

Sepsis and myocardial dysfunction

Sepse e disfunção miocárdica

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ABSTRACT

Sepsis and septic shock are prevalent in the intensive care setting, accounting for more than 40% of mortality in this scenario. The appropriate management and recognition of sepsis-induced myocardial dysfunction are paramount for its proper treatment and probably impact mortality rates. The objective of this article is to review its definition, pathophysiologic mechanisms, possible treatments and current research on the subject according to a critical view.

Cellular signaling involved in myocardial depression is not fully understood. Disturbances in calcium homeostasis, cardiodepressant circulating factors, inflammatory mediators, nitric oxide and apoptosis act as synergistic pathways that lead to severely depressed cardiac function. The diagnosis of myocardial dysfunction during sepsis carries a worse prognosis and increased mortality.

Myocardial dysfunction plays an important role in morbidity and mortality rate of critically ill patients. Current research in this area will continue to evolve; we will, therefore, soon have more insights into potential novel therapies that can change its mortality rates.

Keywords: Sepsis/complications; Shock, septic; Cardiomyopathies; Intensive care units

RESUMO

Sepse e choque séptico são problemas graves prevalentes nas unidades de cuidados intensivos, responsáveis por mais de 40% da mortalidade nesse cenário. O reconhecimento e o manuseio adequado da disfunção miocárdica induzida pela sepse são de suma importância para o tratamento correto e para que, provavelmente, tenham impacto em índices de mortalidade. O objetivo do presente artigo é revisar a definição, mecanismos fisiopatológicos, possíveis tratamentos e pesquisas atuais sobre o assunto, segundo uma análise crítica. Mecanismos de sinalização celular envolvidos na depressão miocárdica não estão

completamente elucidados. Distúrbios da homeostase de cálcio, fatores cardiodepressores circulantes, mediadores inflamatórios, óxido nítrico e apoptose agem em sinergia e levam a uma grave depressão da função cardíaca. O diagnóstico de disfunção miocárdica durante a sepse tem um prognóstico pior e maior mortalidade. A depressão miocárdica desempenha papel importante na morbimortalidade de pacientes criticamente doentes. Pesquisas recentes nessa área devem evoluir e logo novas terapias potenciais poderão modificar os índices de mortalidade desta condição.

Descritores: Sepse/complicações; Choque séptico; Cardiomiopatias; Unidades de terapia intensiva

INTRODUCTION

Myocardial dysfunction often accompanies the early phase of clinical pictures of severe sepsis and septic shock⁽¹⁾, syndromes that are highly common in Intensive Care Units and which run their course with high mortality despite important advances in the treatment and monitoring of patients⁽¹⁻²⁾.

Sepsis-related myocardial dysfunction appears not to be due to structural abnormalities or to myocardial hypoperfusion, but to the presence of circulating inflammatory mediators such as cytokines. At cell level, the reduction in myocardial contractility is linked to apoptosis phenomena and to nitric oxide-dependent and nitric oxide-independent mechanisms, leading to disruption of calcium homeostasis⁽¹⁾.

The existence of myocardial dysfunction in septic humans was proved in the 1980s by Parrillo's team through nuclear medicine techniques in critical patients⁽³⁾. Heart failure in sepsis is generally masked by a "normal" cardiac output (CO), due to diminished

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systemic vascular resistance and afterload, and although dysfunction is profound, cardiac output (CO) is maintained relatively well by ventricular dilatation and tachycardia.

This septic cardiomyopathy involves both ventricles and is potentially reversible, with complete recovery of ventricular function after seven to ten days in survivors⁽¹⁻²⁾. Depression of myocardial function is characterized by ventricular dysfunction and reduction in the ejection fraction (EF) and is also present in up to 40% of cases, contributing to morbidity and mortality in this population^(2,4). Characteristically, there is global biventricular dilatation, but changes in segmental contractility have been described.

PATHOPHYSIOLOGY

Sepsis

Septic syndrome derives from the host inflammatory response to infection through activation of the immune system in a complex interaction among inflammatory mediators that perpetuate the initial lesion. The presence of circulating pathogens leads to the release of countless mediators in a cascade, above all cytokines. This uncontrolled immune response, involving cytokines such as Tumor Necrosis Factor Alpha (TNF-alpha) and Interleukin-1 beta (IL-1 beta), can culminate in cardiovascular collapse and death⁽⁴⁻⁵⁾.

The circulating cytokines are predominantly pro-inflammatory (TNF-alpha and IL-1 beta), with the concomitant release of anti-inflammatory cytokines (IL-10). Most can play both roles - take part in immune defense and cause pathological manifestations⁽⁵⁾. Other mediators, the coagulation and complement system, membrane phospholipid products, metabolites of arachidonic acid, free radicals and nitric oxide also take part in the response to septic process.

NF-KappaB takes part in the regulation of countless biological phenomena and pathological states, including apoptosis, cell growth, response to stress, immunological activity and septic shock. There are countless NF-KappaB-dependent genes involved in the pathogenesis of sepsis and associated with cardiovascular dysfunction in this scenario. They act in a wide range of organs and cell types, both with protective effects and with effects that perpetuate the initial insult^(4,6).

Myocardial dysfunction associated with sepsis

The etiology is multifactorial and several possible mechanisms have been implicated: bacterial toxins, cytokines and other mediators (including tumor necrosis factor alpha and nitric oxide), cardiodepressant factors,

oxygen-reactive species, catecholamines. Cardiovascular changes in sepsis include decreased vascular tonus and myocardial contractility; severity is correlated to prognosis in these patients^(7,8).

A hyperdynamic circulatory state develops after fluid resuscitation and is maintained to recovery or death. There is neither clinical nor experimental evidence of myocardial hypoperfusion, and animal septic shock models show unchanged stocks of high-energy phosphates. There is also autonomic dysfunction, with a reduction in the variability of cardiac frequency.

Cytokines

Endogenous inflammatory mediators that are potentially involved are metabolites of arachidonic acid, histamine, platelet activating factor and endorphins. The major pro-inflammatory cytokines causing depression in myocardial contractility *in vivo* in septic shock patients are tumor necrosis factor alpha and interleukin-1 beta, among others. The same thing occurs in *in vitro* models with isolates of myocytes exposed to the serum of septic patients^(5,9-10).

Changes in molecular signaling activated by cytokines and powerful mediators like endothelin-1 (ET-1) are risk factors for myocardial dysfunction in sepsis. Experimental data suggest that rises in ET-1 correlate with hemodynamic cardiovascular changes, induction of apoptosis and activation of phosphorylation changes during sepsis⁽⁹⁾.

The major mechanisms involved in the mediation of organic dysfunction during sepsis (cellular expression of adhesion molecules, induction of inducible nitric oxide synthetase, apoptosis) are known to be regulated by transcription factors (STAT1, IRF1 and NFK-B). The increase in activation of transcription induces apoptosis and activation of caspase in human fetal myocytes, suggesting that the activation of this process and early apoptosis play a role in inducing organic dysfunction in sepsis⁽¹¹⁾.

Nitric oxide

Studies in rats treated with lipopolysaccharides showed that the overproduction of nitric oxide by nitric oxide synthetase (iNOS) inhibits the aerobic metabolism and causes myocardial dysfunction through the induction of morphological and functional changes in the mitochondria, attenuated by aminoguanidine, an iNOS inhibitor. The sustained production of nitric oxide by iNOS leads to contractile dysfunction via cGMP at an early stage, and later reduces mitochondrial function, and myocardial energy production, contributing

significantly to myocardial dysfunction in late stages of septic shock^(10,12).

DIAGNOSIS

The presence of biventricular changes with a reduction in the EF can be demonstrated by non-invasive methods such as echocardiography or radionuclide scintigraphy. Histopathological evidence of interstitial myocarditis was reported, with impaired ventricular compliance and diastolic function⁽¹³⁾.

Reduction in EF occurs between 24 and 48 hours after onset of the septic picture, even in the absence of shock, and invasive monitoring by pulmonary artery catheter (PAC) can show this condition only in a small group with diminished CO^(6,13). Even raised CO does not rule out sepsis-induced myocardial dysfunction, and left ventricular performance is generally diminished. Changes in right ventricular function (RV) also occur, due both to increase in post-chamber of the RV by pulmonary hypertension secondary to the acute pulmonary lesion and/or associated acute respiratory distress syndrome, and to a reduction in the contractile function of the RV. Segmental contractility changes have been reported; however, biventricular dilation is the most common⁽¹⁴⁾ and is potentially reversible.

PROGNOSTIC AND DIAGNOSTIC MARKERS

Brain natriuretic peptide (BNP)

Atrial natriuretic peptide or BNP is a diagnostic and prognostic marker of ventricular dysfunction, and is frequently raised in severe sepsis and septic shock¹⁵. The persistence of high levels early in the course of the disease gives a worse prognosis and greater mortality⁽¹⁵⁻¹⁷⁾.

Troponin

High levels of troponin during septic shock and severe sepsis have a prognostic and diagnostic value⁽¹⁸⁾. The exact mechanism behind raised troponin levels in septic patients remains a controversial issue⁽¹⁹⁾ which has not yet been completely elucidated, and several mechanisms for the release of troponin have been suggested. Among them is the participation of cytokines⁽²⁰⁾ causing an increase in the permeability of the myocyte membrane and release of free troponin into the cytoplasm, with the myocyte contractile complex remaining intact. This has not been confirmed yet by experimental models using endotoxin. Another mechanism that has been put forward is dysfunction of the microcirculation, which happens globally in sepsis and therefore also affects the cardiac tissue.

In a multivariate analysis, Kollef et al.⁽²¹⁾ showed that ventricular dysfunction, and not merely the level of troponin, was a marker of a poor prognosis⁽²²⁻²³⁾. Very high levels of troponin (>10 ng/mL), especially when used in the context of suspected myocardial ischemia, and negative results are valuable diagnostic tests in assessing these patients.

Myocardial damage can be defined by positivity for troponin, the levels of which correlate to the degree of myocardial dysfunction⁽²⁴⁻²⁵⁾, thus being a predictor of greater severity of the disease and higher mortality^(18,22-23), warranting constant follow-up of this marker.

TREATMENT

Depression of myocardial function with a fall in cardiac output is an important cause of death in these patients. Although no specific therapy is available to date, studies on the inhibition of antagonism to interleukin-6 seem promising, above all in septic shock secondary to meningococemia⁽²⁶⁾. Rigorous fluid resuscitation, independently of coadjuvant treatments, therefore remains the major therapy in the management of these patients.

Dobutamine

Sepsis is characterized by a hyperdynamic state with normal or reduced arterial pressure, normal or high CO, and low systemic vascular resistance. Although the CO is generally steady in patients who are adequately resuscitated, changes in myocardial function may require the use of inotropics to normalize hemodynamics.

Dobutamine is deemed to be the agent of choice for inotropic support and increase in cardiac output during septic shock and severe sepsis, according to a consensus conference⁽²⁷⁾, in patients with adequate filling pressures and reduced arterial pressure and CO, if necessary in association with vasoconstrictors.

Levosimendan

Calcium desensitization⁽²⁸⁾ plays an important role in the pathophysiology of myocardial dysfunction associated with sepsis. Studies of the potential mechanisms of sepsis-induced cardiomyopathy show that phosphorylation of cardiac myofilaments reduced the calcium sensitivity of the myofibrils, which may contribute to reduction of cardiac contractility by modulation of the regulatory action of troponin I on troponin C. An agent that improves the myofilament response to calcium may therefore improve hypocontractility.

Levosimendan is used in patients with decompensated heart failure. Its effects are mediated by calcium-dependent bonds with troponin C, which

produces an increase in the strength of cardiomyocyte contraction without increasing the concentration of intracellular calcium, and with little or no increase in myocardial oxygen consumption⁽²⁹⁾.

The use of levosimendan was tested in a prospective randomized controlled study of 28 patients with sepsis-related cardiac dysfunction defined as persistent left ventricular dysfunction after 48 h of conventional treatment with dobutamine (5 micrograms/kg/minute). The data obtained pre- and post-infusion over 24 hours with levosimendan showed a fall in pulmonary artery occlusion pressure and an increase in the cardiac index, a reduction of end-diastolic volume of the LV, an increase in LVEF, as well as a reduction in the levels of lactate, improvement in flow of gastric mucosa and in creatinine clearance. These data corroborate the use of levosimendan as an alternative to an increased dose of dobutamine in patients without adequate clinical response, owing to its beneficial effects on systemic hemodynamics and tissue perfusion parameters⁽²⁸⁾. Its use has been limited by its tendency to reduce systemic vascular resistance and thus lead to greater hypotension in the septic patients⁽³⁰⁾.

There have been reports of cases of reversal of septic shock that was refractory to other measures, and experimental studies with levosimendan show an attenuation of cardiac dysfunction in endotoxemia in experimental models⁽³¹⁾.

Beta blockers

The use of beta blockers has proved beneficial in patients with heart failure. Suzuki et al., by means of a randomized animal study⁽³²⁾ in a model of induced peritonitis in rats, tested whether infusion of esmolol, a selective beta-1 blocker, might have a protective effect in myocardial function, and found a reduction in levels of TNF alpha, without a rise in lactate, and with improvement in cardiac performance and CO in the treated group. The use of beta blockers in sepsis requires sounder evidence of benefit.

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