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# 2.

## **Structural changes of the heart during sepsis-induced myocardial dysfunction**

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## **Abstract**

Cardiovascular dysfunction is common in severe sepsis or septic shock. Although functional alterations are often described, the elevated serum levels of cardiac proteins and autopsy findings of myocardial immune cell infiltration, edema and damaged mitochondria suggest that structural changes to the heart during severe sepsis and septic shock may occur and may contribute to cardiac dysfunction. We explored the available literature on structural (vs functional) cardiac alterations during experimental and human endotoxaemia and/or sepsis. Limited data suggests that the structural changes could be prevented and myocardial function improved by (pre-) treatment with platelet activating factor (PAF), ciclosporin A (CsA), glutamine, caffeine, simvastatin or caspase inhibitors.

## Introduction

Severe sepsis is a complex cardiovascular, immunological and metabolic disorder characterized by hemodynamic changes and dysfunction of one or more organs (1). It is the leading cause of death in critically ill patients with mortality rates approximating 30% (2,3). Myocardial dysfunction including left (LV) and right (RV) ventricular systolic and diastolic dysfunction is one of the key features of the cardiovascular dysfunction in severe sepsis. It occurs in up to half of all patients with severe sepsis and/or septic shock and contributes to mortality (4-17).

The pathophysiological mechanisms underlying sepsis-associated myocardial dysfunction are not fully understood. Parker and colleagues reported that decreased LV ejection fraction (LVEF) and ventricular dilatation as evidenced by increased LV end-diastolic volume index (LVEDVI) returned to normal in survivors over 7 – 10 days suggesting that myocardial depression is a reversible condition (13). Subsequently, it has been argued that functional rather than structural (i.e. histological) changes seem to be responsible for sepsis-associated myocardial depression (18). Hence, many investigators have attempted to identify molecular and functional mechanisms (4,18-20). However, data from patients with severe sepsis or septic shock indicate that structural changes of the heart during severe sepsis and septic shock may also occur. Increased levels of cardiac Troponin I (cTnI) and T (cTnT) suggestive of myocardial cellular injury during the acute phase of patients with severe sepsis or septic shock have been linked to mortality (21-32). Furthermore, autopsy specimens of adults dying from severe septic shock showed myocardial infiltration of polymorphonuclear neutrophils (PMNs) and monocytes/macrophages suggesting myocarditis, disruption of the contractile apparatus, increased amounts of interstitial collagen and damaged mitochondria. These findings raise several questions (24,27-29). First of all, the functional consequences of these structural alterations during the acute phase of illness are unclear. Second, it is unknown whether the structural alterations are reversible or even preventable. Speculatively, persistence of structural alterations may amongst others contribute to the morbidity, decreased health-related quality of life (HR-QoL) and increased mortality on the long term observed in patients after being hospitalised with severe sepsis or septic shock (33-35). Indeed, one small pediatric study has shown impaired LV function during follow-up (between 0.8 and 12.7 years after discharge) in 12% of children who survived septic shock (36).

The purpose of this narrative review therefore is to explore the available literature on structural cardiac alterations during experimental or human endotoxemia and/or sepsis – with a focus on myocardial infiltration of immune cells and edema, cell death and mitochondrial injury – in order to

assess potential pathophysiologic contributions and reversibility.

## Methods

MEDLINE was electronically searched from inception to August 2011 using the following keywords: sepsis, shock, septic shock, heart failure, myocardial dysfunction, inflammation, edema, apoptosis and mitochondria. Terms were combined using Boolean operators where appropriate. Only studies published in English were retrieved.

## Results

### *Infiltration by immune cells and edema*

Myocardial infiltration of immune cells is a recognized feature of severe sepsis. The predominant cell types found in human autopsy specimens include PMNs and monocytes/macrophages (24,27-29,37). These human findings were confirmed in endotoxemia induced by lipopolysaccharide (LPS) or sepsis induced by caecal ligation and puncture (CLP) in animals by either light microscopy or electron microscopy (EM). These observations are universal irrespective of the experimental sepsis model studied and suggest sepsis/LPS-induced myocarditis (Table 1) (38-46). This may contribute to inflammatory myocardial edema that causes an increase in interstitial pressure with a subsequent increase in myocardial stiffness and/or a decrease in contractility as seen in patients after cardiopulmonary bypass or ischaemia-reperfusion injury (47). Marked swelling of cardiac endothelial cells with prominent leucostasis and fibrin thrombi in blood vessels and infiltration by PMNs may form the basis of inflammatory myocardial edema during experimental sepsis (41,42).

The causative mechanisms underlying myocardial infiltration by immune cells and edema during sepsis are unclear but are most likely multifactorial. Activated endothelium attracts inflammatory cells that will infiltrate the myocardial interstitium (48). The presence of Toll-like receptor (TLR)-2 and TLR-4 in the heart seems mandated (49-51). TLRs are pattern-recognition receptors (PRR) recognizing bacterial ligands and triggering the initial inflammatory response (52). LV function was not depressed in mice with defective TLR-4 signaling during endotoxemia (49). Cardiomyocyte expression of TLR-4 may be of less importance, but its presence on macrophages and PMNs is necessary to cause myocardial dysfunction (50). Myocardial dysfunction in gram-positive sepsis is amongst others mediated via TLR-2 (51). Alternatively, activation and dysfunction of the endothelium with expression of cell

Ref.	Setting, duration	Model	Main findings	Reversibility
(38)	Dogs, h	LPS i.v.	Myocardial cell swelling and decreased interstitial volume	Not reported
(39)	Sprague-Dawley rats, 48 h	CLP	Significant decrease in myocardial collagen and increased interstitial space	Not reported
(40)	Albino rats, 13 days	LPS i.p.	Absent glycocalyx, disorganized basement membrane, edema of interstitial tissue	Not reported
(41)	Rabbits, 5 h	LPS i.v.	Increased concentration of leukocytes in myocardial capillaries, focal diffuse areas of myocyte swelling, nuclear swelling, hypochromasia, cytoplasmic vacuolation, zonal contraction banding, decreased LV contractility defined by $E_{max}$	Not reported
(42)	Beagles, 48 h	LPS in fibrin clots	Decreased LV shortening, less increase in myocardial work compared with controls, neutrophilic infiltrate, endothelial cell edema, capillary intraluminal fibrin deposition, focal myofibrillar loss, sarcolemmal scalloping, interstitial edema	Not reported
(44)	Sheep, 72 h	CLP	Intercellular and intracellular edema	Not reported
(46)	Dogs, 6.5 h	LPS i.v.	Edema	Not reported
(64)	Sprague-Dawley rats, 48 h	LPS i.v.	Interstitial edema, infiltration by white blood cells, decreased myocardial function (LV developed pressure and $dP/dt_{max}$ and $dP/dt_{min}$ )	Not reported
(65)	Sprague-Dawley rats, 14 h	LPS i.v.	Interstitial edema, infiltration by white blood cells, decreased myocardial function (LV developed pressure and $dP/dt_{max}$ and $dP/dt_{min}$ )	Not reported
(66)	Rats, 48 h	LPS i.p.	Decreased LVEF, subepicardial inflammation, increased interstitial space	Fluid resuscitation improved LVEF but had no effect on interstitial space and cardiac wet-to-dry ratio
(69)	Rats, 30 m	LPS i.v.	Mild interstitial edema	Pre-treatment with PAF antagonist reduced edema
(76)	Pigs, 48 h	LPS i.v.	Marked swelling with increase in fine granular matrix and pinocytotic vesicles, leucostasis. At 48 h intracellular edema, open intercalated discs, enlargement of T-tubules	Not reported
(55)	Mice, 4 h	LPS i.p.	Time-dependent increase in neutrophil accumulation in the interstitial space	Not reported

**Table 1. Summary of data from experimental studies on myocardial inflammation and edema.** Abbreviations: LPS lipopolysaccharide; CLP cecal ligation and puncture; i.v. intravenous; i.p. intraperitoneal; h hours; mins minutes;  $E_{max}$  maximum elastance; LV left ventricle; LVEF left ventricular ejection fraction; PAF platelet activating factor

adhesion molecules such as vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1 and has also been suggested to play a pivotal role in sepsis-induced microvascular dysfunction and leakage (53-57). We also found myocardial infiltration by immune cells in association with increased deposition of advanced glycation end (AGE) products during CLP-induced sepsis (58-61) suggesting a role for AGE receptors (RAGE). These receptors trigger a cascade of signaling mechanisms with subsequent endothelial activation shown by expression of VCAM-1, induction of vascular leakage, and increased chemotaxis of mononuclear phagocytes and release of pro-inflammatory mediators resulting in cellular dysfunction (48,62). Next, other mediators are produced by the endothelium including endothelin (Et)-1 (48). Activated endothelium attracts inflammatory cells that will infiltrate the myocardial interstitium (63). Activated PMNs produce reactive oxygen species (ROS) and degradative enzymes (50,55). This implies that in fact the infiltration of leukocytes rather than toxic microbial products are associated with myocardial dysfunction although this assumption is disputed by others (41,64-68).

The functional correlate of myocardial infiltration of immune cells and edema during endotoxemia and/or sepsis has been evaluated by several investigators. Both *in vivo* evaluations in rabbits and rats as well as *ex vivo* evaluation of rat hearts in a Langendorff setup have shown depressed myocardial contractility as defined by decreased LV shortening or decreased LV developed pressure,  $dP/dT_{max}$  or a decreased maximum elastance ( $E_{max}$ ). However, the presence of edema per se may not fully explain impairment of myocardial function. Piper and colleagues observed *ex vivo* depressed myocardial contractility in the absence of edema 24 hours after CLP (68).

No studies have evaluated the reversibility of either infiltration by immune cells or edema. In addition, there is only one study on attenuation of infiltration by immune cells or edema by pretreatment with a platelet activating factor (PAF) antagonist, which attenuated capillary congestion and increased LV wall thickness caused by mild edema (69).

### *Mitochondrial injury*

Mitochondria may play a pivotal role during sepsis (70). In patients with severe sepsis, the degree of mitochondrial dysfunction in skeletal muscle biopsies correlates with outcome (71-73). Mitochondrial dysfunction and ineffective oxygen utilization (i.e. cytopathic hypoxia) may originate from injury to or a decreased number of mitochondria without sufficient new mitochondria formation.

Mitochondrial damage in the heart has been found in human autopsy specimens of patients

with severe sepsis (28). In addition, there are numerous reports of myocardial mitochondrial damage during endotoxemia or CLP-induced sepsis although not all findings were universally confirmed (Table 2) (40,42,44,46,74-86). Damages observed in the mitochondria include edema, patchy disruption of the inner and outer membranes, vacuolar distension of the cristae, enlargement of the cristae with ballooning, cristolysis, the presence of large myelin figures in the cytoplasm and decreased electron density. The number of myocardial mitochondria was also found to be decreased (46,75,79,81-85,87).

In a number of studies mitochondrial injury was associated with dysfunction of one or more complexes of the respiratory chain measured by various means including a decreased respiratory control index or ratio (indicating decreased coupling of phosphorylation to oxygenation), decreased total enzyme activity, depressed State 3 respiration (reflecting inhibition of the electron transport chain) or increased State 4 respiration (reflecting abnormal permeability of the inner mitochondrial membrane), although others were unable to confirm these findings (42,74,77,78,85). Despite the conflicting results, the functional consequences for the heart have been highlighted by several investigators showing depressed myocardial contractility associated with mitochondrial injury and dysfunction (29,42,63,70,72,87-94).

The mechanisms leading to mitochondrial damage and subsequent dysfunction during sepsis are not clear. Various stressors such as ischemia and hypoxia, as a result of maldistribution of coronary flow and above mentioned cellular sequestration, may promote opening of the mitochondrial permeability transition pores (mPTP) (72,74,95). Also, calcineurin and pro-apoptotic members of the B-cell lymphoma (Bcl)-2 family increase permeability of the mitochondrial membrane (72). All of this leads to movement of ions and solutes such as cytochrome *c* between the mitochondrial intermembrane space and cytoplasm (96). The mitochondrial matrix expands and the outer mitochondrial membrane ruptures with subsequent further release of pro-apoptotic factors into the cytoplasm (97). In addition to this, opening of the mPTP also promotes mitochondrial autophagy (67,85). Autophagy is an often reversible process in which the cell degrades self-components in order to recycle or eliminate excessive cytoplasmic content. Occurrence of autophagy in the heart has been demonstrated in experimental sepsis by two groups of investigators. Myocardial autophagy usually serves as a pro-survival mechanism, but excess or persistent autophagy can destroy essential cellular components leading to cell death and impaired myocardial function (98,99). Nonetheless, opening of the mPTP or autophagy has yet to be demonstrated in human sepsis.

Mitochondrial injury and dysfunction can be at least partially reversible by two mechanisms.



Ref.	Setting, duration	model	Main findings	Reversible ?
<i>Mitochondrial damage</i>				
(40)	Albino rats, 13 days	LPS i.p.	Condensed mitochondrial matrix with reduced mean population of dense granules per mitochondrion, swelling of mitochondria, shortened cristae, breaks in membranes, at 24 h. These abnormalities were not seen at 13 days.	Not reported
(42)	Beagles, 48 h	LPS in fibrin clots	Decreased LV shortening, mitochondrial swelling, myelin figures	Not reported
(44)	Sheep, 72 h	CLP	Degenerative mitochondrial changes (enlargement and ballooning of cristae)	Not reported
(74)	Sprague-Dawley rats, 4 h	LPS i.p.	Decreased LV developed pressure, $dP/dT_{max}$ and $dP/dT_{min}$ , reduced cytochrome c	Attenuation of dysfunction by CsA but not FK506. CsA prevented mitochondrial cytochrome c release through inhibition of the MPT.
(76)	Pigs, 48 h	LPS i.v.	Widened cristae and reduced number of granulations in mitochondria. At 48 h mitochondrial edema, vacuolar distension of mitochondrial cristae and cristolysis	Not reported
<i>Mitochondrial damage and dysfunction</i>				
(75)	Baboons, 72 h	E.Coli i.v.	Non-survivors had decreased activity of complex I + III and II + III, complex III, cytochrome c oxidase and succinate. Complex II mainly involved.	Not reported
(77)	Cats, 24 h	LPS i.v.	Significant reductions in $dP/dt_{max}$ and $dP/dt_{min}$ , significant increase in LV relaxation time. Swelling of and decreased protein-to-fluid ratio within mitochondria. Decreased respiratory control ratio due to increase in state 4 respiration. Increased protein nitration.	Contractility improved by ciclosporin A and FK506. Mitochondrial abnormalities only attenuated by CsA. Mitochondrial function restored by CsA and FK506. Calcineurin inhibition increased tissue protein carbonylation due to increased oxidant production.
(78)	Mouse, 24 h	CLP	Reduced contractility, decreased respiratory control ratio, no increase in plasma nitrite/nitrate	Treatment with CsA and NIM811 attenuated mortality, myocardial dysfunction and improved mitochondrial function

**Table 2. Summary of data from experimental studies on heart mitochondrial damage and dysfunction.** Abbreviations: LPS lipopolysaccharide; CLP cecal ligation and puncture; i.v. intravenous; i.p. intraperitoneal; h hours; mins minutes;  $E_{max}$  maximum elastance; LV left ventricle; s.c. subcutaneous; i.t. intra-tracheal

Ref.	Setting, duration	Model	Main findings	Reversible ?
(81)	Sprague-Dawley rats, 18 h	CLP	Decrease in respiratory rate and respiratory control indices, enlargement of mitochondria, destruction of cristae, myelin figures visible	Not reported
(82)	Sprague-Dawley rats, 18 h	LPS i.p.	Significant decrease in rate of respiration, large myelin figures in cytoplasm	Not reported
(83)	Sprague-Dawley rats, 48 h	LPS i.p.	Patchy disruption inner and outer membranes of mitochondria, variable swelling, distorted cristae, differences in number of mitochondria, depressed State 3 respiration, diastolic dysfunction ex-vivo, increased mitochondrial oxidative stress, decreased mtDNA copy number,	Not reported
(84)	Rabbits, 24 h	LPS s.c.	Dose-dependent decrease in state 3 respiration rates, no changes in permeability inner membrane, decreased activity complex I + III, ex-vivo increased coronary vascular resistance	Not reported
(85)	Sprague-Dawley rats, 12 h	CLP	Decreased cardiac work, reduced ratio of hydraulic work to oxygen consumed associated with decreased tissue energy levels, less electron density in mitochondria, decreased total enzyme activity in mitochondria, reduced mitochondrial density, presence of specific autophagy of mitochondria	Not reported
(95)	Sprague-Dawley rats, 24 h	Str. Pneumonia type 3 i.t.	Decreased outer membrane integrity, release of cytochrome c, downregulation of superoxide dismutase	
(108)	C57B1/6 mice, 48 h	CLP, double CLP	Irrversible inhibition cytochrome c oxidase, decreased steady-state levels of cytochrome c oxidase subunit I with double CLP	Not reported

**Table 2. (continued)**

First, inhibiting opening of the mPTP by (pre-)treatment with ciclosporin A (CsA), a calcineurin inhibitor that amongst others regulates that apoptotic process by blocking the mPTP, or restoring cytochrome c oxidase (the terminal oxidase of the respiratory chain) by caffeine or glutamine may improve mitochondrial structure and function, myocardial function and survival during experimental sepsis (74,77,78,100-102). Also pre-treatment with resveratrol or mitochondrially targeted anti-oxidant MitoQ inhibited endotoxin-induced mitochondrial and cardiac abnormalities during experimental endotoxaemia (103-105). Alternatively, reversibility may also occur through the formation of new mitochondria (biogenesis) although an actual increase in the number of mitochondria has yet to be

Ref.	Setting, duration	Model	Main findings	Reversible ?
<i>Necrosis of myocardial cells</i>				
(76)	Pigs, 48 h	LPS i.v.	Focal necrosis	Not reported
(112)	Rats, 18 h	CLP	Increased subendocardial necrosis	Not reported
<i>Apoptosis of myocardial cells</i>				
(64)	Sprague-Dawley rats, h	LPS i.v.	Interstitial edema, infiltration by white blood cells, myocardial apoptosis, increased activity caspase-3 like, caspase-8 like and caspase-9 like, increased systemic inflammation (TNF- $\alpha$ , IL-1 $\beta$ , IL-6), decreased myocardial function (LV developed pressure and dP/dt <sub>max</sub> and dP/dt <sub>min</sub> )	Broad-spectrum Caspase inhibitor and Caspase-3 inhibitor but not Caspase-1 inhibitor prevented apoptosis and myocardial dysfunction but treatment afterwards did not have this effect
(65)	Sprague-Dawley rats, 14 h	LPS i.v.	Interstitial edema, infiltration by white blood cells, myocardial apoptosis, increased activity caspase-3 like, caspase-8 like and caspase-9 like, increased systemic inflammation (TNF- $\alpha$ , IL-1 $\beta$ , IL-6), decreased myocardial function (LV developed pressure and dP/dTmax and dP/dTmin)	Caspase inhibitors prevented apoptosis and myocardial dysfunction
(74)	Sprague-Dawley rats, 4 h	LPS i.p.	Decreased LV developed pressure, dP/dTmax and dP/dTmin, increased systemic inflammation (TNF- $\alpha$ , IL-1 $\beta$ , IL-6), increased heart myeloperoxidase (MPO) activity, occurrence of nuclear apoptosis, increased caspase-3 activity, reduced cytochrome c	Attenuation of dysfunction CsA but not FK506. Attenuation of systemic inflammation and heart MPO activity by CsA and FK506. Protection against nuclear apoptosis by CsA (not FK506). Caspase-3 activity not attenuated. CsA prevented mitochondrial cytochrome c release through inhibition of the mitochondrial permeability transition.
(78)	Mouse, 24 h	CLP	Increased mortality, reduced contractility, increased heart caspase 3 and 9 activity	Treatment with CsA and NIM811 attenuated mortality, myocardial dysfunction and decreased caspase 3 and 9 activity especially in Bcl-2 transgenic mice.
<i>Necrosis of myocardial cells</i>				
(80)	Sprague-Dawley rats, 48 h	LPS i.p.	Increased caspase-3 activity, increased apoptosis through increased Bax mRNA expression, loss of mitochondrial cytochrome c, decreased myocardial contractility of isolated cardiomyocytes	Not reported

**Table 3. Summary of data from experimental studies on myocardial cell death.** Abbreviations: LPS lipopolysaccharide; CLP cecal ligation and puncture; i.v. intravenous; i.p. intraperitoneal; h hours; m minutes;  $E_{max}$  maximum elastance; LV left ventricle

Ref.	Setting, duration	model	Main findings	Reversible ?
<i>Necrosis of myocardial cells</i>				
(85)	Sprague-Dawley rats, 12 h	CLP	Presence of specific autophagy of mitochondria (mitochondria enclosed in vacuoles and presence of myelin figures with dense vacuole formation). Increased caspase-3 activity and cardiac TNF- $\alpha$	Not reported
(114)	Sprague-Dawley rats, 4 h	Staph. Aureus toxin i.v.	Decreased myocardial function (Langendorff), increase in p53 expression and myocyte apoptosis	Pre-treatment with simvastatin attenuated p53 expression and apoptosis

**Table 3. (continued)**

visualized (83,106). Recent work in muscle biopsies of survivors of critical illness showed mitochondrial biogenesis and antioxidant defense response (107). At present, no studies have identified spontaneous reversibility of mitochondrial injury or dysfunction.

Some authors have suggested that mitochondrial dysfunction might actually reflect myocardial hibernation (108,109). Suggestive is the observation of a more depressed uptake of substrates such as glucose, free fatty acids and ketone bodies among survivors of septic shock compared to non-survivors (110). This concept warrants further study.

#### *Cardiomyocyte cell death*

Death of cells can occur through swelling (i.e. necrosis) or shrinkage (i.e. apoptosis) of cells and its organelles (111). Necrosis is probably of less importance as it has been found only in a small proportion of human autopsy specimens and its occurrence during experimental sepsis has not been universally confirmed (Table 3) (24,27,28,42,68,76,112). Although myocardial apoptosis was not found in human autopsy specimens, its occurrence and associated myocardial dysfunction was frequently observed during endotoxemia or CLP-induced sepsis (Table 2) (64,65,74,78,80,85,113-117).

Apoptosis (i.e. programmed cell death) is initiated through the death receptor pathway (i.e. the extrinsic pathway) or the mitochondrial pathway (i.e. the intrinsic pathway). Presumably, activation of both pathways may eventually result in disruption of the actin/myosin contractile apparatus and loss of integrity of cardiomyocytes detectable by increased serum cTnT and cTnI (21-23). The extrinsic apoptotic pathway is activated through tumor necrosis factor (TNF)- $\alpha$  and its receptor (TNF-R) or the pro-apoptotic factor p53 next to infiltration by immune cells and edema (114,118). TNF- $\alpha$  is not only produced by activated macrophages but also by cardiomyocytes and has

been attributed a major role in the pathophysiology of sepsis and depressed myocardial contractility (4,119-123). During LPS-induced endotoxemia and CLP-induced sepsis myocardial apoptosis was found both through activation of the extrinsic and the intrinsic apoptotic pathway. Some investigators however have questioned the occurrence of apoptosis during experimental sepsis or were unable to demonstrate increased caspase-3 activity coinciding with an increase in positive TUNEL staining (115,124).

Both activation of the extrinsic and intrinsic apoptotic pathway are associated with impaired myocardial contractility *ex-vivo* of isolated hearts or cardiomyocytes (64,65,74,78,80). Some investigators have demonstrated that pre-treatment with broad-spectrum caspase inhibitors, CsA or simvastatin inhibits apoptosis and subsequent myocardial dysfunction (74,78,114). Larche and co-workers have shown decreased caspase 3 and 9 activity and attenuated myocardial dysfunction in a mouse model of CLP-induced sepsis after treatment with CsA (78).

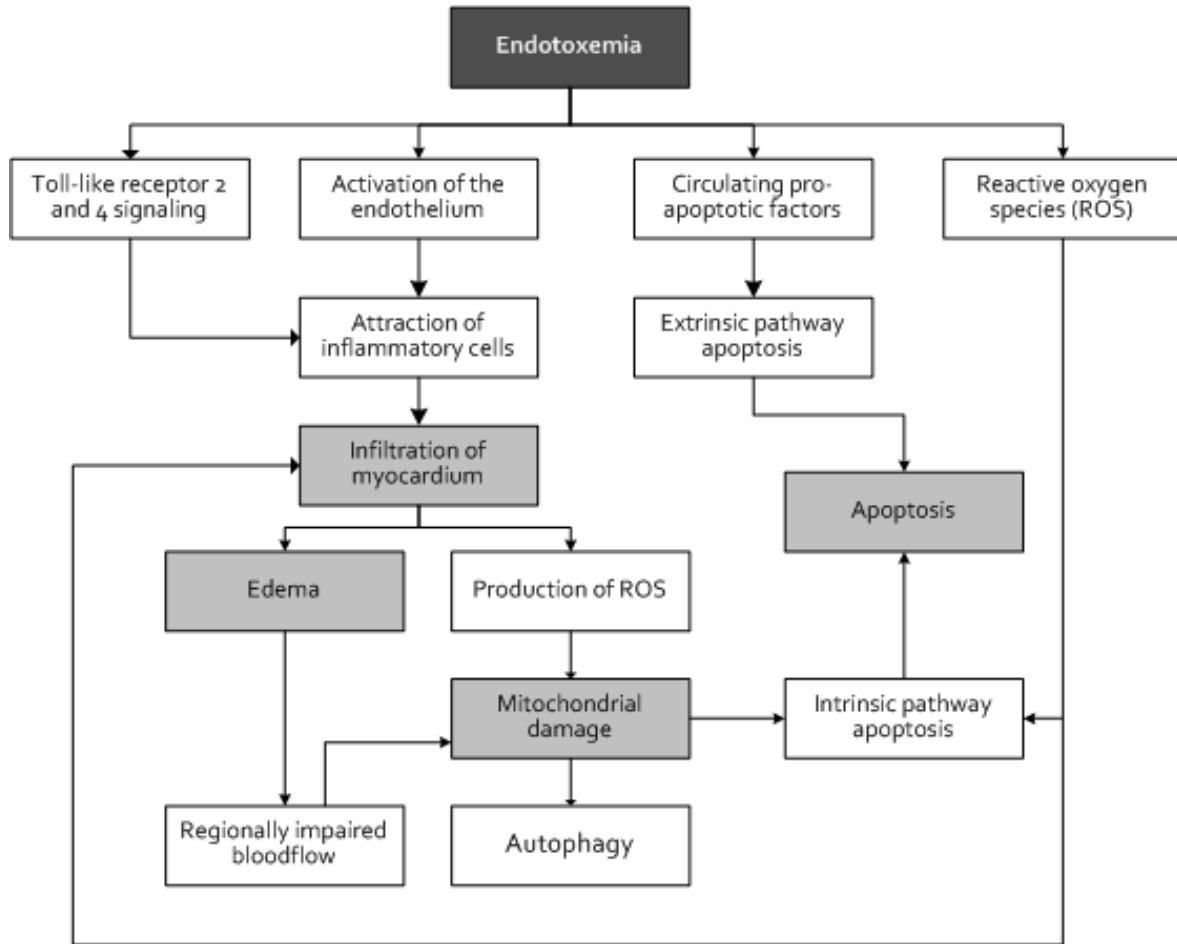
#### *Disruption of the contractile apparatus*

Human autopsy findings showed scattered foci of partial lack of or irregularly disorganized cross-striations within cardiomyocytes and scattered foci of disruption of the myofibrillar proteins actin and myosin (27). Likewise, experimental work showed that activation of the endopeptidase matrix metalloproteinase (MMP)-2 resulted in myofibrillar disruption and decreased cardiac contractility and may thus contribute to sepsis-induced myocardial dysfunction (125).

### Putting the experimental data in perspective

As outlined above, it may thus be concluded that myocardial infiltration by innate immune cells such as PMNs and monocytes/macrophages, edema, and mitochondrial injury and dysfunction contribute to cardiac dysfunction during sepsis and most probably interact with each other (as summarized in Figure 1), albeit that there is heterogeneity in experimental findings resulting from differences in animal species, duration of the experiments, and sepsis model studied. For instance, the majority of studies used endotoxemia, whereas the CLP-model may be a clinically more relevant sepsis model (126). Also, the majority of models reflect the acute phase of sepsis.

Severe sepsis in humans has various clinical manifestations such as hyperdynamic sepsis or low cardiac output state. Therefore, the findings of the experimental studies cannot be easily extrapolated to the clinical situation. Confirmation in human sepsis of many of the above mentioned patho-



**Figure 1. Proposed mechanisms underlying structural changes of the heart during sepsis.** Various pathways are suggested: during endotoxemia the endothelium is activated and this will lead to attraction of inflammatory cells that invade the myocardium. This leads to edema which can result in decreased myocardial compliance, but may also impair regional blood flow that will result in cytopathic hypoxia and subsequent mitochondrial damage. In addition, locally produced reactive oxygen species (ROS) further contribute to mitochondrial damage. The damaged mitochondria undergo autophagy, but also activate the intrinsic apoptotic pathway through mitochondrial permeability transition. Furthermore, circulating pro-apoptotic factors such as TNF- $\alpha$  activate the extrinsic apoptotic pathway. Finally, circulating reactive oxygen species further contribute to activation of the intrinsic apoptotic pathway.

physiological mechanisms is warranted. Furthermore, the short-term as well as long-term functional consequences need to be evaluated in human sepsis. Also, the reversibility of structural cardiac alterations has hardly been studied although some authors have shown that possible interventions such as statins, CsA, caffeine, glutamine, anti-oxidants or exogenous cytochrome c t may attenuate myocardial dysfunction in the various sepsis models (63,74,77,78,100,101,127,128). Yet, before these interventions become readily established as treatment their effects need to be confirmed by others.

On the other hand, statins are already available. Statins prevent the formation of mevalonaat by inhibiting the enzyme hydroxymethylglutharyl coenzyme A. Apart from their lipid-lowering ability,

statins exert pleiotropic effects including anti-inflammatory, antioxidant, immunomodulatory and antiapoptotic features (114,129). They suppress the control of leucocyte activation and septic inflammation, depress the production of mediators such as TNF $\alpha$  and inhibit leucocyte rolling, adherence and transmigration. Hence, their use could attenuate infiltration of immune cells in the myocardium and reduce myocardial edema with subsequent improvement in myocardial function. This concept is supported by one group of investigators showing that (pre-) treatment with simvastatin decreased endothelial adhesion of leucocytes and preserved cardiac function and haemodynamics in CLP-induced septic mice (130,131). Two systematic reviews based on observational studies suggested a beneficial effect of statins on survival (132,133). In contrast, in a recent randomized controlled trial of patients with community-acquired pneumonia or sepsis such a protective effect could not be demonstrated (134). One study provided data on the effect of statins on hemodynamics or myocardial function (135). A retrospective evaluation of 53 patients with sepsis of whom 16 received statins showed a significantly lower rate of cardiovascular dysfunction defined as hypotension requiring vasopressor therapy (38% vs 73%). Although studies are underway investigating the efficacy of statins in human sepsis, none of them is designed to study the effects on myocardial function (133). Hence, the use of statins to improve myocardial function in human sepsis cannot be recommended at present.

## Conclusions

Myocardial infiltration by immune cells, edema, and mitochondrial injury may contribute to cardiac dysfunction during sepsis. However, it is difficult to extrapolate the experimental findings to a clinical situation because of heterogeneity of studies. Hence, future investigations are warranted to confirm the occurrence and functional consequences of structural cardiac alterations in patients with severe sepsis or septic shock.

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