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WHAT'S NEW IN INTENSIVE CARE

Long-term impact of sepsis on cardiovascular health

R. T. Mankowski[1], S. Yende[2,3] and D. C. Angus[2*]

Introduction

Sepsis is life-threatening, acute organ dysfunction due to a dysregulated host response to infection [1]. Advances in critical care medicine have decreased early hospital mortality, in turn increasing the number of patients who survive. Unfortunately, these survivors are at increased risk of chronic critical illness and post-discharge sequelae [2], such as long-term disability, physical and cognitive impairments, and worsening of chronic diseases such as cardiovascular disease [3]. Many patients who develop sepsis already have pre-existing chronic health issues, further complicating our understanding of the relationship between chronic diseases and sepsis. There are several chronic disease trajectories following sepsis, including partial or complete return to pre-sepsis health status, slow progressive worsening, and relapsing and rapidly progressive impairment [4]. The recovery trajectories appear to vary and may be influenced by pre-sepsis health status and severity of organ dysfunction and host immune response during the sepsis episode itself [4]. Furthermore, a bidirectional relationship may exist between chronic diseases and sepsis. In particular, a chronic disease may increase the risk of infection and, in turn, the infection may accelerate the chronic condition [4]. This complex relationship complicates research design of preclinical and clinical studies [4].

Here, we focus on cardiovascular disease after sepsis because it is a leading cause of hospital readmission (e.g., for exacerbation of heart failure or acute coronary syndrome), impaired quality of life, and late death after sepsis. Although cardiovascular disease is defined broadly as a group of disorders of the heart and blood vessels [5], we focus on four conditions: stroke and myocardial infarction (MI) because they are common manifestations of atherosclerotic heart disease, and heart failure and atrial fibrillation because they have been studied in patients with sepsis and severe pneumonia, the most common cause of sepsis.

Relationship between sepsis and cardiovascular disease

For decades, infections were considered precipitants of cardiovascular disease [6]. Recent epidemiologic studies showed that new-onset stroke (18%), MI (7%) [7], and heart failure (8.6%) [8] are common during the first year after hospital discharge for sepsis and pneumonia. Although accurate estimates for atrial fibrillation after hospital discharge are not available, new-onset atrial fibrillation is common during sepsis hospitalization (7%) [9]. While most studies focused on long-term cardiovascular disease after sepsis and pneumonia, the higher risk may be observed among patients who are critically ill without evidence of infection [7]. Additionally, the relationship between different cardiovascular events during sepsis and after hospital discharge is complex (Fig. 1). For instance, new-onset atrial fibrillation during sepsis was associated with higher risk of subsequent heart failure [9], but the incidence of heart failure over 2 years after sepsis between survivors with and without left ventricular (LV) dysfunction during sepsis [10] is similar.

The mechanisms underlying the increased risk of cardiovascular disease after sepsis are poorly understood. The role of inflammation has been extensively studied. Persistent systemic inflammation induced by infections is associated with cardiovascular disease [6, 11], and increased circulating concentrations of pro-inflammatory biomarkers, catecholamine release, and multi-organ failure during sepsis may contribute to chronic systemic inflammation

*Correspondence: angusdc@ccm.upmc.edu
[2] The Clinical Research, Investigation and Systems Modeling of Acute Illness Laboratory, Department of Critical Care Medicine, University of Pittsburgh, 614 Scaife Hall, 3550 Terrace Street, Pittsburgh 15261, Pennsylvania, USA
Full author information is available at the end of the article

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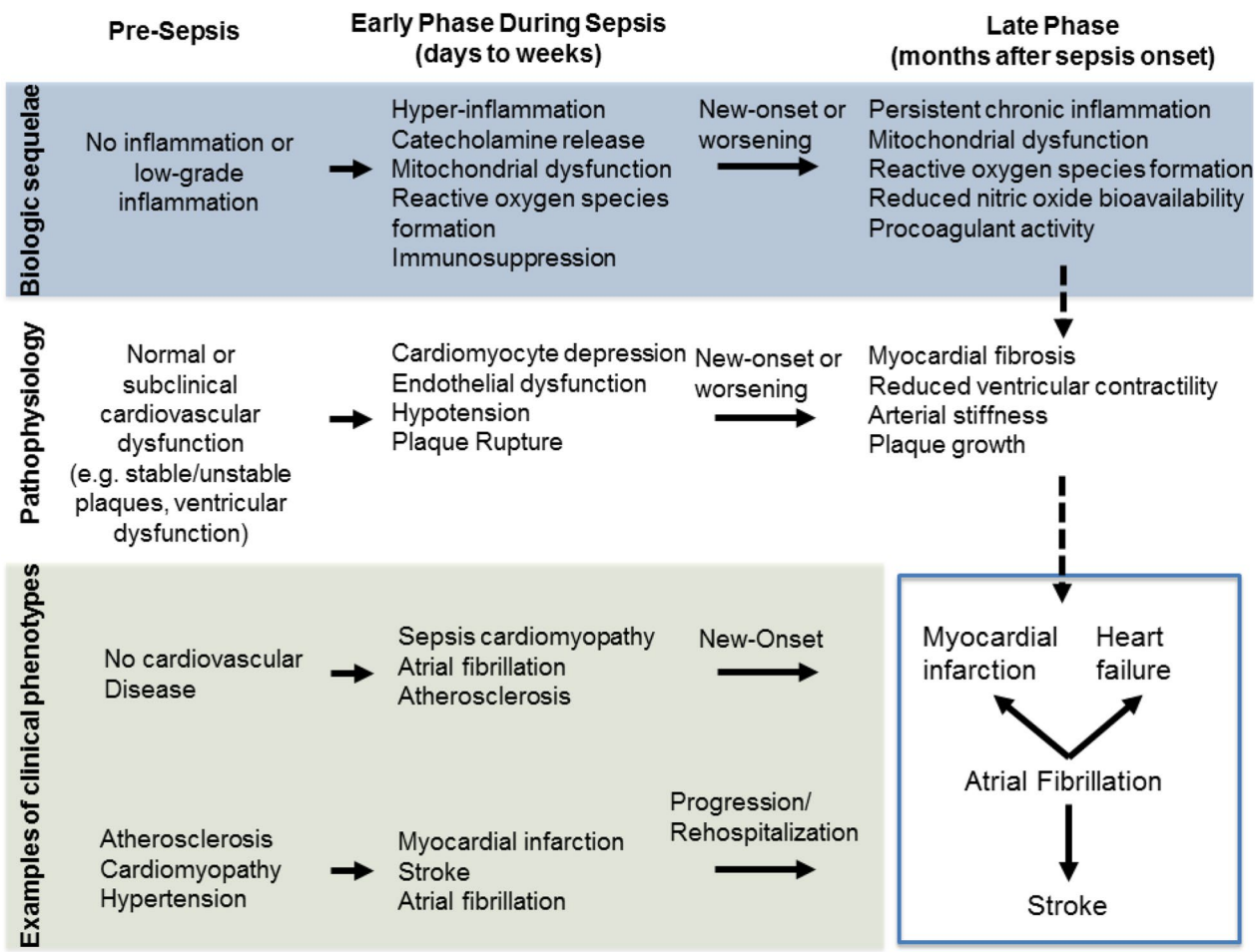

Fig. 1 Conceptual mechanistic model of the long-term impact of a sepsis incident on cardiovascular disease development and/or worsening of pre-existing dysfunction/disease. The figure presents the impact of a sepsis (early phase) on long-term (late phase) cardiovascular disease development in three domains: biologic sequelae due to sepsis (blue), pathophysiology of cardiovascular dysfunction (white), and examples of cardiovascular disease phenotypes (green). The magnitude of long-term cardiovascular disease risk is likely dependent on pre-sepsis health state and clinical or subclinical cardiovascular dysfunction/disease (pre-sepsis) and biological mechanisms and pathophysiologic changes during the episode of sepsis and recovery. Dashed arrows demonstrate how late biologic sequelae (deteriorating processes initiated or accelerated by a sepsis incident) may lead to the late clinical phenotypic changes. Over time, persistent systemic inflammation, progressive mitochondrial dysfunction, formation of reactive oxygen species, reduced nitric oxide bioavailability, and procoagulant activity (late phase biologic sequelae) may lead to dysfunctional cardiovascular remodeling, which contributes to the development/progression of cardiovascular disease. We also demonstrated that potential interactions between cardiovascular diseases such as development of atrial fibrillation might contribute to the development of stroke, MI, or heart failure

[12]. Persistent systemic inflammation may convert stable atherosclerotic plaques to unstable plaques, lead to plaque rupture, and stroke or MI (Fig. 1). Experiments exposing cultured cardiomyocytes to pro-inflammatory cytokines (e.g., tumor necrosis factor-alpha [TF-α], interleukin 1 beta [IL-1β], and IL-6) demonstrated that acute release of pro-inflammatory cytokines plays an important role in cardiomyocyte depression [13].

Additionally, preclinical results showed that a bacterial pathogen invading myocardium was the primary inducer of inflammation, cardiomyocyte death, fibrosis, and ventricular dysfunction in the myocardium in a pneumonia model in human primates [14]. In contrast, several clinical reports have shown no correlation between pro-inflammatory cytokines and functional measures such as echocardiography [13]. Future studies should examine the role of chronic inflammation in ventricular function during recovery, particularly subclinical impairments of ventricular dysfunction.

Other potential mechanisms include the role of procoagulant activity, which may contribute to formation/progression of atherosclerosis and plaque rupture and lead to stroke and MI [15]. Taken together, sepsis and pneumonia are associated with increased long-term risk

of cardiovascular disease. However, studies are needed to characterize both cardiac and vascular function impairments during the acute episode of sepsis and during recovery. In addition, higher risk of cardiovascular disease after sepsis warrants designing studies testing interventions aimed at reducing cardiovascular burden and preventing cardiovascular disease development [7].

Limitations and implications for future studies

Most studies reporting long-term cardiovascular disease incidence in sepsis survivors are limited by cross-sectional and retrospective designs. In addition, many studies lack pre-sepsis cardiovascular profiles and long-term follow-up functional measures that could better characterize asymptomatic and subclinical cardiovascular dysfunction during and after sepsis. Better infrastructure to follow sepsis survivors, especially in the first 12 months, would contribute to our understanding of the impact of acute sepsis on cardiovascular health and could help with the design of interventions to prevent cardiovascular disease, regardless of the pre-sepsis health status. Non-invasive, reproducible, and sensitive methods to measure cardiac function (e.g., speckle-tracking echocardiography), endothelial function (e.g., flow-mediated dilation), and arterial stiffness (e.g., pulse wave velocity) might be appropriate diagnostic tools to improve our understanding about the interplay between ventricular and vascular dysfunction (i.e., arterial-ventricular coupling) and its contribution to cardiovascular dysfunction after sepsis. These techniques could help to study relationships between sepsis and cardiovascular dysfunction, and potential interactions between cardiovascular diseases, such as development of atrial fibrillation contributing to the development of stroke, MI, or heart failure (causal diagram in Fig. 1).

Decline in physical and cardiovascular health status due to sepsis and pre-existing conditions may also require understanding the role of lifestyle interventions such as antioxidant and anti-inflammatory nutraceutical agents and physical activity interventions to target the consequences of sepsis.

Finally, there is also a need for animal models to circumvent some of the complexities and difficulties of obtaining cardiovascular specimens and assessments in humans, and to generate preclinical evidence of the potential consequences of interventions designed to manipulate cardiovascular health status. Longitudinal animal models of sepsis in rodents of various phenotypes (e.g., healthy, atherosclerosis, cardiomyopathy, or sarcopenia) could be helpful to better understand the interplay between health status before and cardiovascular disease after sepsis, and study the effects of potential interventions to prevent or reduce the cardiovascular burden of sepsis.

Conclusions

Cardiovascular disease incidence after sepsis is one of the emerging health issues. Many studies show that sepsis increases risk of cardiovascular disease, particularly heart failure and atherosclerosis. While increased systemic inflammation may explain the link between them, definitive evidence is currently lacking. Future preclinical and clinical studies warrant characterizing cardiovascular dysfunction after sepsis and designing interventions to prevent cardiovascular disease development.

Author details
[1] Department of Aging and Geriatric Research, University of Florida, Gainesville, Florida, USA. [2] The Clinical Research, Investigation and Systems Modeling of Acute Illness Laboratory, Department of Critical Care Medicine, University of Pittsburgh, 614 Scaife Hall, 3550 Terrace Street, Pittsburgh 15261, Pennsylvania, USA. [3] Veterans Affairs Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA.

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