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EDITORIAL COMMENT

A new path to prevent sepsis-induced cardiac dysfunction

Um novo caminho para prevenir a disfunção cardíaca induzida por sepsis

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Worldwide, more than 30 million people annually are affected by sepsis, a life-threatening systemic inflammatory disease.[1] Described as an uncontrolled inflammatory response by the host to an infection, it can result in multiple organ dysfunction, the heart being one of the most susceptible organs.[2] In the early stages of infection, cells secrete inflammatory factors and cytokines that initiate a systemic inflammatory response, encompassing increased capillary permeability and disturbances in the coagulation cascade, among other effects.[3] These events impact significantly on the heart, leading to cardiac dysfunction, particularly impaired contractility and diastolic dysfunction. Cardiac dysfunction is a common and widespread complication of sepsis that is responsible for about 70% of mortality due to sepsis.[3]

Lipopolysaccharide (LPS), a known bacterial endotoxin, is released by the lysis of Gram-negative bacteria and is a strong inducer of sepsis and subsequent organ dysfunction.[3] Previous studies demonstrated that LPS induces the release of proinflammatory cytokines, resulting in the development of septic shock (sepsis-associated acute circulatory failure) through binding to the toll-like receptor-4 (TLR-4), a highly expressed receptor on the surface of cardiomyocytes.[3] Additionally, it has been demonstrated that macrophages and neutrophils infiltrate myocardial tissue during the early stages of sepsis-induced cardiac dysfunction, which can promote the intracellular production of reactive oxygen species (ROS), leading to cardiomyocyte damage and impaired myocardial contractile function.[4] This imbalance in ROS production can disrupt the myocardial mitochondrial cell membrane, inhibit mitochondrial oxidative phosphorylation and inhibit the tricarboxylic acid cycle, thereby decreasing the production of adenosine triphosphate (ATP), which impairs the energy supply to cardiomyocytes.[4] Excessive inflammation, allied to oxidative stress and mitochondrial dysfunction in cardiomyocytes, activates and accelerates the intracellular apoptotic pathway, resulting in the apoptosis of these cells.[4]

Currently, sepsis and its complications still impose an overwhelming burden on clinical practice due to the relatively limited effectiveness of therapeutic strategies. The available treatments for sepsis-induced cardiac dysfunction aim at maintaining hemodynamic stability and supporting normal cardiac function, while more specific drugs are still limited.[5] Thus, the identification of effective new therapeutic strategies is an urgent need for human health.

The renin–angiotensin system (RAS) is essential for maintaining normal systemic performance. Two major cascades,

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the angiotensin-converting enzyme (ACE)/angiotensin II (Ang II)/angiotensin II type 1 receptor (ATR1) cascade, and the angiotensin-converting enzyme 2 (ACE2)/angiotensin (1–7) (Ang (1–7)/Mas receptor (MasR) cascade, which have antagonistic roles within the RAS, are essential not only in maintaining systemic blood pressure, but also in modulating inflammation, immunoreaction, ROS production, cell growth and apoptosis, all key elements of sepsis.[6] Therefore, the development of innovative and powerful therapeutic tools targeting the RAS appears to hold a promising future for the treatment of sepsis.

Some studies have demonstrated that RAS components such as ACE2, Ang (1–7) and their receptors have a cardioprotective effect.[7] Irbesartan is one of the non-peptide Ang II receptor antagonists used worldwide in the treatment of hypertension and diabetic nephropathy. It functions by selectively blocking AT1 receptors, reducing the effect of Ang II.[8] Among the main Ang II receptor blockers, irbesartan shows the longest duration of its antagonistic effects, which makes its use preferable.[9] Furthermore, other studies have demonstrated that this blocker has a cardioprotective effect.[10] However, the exact mechanisms whereby irbesartan exerts its function are not completely understood.

The study by Tepebasi et al. published in this issue of the *Journal*[11] provides evidence that irbesartan has a protective effect against LPS-induced cardiac damage, reducing myocardial damage, oxidative stress and indicators of apoptosis. Using a well-established LPS-induced sepsis model that is known to induce systemic inflammation, as well as to cause cardiotoxicity associated with oxidative stress and apoptosis, mimicking in vivo sepsis-induced cardiac dysfunction, the study demonstrates that animals administered LPS presented degeneration of myocardial cells and endothelial cell injury and loss, together with increases in markers of oxidative stress and apoptosis. Strikingly, irbesartan mitigated most of the features induced by LPS, including the loss of endothelial cells and increased levels of oxidative stress and apoptosis markers.

Overall, the paper by Tepebasi et al.[11] is a valuable contribution, since it brings important insights about the mechanisms by which irbesartan reduces the cardiac damage induced by LPS, highlighting the importance of studying RAS inhibitors for the treatment of sepsis-induced cardiac dysfunction.

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Conflicts of interest

The author has no conflicts of interest to declare.

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