Mechanisms of sepsis-induced cardiac dysfunction

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Objectives: **To review mechanisms underlying sepsis-induced cardiac dysfunction in general and intrinsic myocardial depression in particular.**

Data Source: **MEDLINE database.**

Data Synthesis: **Myocardial depression is a well-recognized manifestation of organ dysfunction in sepsis. Due to the lack of a generally accepted definition and the absence of large epidemiologic studies, its frequency is uncertain. Echocardiographic studies suggest that 40% to 50% of patients with prolonged septic shock develop myocardial depression, as defined by a reduced ejection fraction. Sepsis-related changes in circulating volume and vessel tone inevitably affect cardiac performance. Although the coronary circulation during sepsis is maintained or even increased, alterations in the microcirculation are likely. Mitochondrial dysfunction, another feature of sepsis-induced organ dysfunction, will also place the cardiomyocytes at risk of adenosine triphosphate depletion. However, clinical studies have demonstrated that myocardial cell death is rare and that cardiac function is fully reversible in survivors. Hence, functional rather than structural changes seem to be responsible for intrinsic myocardial depression during sepsis. The underlying mechanisms include down-regulation of β-adrenergic receptors, depressed postreceptor signaling pathways, impaired calcium liberation from the sarcoplasmic reticulum, and impaired electromechanical coupling at the myofibrillar level. Most, if not all, of these changes are regulated by cytokines and nitric oxide.**

Conclusions: **Integrative studies are needed to distinguish the hierarchy of the various mechanisms underlying septic cardiac dysfunction. As many of these changes are related to severe inflammation and not to infection *per se*, a better understanding of septic myocardial dysfunction may be usefully extended to other systemic inflammatory conditions encountered in the critically ill. Myocardial depression may be arguably viewed as an adaptive event by reducing energy expenditure in a situation when energy generation is limited, thereby preventing activation of cell death pathways and allowing the potential for full functional recovery. (Crit Care Med 2007; 35:1599–1608)**

KEY WORDS: sepsis; heart failure; β-adrenergic receptors; mitochondria; nitric oxide; calcium signaling

Sepsis, the systemic inflammatory response syndrome to infection, is the leading cause of death in the critically ill (1, 2), predominantly as a consequence of multiple organ failure. Myocardial dysfunction is a recognized manifestation of this syndrome (3–6). In light of a greater understanding of the underlying pathophysiology, a reappraisal of the literature is warranted. We will review both clinical and preclinical studies and integrate recent insights into subcellular mechanisms. Our aim is to provide a detailed overview on sepsis-induced cardiac dysfunction in general and on intrinsic myocardial depression in particular. The wide variety of possible pathophysiologic mechanisms and space limitations do not permit total coverage, but we hope that a synthesis of current knowledge relating to the major areas has been encapsulated in this review (Fig. 1).

PATIENT STUDIES

Despite awareness of sepsis-induced myocardial dysfunction for several decades, its frequency remains unknown. Large epidemiologic studies are lacking, and no consensus exists for a suitable definition. A reduced ejection fraction (EF) was recorded in 25% of nonshocked (7) and 50% of shocked septic patients (8) as assessed by ventriculography and thermodilution. However, cardiac output was normal or increased in all patients despite moderate to severe myocardial depression. Notably, survivors had lower EF and higher end-diastolic volumes compared with nonsurvivors, suggesting a protective effect of myocardial depression. The decrease in EF was reversible, with full recovery of cardiac function seen in survivors at 7–10 days. Right heart dilation and decreased right ventricular EF have also been described in some studies (9, 10) although not in other studies (11).

More recent studies have predominantly used echocardiography. In newly presenting hypotensive patients, hyperdynamic left ventricular (LV) function (EF >55%) during initial resuscitation was an independent predictor of sepsis (12). In a sequential study (13), hemodynamically unstable patients in septic shock had normal LV end-diastolic volume but depressed LVEF and severely reduced stroke volumes. One in six had severe hypokinesia with LVEF <30%. LV end-diastolic volume subsequently increased in survivors but tended to decrease in nonsurvivors. In other studies of septic shock lasting ≥48 hrs, 24% to 44% had systolic LV dysfunction (14–16). Those with myocardial depression had received more fluids during the first 24 hrs of intensive care unit stay and suffered a higher overall mortality than patients without myocardial dysfunction (16). A

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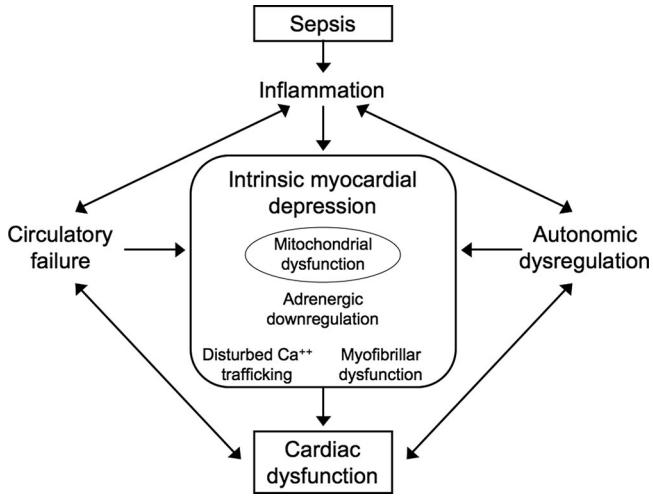

Figure 1. Sepsis-induced cardiac dysfunction. Cardiac performance during sepsis is impaired due to changes in the macro- and microcirculation, autonomic dysfunction, and inflammation-induced intrinsic myocardial depression. The mechanisms of myocardial depression include down-regulation of adrenergic pathways, disturbed intracellular calcium (Ca^{2+}) trafficking, and impaired electromechanical coupling at the myofibrillar level. Mitochondrial dysfunction seems to plays a central role in this sepsis-induced organ dysfunction.

further 44% showed echocardiographic features of diastolic dysfunction (15).

Various biomarkers have identified septic patients with cardiac injury or dysfunction. Serum levels of troponin I or T, both sensitive markers of cardiomyocyte damage, are elevated in 31% to 85% of critically ill patients with sepsis (17–21). Elevated troponin levels were associated with higher catecholamine requirements (18), lower stroke work index (18) and LVEF (20), and a higher mortality (17–20). Apart from necrosis, cytoplasmic troponin can leak into the circulation after reversible damage to the cardiac contractile apparatus (22). As discussed later, widespread myocardial necrosis is not a feature of human sepsis.

Elevated B-type natriuretic peptide levels have also been used to identify cardiac dysfunction in septic patients (16, 23), although many factors influence B-type natriuretic peptide levels, including age, gender, renal function (24), and possibly inflammation (25). We reported a similar increase in B-type natriuretic peptide levels in patients with severe sepsis, septic shock, and acute heart failure (26). High B-type natriuretic peptide levels in sepsis also correlated with adverse outcomes (16, 27).

ANIMAL MODELS

In vivo and *ex vivo* assessments have been performed using LV pressure measurements (28–30), conductance catheters (31, 32), echocardiography (28, 30, 33, 34), positron emission tomography (34), magnetic resonance spectroscopy (35), radionuclide studies (35, 36), and the Langendorff perfused heart model (37, 38). Investigators have also performed light and electron microscopy of cardiac tissue (35) and assessed isolated papillary muscles (39, 40), permeabilized muscle fibers (41), and single cardiomyocytes (42, 43). These models have varied in type (e.g., endotoxin, infusion of live bacteria, cecal ligation and puncture) and severity of insult, species, duration of study, anesthesia, and the degree (or absence) of volume resuscitation. The physiologic and immunologic response will vary as a consequence (44) and will affect outcome (45).

MECHANISMS

Circulatory and Microvascular Changes

Early sepsis and septic shock are characterized by circulatory abnormalities that usually relate to intravascular volume depletion and vasodilation. Consequent underfilling of the heart leads to a reduced cardiac output. This potentially causes an oxygen supply-demand imbalance in various organ beds (46) that is often reversed by fluid resuscitation (47). Insufficiently resuscitated animal models are therefore likely to demonstrate reduced cardiac performance (34, 48, 49). Myocardial edema due to inflammation-induced vascular leakage may also influence cardiac compliance and function (34, 50). In addition, ventricular function is influenced by changes in afterload. Pulmonary hypertension will worsen right heart function (51), whereas right heart dilation will impair left heart function (52). Finally, intrinsic cardiac contractility is affected, with a decreased ventricular performance in response to fluid resuscitation (53).

Macrocirculatory coronary blood flow is increased in patients with established septic shock (54, 55), but debate is ongoing as to the role of the microcirculation. In endotoxemic dog hearts, heterogeneous cardiac microvascular blood flow (56), swelling of endothelial cells, and nonocclusive intravascular fibrin depositions (35) are reported. Nevertheless, Hotchkiss et al. (57) found no cellular hypoxia in septic rat hearts using the marker ^{18F}fluoromisonidazole.

Vascular endothelial cells and cardiac myocytes interact closely. Endothelial cell activation led to increased production of nitric oxide (NO), endothelin, and prostaglandins that had paracrine regulatory effects on cardiac function (58). NO from activated endothelial cells also impaired isometric contractions of isolated cardiac trabeculae (59, 60). On the other hand, activated cardiomyocytes from septic mice influenced endothelial barrier function and promoted transendothelial migration of circulating neutrophils into the cardiac interstitium (61).

Autonomic Dysregulation

Some authors argue that severe sepsis is characterized by an autonomic failure, perhaps related to apoptosis in cardiovascular autonomic centers (62), that can precede the onset of shock (63–65). Tachycardia, a typical sepsis feature, is viewed as a response to cardiac underfilling, adrenergic stimulation, and fever. Sepsis-related tachycardia has several adverse effects on the heart, including restricted diastolic ventricular filling, increased oxygen requirements, and, potentially, a tachycardia-induced cardiomyopathy. Indeed, heart rate on presentation predicted survival in septic shock patients (66).

Metabolic Changes

Metabolic changes in the normal and diseased heart have been reviewed exten-

sively (67). During sepsis, profound metabolic changes are suggested by intracardiomyocyte accumulation of lipids and glycogen in nonsurvivors (22) and in mice (68). Whereas sepsis is characterized by hyperlactatemia, the hearts of septic patients show a net lactate extraction between arterial and coronary sinus blood (54) and a diminished myocardial uptake of glucose, ketone bodies, and free fatty acids (55). In septic patients, oxygen consumption and resting metabolic rate are enhanced compared with normal metabolism (69). However, with the development of organ dysfunction and the progression of shock, both oxygen consumption and resting metabolic rate decrease. This suggests that septic patients with established organ dysfunction or shock can tolerate lower values of oxygen delivery. Prolonged sepsis is also associated with a progressive increase in tissue oxygen tension that parallels the severity of illness (70, 71). The implication is that the problem lies more in reduced cellular oxygen utilization than in its delivery to tissues. As >90% of total body oxygen consumption is used by mitochondria for adenosine triphosphate (ATP) production, mitochondria may play a fundamental role in the pathogenesis of sepsis-induced organ dysfunction.

Mitochondrial Dysfunction

Many sepsis studies demonstrate the importance of mitochondrial dysfunction (72, 73) (Fig. 2). This has been linked to both severity and outcome (74). Cardiomyocytes demonstrate mitochondrial ultrastructural damage in both septic animals (35, 75–78) and patients (79, 80). Reduced oxygen consumption, suggestive of disturbed mitochondrial respiratory function, is described in animals in late- but not early-stage sepsis (77). Decreased activities of mitochondrial electron transport chain enzyme complexes are also documented in hearts from septic animals (43, 76, 81–83). Underlying mechanisms include the inhibitory effects of reactive nitrogen and oxygen species on oxidative phosphorylation and ATP production. This is related to elevated production of superoxide and NO and depletion of intramitochondrial antioxidants (74). Mitochondrial DNA is more susceptible to endotoxin-induced damage than nuclear DNA (76, 84). However, reactive oxygen species will also stimulate recovery by activating mitochondrial biogenesis within the rat heart (76).

Increased expression of mitochondrial uncoupling proteins (UCP) could reduce mitochondrial membrane potential and ATP synthesis (85, 86). UCP1 in brown adipose tissue is linked with heat production, whereas the roles of UCP2 and UCP3, both found in human heart (87), are less clear, especially during sepsis (88). A UCP-induced proton leak may reduce the efficiency of ATP generation but could also potentially limit superoxide generation (89). Heat shock proteins, strategically positioned in and outside mitochondria, protect vital protein structures and functions during stress conditions (90). Their activation in septic rats reduced cardiac mitochondrial dysfunction (91) and mortality (92). Finally, the mitochondrial permeability transition pore may also play a role in the development of mitochondrial dysfunction, as its inhibition improved mitochondrial respiration, restored the cardiomyocyte membrane potential, improved cardiac function *ex vivo*, and reduced mortality in septic mice (93).

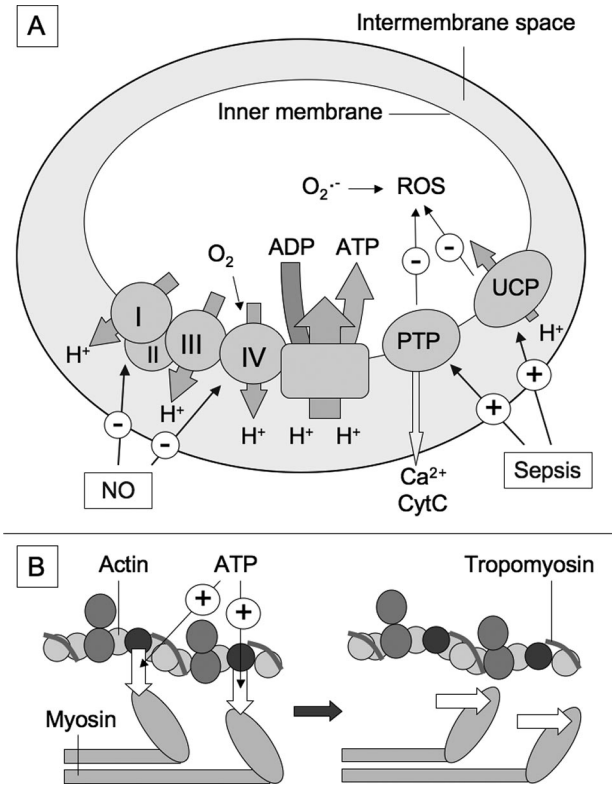

Figure 2. Mitochondrion. *A*, electrons passing along the respiratory chain complexes generate a proton (H^+) gradient across the inner mitochondrial membrane that drives adenosine triphosphate (*ATP*) synthesis. At complex IV, most of the oxygen consumed by mitochondria is reduced to water. Other oxygen molecules react with free electrons at complexes I and III, resulting in production of superoxide ($O_2^{\cdot-}$) and, subsequently, other reactive oxygen species (*ROS*). Uncoupling proteins (*UCP*) dissipate the proton gradient, thereby potentially reducing ATP and ROS production. Opening of the permeability transition pore (*PTP*) results in mitochondrial swelling, proton gradient collapse, calcium efflux, and release of cytochrome *c* (CytC), an activator of apoptosis. Sepsis induces mitochondrial dysfunction at various levels, partly by excessive nitric oxide (*NO*) production. *B*, ATP binds to actin, allowing myosin to detach from its binding site and change its configuration, a process that is crucial for myocardial relaxation. *ADP*, adenosine diphosphate.

Cell Death

Cellular hypoxia (due to circulatory derangements) and dysoxia (due to mitochondrial dysfunction) may both place the cardiomyocyte at risk of energy depletion and cell death if energy demands continue to outstrip supply. In different septic models, variable changes in ATP and phosphocreatine have been reported (35, 75, 94). In some of these studies, myocardial depression was noted in the absence of any changes in high-energy phosphates or cell death. However, nucleotide levels may be preserved by a reduction in energy requirements (74), and a decrease in ATP turnover cannot be excluded.

With regard to myocardial cell death, postmortem studies in septic shock patients revealed increased inflammatory cell infiltration but minimal, if any, myocardial cell death (20, 22, 80, 95, 96). Animal studies have detected subendocardial necrosis after non-fluid-resuscitated sepsis (97), although other studies have shown negligible myocardial necrosis (35) or apoptosis (98–102). Of note, the caspase cascade is nonetheless activated. A caspase inhibitor reduced the degree of depression in *ex vivo* Langendorff heart preparations and in isolated cardiomyocytes (101), hinting at alternative modes of action. In summary, myocardial cell death is a rare event during sepsis and insufficient to account for the functional depression observed. The reversibility of this condition also supports functional rather than anatomical abnormalities.

Inflammatory Signaling

Endotoxin, Toll-Like Receptors, and Cytokines. Endotoxin mediates cardiovascular changes mimicking sepsis in both research animals (103) and human volunteers (104–106). Endotoxin-induced cardiac dysfunction depends on the presence of the cell-wall receptors Toll-like receptor-4 (30, 43, 107) and CD14 (108). Toll-like receptor-4 must be present on macrophages and, to a lesser extent, neutrophils to cause myocyte dysfunction during endotoxemia (43, 109). Likewise, Toll-like receptor-2 is necessary for myocardial dysfunction after a Gram-positive challenge (110). These studies thus invoke a mechanism involving cytokine release from macrophages, supporting earlier work from Parrillo et al. (42) identifying the presence of a circulating myocardial depressant substance in humans with septic shock. Serum from these patients taken during the acute phase, but not the recovery period, significantly depressed contractions in isolated rat cardiomyocytes. These *in vitro* changes paralleled serial changes seen in the patients' LVEF. Immunoabsorption of both tumor necrosis factor α and interleukin-1β from the patient sera resulted in loss of depressant activity in the rodent cells (111). This study also showed a dose- and time-dependent decrease of myocardial cell shortening after cytokine treatment, which reversed on washing the cells with cytokine-free media. Interleukin-6 has also been shown to have an important role in myocardial depressant activity in children with meningococcal septic shock (112). This supported earlier work in *in vitro* models (113, 114). Macrophage migration inhibitory factor, another proinflammatory cytokine elevated in patients with septic shock, is also implicated in the pathogenesis of myocardial dysfunction (115–117). In summary, myocardial function is depressed by various cytokines produced and liberated from activated immune cells after contact with bacterial compounds.

Nitric Oxide. NO, a small, highly reactive molecule with a half-life of a few seconds, is produced in virtually all cell types within the heart. All three isoforms of NO synthase (NOS) are found in cardiomyocytes. NO has a multifaceted role in cardiac physiology, both in health and disease states, and its biology is highly complex (see Refs. 118–120 for reviews). It is responsible for direct effects on vascular tone, depression of mitochondrial respiration, and further release of proinflammatory cytokines. NO is also endowed with pro- or antiapoptotic signaling capabilities, depending to some extent on its concentration and cellular context, for example, generation of reactive oxygen species (121, 122).

The inducible NOS-2, transcriptionally up-regulated by cytokines, pathogen antigens, and redox-sensitive transcription factors, produces NO, a well-recognized myocardial depressant (123–125). Conflicting results from selective and nonselective inhibition of inducible NO synthase indicate that the constitutive NOS isoforms (NOS-1 and NOS-3) have a potential role in regulating cardiomyocyte homeostasis and function (39, 126, 127). Whereas NOS-2 activation depressed cardiac function, overexpression of NOS-3 had the opposite effect in septic mice (128). These differences may be related to variable dose-related, temporal, and subcellular compartmental effects on β-adrenergic responsiveness, calcium handling, and contractility (129).

NO activates soluble guanylyl cyclase, thus elevating intracellular 3'5'-cyclic guanosine monophosphate and, in turn, a family of 3'5'-cyclic guanosine monophosphate kinases. NO also reacts with superoxide to form peroxynitrite ($ONOO^-$). NO and $ONOO^-$ can react with iron and thiol-containing proteins to modulate the role of that protein either reversibly or irreversibly, for example, enzyme activity. $ONOO^-$ induced a delayed and irreversible cardiac depression in a perfused heart model (130). Myocardial ATP levels remained normal, as did creatine kinase release, indicating a lack of myocyte death. The same group also reported similar findings, with increased ventricular NOS-2 activity and levels of NO and $ONOO^-$, in hearts perfused with either cytokines (123) or endotoxin (131). A peroxynitrite decomposition catalyst, a NO synthase inhibitor, and a superoxide scavenger were all able to prevent this decline in cardiac function. Some of these results may be explained by $ONOO^-$-induced activation of matrix metalloproteinases (132).

Conservation of the NOS-2 gene during evolution suggests that the NO response to sepsis could be adaptive and, at least in part, protective to the heart. Indeed, selective NOS-2 inhibition increased cardiac oxygen consumption in failing dog hearts (133). NO also induces coronary and systemic vasodilation, thereby facilitating myocardial blood supply and reducing cardiac afterload. NOS-2 inhibition increased systemic and pulmonary blood pressure but decreased cardiac output in endotoxin-treated animals (51, 134, 135) and in septic shock patients (136, 137). Furthermore, NO may increase ventricular compliance, allowing the septic heart to fill more easily during diastole (138, 139). By inhibiting the electron transport chain, NO and $ONOO^-$ could decrease superoxide production (89). NO can additionally act as a free radical scavenger, preventing the formation of even more toxic reactive oxygen species (140). Finally, if organ failure is related to mitochondrial damage, recovery will be contingent on restoration of new active mitochondrial protein. This process, mitochondrial biogenesis, is triggered by NO (141, 142).

Contractile Dysfunction

Adrenergic Signaling. Short-term β-adrenergic stimulation with catecholamines increases cardiac contractility and heart rate. However, prolonged and excess stimulation can lead to myocardial damage by calcium overload and consequent cell necrosis (143). During sepsis, various studies have documented elevated catecholamine levels in patients (63, 144, 145) and animals (33, 146). Circulating catecholamines may be autooxidized by superoxide and thus inactivated (147). In a septic shock rat model, administration of a superoxide dismutase mimetic increased plasma catecholamine concentrations and β-adrenergic respon-

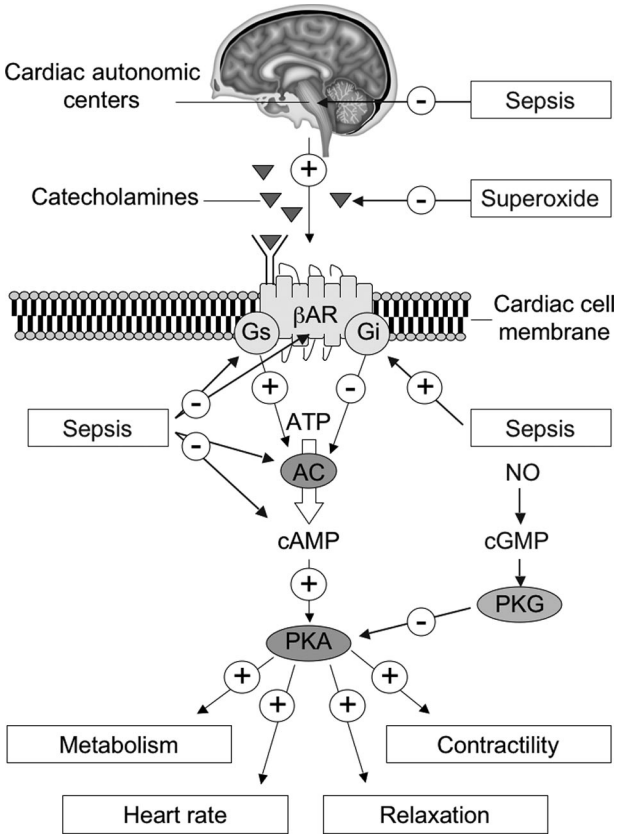

Figure 3. Adrenergic signaling. After stimulation of cardiac autonomic centers, secreted catecholamines stimulate β-adrenergic receptors (*βAR*) on cardiomyocytes. These receptors are coupled to adenylate cyclase (*AC*), which transforms adenosine triphosphate (*ATP*) to cyclic adenosine monophosphate (*cAMP*). G-proteins, both stimulatory (*Gs*) and inhibitory (*Gi*), modify signal transmission across the cell membrane. cAMP activates protein kinase A (*PKA*), which phosphorylates key enzymes that stimulate metabolism, stimulate cardiomyocyte contraction and relaxation, and influence heart rate. Sepsis induces a disruption at various levels of this signaling cascade, partly via nitric oxide (*NO*), cyclic guanosine monophosphate (*cGMP*), and protein kinase G (*PKG*).

siveness. At the cardiomyocyte level, various adaptive mechanisms responding to elevated catecholamine levels have been identified (Fig. 3). In septic rats, myocardial β-adrenergic receptor density was found to be decreased (148, 149). Others found a blunted contractile response in rat cardiomyocytes after cytokine stimulation despite a normal receptor density (150). Notably, responses to increased extracellular calcium ion concentrations were normal. The underlying mechanism was identified to be a disruption of signal transduction across the cell membrane (151). In endotoxemic rabbits, stimulatory G-proteins were decreased (152), whereas in both nonsurvivors of septic shock (153) and septic animals (154), inhibitory G-proteins were increased. These changes result in decreased activity of adenylyl cyclase and reduced levels of cyclic adenosine monophosphate. In summary, β-adrenergic stimulation during sepsis is blunted by alterations occurring at different levels of the signaling cascade. In both patients with reduced LV function (155) and septic mice (156), down-regulation of the β-adrenergic response was associated with elevated levels of NO.

Calcium Trafficking. Intracellular calcium trafficking is depicted in Figure 4. Endotoxin (157, 158) and cytokines (159) alter and suppress L-type calcium currents in isolated rat cardiomyocytes, perhaps via changes in autonomic regulation of this channel. This is accompanied by reduced systolic intracellular calcium concentration and diminished cell contraction. Additionally, endotoxin opens ATP-dependent potassium channels, thereby shortening action potentials and reducing calcium overload (160). Ryanodine receptor density is also decreased in septic models, with a consequent impairment of calcium-induced calcium release (161, 162). Ryanodine receptor activity and isolated papillary muscle contractility were decreased at 24 hrs but not 4 hrs after endotoxin (163). These effects could be reversed by selective NOS-2 inhibition. Recombinant human tumor necrosis factor-α decreased contractility in *in vitro* models (164), secondary to a decrease in intracellular calcium concentration, perhaps via activation of the sphingomyelin pathway (165–167). Tumor necrosis factor-α-dependent degradation of sphingomyelin to sphingosine blocks the ryanodine receptor and impedes calcium release from the sarcoplasmic reticulum.

Diastolic calcium uptake into the sarcoplasmic reticulum was unaffected during the early phase of sepsis but decreased later on (168, 169). This was associated with defective phosphorylation of sarcoplasmic reticulum proteins, including phospholamban, and an increase in tissue cyclic adenosine monophosphate, implicating changes in β-adrenergic signaling.

The phosphatase calcineurin stimulates cytokine gene transcription and opens the mitochondrial permeability transition pore. Inhibition of calcineurin normalized cardiac performance 4 hrs after endotoxin, preventing cardiomyocyte apoptosis (170) and improving mitochondrial morphology and function (171). However, these changes were accompanied by a probable increase in reactive oxygen species (171).

In summary, reductions in cytosolic calcium levels reduce contractility during late sepsis. Calcium trafficking is also linked to mitochondrial function and integrity. It remains to be determined how these effects on calcium signaling are linked to time-dependent changes in NO, the β-adrenergic response, and any protective effects on the myocardium during prolonged sepsis.

Myofibrillar Dysfunction. In nonsurvivors of long-standing septic shock, immunohistochemical analysis of cardiomyocytes suggested partial disruption of myofilaments (22). This may be due to enhanced matrix metalloproteinase activity as these enzymes can degrade both the contractile apparatus and the cytoskeleton (172, 173). Reversal of these structural changes is likely to be slow, especially if *de novo* protein synthesis is required. An altered calcium sensitivity of cardiac myofibrillar proteins is seen in animal models of sepsis (174, 175), leading to reduced contractility of isolated papillary muscles (40). In summary, alterations of the contractile apparatus, including reduced calcium sensitivity, are also likely to contribute to the myocardial depression during sepsis.

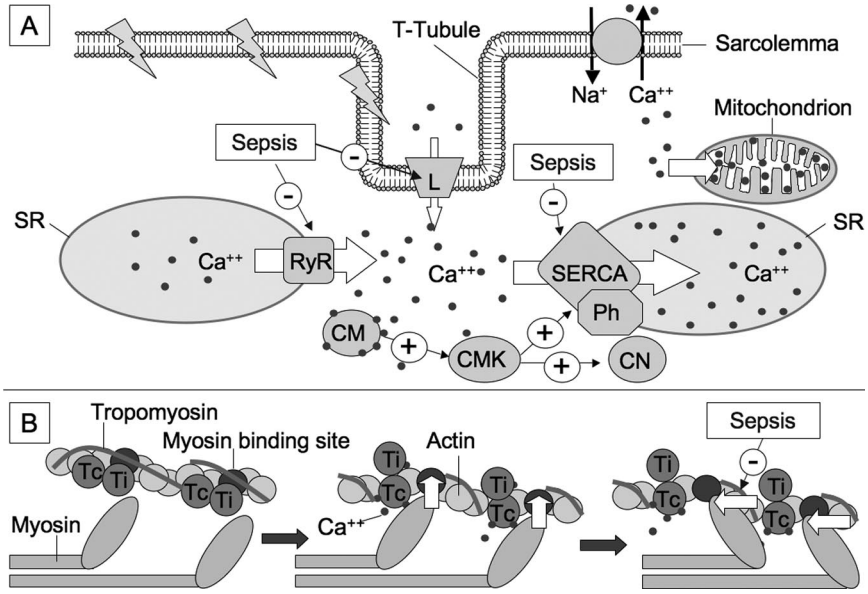

Figure 4. Calcium trafficking. *A*, depolarization of the cardiomyocyte sarcolemma opens L-type voltage gated calcium channels (*L*), leading to Ca^{2+}-induced Ca^{2+} release by ryanodine receptors (*RyR*) from the sarcoplasmic reticulum (*SR*). The intracellular Ca^{2+} concentration determines the force of contraction. To allow diastolic relaxation, Ca^{2+} must be removed from the cytosol back into the SR by the energy-dependent SR-calcium-adenosine triphosphatase (SERCA). SERCA activity is regulated by phospholamban (*Ph*). A proportion of Ca^{2+} is removed into mitochondria, and some is transported extracellularly by a Na^{+}-Ca^{2+} pump. Some Ca^{2+} binds to calmodulin (*CM*), a regulatory protein that lowers cytosolic Ca^{2+} directly, and via calmodulin-kinase (*CMK*), which stimulates Ca^{2+} reuptake into the SR. CMK also activates calcineurin (*CN*), which interacts with the mitochondrial permeability transition pore, enabling mitochondria-related death pathways. Sepsis inhibits intracellular Ca^{2+} trafficking at various sites. *B*, cytosolic Ca^{2+} binds to troponin C (*Tc*), modulating the inhibitory action of troponin I (*Ti*) and tropomyosin, hence exposing the binding site for myosin. After interaction between actin and myosin, the myosin head changes its conformation, resulting in a power stroke that moves the actin filament against the myosin filament. Sepsis decreases calcium sensitivity and causes damage to the contractile apparatus via activation of matrix metalloproteinases.

CONCLUSIONS

Myocardial depression is a well-recognized manifestation of organ dysfunction in sepsis. Echocardiographic studies suggest that 40% to 50% of patients with prolonged septic shock develop myocardial depression, as defined by a reduced ejection fraction. The degree of myocardial structural derangement and functional impairment relates to the severity of illness. As sicker patients usually receive higher doses of vasoactive drugs, the physiologic cardiac response may be masked considerably. Various mechanisms can explain the development of septic myocardial depression, most of which are regulated by cytokines and NO. Future integrative studies are needed to distinguish the importance and hierarchy of these mechanisms. As many of the changes described here are related to severe inflammation and not to infection *per se*, a better understanding of septic myocardial dysfunction may be usefully extended to other systemic inflammatory conditions encountered in the critically ill.

Finally, it is worth considering that myocardial depression could protect the heart by reducing cellular energy expenditure in a situation when energy generation is impaired due to mitochondrial dysfunction and microcirculatory abnormalities. Analogies can be drawn to ischemia-induced hibernation, a well-recognized phenomenon in patients with ischemic heart disease, serving as a regulatory event that maintains myocardial integrity and viability (176). Similar cellular changes to those seen during hibernation have been reported in septic animals in conjunction with diminished cardiac performance (68). This concept merits further investigation as it may carry major implications for patient management.

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