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Editorial

Sepsis-Induced Myocardial Dysfunction and Mammalian Target of Rapamycin Signalling Pathways

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See article by Cheng et al., pages 875–883 of this issue.

Sepsis-induced myocardial dysfunction[1] is increasingly recognized as a significant contributor to hemodynamic changes accompanying septic shock, occurring in as many as half of all septic shock patients.[2,3]

Sepsis-Induced Myocardial Dysfunction

Hemodynamic manifestations

The functional manifestations of sepsis-induced myocardial dysfunction are not straightforward nor is the underlying pathophysiology. First, systolic contractility is diminished; often quantitated as decreased left ventricular ejection fraction. Second, appreciation of decreased systolic contractility is clouded by the fact that left ventricular afterload during septic shock is reduced by decreased systemic vascular resistance and, further, ventricular contractility might be artificially enhanced by the use of vasopressor/inotropes, which typically have a degree of inotropic activity. Thus, a normal ejection fraction observed when mean arterial pressure is low while treating with dopamine, epinephrine, or norepinephrine, should be interpreted as sepsis-induced myocardial dysfunction because, under these afterload and vasopressor/inotrope circumstances, left ventricular ejection fraction would be increased above normal in the absence of sepsis. Third, a substantial decrease in systolic contractility will result in impaired ejection ending at an increased end-systolic volume (dilation at end-systole). In survivors of sepsis the diastolic left ventricle also often dilates and becomes more compliant, allowing stroke volume (end-diastolic volume minus end-systolic volume) to be preserved or increased in the face of decreased systolic contractility.[1] Dilation is observed in survivors more than in nonsurvivors.[4] This leads to the classical hyperdynamic, increased cardiac output, picture of septic shock. Fourth, in nonsurvivors the diastolic ventricle can become less compliant so that stroke volume is diminished by a decrease in end-diastolic volume (noncompliant ventricle) and an increase in end-systolic volume (due to decreased systolic contractility). This leads to the terminal hypodynamic phase of septic shock. Thus: (1) decreased contractility; (2) masking of decreases in contractility by loading conditions and therapeutic interventions; (3) increased diastolic compliance and ventricular dilation; and (4) decreased diastolic compliance are all components of the complex functional picture of sepsis-induced myocardial dysfunction.

Additional confounders during sepsis-induced myocardial dysfunction are troponin increases, electrocardiogram changes, and heterogeneous wall motion abnormalities[5], all of which raise the possibility of myocardial ischemia. Indeed, these findings must be distinguished from true demand ischemia due to high heart rate, decreased coronary perfusion pressure, and the use of catecholamine vasopressors, which increase myocardial oxygen demand in this population of patients who not uncommonly have underlying coronary artery disease. Sepsis also results in increased pulmonary vascular resistance, which might contribute to right ventricular dysfunction.[6] With aggressive fluid resuscitation, right ventricular dilation and right-to-left septal shift can occur, which further contribute to left ventricular dysfunction and asynchronous left ventricular systolic contraction.

Pathophysiology

The pathophysiology underlying sepsis-induced myocardial dysfunction is no less complex. The sepsis-induced inflammatory response involves a very large number of inflammatory mediators and changes in expression of thousands of genes.[7] Pathogen-associated molecular patterns from infecting organisms are initially detected by innate immune receptors (eg, toll-like receptors) expressed on leukocytes but also on cardiomyocytes.[8,9] Leukocytes activated by pathogen-associated molecular patterns contribute in multiple ways[10] including by release of cytokines (eg, tumour necrosis factor α), which contribute to myocardial dysfunction,[11] in part because of production of nitric oxide through activation of inducible nitric oxide synthase.[12] Nitric oxide and reactive

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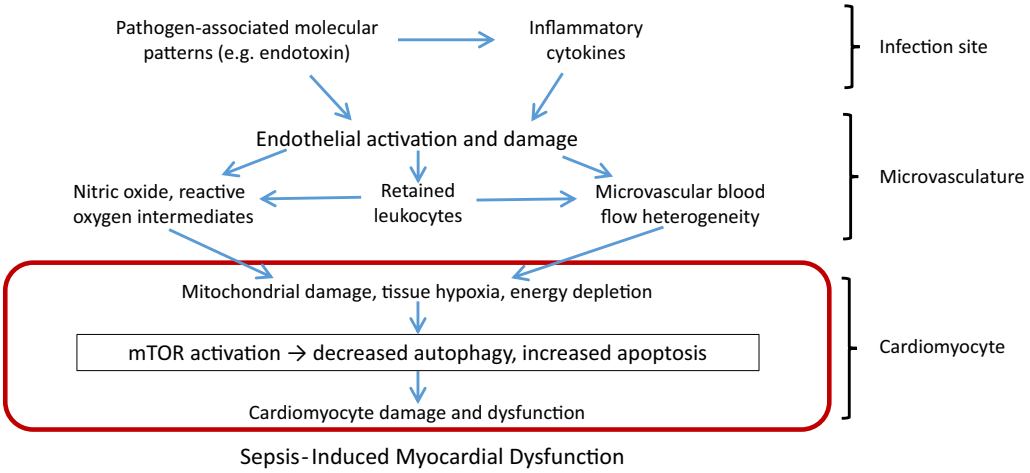

Figure 1. Mammalian target of rapamycin (mTOR) might contribute to sepsis-induced myocardial dysfunction. Pathogen-associated molecular patterns at the site of infection trigger a systemic inflammatory response. Activation and dysfunction of the coronary microvascular endothelium leads to mitochondrial damage, tissue hypoxia, and energy depletion, which activate the mTOR pathway. The mTOR pathway, in turn, might contribute to myocardial damage and dysfunction.

oxygen intermediates play a role[13] by increasing activity of cardiomyocyte apoptotic pathways[14] and related mitochondrial dysfunction.[15] Endothelial activation alters blood flow and endothelial permeability so that impaired myocardial oxygen extraction and myocardial edema might play a role.[16] Expression and activation of cell adhesion molecules by activated cardiomyocytes contribute to decreased cardiomyocyte contractility[17] by altering function of the actin cytoskeleton, which impairs coordinated systolic calcium flux.[18]

Therapeutic challenges

Involvement of many inflammatory pathways means that developing targeted interventions to treat sepsis-induced myocardial dysfunction has been very challenging—there is no single target. The current Surviving Sepsis Campaign Guidelines recommendations for treating sepsis-induced myocardial dysfunction are considered "weak recommendations" with "low quality of evidence."[19] Indeed, the current recommendation to use dobutamine to increase contractility is countered by recent data suggesting that β-adrenergic agonist activity might be harmful in septic shock[20] and the use of β-blockers has been suggested.[21] Because there is no single molecular target, a key goal is to identify regulatory molecules that are central upstream hubs in the complex intramyocardial inflammatory signalling cascade. Mammalian target of rapamycin (mTOR) might fit this description.

The Role of mTOR

mTOR integrates signalling from a variety of upstream pathways such as energy status, oxidative stress, amino acid availability, insulin, and growth factors and subsequently plays a central role in promoting cell growth, promoting apoptosis, inhibiting autophagy, and regulation of the actin cytoskeleton, among many other effects.[22] Because it plays a central role in integrating upstream signals that lead to regulation of many downstream metabolic pathways relevant to the septic intramyocardial inflammatory response, mTOR is an interesting molecule to consider. mTOR complex 1 and mTOR complex 2 activity regulate the myocardial inflammatory response after myocardial infarction.[23] Increased mTOR complex 1 activity decreases cell survival by decreasing autophagy and promoting proteasome activity.[24] Decreased autophagy appears to contribute to cardiomyocyte necrosis after ischemia-reperfusion.[24] Thus, it is reasonable to postulate that mTOR plays a role in sepsis-induced myocardial dysfunction (Fig. 1).

Recently, involvement of the mTOR pathway has been investigated in animal models of sepsis-induced myocardial dysfunction. In a lipopolysaccharide model of inflammation in mice, lipopolysaccharide administration caused myocardial dysfunction and activated intramyocardial adenosine monophosphate-activated protein kinase (AMPK), resulting in activation of mTOR and inhibition of autophagy.[25] These findings are consistent with the recent observation by Han et al. that inhibition of mTOR led to increased autophagy and reduced myocardial dysfunction in a cecal ligation and puncture model of sepsis in rats.[26]

Novel Findings of the Study by Cheng et al.[27]

The key issue that Cheng et al. (in this issue of the *Canadian Journal of Cardiology*) address is whether mTOR is involved in sepsis-induced myocardial dysfunction in human septic shock. First, they confirm that patients with sepsis-induced myocardial dysfunction have higher mortality rates. Second, these investigators measured several key molecules in the mTOR pathway to test for potential involvement in sepsis-induced myocardial dysfunction. They did not find a difference in mTOR concentrations in peripheral blood. Whether there was a difference in intramyocardial mTOR was not assessed. However, a downstream target of increased intracellular mTOR activity, phosphorylated ribosome S6 protein kinase (PS6K), was increased in the peripheral blood of patients who had sepsis-induced myocardial dysfunction. Third, these investigators tested for evidence of downstream involvement that could plausibly contribute to sepsis-induced myocardial dysfunction. That is, if intracellular mTOR

activity were increased then autophagy should be decreased, which might causally contribute to myocardial damage and dysfunction. Indeed, in patients having sepsis-induced myocardial dysfunction, Cheng et al. found decreased circulating levels of (microtubule-associated protein light chain 3 type II (LC3B), a major protein in the autophagy pathway. Additional evidence for increased intracellular mTOR activity is the finding of increased circulating levels of B-cell CLL/Lymphoma 2-interacting mediator of cell death (BIM), a protein downstream of mTOR that promotes apoptosis. On the basis of these observations these investigators postulate that intracellular mTOR activity, primarily mTOR complex 1, is increased (increased PS6K levels) leading to decreased autophagy (decreased LC3B levels), and increased apoptosis (increased BIM levels), all of which could reasonably contribute to myocardial damage and dysfunction of sepsis.

Limitations

A number of limitations must be considered. First, it is challenging in individual patients to definitively determine that observed myocardial dysfunction is sepsis-induced rather than demand ischemia. Nevertheless, these investigators did the best they could with clinical judgement. Second, are blood concentrations directly connected to the myocardium or do other organs contribute to blood levels of mTOR, PS6K, LC3B, and BIM? In this regard, non-survivors had responses directionally similar to patients with sepsis-induced myocardial dysfunction for all of these molecules. Therefore, the current findings might not be particularly specific for myocardial dysfunction and might simply reflect severity of illness and multiple organ involvement. Third, there does seem to be a disconnect between the previously reported animal study that showed decreased intramyocardial mTOR expression after cecal ligation and puncture.[26]

Implications and Conclusions of the Study by Cheng et al.[27]

Whether the mTOR pathway causally contributes to sepsis-induced myocardial dysfunction, possibly through decreased autophagy, is uncertain, but the results of Cheng et al. raise this as a very reasonable hypothesis. If this hypothesis were to be supported by further evidence with data arising directly from the myocardium, then mTOR inhibition could be considered for treatment or prevention of sepsis-induced myocardial dysfunction. There are many "ifs" in this logic so we are far from targeted therapeutic intervention for sepsis-induced myocardial dysfunction.

Although the current results are challenging to fully interpret, the key conclusion that can be drawn is that the mTOR pathway is involved in human sepsis. Cheng et al. have made a valuable contribution in understanding the potential role of the mTOR signalling pathway in sepsis-induced myocardial dysfunction.

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