Molecular Events in the Cardiomyopathy of Sepsis

Michael A Flierl,[1] Daniel Rittirsch,[1] Markus S Huber-Lang,[2] J Vidya Sarma,[1] and Peter A Ward[1]

[1]Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, United States of America; [2]Department of Trauma, Hand and Reconstructive Surgery, University of Ulm Medical School, Ulm, Germany

Septic cardiomyopathy is a well-described complication of severe sepsis and septic shock. However, the interplay of its underlying mechanisms remains enigmatic. Consequently, we constantly add to our pathophysiological understanding of septic cardiomyopathy. Various cardiosuppressive mediators have been discovered, as have multiple molecular mechanisms (alterations of myocardial calcium homeostasis, mitochondrial dysfunction, and myocardial apoptosis) that may be involved in myocardial dysfunction during sepsis. Finally, the detrimental roles of nitric oxide and peroxynitrite have been unraveled. Here, we describe our present understanding of systemic, supracellular, and cellular molecular mechanisms involved in sepsis-induced myocardial suppression.

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INTRODUCTION

Early pioneering reports sought to distinguish between two distinct clinical profiles of septic shock and associated "warm shock" with warm, dry skin, a pounding pulse despite hypotension, and high cardiac output. This was observed in the initial phase of hospitalization due to septic shock. In contrast, "cold shock" seemed to be related to low cardiac output and was correlated with the later clinical stages of septic shock before patients succumbed to sepsis (1–3). Based on these findings, it was concluded that patients during septic shock initially encountered an early hyperdynamic phase from which they either recovered or declined into a hypodynamic phase associated with myocardial depression, heart failure, and death (4). This principle was initially supported by experimental models, demonstrating that septic shock associated with reduced cardiac output and elevated systemic vascular resistance led to the death of animals (5,6). However, these concepts were substantially challenged when Wilson *et al.* (7) linked septic shock in humans with normal, or even elevated, cardiac output (and very rarely with low cardiac output) and decreased systemic vascular resistance in adequately resuscitated septic patients. Subsequent studies using pulmonary artery catheters confirmed that sufficient fluid resuscitation in septic shock patients manifested a hyperdynamic circulatory state with high cardiac output, decreased systemic vascular resistance, normal stroke volume, and high heart rate (8–11)—even in nonsurvivors (12). Therefore, it was concluded that the initial depiction of cold shock–associated decreased cardiac output was likely related to hypovolemia due to inadequate volume loading of septic shock patients, rather than being involved in mechanisms leading to lethality.

First evidence for myocardial suppression in patients with septic shock was published in 1984 (13). All observed patients presented with high cardiac output maintained their stroke volume index, and displayed decreased systemic vascular resistance. It was further reported that 75% of patients exhibited decreased left ventricular ejection fraction after the onset of septic shock over a two-day period. However, one of the most striking findings in the study was that depression of the left ventricular ejection fraction, as well as the observed acute left ventricular dilatation, were reversible and returned to normal levels after 7 to 10 days in surviving patients (13). This was later confirmed in further patient studies and experimental settings (14–17). In more recent studies, predominantly using echocardiography, cardiac dysfunction during sepsis and septic shock has been confirmed (18–21). To date, it is now generally accepted that, after adequate volume resuscitation, patients develop a hyperdynamic circulatory state associated with high cardiac output, decreased systemic vascular resistance, and biventricular dilatation. Here, we describe supracellular, systemic, and various molecular mechanisms that might be involved in septic cardiomyopathy, such as circulating cardiosuppressing mediators, alterations of calcium flux in cardiomyocytes,

Address correspondence and reprint requests to *Peter A Ward, Department of Pathology, The University of Michigan Medical School, 1301 Catherine Road, Ann Arbor, MI 48109-0602, USA. Phone: (734) 647-2921; Fax: (734) 764-4308; E-mail: pward@umich.edu.*
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involvement of nitric oxide and peroxynitrite, as well as mitochondrial dysfunction and apoptosis.

SYSTEMIC, SUPRACELLULAR MECHANISMS

Decreased Coronary Blood Flow

One of the first suggestions was that reduced coronary perfusion in the septic heart might be responsible for a setting of global cardiac ischemia. This hypothesis was soon abandoned after direct measurements of coronary blood flow were obtained, showing no reduced, but rather increased, coronary blood flow (22,23). In later studies, however, increased levels of plasma troponin were observed and correlated with the severity of myocardial depression during sepsis and septic shock (24). Myocardial necrosis could not be observed in patients who died from septic shock (3,25), however, raising the question whether increases in troponin were due to cytokine-induced, transient increases in cardiomyocyte membrane permeability to troponin. To date, this remains to be determined.

Alterations of Microvasculature

There is now increasing evidence that sepsis and septic shock leads to changes of the myocardial microvasculature. In a canine model of endotoxemia, maldistribution of heterogeneous coronary blood flow has been reported (26). These findings might be caused by endothelial swelling and nonocclusive intravascular fibrin deposits in the microvasculature (27). In parallel, activated cardiomyocytes from septic mice promoted transendothelial migration and activation of circulating neutrophils into the interstitium (28) where these cells may augment the sepsis-induced intracardial inflammation, and contribute to an increased vascular leakage, which has been described to also impair cardiac function and compliance secondary to myocardial edema (29,30). Yet, studies have failed to confirm cellular hypoxia in a murine sepsis model (31).

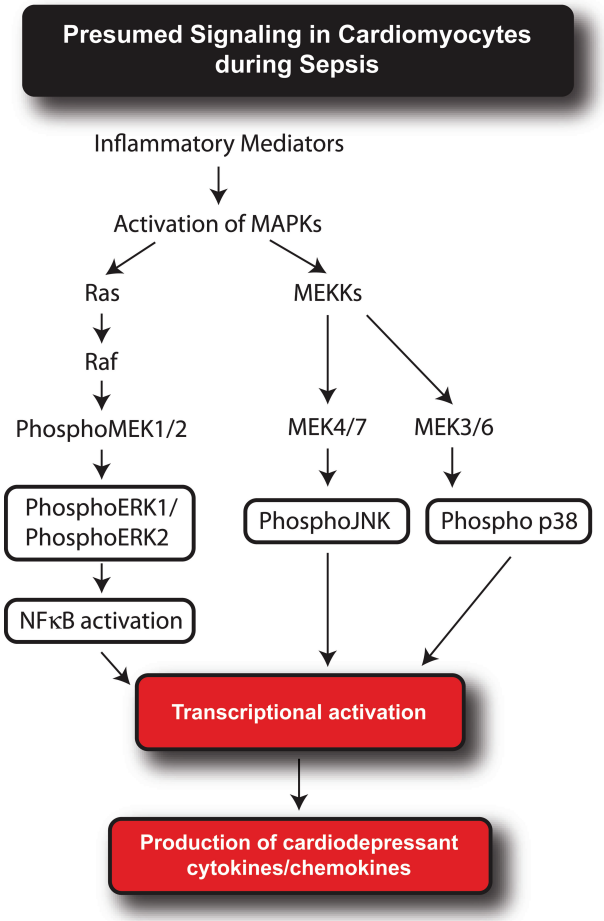

Figure 1. Flowchart of the presumed intracellular signaling in cardiomyocytes leading to myocardial production of cardiodepressant mediators.

Cardiosuppressing Circulating Proinflammatory Mediators

Another hypothesis suggested circulating myocardium-depressing factors as the cause of septic cardiomyopathy (32). Parrillo *et al.* (33) confirmed the existence of a cardiodepressant substance by incubating isolated rat cardiomyocytes with serum obtained from septic shock patients, leading to decreased amplitude and velocity of cardiomyocyte shortening. Levels of cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and the complement anaphylatoxin, C5a, are known to be elevated in the circulation during sepsis and have been found to directly depress myocardial contractility *in vitro* (34–36). It is noteworthy that cardiomyocytes are able to generate TNF-α, IL-1β, IL-6, cytokine-induced neutrophil chemoattractant (CINC)-1, macrophage migration inhibitory factor (MIF), and high-mobility group box (HMGB)-1 during endotoxemia, sepsis, and burn injury (37–39). This is a seemingly paradoxical phenomenon because such cardiomyocyte products would impair cardiomyocyte performance (Figure 1). Our understanding of this negative feedback loop to date remains elusive, but in many respects it is analogous to products of the inflammatory response that are tissue-damaging as opposed to products that are tissue-protective (40). During sepsis the complement anaphylatoxin C5a has been described to be involved in immunoparalysis (41), multiple organ failure (42), thymocyte apoptosis (43), and imbalance of the coagulation system (44). Recently,

C5a has also been found to play a major role in septic cardiomyopathy (36). Following experimental sepsis, reductions in left ventricular pressures occurred *in vivo* and in cardiomyocyte contractility *in vitro*, both of which could be reversed by *in vivo* administration of a blocking antibody to C5a (Figure 2). *in vitro* addition of recombinant rat C5a induced dramatic contractile dysfunction in both sham and septic cardiomyocytes, suggesting that excessive *in vivo* generation of C5a during sepsis causes dysfunction of cardiomyocytes (36).

Despite all these findings, isolated rabbit papillary muscles or rat cardiomyocytes harvested during the acute phase of sepsis and *ex vivo* studies show a persistent decrease in contractility in spite of the absence of direct contact with septic plasma (36,45,46). This raises questions as to whether cardiodepressant factors in serum represent an exclusive pathophysiological mechanism of sepsis-associated cardiomyopathy.

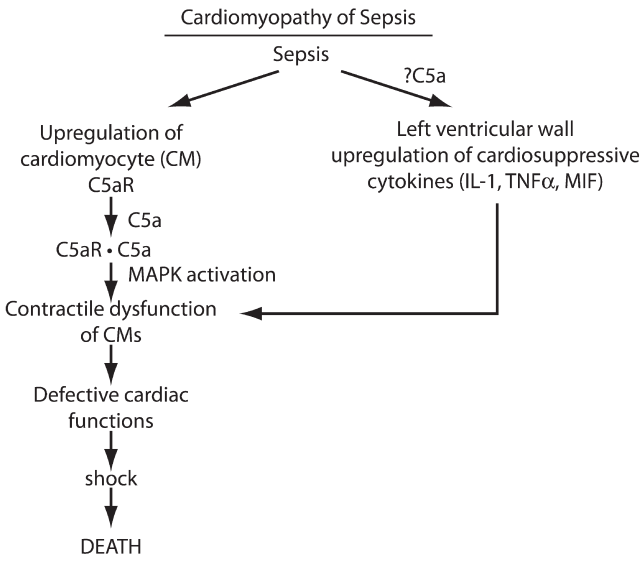

Figure 2. Myocardial contractile dysfunction sepsis might, in part, be triggered by C5a. Question marks illustrate open, to date unanswered, questions.

Metabolic Changes

Various profound metabolic changes have been described in the cardiomyocyte during sepsis and septic shock. Patients in severe sepsis and septic shock display a 30% increase of oxygen consumption and baseline metabolism compared with normal basal values, but both are markedly reduced compared with "uncomplicated" sepsis (47). Once organ dysfunction develops, however, oxygen consumption and resting metabolic rate decrease, suggesting that, during multiple organ failure, patients seem to tolerate lower values of oxygen supply (48). Moreover, prolonged sepsis has been found to be associated with progressive increase in tissue oxygen tension paralleling the severity of illness (49,50). It has therefore been speculated whether, during severe sepsis, cells utilize less oxygen, rather than suffering from a defective oxygen delivery to tissues. Whereas sepsis is generally associated with increased blood levels of lactate, septic human hearts exhibited a net lactate extraction between arterial and coronary sinus blood (22). In a recent human autopsy study of patients who had succumbed to severe sepsis, buildup of lipids was found inside cardiomyocytes (51). During sepsis, human cardiomyocytes have also displayed diminished uptake of ketone bodies, free fatty acids, and glucose (23). In parallel, septic mice presented with increased intracardiomyocyte deposits of glycogen (52).

Autonomic Dysfunction

Septic shock has been found to be associated with neuronal and glial apoptosis within cardiovascular autonomic centers (53,54), raising the question whether failure of cardiac modulation by the autonomic nervous system might contribute to septic cardiomyopathy. Other reports linked high levels of circulating catecholamines with the onset of septic shock but found impaired sympathetic modulation on heart and vessels, suggesting that central autonomic regulatory impairment contributes to circulatory failure (55). Moreover, impaired function of the autonomic nervous system is associated with an increased risk for death from critical illness (56). Thus, innovative pathophysiologic concepts targeting autonomic dysfunction in life-threatening disease emerge as a new clinical and scientific challenge (57–60).

CELLULAR MOLECULAR MECHANISMS

In addition to the circulating cardiodepressing factor theory, a second concept was developed, focusing on intrinsic alterations in the myocardium as a predominant mechanism of septic cardiomyopathy (see below). It remains to be determined if and to what extent cytokines, chemokines, and C5a participate in the initiation of these intracellular events, which would link the two hypotheses.

Calcium Flux and Cardiomyofilaments

There is now increasing evidence that sepsis induces significant alterations in the myocardial calcium homeostasis in two ways. First, abnormalities in the myocardial calcium current have been described in endotoxemic guinea pigs (61), as well as in cultured rodent cardiomyocytes exposed to the cardiodepressive IL-1β (62). In line with these findings, myocardial L-type calcium channels have been found to be decreased during endotoxemia (63). Second, a reduction in myofilament calcium sensitivity has been

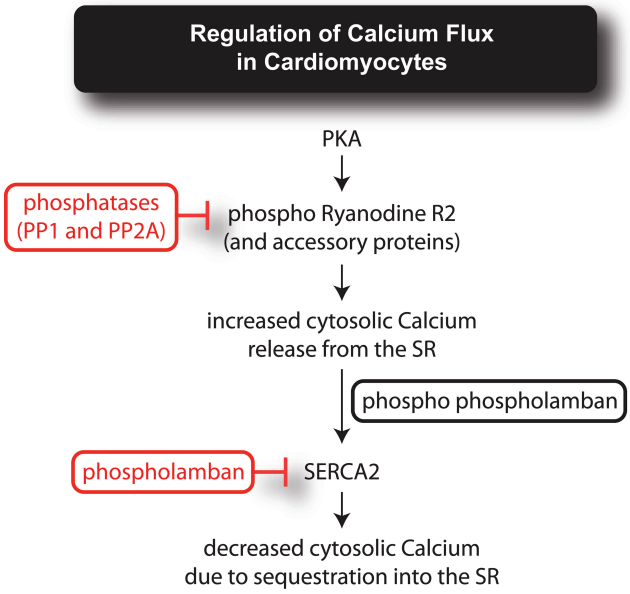

Figure 3. Physiologic regulation of calcium flux in cardiomyocytes.

reported in endotoxemic rabbits (64,65). The exact mechanisms of these observations are only partially understood, but the decreased response of myofilaments to calcium may be involved in the impaired myocardial contractility and depression of systolic function in septic patients. Indeed, reduced calcium sensitivity of myofilaments seems to be associated with increased cardiomyocyte length and increased ventricular distensibility (66). Recently, scattered foci of disruptions in the actin-myosin contractile apparatus were described in septic human hearts (51). Moreover, myocardial Ca^{2+} transport across membranes of the sarcoplasmic reticulum (SR) plays a central role in cardiac contraction-relaxation sequence (Figure 3). The density of the calcium release–triggering ryanodine receptor is decreased on the SR during experimental sepsis, associated with subsequent impairment of Ca^{2+} release from the sarcoplasmic reticulum (67). Transient increases of intracellular Ca^{2+} activate myofilament proteins to cause myocardial contraction. The sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2) subsequently translocates cytoplasmatic Ca^{2+} back into the SR, a process that is tightly controlled by a closely associated SR membrane protein, phospholamban (PLB) (68). Dephosphorylated PLB activates and enhances SERCA2 activity, whereas phosphorylation of PLB greatly diminishes SERCA2 functionality and myocardial relaxation (68,69). Thus, PLB and SERCA2 interactions play a primary role in regulating cardiac contractility and relaxation. Calcium uptake by sarcoplasmic reticulum has been shown to be impaired during the hypodynamic phase of sepsis in the rat heart (70). The resulting decrease in myocardial contractility during the hypodynamic phase might also, in part, be induced by a decrease in phospholamban phosphorylation, which leads to decreased Ca^{2+} transport across the SR (71). In sharp contrast, during the early hyperdynamic phase of sepsis, the interaction between phospholamban phosphorylation and Ca^{2+} transport across the SR seems to be largely disrupted, represented by an increase in phospholamban phosphorylation (71).

Toll-like Receptors and CD14

Toll-like receptors (TLRs) have been identified as primary receptors of innate immunity that distinguish between different patterns of pathogens and evoke a rapid innate immune response (72). To date, nine TLRs have been identified and characterized (72). Various studies have identified the expression of human TLRs, including TLR2, TLR4, and TLR6 in the heart (73–75). The importance of myocardial TLR signaling was established when TLR4 or IRAK1 (IL-1 receptor–associated kinase 1; a downstream signaling component of TLR4) deficient mice were found to be protected from LPS-induced cardiac dysfunction, as determined by echocardiogram (76,77). When mice were subjected to LPS challenge, the rapid and robust induction of NF-κB, subsequent increase of TNF and IL-1β mRNA, and protein expression in cardiomyocytes were significantly ameliorated and delayed in TLR4-mutant mice (78). These findings indicate that TLR4 signaling is responsible, at least in part, for the induction of myocardial proinflammatory mediators during endotoxemia.

CD14 is a 55-kD glycosylphosphatidylinositin-anchored receptor that binds LPS with affinity and is critically involved in mediating LPS responses (79). Subsequently, CD14-deficient mice were shown to be protected against LPS-induced septic shock (80). Cardiomyocytes from CD14-deficient mice exhibited decreased activation of NF-κB, blunted consequent downstream expression of myocardial mRNA, and protein levels of TNF and IL-1β during endotoxemia (81). Moreover, endotoxemic $CD14^{-/-}$ mice maintained normal cardiac function, whereas wild-type littermates displayed decreased left ventricular shortening and diminished velocity of circumferential shortening and left ventricular pressure/time (dP/dt_{max}) (81). Because CD14 lacks a transmembrane domain, however, the exact mechanism by which LPS binding to CD14 induces cell activation remains to be determined.

β-Adrenergic Receptors

Catecholamines are known to increase cardiac contractility and heart rate via interaction with β-adrenoceptors expressed

on the myocardium. However, if these receptors are excessively stimulated or engaged over an extended period of time, myocardial damage by calcium overload and subsequent cell necrosis have been reported (82). Septic patients are known to be exhibit increased levels of catecholamines (55,83,84). These findings have been confirmed in various animal studies (85,86). In a murine model of sepsis, decreased density of β-adrenoceptors on the myocardium was reported (87,88). However, other reports linked the myocardial contractile dysfunction to cytokine stimulation, as β-adrenoceptor density was found to be normal (89). Importantly, there seems to be significant disruption of the myocardial signal transduction following β-adrenoceptor stimulation. Endotoxemic rabbits displayed decreased levels of stimulatory G-proteins (90), and septic rats exhibited increased expression of inhibitory G-protein (91), which was also reported in the myocardium of human nonsurvivors of septic shock (92). These events are likely to decrease the activity of the adenylyl cyclase, resulting in decreased intracellular levels of cyclic adenosine monophosphate (cAMP), paralyzing the cardiomyocyte. Thus, it remains to be determined whether a blunted β-adrenoceptor stimulation, disruption of the signaling cascades further downstream, or a combination of both are involved in septic cardiomyopathy.

MAPK Signaling Cascades

Many extracellular stimuli recognized by mammalian cells engage a highly complex intracellular signaling network, at the center of which are involved the mitogen-activated protein kinases (MAPKs). The most extensively studied members of the MAPKs are extracellular signal-regulated kinase 1/2 (ERK1/2), p38 MAPK, and c-Jun N-terminal kinase (JNK) (93). In cardiomyocytes, MAPK activation has been linked to a wide array of cellular events, including apoptosis (94,95), ischemia/reperfusion injury (96), and ischemic heart failure (97). It remains to be determined if myocardial MAPK activation also occurs during sepsis (Figure 1), and if MAPKs are also engaged in other myocardial defects like disturbance of sarcoplasmic calcium flux, etc. (see above).

Matrix Metalloproteinases

Matrix metalloproteinases (MMPs) comprise a large family of zinc-dependent endopeptidases that have been recognized for their ability to degrade components of the extracellular matrix. Increased MMP activity has been associated with a wide variety of cardiovascular pathologies, including acute and chronic heart failure and atherosclerosis (98–101). MMP-2 activation and release has been found to mediate acute cardiac failure following ischemia-reperfusion injury through cleavage of troponin I (102,103). Recent studies have also demonstrated an important role for MMPs during septic cardiomyopathy. Endotoxemic rats were found to have significantly depressed cardiac function, loss of ventricular 72-kD MMP-2, and release of MMP-9 (104). MMP inhibitors significantly preserved cardiac function during LPS-induced septic shock and reversed these observations (104). In an ovine sepsis study, cardiac MMP-2 and MMP-9 activity positively correlated with heart rate and negatively correlated with left ventricular stroke work index, and increased MMP-2 and MMP-9 activities were positively correlated with cardiomyocyte apoptosis (105).

Nitric Oxide and Peroxynitrite

Excessive production of nitric oxide (NO) is an important player during hypotension and catecholamine resistance in septic shock (106). However, its role and impact on septic cardiomyopathy is still a matter of debate. Whereas disproportionate levels of NO sustain the ability of the left ventricle to fill during diastole, and thereby crucially support adequate myocardial perfusion (107,108), cardiodepressant activity of proinflammatory cytokines also seems to involve NO synthase (NOS): exposure of rat cardiomyocytes to septic sera depressed contractility (see below), but NOS inhibition restored contractility to control levels (109). Moreover, intracoronary infusion of the NO donor sodium nitroprusside impaired systolic pressure development despite improved diastolic relaxation and distensibility (110). Finally, deficiency or selective blockade of inducible NOS (iNOS) protected against the development of cardiac dysfunction in endotoxemic mice (111,112). In a cecal ligation and puncture (CLP) sepsis model, genetic iNOS deletion or pharmacological iNOS blockade enhanced cardiac norepinephrine responsiveness associated with improved systolic function, but seemed to be associated with compromised left ventricular relaxation (113). In septic patients, administration of a nonspecific NOS inhibitor increased arterial pressure but decreased cardiac output (114). The adverse effects of NO might also, in part, be related to interactions between NO and superoxide anions with subsequent production of peroxynitrite. Peroxynitrite, rather than NO *per se*, has been shown to impair muscle contractility during sepsis by its ability to denature proteins, perturb calcium flux, and depress mitochondrial respiration during experimental sepsis (115,116). In contrast, neutralization of peroxynitrite improved cardiac dysfunction in a rodent model of sepsis (117). In human septic hearts, increased expression of iNOS and significant amounts of peroxynitrite were found (51). Finally, NO, produced in large amounts during sepsis, can bind to complex IV of the respiratory chain and then compete with oxygen, inhibiting this complex and increasing production of reactive oxygen species (ROS) (3). High concentrations of NO also seem to block other complexes of the respiratory chain. Peroxynitrite can also be very toxic for the respiratory chain and particularly inhibits complexes I, II, and III (3).

Mitochondrial Dysfunction

Sepsis and septic shock severely impair the "cellular power plants," mitochondria (118,119). Recent evidence

suggests that the severity of myocardial dysfunction and maybe even severity and outcome of sepsis (120) could be related to mitochondrial dysfunction (121–123). During sepsis, myocardial mitochondria display ultrastructural damages in rodents (124,125) and humans (126). Septic animal hearts exhibited reduced activities of mitochondrial electron transport chain enzyme complexes (127–129). The increased mitochondrial production of superoxide and NO (130) in combination with the depletion of intramitochondrial antioxidants during sepsis might severely inhibit oxidative phosphorylation and ATP generation (120). This acquired defect in oxidative phosphorylation prevents cells from using molecular oxygen for ATP production and potentially causes sepsis-induced organ dysfunction (131). This concept has been termed "cytopathic hypoxia" (132,133). Interestingly, mitochondrial DNA seems to be more receptive to LPS-induced damage than nuclear DNA (124,134). Finally, the mitochondrial permeability transition pore seems to be involved in sepsis-induced mitochondrial damage in the myocardium, because its inhibition significantly improved cardiac function and reduced mortality in rodents (135).

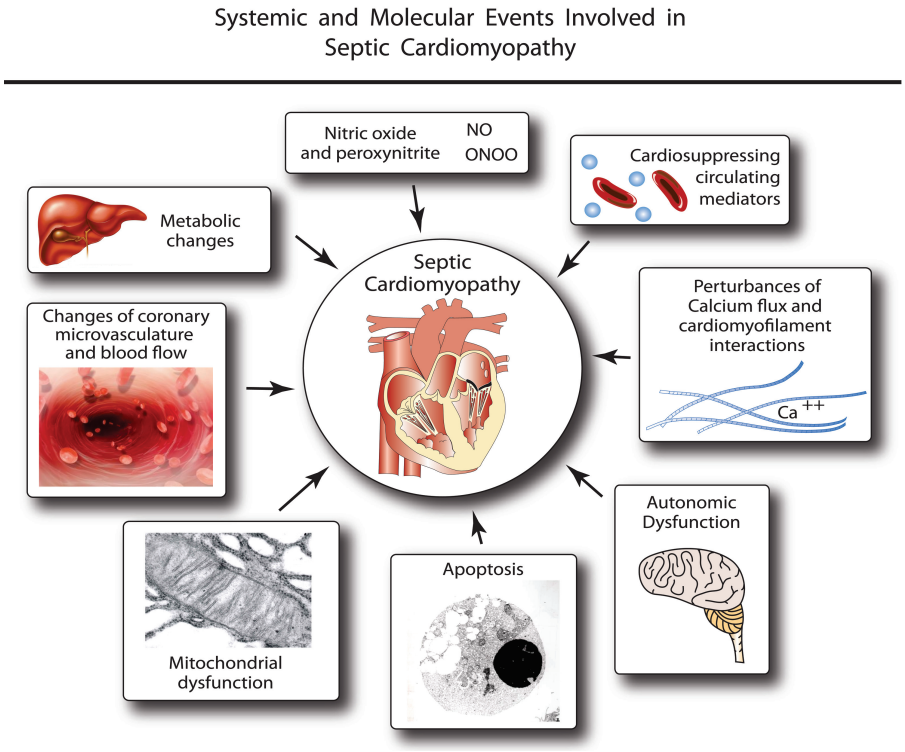

Figure 4. A depiction of supracellular, systemic, and molecular events involved in the cardiomyopathy of sepsis. See text for details.

Apoptosis

There is now increasing evidence that apoptosis is involved in septic cardiomyopathy (136–138). Activation of various caspases, the effectors of apoptosis, and mitochondrial cytochrome c release have been reported in cardiomyocytes following septic challenge (139–141). Caspase 3 activation via endotoxin might also be associated with altered calcium myofilament responses, cleavage of contractile proteins, and sarcomere disorganization (142). Therefore, it is not surprising that anti-apoptotic strategies have reversed cardiac dysfunction (inhibition of caspases [particularly caspase 3] averted endotoxin-induced cardiac dysfunction and heart apoptosis) (137,143). Cyclosporin A, which inhibits mitochondrial permeability transition and cytochrome c release, or overexpression of anti-apoptotic Bcl-2 both prevented sepsis-induced myocardial dysfunction (135,144,145). Yet, there seem to be additional parameters involved in the caspase inhibitor–mediated cardioprotection, besides decreasing apoptotic cell death. Blockade of caspase activation may decrease cytokine/chemokine production and indirectly influence intracellular calcium homeostasis (3). However, the time course of septic cardiomyopathy in humans (potential recovery after 7 to 20 days) profoundly challenges a central role of apoptotic cell death as a major cause of myocardial impairment. We need to understand more precisely the involvement of apoptosis in this setting.

CONCLUSIONS

Although tremendous research efforts have attempted to uncover the molecular mechanisms resulting in septic cardiomyopathy (Figure 4), various pieces of the puzzle so far fail to come together as a big picture. Why? Despite the identification of various mechanisms contributing to sepsis-induced cardiac dysfunction (such as cardiodepressant mediators, mitochondrial dysfunction, or apoptosis), we are far from understanding their exact impact. Each theory has a major flaw that challenges its principles. Cardiodepressant mediators, such as TNF-α, IL-1β, IL-6, MIF, etc., are known to be elevated early during sepsis, but return to normal levels within 2 to 3 days. Thus, cytokine/chemokine involvement in early cardiodepression seems possible. However, because cardiodepression is usually reversed only 7 to 10 days after sepsis onset in humans, myocardial suppression by cytokines/chemokines during the late stages of sepsis seems highly unlikely, unless these mediators are predominantly stored inside cardiomyocytes and exert their functions mainly without being secreted. However, this would infer functions of mediators without their interactions with surface receptors. Moreover, if

apoptosis is a driving force in cardiac dysfunction during sepsis, as various studies suggest, we have yet to understand how septic cardiosuppression can be reversible after 7 to 10 days. Thus, is apoptosis signaling somehow stopped at a pre-apoptotic level; and if so, by what molecular mechanisms? It seems that the abnormalities leading to contractile myocardial dysfunction during sepsis are transient and that a "corrective switch" exists, once profound sepsis is overcome, reversing cardiomyopathy.

The explanations for all of these questions and challenges might lie in the fact that the sepsis-induced depressed cardiac performance recapitulates the changes that occur during cardiac hibernation, an adaptive and reversible response otherwise seen in ischemia and hypoxia (52). Although these changes occurred in the setting of preserved arterial oxygen tension and myocardial perfusion, sepsis-associated myocardial depression might in fact be a form of cardiac hibernation, triggered by the same metabolic changes (increased glucose uptake, glycogen deposits, and increased steady-state levels of GLUT4) that have been described during ischemia and hypoxia (52). Hibernation is currently considered not only as a simple consequence of an oxygen deficit, but rather as an adaptive response to maintain cardiomyocyte viability in the setting of reduced blood flow (146). In stunning parallel with septic cardiomyopathy, the hibernating myocardium exhibits reduced calcium responsiveness (147), ultrastructural changes including loss of myofibrils (148), loss of mitochondria (149), and apoptosis-induced cell loss (150,151). Moreover, there is evidence that TNF-α and iNOS contribute to myocardial hibernation (152). Interestingly, these changes seem to be dose dependent, with moderate increases leading to reversible myocardial dysfunction, and greater increases resulting in irreversible injury (148). Thus, a crucial question is whether exceeding a certain threshold level of TNF-α, iNOS, or further unidentified mediators triggers the conversion from reversible to irreversible myocardial dysfunction. This remains to be determined.

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