demonstrated reversible membranous bleb formation in rat cardiomyocytes during limited periods of hypoxia and consecutive release of myocardial enzymes in cell supernatant. In addition, in a histopathological study (13) in patients who died from septic shock, contraction band necrosis was revealed in only half of cases with positive pre-mortem troponin, but also in one troponin-negative patient, suggesting that troponin release does not necessarily indicate myocardial cell necrosis. Unfortunately, there is no study in which changes in left ventricular function and troponin have been assessed simultaneously over time.

Interestingly, in ≈50% of patients with advanced heart failure of ischemic but also non-ischemic origin, low-level elevation of cTnI was found (44). Raised cTnI was associated with more severe left ventricular dysfunction, worse hemodynamics, and worse outcome (44). In these patients, activation of pro-apoptotic pathways with subsequent cell breakdown and troponin release has been proposed as a possible mechanism (44). Thus, apoptosis might be an alternative explanation for troponin release in patients with severe sepsis.

In this context, it is important to recognize that completion of a marathon has been shown to be a sufficient inflammatory stimulus to induce troponin release in healthy people, and that troponin release is related to left ventricular diastolic dysfunction, increased pulmonary pressures, and right ventricular dysfunction in these runners (45). Whereas authors agree that troponin elevation in sepsis is an ominous sign (41), the widespread use of natriuretic peptide testing also led to puzzling findings in patients with sepsis. B-type natriuretic peptide (BNP) and N-terminal-proB-type natriuretic peptide (NT-proBNP) are polypeptides secreted by cardiomyocytes in response to wall stress and other stimuli. These peptides exert diuretic, natriuretic, vasodilatory, and sympathicolytic effects, and thereby counteract the deleterious effects of the renin–angiotensin–aldosterone and sympathetic nervous systems in heart failure. In these patients, elevated BNP levels reflect the endogenous response to cardiac overload, making BNP useful as a marker of disease severity. Notably, BNP and NT-proBNP levels have been shown (46,47) to be similarly elevated in patients with septic shock and those with decompensated heart failure and even cardiogenic shock. However, the clinical significance of these findings is not yet clear. Very conflicting data on the relationship between BNP and NT-proBNP and pulmonary capillary wedge pressure, LVEF, and LVSWI have been obtained in ICU patients. In addition, some authors reported that BNP/NT-proBNP levels provided prognostic information in the setting of severe sepsis and septic shock, whereas others did not (41).

Although measurement of BNP and NT-proBNP is currently of limited value in the management of ICU patients, we cannot discount the fact that elevated BNP/NT-proBNP levels reflect structural and functional changes within the myocardium that cannot be assessed by routine techniques. Marathon running has been shown to induce a significant increase in circulating NT-proBNP which is accompanied by subtle changes in left ventricular diastolic function, pulmonary pressures, and right ventricular function (45). These findings, along with the observations that changes in tissue Doppler parameters were detectable before changes in standard size and function measurements by conventional echocardiography in a murine model of doxorubicin-induced cardiotoxicity, and that tissue Doppler findings predicted mortality (48), give rise to the speculation that subtle changes in myocardial structure and function may have been missed in previous studies in patients with sepsis.

**Effects of therapy**

In the last few years, several mediators of sepsis have been suspected to be responsible for myocardial depression, and several antagonists of such ‘depressant factors’ have been tested in clinical trials.
However, all these studies resulted in disappointing findings, suggesting that these factors did not (or at least not solely) mediate the phenomenon.

**Delivery-dependent phase**

Apart from early antibiotic treatment, only a few treatment modalities in patients with septic shock have resulted in a positive result in randomized trials. Among these, the early goal-directed therapy (EGDT) study is a key study in the understanding of cardiovascular dysfunction in severe sepsis and septic shock (8). Patients admitted to the emergency department who presented with SIRS and septic shock (8). Patients admitted to the emergency department who presented with SIRS in the context of suspected sepsis with a systolic blood pressure ≤90 mmHg or a serum lactate level ≥4 mmol/l who were receiving appropriate antibiotic therapy were randomized to undergo standard therapy relying on measurement of central venous pressure (CVP; goal ≥8–12 mmHg), MAP (goal >65 mmHg), and urine output (goal >0.5 ml/kg/h) or EGDT relying on continuous ScvO2 monitoring (goal ≥70%), in addition to determination of CVP, MAP, and urine output as in the standard group. Repeated crystalloid boluses were administered to achieve a CVP of 8–12 mmHg and, if the MAP was still <65 mmHg, vaspressors were applied. If the MAP was >90 mmHg, vasodilators were given until it was <90 mmHg. If the ScvO2 was <70%, red cells were transfused to achieve a hematocrit level of ≥30%. If ScvO2 was <70% despite optimization of CVP, MAP, and hematocrit, dobutamine infusion was started. Therapy according to this protocol was applied for at least 6 h before patients were admitted as inpatients. Then, monitoring of ScvO2 was discontinued. In patients assigned to standard therapy, ScvO2 values were also recorded but not shown to the treating physicians.

Patients undergoing EGDT received more fluids, more red cell transfusions, and more inotropic agents during the first 6 h of therapy. During the interval from 7 to 72 h after randomization, patients assigned to EGDT had higher ScvO2, lower lactate, and higher pH compared to the standard group. In-hospital mortality was significantly lower in the EGDT group compared to the standard group (30.5% vs 46.5%; p = 0.009) (8).

This study has thus shown improved hemodynamics and better outcome as a result of early optimization of preload (although CVP is an inaccurate estimate of left ventricular end-diastolic pressure), afterload, oxygen transport capacity, and myocardial contractility. Dobutamine was given to 14% of patients in the EGDT group (8), based on the assumption that in these patients the CI was too low to meet the body’s demands even after correction of CVP, MAP, and hematocrit. These patients may have suffered from overt myocardial depression. Whether changes in cardiac function were also present in the other patients is unknown but very likely.

**Delivery-independent phase**

The benefit of a similar goal-directed approach after the initial phase of septic shock, i.e. during the delivery-independent phase, is unproven. On the contrary, achieving supranormal hemodynamic targets was found to increase mortality compared to those who were treated according to more physiologic targets (49,50). In the EGDT study, dobutamine was administered very early, i.e. during the delivery-dependent phase, and at comparatively low doses, which may explain the benefit derived from its use. Higher doses and application in the delivery-independent period often result in tachycardia, arrhythmia, and ECG signs of ischemia, probably due to the increased myocardial oxygen demand despite unchanged and impaired oxygen extraction. In contrast, experimental data suggest that late in the course of sepsis the opposite treatment may be useful: in a rat model of sepsis (51), esmolol infusion has been shown to lower circulating TNF-α levels and exert beneficial effects on hemodynamics, raising questions about potential similarities to beta blocker treatment in chronic heart failure.

Apart from early optimization of the oxygen supply, microcirculatory and mitochondrial dysfunction is an important target during the delivery-independent phase. Interestingly, the composite treatment of EGDT was also associated with a greater reduction in circulating IL-8 and D-dimer levels as compared to standard therapy, indicating that EGDT not only improved the oxygen supply but also resulted in a greater attenuation of inflammation compared to standard therapy. Although patients in the EGDT group received more liberal volume therapy within the first 6 h compared to the standard group, they required intubation and mechanical ventilation less often in the following period (6).

One component of the EGDT concept was vasodilator therapy in patients with MAP > 90 mmHg (9% of patients). Experimental findings from a pig model (52) suggest that recruitment of the microcirculation is achievable by nitric oxide donors. Interestingly, a small observational study in humans (53) revealed an improvement in sublingual microcirculatory perfusion after the administration of nitroglycerin.
A multifactorial therapy promoting both anti-inflammatory and anticoagulant effects in patients with sepsis is the administration of recombinant activated protein C (rAPC; drotrecogin-α), which has been shown to reduce mortality in patients with severe sepsis and a high risk of death (54). The fact that D-dimer levels were reduced significantly more in patients receiving rAPC as compared to the control group may indicate that its effect was due at least in part to an improvement in microvasculature dysfunction. One might hypothesize that rAPC affects not only the microcirculation of the extracardiac organs but also the heart itself, and thus represents a kind of myocardial reperfusion strategy. Interestingly, in a recently published study (55), lower cTnI levels were found in patients with severe sepsis treated with rAPC (n=23) on Day 2 of therapy compared to a similar group of patients who did not receive the drug (n=34). There was a non-significant trend towards lower mortality in the rAPC group (22% vs 32%; non-significant trend towards lower mortality in the sepsis treated with rAPC (n=30/C30). Interestingly, in a recently published study (55), lower cTnI levels were found in patients with severe sepsis treated with rAPC (n=23) on Day 2 of therapy compared to a similar group of patients who did not receive the drug (n=34). There was a non-significant trend towards lower mortality in the rAPC group (22% vs 32%; p=0.11) (55). However, it remains unproven whether the smaller release of troponin in the rAPC group indicates less microvascular injury with subsequently lower mortality following the application of the therapy, or whether the lower cTnI levels reflect the better prognosis of the rAPC group independent of the effect of the drug. As mentioned earlier in this article, apoptosis may be involved in myocardial dysfunction and troponin release in sepsis and, very recently (56), rAPC has been shown to exert anti-apoptotic effects on circulating mononuclear cells in humans. Of note, rAPC was not effective in patients with severe sepsis but a low risk of death based on initial APACHE II score (57). This could be seen as an analog to the failure of thrombolyis and glycoprotein IIb/IIIa antagonists to improve outcome in patients with suspected acute coronary syndrome but with low risk. Interestingly, orthogonal polarization spectral imaging now allows direct observation of the microcirculation at the bedside (7). It is, however, unknown whether changes in the sublingual mucosa provide any information about changes within the myocardium, and whether the use of this technique can improve patient management by better tailoring of therapy.

Mitochondrial dysfunction might be a new target for innovative sepsis therapies. Pharmacological prevention of mitochondrial permeability transition, a key feature of mitochondrial dysfunction, has recently been shown (58) to attenuate myocardial dysfunction and improve survival in a murine model of sepsis.

Conclusions and outlook

There is clear evidence of myocardial dysfunction in patients with severe sepsis and septic shock. However, both the clinical picture and the underlying mechanisms require better characterization. Tailored therapies addressing microvascular and metabolic dysfunction may contribute to an improvement in the outcome of patients with sepsis complicated by myocardial dysfunction.

References

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