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Septic shock: a heart story since the 1960s

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1960s and 1970s: general hemodynamic in septic shock

Before the advent of pulmonary arterial catheter two distinct clinical profiles of septic shock had been described [1, 2]. One was characterized by warm, dry skin and a bounding pulse despite hypotension ("warm" shock) and the other by cold skin ("cold" shock). Authors were under the impression that "warm" shock was seen in the initial phase of hospitalization in septic shock patients while "cold" shock was more often observed later, before patients died. Invasive measurements were available in few patients showing that "warm" shock was associated with high cardiac output (CO) and "cold" shock with a low CO (Fig. 1a). It was then concluded that patients in septic shock initially went through an early hyperdynamic phase after the onset of illness and eventually either recovered or deteriorated into heart failure or myocardial depression related to sepsis leading to hypodynamic shock and death [3]. The latter concept was supported by animal models designed by Weil (Fig. 2) using intravenous bolus injections of high doses of endotoxin or live organisms [4, 5] (Fig. 1b), showing septic shock characterized by reduced CO and elevated systemic vascular resistance (SVR) leading to animal death (Fig. 1b).

However, a concomitant publication by Wilson et al. [6] described septic shock in humans as associated predominantly with normal or elevated CO and very rarely with low CO (Fig. 1c). They were among the first to provide a description of septic shock as having high CO and low SVR, distinguishing it from cardiogenic and hemorrhagic shock that both combined low CO and high SVR. Despite these data the view by Wilson et al. of the nature of cardiovascular dysfunction in septic shock did not become accepted until the widespread use of pulmonary artery thermodilution catheters, allowing measurement of both CO and pulmonary artery wedge pressure. The recognition of inadequate volume resuscitation of patients in septic shock [7] followed, and subsequent studies using pulmonary artery catheter consistently showed that adequately volume-resuscitated patients in septic shock typically manifest a hyperdynamic circulatory state with high CO, decreased SVR, normal stroke volume, and high heart rate [7, 8, 9, 10, 11, 12] even in nonsurvivors [11]. Refined animal models using bolus or chronic endotoxin infusion, cecal ligation, and puncture or infected peritoneal clot implantation found increased CO and low SVR in "resuscitated" animals [13, 14, 15, 16] and low CO in "unresuscitated" animals [17, 18].

In summary, the very initial description of "cold" shock associated with low CO in septic shock patients was very likely due to measurements performed in the context of hypovolemia (at least "relative" hypovolemia). It is now generally accepted that after adequate volume loading, severe sepsis and septic shock are often associated with high CO.

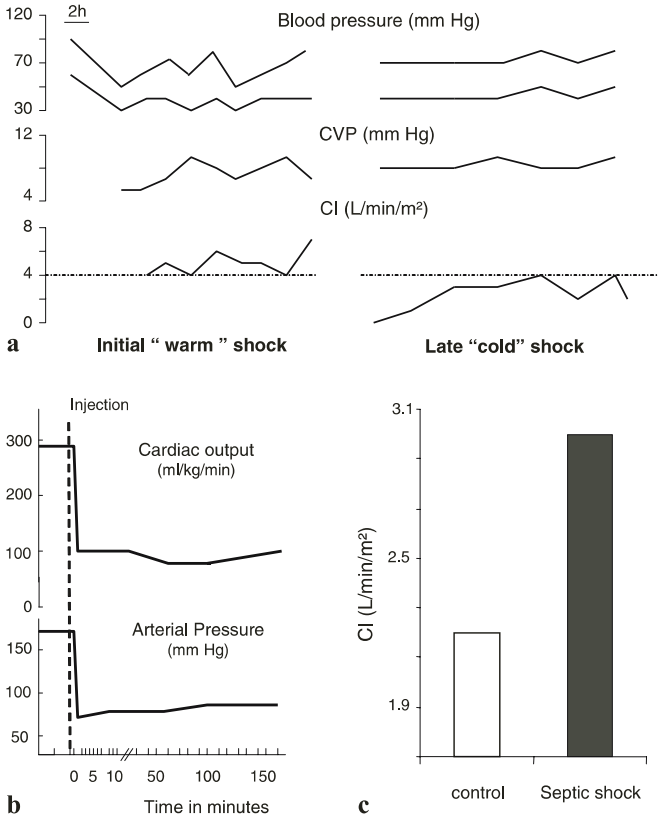

Fig. 1 General hemodynamic in septic shock as viewed before the advent of pulmonary arterial catheter. **a** Description in 1967 of a case of a hyperdynamic or "warm" shock (high cardiac index, *CI*; hypotension) and a case of hypodynamic or "cold" shock (low CI, hypotension). (From [1] with permission) **b** Experimental model supporting the "cold" shock model. (From [4] with permission) **c** First description showing that normal or elevated CI is present predominantly in septic shock patients. This view was fully adopted after the widespread of pulmonary artery catheters with thermodilution capacity. (Adapted from [7])

1980s: evidence of a myocardial depression in septic shock

The clue of the sepsis-induced cardiac dysfunction in patients with septic shock came from Parrillo (Fig. 3) with the study by Parker et al. [19] in 1984. Indeed, using portable radionuclide cardiac imaging and simultaneous thermodilution CO studies on patients with septic shock, they showed that all patients had a high CO and maintained stroke volume index and low SVR. Parker et al. [19] further showed that 15 of the 20 studied patients had a depression of left ventricular ejection fraction (LVEF) below 0.45 during the first 2 days after the onset of septic shock. Interestingly, survivors had an LVEF that remained low for 4 days and then rose to normal values within 7–10 days. Acute left ventricular dilatation has been also seen in these resuscitated patients with septic shock, and these acute changes in ventricular volume were reversible in 7–10 days in survivors [19]. These data reflecting left but also right ventricular dysfunction (i.e., reduced right ventricle ejection fraction and increased right ventricle end-diastolic volume) have been confirmed by further studies [20] and by experimental studies [15, 16, 21, 22]. Indeed, Natanson et al. [15] confirmed in dogs implanted with a viable *Escherichia coli* clot into the peritoneum that LVEF is decreased in septic animals. The maximal decrease in LVEF occurred on day 2, remained depressed for 2–3 days, and recovered by 7–10 days (Fig. 4a). Similar cardiac abnormalities (decreased LVEF, dilated left ventricle, maintained or increased CO on day 2, which all revert to normal values in 7–10 days) were observed regardless to the type of bacteria (Gram-negative or Gram-positive) and its viability [21]. The importance of the bacterial inoculum plays also a crucial role since increasing the number of bacteria at the nidus of infection was associated with a dependent, progressive decrease

Fig. 2 Photograph of M.H. Weil

Fig. 3 Photograph of J.E. Parrillo

in systolic cardiac performance and a similar, stepwise diastolic ventricular dilatation (Fig. 4b) [16].

It is now clear that systolic function deteriorates at the early phase of septic shock in humans, as confirmed by echocardiographic studies [23]. The question of left ventricular diastolic dysfunction in septic shock remains less clearly defined. Reduced compliance manifested as reduced rapidity of ventricular filling [24] has been described in patients with septic shock [25].

Septic myocardial depression can also be illustrated in the context of reduced ventricular response to fluid loading. Response to volume infusion among patients with septic shock is altered, as suggested by the findings by Ognibene et al. [26] showing no significant increase in left ventricular systolic work index despite increases in pulmonary artery wedge pressure and left ventricle end-diastolic volume index. The effect of septic shock on right ventricle function has been also studied (review for details see [27]). Parker et al. [28] showed right ventricular dilatation and marked depression in right ventricular ejection fraction, which normalized 7–14 days after the onset of sepsis. Accordingly, myocardial depression simultaneously affects both ventricles (Fig. 4c, d).

In summary, if adequately fluid resuscitated, patients with septic shock develop a hyperdynamic circulatory state with increased CO and decreased SVR associated with biventricular dilatation. Despite the fact that CO is normal or increased ventricular function is abnormal (depressed ejection fraction of both ventricles). In survivors these changes revert to normal within 7–10 days. Patients with septic shock also show a depressed response to volume resuscitation (depressed Frank–Starling curve) and alterations in diastolic function.

1990s and thereafter: evidence of an "intrinsic" sepsis-induced cardiac dysfunction

Supracellular hypotheses, such as decreased coronary blood flow or circulating factors, were frequently suggested as predominant mechanisms of sepsis-induced myocardial depression until the early 1990s, when

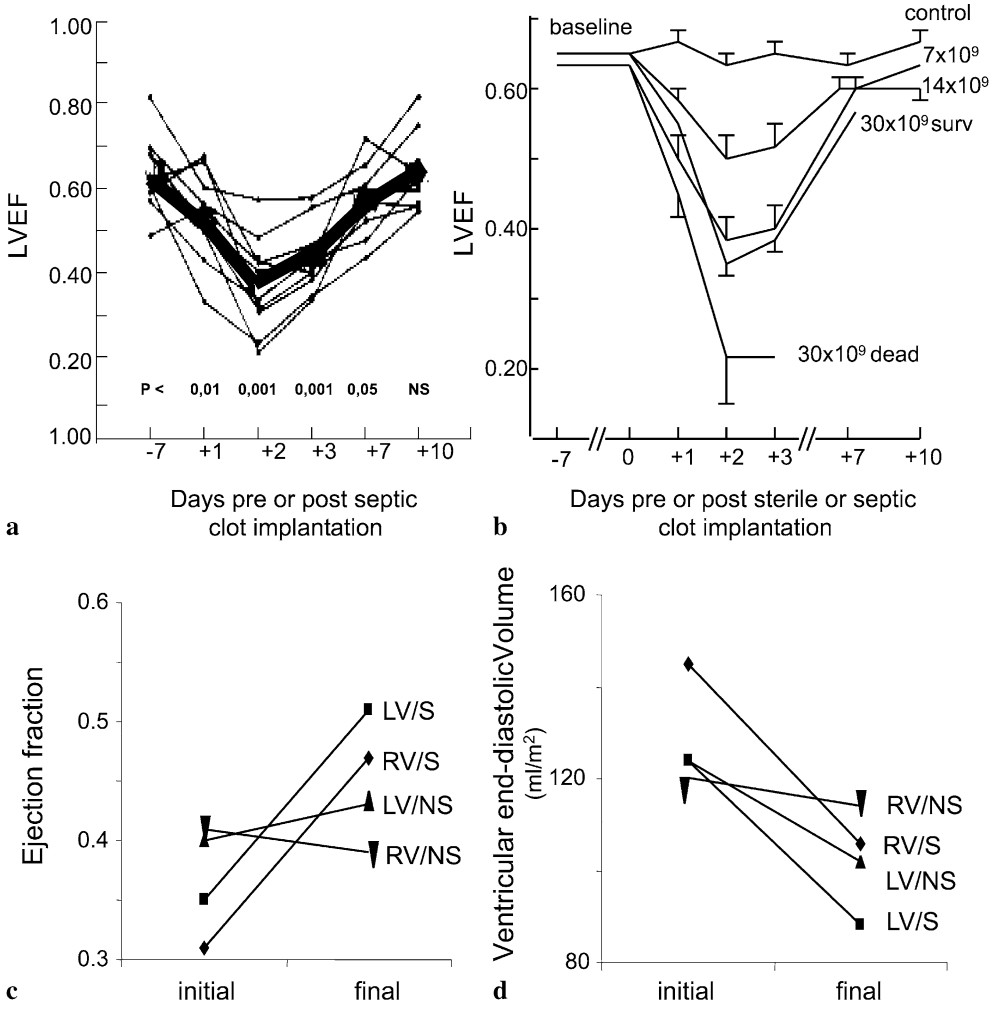

Fig. 4 Sepsis-induced cardiac dysfunction in septic shock. **a** Time-course of left ventricular ejection fraction (*LVEF*) in dogs implanted with a viable *Escherichia coli* clot into the peritoneum [15]. **b** Dose-response curve of LVEF after septic inoculation with increasing inoculum of alive bacteria (*surv*) or dead bacteria (*dead*) [16]. **c** Left and right ventricular ejection fraction in survivors (*LV/S*, *RV/S*, respectively) and in nonsurvivors (*LV/NS* and *RV/NS*, respectively) from septic shock (adapted from [19]). **d** Left and right ventricular end diastolic volume index in survivors (*LV/S* and *RV/S*, respectively) and in nonsurvivors (*LV/NS*, and *RV/NS*, respectively) patients before and after treatment of septic shock (adapted from [28]). Clinical data confirm that sepsis-induced cardiac dysfunction is reversible with time

increasing and very convincing evidence definitively assessed the major role of "intrinsic" cellular alterations in septic heart.

Supracellular hypothesis

Decreased coronary blood flow

Global ischemia caused by reduced coronary blood flow has for decades been suggested to explain depression in septic heart. However, direct measures of coronary blood flow and cardiac metabolism studies in the late 1980s showing changes in those parameters ruled out this hypothesis [29, 30]. Recent studies report increased levels of plasma troponin in severe sepsis and septic shock, with a close relationship with the severity of myocardial depression. However, neither our group nor others have been able to detect any necrosis in myocardium or skeletal muscle of patients who died from septic shock (personnel observations and [31]). Accordingly, plasma troponin increase does not seem related to cell death per se but rather to other mechanisms such as a transient increase in cardiac myocyte membrane permeability to troponin due to cytokine effects [32].

Circulating factors

In 1971 Wangensteen et al. [33] suggested that myocardial depression is due to circulating myocardial depressant factor(s). Later Parrillo (Fig. 3) et al. [34] confirmed the existence of "circulating myocardial depressant factor(s)" in humans by showing that serum obtained during the initial phase of septic shock decreases both the amplitude and the velocity of shortening of cardiomyocytes from newborn rats (Fig. 5). Cytokines such as tumor necrosis factor (TNF) α and interleukin (IL) 1β have been suggested to be these "circulating myocardial depressant factor(s)" since both cytokines are released in plasma during sepsis [35] and have been shown to have direct, although short-term, depressant effect on myocardial contractility in vitro [36]. However, although a cytokine effect might explain a myocardial depressant activity at the initial phase of sepsis and explain the Parrillo et al. [34] findings, it can hardly explain a delayed and prolong depressant effect on heart contractility. Indeed, as described above, cardiac performance in both animals and humans is altered during 7–10 days whereas TNF-α and IL-1β plasma levels return to normal values within 48 h of sepsis onset. Moreover, several studies using isolated rabbit papillary muscle [37, 38] or isolated rat cardiomyocytes [17, 39] harvested in the acute phase of sepsis and studied ex vivo show a persistent decrease in contractility of similar amplitude to in vivo measurements (Fig. 6) despite the absence of direct contact with plasma.

In summary, the above studies argue against a major role of "circulating myocardial depressant factor(s)" but

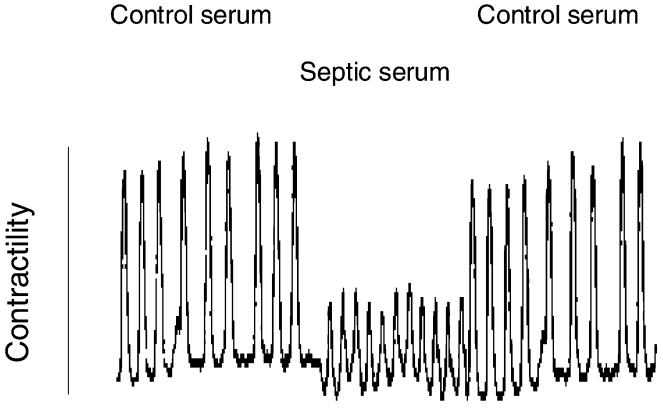

Fig. 5 "Myocardial depression factor." Serum obtained from patients during the acute phase of septic shock and incubated with cardiomyocytes decreased the extent and velocity of myocyte shortening whereas serum obtained from nonseptic patients restored immediately contractile force. (From [34] with permission)

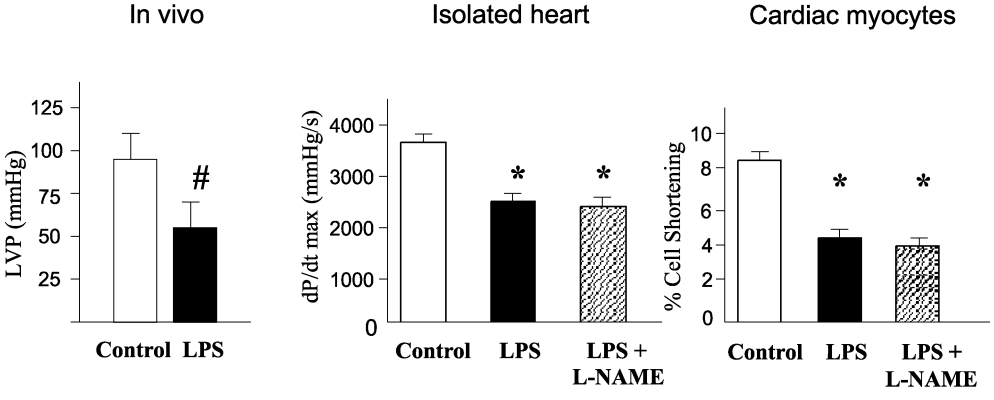

Fig. 6 Cardiac contractility remains decreased in LPS animals regardless of the presence or the absence of plasma. This argues against a role of a "circulating myocardial depressant factor" but rather supports an "intrinsic" alteration in the myocardium as the predominant mechanism of septic cardiac dysfunction. Inhibition of NO synthases does not restore contractility, suggesting that NO does not play an acute and direct role in septic cardiomyopathy; $^{\#}p < 0.05$, $^{*}p < 0.001$. (Adapted from [39, 60])

rather support the concept of an "intrinsic" alteration in the myocardium as the predominant mechanism of septic cardiac dysfunction (Fig. 5). Although cytokines cannot explain the sustained myocardial depression, they may participate in initiating cellular events that lead to the prolonged "intrinsic" septic cardiomyopathy. Thus in the 1990s and thereafter research focused largely on assessing mechanisms of sepsis-induced alteration in myocardial function at the cellular level.

"Intrinsic" cellular mechanisms

beta-Adrenergic receptors

Studies reporting the role of a β-adrenergic pathway during sepsis are contradictory. Indeed, studies using isolated cardiomyocytes which are exposed to endotoxin show a marked decrease in contractile response to isoproterenol [40]. However, these data were not confirmed by models using myocytes isolated from septic animals.

An experimental study culturing neonatal cardiomyocytes with plasma obtained from septic patients treated with norepinephrine during 48 h reported a 35% decrease in β-adrenoceptor density, a 60% increase in the level of inhibitory G protein α-subunits, and a 50% decrease in isoproterenol-stimulated adenylyl cyclase activity [41]. However, our data challenge these results. We found that β-adrenergic stimulation of calcium current is increased 12 h after endotoxin challenge but is decreased after 36 h [17]. This dual response suggests time-dependent changes in the adenylyl cyclase pathway: adenylyl cyclase activity is increased during the early phase of sepsis but is decreased during the last phase because the number of β-adrenergic receptors is decreased (internalization) and Giα subunit expression, which inhibits adenylyl cyclase, is also increased. The lack of β-agonist agents efficacy in the late phase of sepsis has also been described in humans [42].

In summary, β-adrenergic pathway is altered in septic patients and may participate in both the "intrinsic" decrease in cardiac contractility and the deteriorated response to β-adrenergic agent.

Calcium and cardiomyofilaments

During sepsis-induced cardiomyopathy two main changes can occur in calcium homeostasis at the cardiomyocyte level: (a) abnormalities in calcium current and (b) decrease in myofilament calcium sensitivity. In endotoxin-treated animals the number of L-type calcium channels is decreased [43], and this decrease is related directly to left ventricular depression in vivo [42]. However, the role of these modifications in the pathophysiology of the sepsis-induced cardiomyopathy remains unclear.

Decrease in myofilaments calcium sensitivity plays a crucial role in sepsis-induced cardiac dysfunction. Tavernier et al. [44] showed a decrease in cardiomyofilament calcium sensitivity which has been confirmed in various models (Fig. 7a and Fig. 7b) [37, 39]. This decreased calcium sensitivity of myofilaments is dose dependent and reversible with time. The exact mechanism is still unknown, but proteins phosphorylation may be involved [37]. Phosphorylation of troponin I has been reported [39], resulting in a reduced ability of calcium to activate the myofilaments, as recently confirmed [45]. Nitric oxide, by stimulating GMP-dependent kinase, may induce troponin I phosphorylation in vitro and then a decrease in myofilaments calcium sensitivity. The decreased response of myofilaments to calcium may induce a decreased contractility and the depression of systolic function but may also explain the ventricular dilatation observed in septic patients after fluid loading. Indeed, a decrease in myofilament calcium sensitivity is associated with an increase in cardiomyocyte length and an increase in ventricular distensibility [46]. Myofilament phosphorylation may increase sarcomere length (preload)

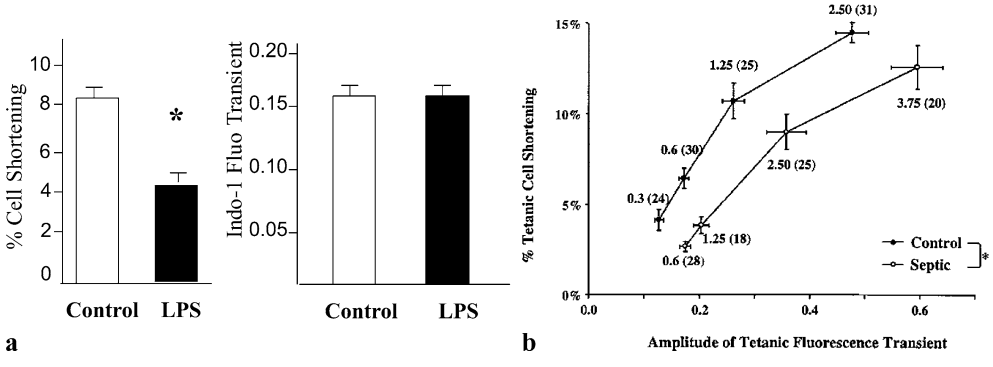

Fig. 7 **a** Cardiac contraction is decreased during sepsis whereas calcium influx is preserved, suggesting an alteration in calcium myofilament responsiveness in septic cardiomyocytes [39]; $*p < 0.05$. **b** There is a decrease in cardiomyofilament calcium sensitivity in cardiomyocytes from endotoxin-treated rats, as suggested by the rightward shift in the relationship between contraction (here shortening) and intracellular calcium (here fluorescence transient); $*p < 0.001$. (From [39] with permission)

and could be the cellular basis of the Frank–Starling relationship. This may explain the conserved loading response observed in septic patients whereas cardiac function is depressed.

Levosimendan, an agent that improves cardiac myofilament response to calcium, has recently been reported to restore contractile cardiac performance in experimental model of sepsis and in patients [18, 47].

Nitric oxide and peroxynitrite pathway

NO, produced mainly by inducible NO synthase (NOS-2), is clearly involved in vascular dysfunction both in animals and humans (Fig. 8). NO plays also a crucial role in the development of the "intrinsic" septic cardiomyopathy by many ways including change in contraction, protein nitration and alteration in mitochondrial respiration.

As shown in vessels, NOS-2 overexpression is associated with an increased production of NO in cardiomyocytes after incubation with lipopolysaccharide (LPS) in vitro. However, although NO seems to have a direct and immediate effect on vascular tone, its effect on cardiac contractility is certainly not direct. Indeed, although the inhibition of NOS does restore vascular tone, it does not restore the contractility of cardiomyocytes, papillary muscle, or isolated heart harvested from animal models treated with LPS (Fig. 6) [35, 37]. Similarly, in septic patients the administration of the nonspecific NOS inhibitor N^{ω}-monomethyl-l-arginine increases arterial pressure but decreases CO [48]. This suggests that if NO and NOS-2 play a role in septic cardiomyopathy, this role is certainly indirect.

In septic patients NO produced in large amount may interact with superoxide anion and produce peroxynitrite. As suggested by our model of muscle dysfunction in septic patients, peroxynitrite, rather than NO per se, decreases muscle contractility [29]. Peroxynitrite by denaturating proteins, by inducing calcium flux abnormalities [49] or by depressing mitochondrial respiration [50] and inhibiting cardiac MM isoform of creatine kinase (CK) and mi-CK [35] could impair cardiac contractility during sepsis. The involvement of peroxynitrite in sepsis-induced cardiomyopathy was recently confirmed by the use of peroxynitrite neutralizers, which improved cardiac dysfunction in septic rats [51].

Sepsis-induced cardimyopathy may also be caused by mitochondrial respiratory changes. Indeed, NO, produced in large amount during sepsis, can bind to complex IV of the respiratory chain and then compete with oxygen, which inhibits this complex and increases reactive oxygen species (ROS) production. At higher concentrations NO inhibits other complexes of the respiratory chain. Peroxynitrite can also be very toxic for the respiratory chain and particularly inhibits complexes I, II, and III of the respiratory chain. Recently it has been shown that complex I is inhibited in skeletal muscle taken from septic patients, and that the inhibition is related to NO production by NOS-2 [52]. Respiratory chain inhibition is even more marked in heart than in skeletal muscle during sepsis.

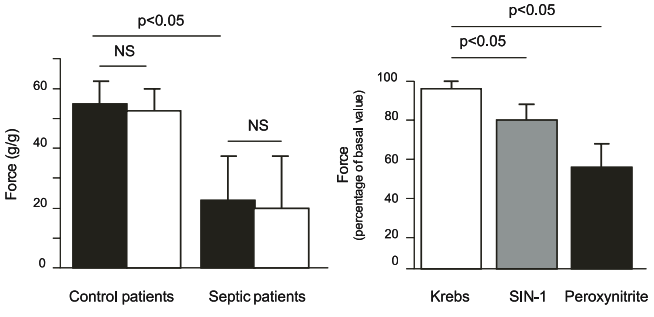

Fig. 8 Role of NO and peroxynitrite in sepsis-induced skeletal muscle dysfunction. Muscle contractility is decreased in septic patients in basal conditions (*closed columns*). NO inhibition by N^{ω}-nitro-L-arginine methylester (*open columns*) does not restore contraction, suggesting that NO is not acutely involved in muscular dysfunction. High peroxynitrite production in skeletal muscle of septic patient [31] together with the decrease in contractility observed after adjunction of a peroxynitrite donor (*SIN-1*) strongly suggest a direct effect of peroxynitrite on muscle dysfunction. (From [31])

Apoptosis

Cell death and particularly apoptosis seem to be involved in sepsis-induced cardiac dysfunction. Caspases, which are proteases, are the effectors of apoptosis. They are activated in response of the activation of TNF-α receptor or after release of cytochrome *c* from mitochondrial intermembrane space. Caspases are activated during endotoxin-induced cardiac dysfunction leading to apoptosis [53, 54]. Moreover, caspases (particularly caspase 3) inhibition prevented endotoxin-induced cardiac dysfunction and heart apoptosis [53, 54]. Although improvement in contractile function following caspases inhibition can be related to decrease in apoptotic cell death, other mechanisms are involved. Indeed caspase inhibition may lead to a decrease in cytokine production and then indirectly influence intracellular calcium homeostasis. Endotoxin-induced caspase 3 activation may also be associated with change in calcium myofilament response, contractile proteins cleavage, and sarcomere disorganization [55]. Cyclosporine A, which blocks mitochondrial cytochrome *c* release, prevents heart dysfunction, suggesting that the mitochondrial membrane permeability (MPT) pore is involved in sepsis-induced cardiomyopathy [56]. Antiapoptotic Bcl-2 overexpression, which may regulate the MPT pore opening, has been reported to be protective against endotoxin-induced myocardial dysfunction [57]. However, the time-course of sepsis-induced cardiac dysfunction (recovery ad integrum in 7–10 days) challenges the role of apoptotic cell death as a major cause of contractile impairment. Namely this

time course suggests that the abnormalities leading to contractile dysfunction are transient, and/or that corrective mechanisms exist to limit their effects.

In summary, cardiac dysfunction during sepsis can be seen as a consequence of multiple cellular alterations. At the early phase of sepsis cytokines, playing the role of "myocardial depressant factor," induce persistent cellular metabolism modifications, including the induction of NOS-2. As a consequence NO produced is directly able to modify myofilaments sensitivity to calcium by inducing troponin I phosphorylation, or to disturb cellular energetic by inhibiting respiratory chain complexes. Moreover, NO, by inducing peroxynitrite production, is indirectly responsible of protein denaturation and inactivation, calcium flux abnormalities, depression of respiratory chain, and inhibition of CK energy shuttle. All these cellular alterations may lead to cardiac dysfunction. New concepts such as apoptosis are also involved. Of interest, we have recently observed in an animal model of sepsis that other cardiovascular mediators, such as protstaglandins and endothelin, released by cardiac endothelium, may contribute to restore cardiac contractile performance [36].

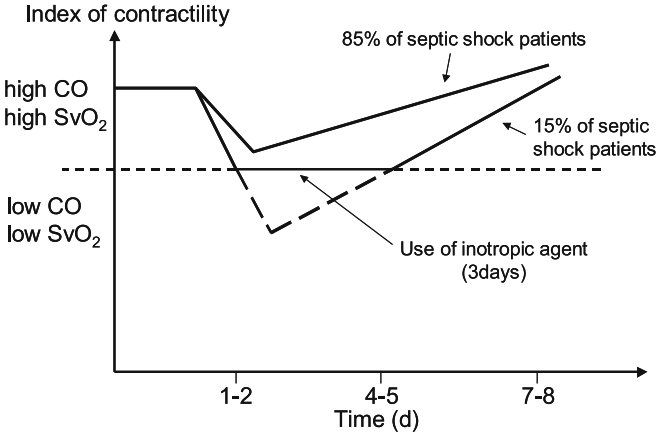

Fig. 9 Hemodynamic profile and need of inotropic agent in human septic shock. In 85% of septic shock patients cardiac output (*CO*) and mixed SvO_2 are above normal despite a decrease in LVEF observed in echocardiography. There is no need of positive inotropic agent in these cases. In the other 15% of septic shock patients [59] CO and SvO_2 are both decreased despite adequate volume loading. An inotropic agent is therefore required for an average of 3 days

Conclusions

Although CO is maintained or increased during septic shock, cardiac contractility is depressed. This paradox can be explained by a maintained stroke volume (possibly due to a dilated ventricle despite a lower ejection fraction) and an increased heart rate. Cardiac contractile impairment is maximal the second day after the onset of sepsis, but remarkably it recovers ad integrum in 7–10 days in survivors. Although cardiac dysfunction occurs in the majority of patients with septic shock, it does not mean that all these patients should receive inotropic support. Indeed, the most frequent scenario in septic shock is a vascular dysfunction accompanied by a "compensated" septic cardiomyopathy. In these patients the CO remains high and is likely adapted to the cellular metabolism (high SvO_2). Use of positive inotropes is then unnecessary and potentially harmful [58]. However, in approx. 15% of patients, as found by Rivers et al. [59], vascular dysfunction is accompanied by a "decompensated" septic cardiomyopathy that needs treatment with positive inotropes. In these patients CO is abnormally decreased and the SvO_2 abnormally low (Fig. 9). For a short period (2–3 days) inotropic support is necessary to increase CO and improve cellular oxygenation.

In summary, this present review describes various mechanisms likely to be involved in sepsis-induced intrinsic cardiomyopathy. These modifications observed in heart may be extended to other organs and may be involved in the pathophysiology of multiple organ failure. Future studies should assess whether mechanisms such as peroxynitrite production and apoptosis are of importance in humans, and whether recent therapies such as activated protein C and low-dose corticosteroids have any impact to prevent or restore myocardial function.

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