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REVIEW ARTICLE

From Echocardiographic Evaluation to Biomarkers Measurement: The Role of Myocardial Dysfunction in Mortality Associated with Sepsis

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Abstract

Sepsis remains the leading cause of mortality and critical illness worldwide. Myocardial dysfunction is one of the most clinically relevant manifestations of sepsis and results from a complex interaction among genetic, molecular, metabolic, and structural changes. Despite the prominence given to the occurrence of systolic dysfunction during sepsis, the association between diastolic dysfunction and mortality is controversial, while diastolic dysfunction and right ventricular dysfunction are identified as independent predictors of mortality in the most recent studies. Elevation of biomarkers during sepsis may result from several mechanisms, and although the role of the B-type natriuretic peptide (BNP) and the N-terminal portion of its prohormone (NT-proBNP) as independent predictors of mortality is well defined, the same cannot be said about cardiac troponins due to conflicting results among currently available studies.

The objective of the present review is to discuss the pathophysiological mechanisms of myocardial dysfunction induced by sepsis in adults and the role of echocardiography and cardiac biomarkers as tools for prognostic evaluation in this clinical setting.

Introduction

Sepsis is a set of physiological, pathological, and biochemical abnormalities that can occur in response to infection caused by any pathological agent. Despite the advances in the treatment and support of critically ill patients, sepsis continues to be the main cause of mortality and severe disease throughout the world, with an estimated incidence of 17 million cases per year.[1]

Myocardial dysfunction is one of the manifestations of greater clinical relevance in sepsis and one of the organic dysfunctions that most early occurs in septic shock.[2] By definition, it consists of reversible systolic and/or diastolic dysfunction of the left ventricle (LV) and/or right ventricle (RV) (Figure 1).[3,4]

In recent years, myocardial dysfunction induced by sepsis became a focus of exhaustive investigation as an independent predictor of mortality in this clinical context, especially after the growing use of biomarkers of myocardial injury as indicators of poor prognosis in cardiovascular diseases.[5]

The objective of this review is to discuss the pathophysiological mechanisms of myocardial dysfunction induced by sepsis in adults and the role of echocardiography and cardiac biomarkers as tools for prognostic evaluation in this clinical scenario.

Keywords

Sepsis; Mortality; Biomarkers; Cardiac dysfunction.

Pathophysiology

Sepsis-induced myocardial dysfunction is believed to result from a complex interaction among genetic, molecular, metabolic, and structural alterations that may have unique and independent contributions or very confusing and intricate interrelationships (Figure 2).[6] The involved factors include:

- Action of myocardial depressants: the combined action of tumor necrosis factor-alpha (TNF-α) with interleukin 1-beta (IL-1 β) is cardiodepressant and can play an important role in the early reduction of myocardial contractility observed in the course of sepsis.[7] Furthermore, both induce the release of additional factors that may similarly affect the myocardial function, as for example, nitric oxide (NO), which in turn is also a cause of

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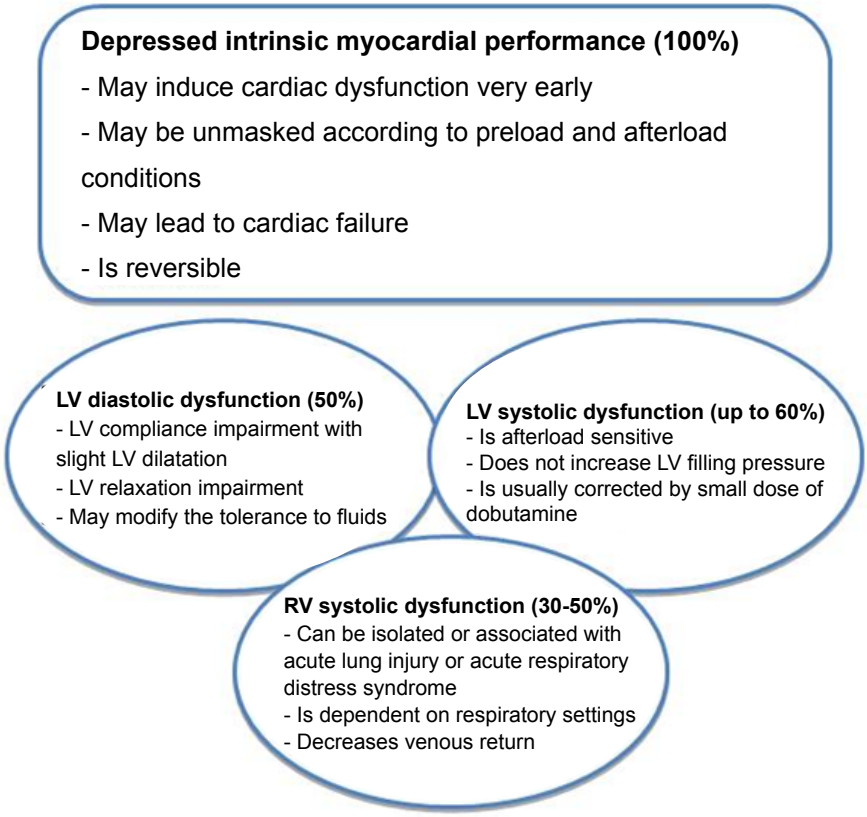

Figure 1 - Main mechanisms of cardiac dysfunction, along with its consequences and impact.
Adapted from Vieillard-Baron A, Cecconi M. Understanding cardiac failure in sepsis. Intensive Care Med 2014;40:1561.

reduced glutathione, oxidative stress, and mitochondrial dysfunction.[8,9] Although its exact role in the pathogenesis of myocardial dysfunction in sepsis is unknown, endothelin-1 has been demonstrated in animal models to directly affect the myocardial performance as well.[10]

- Alterations of calcium channels: the involvement of these channels with myocardial dysfunction can be explained by the relationship between intracellular calcium concentrations and cardiac contractility, but experimental models have shown that despite the reduction in L-type calcium channels observed in sepsis leading to a reduction in cardiac repolarization, there is no clear association between the resulting shortening of the duration of action potential and a possible reduction in myocardial contractility.[11]

- Toll-like receptors: toll-like receptors (TLRs) recognize specific pathogenic molecular patterns and play an important role in innate immunity. Experimental models have demonstrated that the activation of nuclear factor κB mediated by TLR4 plays an important role in the development of myocardial depression[12] and that TLR3 knockout mice maintain a normal cardiac function even during sepsis.[13]

- Adrenergic hyperstimulation: in the early stage of sepsis, there is a massive release of catecholamines from the autonomous nervous system, intestine, leukocytes, and macrophages, resulting in hyperstimulation of alpha and beta-adrenergic receptors, which finally leads to their downregulation and resistance to circulating catecholamines.[14,15]

- Mitochondrial dysfunction: an adequate supply of adenosine triphosphate (ATP) is fundamental to the maintenance of myocardial contractility, and several mechanisms of mitochondrial lesion can play an important role in the development of myocardial dysfunction during sepsis, such as edema of the mitochondrial matrix, oxidative stress, alteration of membrane permeability, imbalance between biogenesis processes (growth and division), and mitophagy (removal of dysfunctional mitochondria by autophagy).[16]

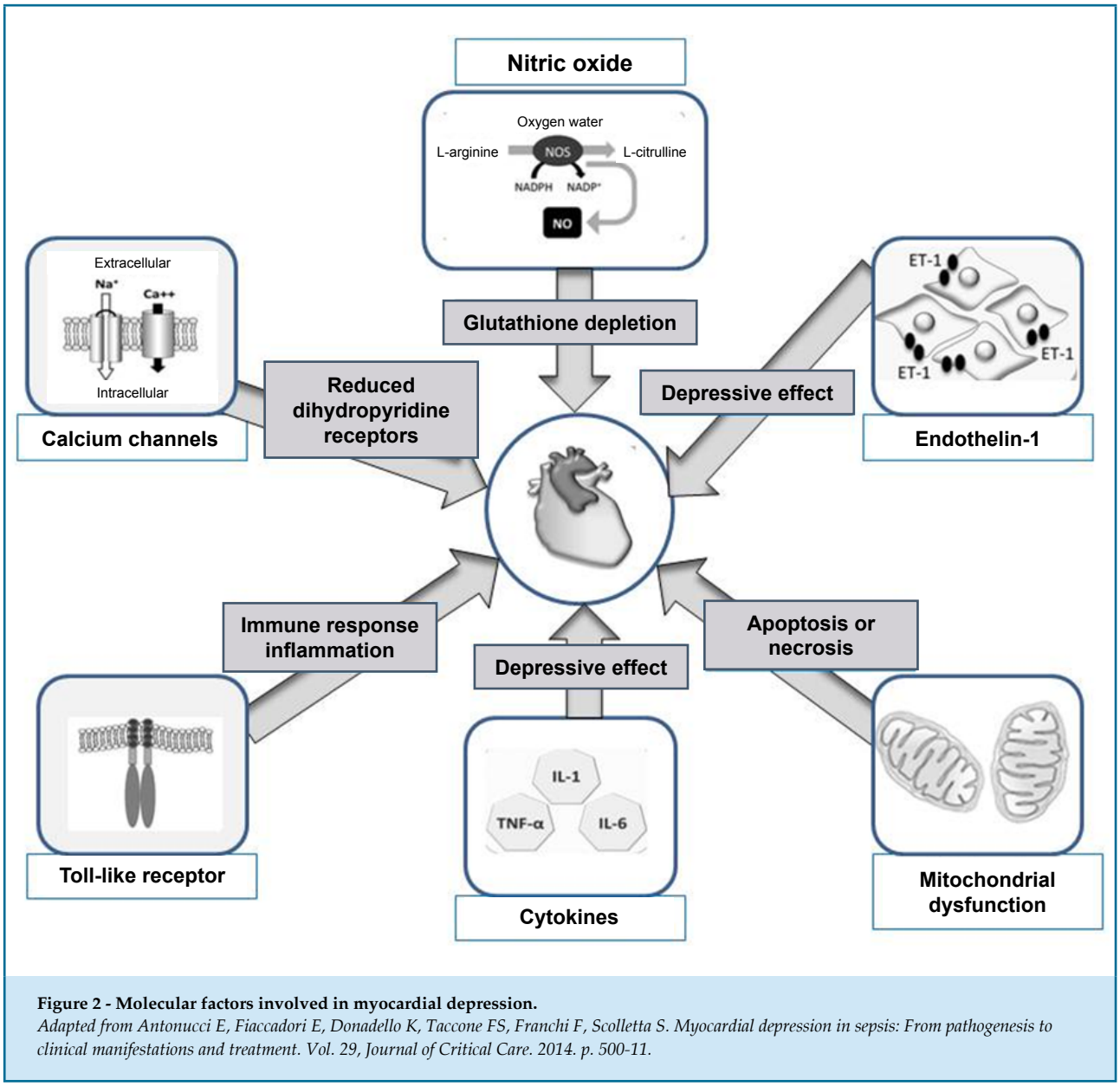

Figure 2 - Molecular factors involved in myocardial depression.
Adapted from Antonucci E, Fiaccadori E, Donadello K, Taccone FS, Franchi F, Scolletta S. Myocardial depression in sepsis: From pathogenesis to clinical manifestations and treatment. Vol. 29, Journal of Critical Care. 2014. p. 500-11.

Joseph et al.[17] demonstrated that the activation of the NADPH oxidase 2 – an enzyme complex found in the plasma membrane and involved in the maintenance of immune function, cell growth, and apoptosis – is one of the responsible factors for the oxidative stress induced by sepsis, and that its inhibition decreases not only the production of oxygen-derived reactive species, but also preserves the mitochondrial function and homeostasis of intracellular calcium, relieving the systolic dysfunction induced by sepsis in vivo.[17]

- Necrosis and apoptosis of cardiomyocytes: focal myocardial necrosis and subendocardial necrosis have been identified in experimental models of sepsis, while necrosis of the contractile bands was identified by Schmittinger et al.[18] in a prospective study involving the histological analysis of 20 biopsied human hearts.

- Myocardial infiltration: myocardial infiltration by neutrophils, monocytes, and macrophages is the main histological finding in septic cardiomyopathy. This inflammatory process is associated with interstitial edema, fibrosis, and formation of thrombi in the microcirculation.[18,19]

Left ventricular systolic dysfunction and mortality

LV systolic dysfunction has been the most studied and reported dysfunction in the literature, and despite

reduced myocardial contractility occurring in 100% of the cases of severe sepsis,[20] studies estimate that only 20 to 60% of the patients with septic shock have decreased LV ejection fraction (LVEF)[21-23] in the first 3 days of treatment, with a gradual return to the baseline value around the tenth day from the onset of sepsis among the survivors.[21]

Despite the importance given to the occurrence of systolic dysfunction during sepsis, its association with mortality is controversial. Ognibene et al.[24] observed that, paradoxically, patients with lower LVEF and greater LV end-diastolic volume (LVEDV) had a greater chance of surviving and recovering their myocardial function in the course of sepsis.[24] Additionally, Vieillard-Baron et al.[22] identified that acute and reversible left ventricular dysfunction was not associated with worse prognosis.

Narvaéz et al.[25] reported a 22.8% incidence of septic cardiomyopathy among patients with severe sepsis or septic shock, with no difference in mortality when compared with patients with LVEF ≥ 50% and normalization of LV function after recovery from the acute event.[25] De Geer et al.,[26] using speckle tracking, observed that the global longitudinal strain is often reduced in patients with septic shock, either alone or associated with a reduction in the LVEF or the average mitral annular motion velocity measured by tissue Doppler (e').[26] The authors also observed that the global longitudinal strain presents a strong correlation with NT-proBNP levels on the first day of hospitalization, but is not significantly different between survivors and nonsurvivors, therefore, is not a good predictor of mortality.[26]

In a recent meta-analysis that included seven prospective observational studies evaluating the relationship between systolic dysfunction associated with sepsis and mortality, the presence of a new-onset systolic dysfunction was not a sensitive or specific predictor of mortality due to the heterogeneity and low statistical power of the studies involved.[27]

The assessment of the systolic function during sepsis can be a complex and challenging task,[28] which may lead to the myocardial depression not being readily identified[29] or the LVEF to be even overestimated, depending on the moment it is assessed.[30] This occurs because the heart, despite being a central component of the cardiovascular system, is affected during sepsis by disorders of capillary permeability and peripheral vascular tonus, with fluid loss to the third space, absolute hypovolemia, and consequent decrease in preload, in addition to peripheral vasodilation with a direct reduction of the afterload and relative hypovolemia, leading to an additional decrease in preload.[28]

Since myocardial contractility is invariably reduced in sepsis, the LVEF ends up reflecting the balance between preload and afterload; in this way, despite the reduction of the intravascular volume directly affecting even more the myocardial function,[31] the arterial vasodilation, by reducing the afterload, may temporarily mask the myocardial depression and allow the LV systolic function to be preserved, i.e., overestimated despite a severely compromised intrinsic contractility, while the correction of the vasoplegia by volume resuscitation and the use of vasopressors unveil the contractile deficit.[30] In fact, Boissier et al.,[32] using tissue Doppler and speckle tracking, showed that most patients with septic shock have reduced LV strain, and observed an inverse correlation between most indices of contractility and afterload.[32] In addition, the diagnosis of systolic dysfunction in this clinical scenario can be hindered by the high prevalence of heart failure with reduced ejection fraction (HFREF) in the population, often done retrospectively by the observation of improvement in ventricular function through serial echocardiographic assessments.

Left ventricular diastolic dysfunction and mortality

Diastolic dysfunction is equally prevalent in the presence of sepsis, occurring in approximately 40% of the patients,[33,34] although this number may vary according to the criteria used to evaluate the diastolic function. This has been observed in a study conducted by Clancy et al.,[35] in which 60% of the patients evaluated on the first day of an episode of severe sepsis or septic shock presented diastolic dysfunction and 23% presented indeterminate diastolic function according to the guidelines published in 2016 by the American Society of Echocardiography along with the European Association of Cardiovascular Imaging, while 21% and 74% had diastolic dysfunction or indeterminate diastolic function, respectively, according to the 2009 guidelines of the American Society of Echocardiography.[35]

It is not yet clear whether diastolic dysfunction is induced by this condition or changed by its treatment (with volume expansion and use of vasopressors) or, even, if it is a preexisting condition aggravated by the infection.[31] The prevalence of diastolic dysfunction is known to increase significantly with age,[36] especially with the occurrence of comorbidities like hypertension and ischemic cardiopathy, characteristics often present

in the target populations of the studies. The isolated presence of diastolic dysfunction is already in itself a marker of poor prognosis. Redfield et al.[37] demonstrated by multivariate analysis that the isolated presence of any degree of diastolic dysfunction was strongly predictive of mortality, while Flu et al.[38] showed that isolated diastolic dysfunction was associated with a higher risk of cardiovascular events in 30 days and cardiovascular mortality in the long term in patients undergoing open vascular surgery.[38] Nevertheless, little is known about how the presence of diastolic dysfunction increases the risk of mortality in sepsis, but a very plausible hypothesis is that the abnormal relaxation of the LV potentiated by tachycardia induced by sepsis and/or decreased complacency could promote changes in cardiac hemodynamics in such a way that the normal cardiac output could only be maintained through increased LV filling pressures and greater atrial participation in ventricular filling.[39]

Once the left ventricular pressure rises disproportionately in response to a relatively small increase in volemia, such patients can progress with pulmonary venous congestion secondary to an overload of fluids required for volume resuscitation and enhanced by the widespread increase in capillary permeability secondary to endothelial dysfunction induced by sepsis.[40]

Regardless of the limitations presented, diastolic dysfunction has been singled out as an independent predictor of mortality by studies with tissue Doppler techniques for the evaluation of the properties of relaxation of the myocardium. Sturgess et al.,[41] in a prospective observational study with patients admitted to intensive care with septic shock, concluded that after adjustment for disease severity, presence of cardiac disease, volemic management, and degree of diastolic dysfunction, the ratio between the speed of early diastolic transmitral flow by pulsed Doppler (E) and e' – the E/e' ratio – was an important independent predictor of in-hospital survival that allowed a better discrimination of survivors and nonsurvivors than cardiac biomarkers.[41]

Landesberg et al., in a study including 262 patients with severe sepsis and septic shock, observed that diastolic dysfunction was not only common but also represented an important predictor of mortality in this context. The authors observed that patients with isolated systolic dysfunction (LVEF ≤ 50%; 9% of the patients) and diastolic dysfunction (e' < 8 cm/s; 40% of the patients) alone or associated with systolic dysfunction (14% of the patients) showed a significantly higher mortality than those without any type of dysfunction. In this study, a septal e' < 8 cm/s was considered an independent predictor of mortality.[42]

Mourad et al.[43] followed 72 patients with cancer admitted with septic shock to an intensive care unit and found that early diastolic dysfunction was a strong independent predictor of mortality in these patients and, once again, a lateral e' < 8 cm/s was an echocardiographic parameter independently associated with mortality.[43]

In 2014, Landesberg et al.[44] evaluated a new cohort of patients with severe sepsis and septic shock to investigate the manifestation of myocardial dysfunction that best correlates with troponin elevations and explain its association with mortality in sepsis. The authors concluded that diastolic dysfunction and RV dilation were the echocardiographic characteristics that best correlated with troponin levels and best independent predictors of in-hospital mortality than this biomarker, suggesting a potential contribution of these cardiac mechanical properties in the elevation of troponin levels and association with mortality in this clinical context. Once again, a septal e' < 8 cm/s was an important risk marker of mortality.[45]

More recently, Rolando et al., in a prospective observational study with 53 patients with a mean age of 74 years, observed that diastolic dysfunction was present in 83% of this population and that the E/e' ratio was the index of diastolic dysfunction that best correlated with decreased hospital survival on multivariate analysis.[45]

These findings have been corroborated by a meta-analysis comprising 16 studies and 1,507 patients with severe sepsis or septic shock, in which both a lower e' and a higher E/e' ratio had a significant association with mortality.[46]

Right ventricular dysfunction and mortality

Right ventricular systolic dysfunction, characterized by reduced contractility, increased right atrial pressure, and reduced venous return, has been reported in 30 to 50% of the patients during sepsis.[47] This complication may occur isolated or in association with left ventricular systolic dysfunction, justifying in the latter case the maintenance of filling pressures in the left side within the limits of normality, even in the presence of important contractility deficit.[20]

Similar to what occurs with the LV, the RV ejection fraction (RVEF) is directly dependent on the coupling between contractility and afterload, but different from the

systemic vascular resistance, which is initially reduced, pulmonary vascular resistance is increased since the early stages of sepsis by decreased production of NO[48,49] and increased circulating levels of vasoactive substances, such as thromboxane, endothelin, and serotonin.[50-53]

An RV with an intrinsic reduction in contractility induced by sepsis becomes more sensitive to the increase in afterload secondary to pulmonary vascular dysfunction[54] and only manages to maintain, at least initially, its systolic function through increased filling pressures provided by an adequate volume resuscitation; with fluid administration, there is an increase in cardiac index, central venous pressure, pulmonary capillary wedge pressure, and indices of end systolic and diastolic RV volumes, despite a progressive reduction in the ejection fraction of this ventricle.[55]

The failure of this compensatory mechanism becomes particularly more evident in patients on mechanical ventilation and in the presence of acute lung injury. In the first case, the effects of positive pressure on cardiac function lead to decreased venous return (hindering the increased filling pressures), elevation in pulmonary vascular resistance, and reduction in cardiac output due to increased intrathoracic pressure.[56] In the second, the hyperinflation resulting from recruitment maneuver and the pulmonary collapse due to alveolar filling and protective ventilation strategies using very low tidal volumes can also elevate the pulmonary vascular resistance by an increased autonomic tonus reflex and hypoxic pulmonary vasoconstriction, respectively.[57,58]

Regardless of this mechanism of adaptation, the literature has demonstrated an association between right ventricular systolic dysfunction and mortality in sepsis, with studies pointing to a lower RVEF[59,60] and, more recently, to a reduction in peak systolic velocity of the RV free wall on tissue Doppler in patients not surviving to sepsis compared with survivors.[61,62]

Vallabhajosyula et al.,[63] in a historical cohort study of patients with severe sepsis or septic shock admitted to all intensive care units at Mayo Clinic between January 2007 and December 2014, showed that 55% of the patients met the diagnostic criteria for right ventricular dysfunction and, after adjustment for age, comorbidities, disease severity, presence of septic shock, and mechanical ventilation, concluded that the presence of right ventricular dysfunction was associated with worse survival at 1 year (risk ratio of 1.6, 95% confidence interval [95%CI] 1.2 – 2.1, p = 0.002).[63] More recently, Orde et al.[64] showed that right ventricular dysfunction was present in 32% of the patients with severe sepsis or septic shock evaluated by conventional echocardiography, and that this number rose to 72% when the evaluation was performed with speckle tracking; this "unmasked" dysfunction, especially when severe, was associated with a high mortality rate.[64]

Biomarkers and sepsis

Cardiac troponins (I and T) are important independent predictors of mortality in acute coronary syndrome without ST-segment elevation[65] and other clinical conditions, such as end-stage renal disease,[66] stroke,[67] and pulmonary embolism.[68]

The elevation in troponin levels is relatively common in sepsis, occurring in approximately 60% of the patients;[69] even though it is unclear why this happens, the manifestations of myocardial dysfunction that most correlated to the elevation in troponin levels have been recently demonstrated to be diastolic dysfunction and right ventricular dilation.[44]

The role of the troponins as a prognostic factor in sepsis is still under debate, with some studies[70-72] having shown negative results in terms of increased mortality, and others concluded otherwise. John et al.[73] showed a higher mortality at 28 days in patients with positive troponin I (32% versus 14%, p < 0.0001),73 while Vallabhajosyula et al.,[74] in a retrospective cohort study, observed a relationship between troponin T elevation (≥ 0.01 ng/mL) on admission, in-hospital mortality (odds ratio [OR] 1.6, p = 0.003), and mortality at 1 year (OR 1.4, p = 0.04).[74]

BNP and NT-proBNP are two molecules secreted in response to atrial wall stretching and extensively used in the diagnosis and prognosis of heart failure. In the clinical context of sepsis, proinflammatory cytokines are believed to also exert an important role in the elevation of BNP levels. In vitro studies have shown the importance of interleukins 1 and 6 and TNF-α in inducing BNP secretion by cardiomyocytes,[75,76] explaining the higher plasma concentrations of this biomarker even in individuals without heart failure, and its correlation with the levels of C-reactive protein, a traditional marker of inflammatory activity.[77]

In sepsis, the interpretation of increased levels of BNP and NT-proBNP can be hampered by the inflammation and other factors like age and renal insufficiency, although studies have demonstrated their importance

as independent markers of mortality in this clinical scenario.[77,78] Brueckmann et al.,[79] for example, followed 57 patients diagnosed with severe sepsis and observed that patients with NT-proBNP levels > 1400 pmol/L showed a 3.9 times greater risk (relative risk [RR] 3.9, 95%CI 1.6 – 9.7) of dying from sepsis than patients with lower NT-proBNP values ($p < 0.001$).[79] Khoury et al.[80] studied 259 patients with sepsis and without cardiac failure and concluded using multivariate analysis that BNP is a strong predictor of in-hospital mortality at 90 days and 60 months, in addition to a better prognostic predictor than the Sepsis-related Organ Failure Assessment (SOFA) score for mortality at 90 days, and a better prognostic predictor of mortality at 60 months in low-risk groups.[80]

Final considerations

Evidence points to an association between myocardial dysfunction and sepsis as a relatively frequent event. The relationship between systolic dysfunction and mortality is still not defined, nor is the mechanism by which the diastolic dysfunction and the right ventricular dysfunction affect so adversely the evolution of patients with sepsis. There are no studies evaluating the effects of a differentiated strategy of treatment on the outcome of these patients. These gaps offer the opportunity for research and development of knowledge that can contribute to the treatment of such patients and, in the final analysis, improve their prognosis.

Author contributions

Conception and design of the research: Campista MS. Writing of the manuscript: Campista MS, Guedes MA. Critical revision of the manuscript for intellectual content: Jorge AJL, Campista MS, Martins WA. Supervision / as the major investigador: Jorge AJL.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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