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Long-Term Impact of Sepsis on Cardiovascular Health

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Abstract

Recent retrospective epidemiological studies demonstrated that new-onset cardiovascular disease is one of the most emerging issues among sepsis survivors. Sepsis incident may also accelerate cardiovascular dysfunction/disease existing prior to sepsis. This review summarizes recent key literature on long-term cardiovascular outcomes after sepsis and pneumonia, and highlights potential biologic and pathophysiologic mechanisms that contribute to long-term cardiovascular disease after a sepsis incident. Prospective pre-clinical and clinical studies are warranted to characterize cardiovascular dysfunction after sepsis, the role of chronic biologic sequelae in pathophysiology of post-sepsis cardiovascular disease, and design interventions to prevent and reduce long-term cardiovascular burden of sepsis.

Keywords

Critical Care; Outcomes; Chronic Disease; Older Adults; Epidemiology

Sepsis is a life-threatening, acute organ dysfunction due to a dysregulated host response to infection [1]. Advances in critical care medicine have decreased early hospital mortality, thus the number of patients who survive and develop chronic critical illness and discharged from the hospital with sequelae of critical illness is increasing [2]. These survivors frequently experience long-term disability, physical and cognitive impairments, and worsening of chronic diseases such as cardiovascular disease [3].

Given the high burden of chronic diseases among sepsis patients, there has been increasing interest in understanding 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 pre-clinical and clinical studies [4].

This review focuses on the long-term impact of sepsis on chronic diseases. We chose to focus on cardiovascular disease after sepsis because it is one of the leading causes of death among sepsis survivors, increases readmission rates (e.g., heart failure and acute coronary syndrome), and worsens quality of life.

Relationship between sepsis and cardiovascular disease

For decades, infections were considered precipitants of cardiovascular disease [5]. Epidemiologic studies reported higher long-term risk of heart failure, myocardial infarction, stroke, coronary revascularization, and atrial fibrillation for many years after pneumonia and sepsis [6, 7]. Additionally, the relationship between different cardiovascular events during sepsis and after hospital discharge is complex (Figure 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 [8] 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 [5, 10], and increased circulating concentrations of pro-inflammatory biomarkers, catecholamine release, and multi-organ failure during sepsis may contribute to chronic systemic inflammation [11]. Persistent systemic inflammation may convert stable atherosclerotic plaques to unstable plaques, lead to plaque rupture, and stroke or acute myocardial infarction (Figure 1). Experiments exposing cultured cardiomyocytes to pro-inflammatory cytokines (e.g. tumor necrosis factor- α [TF- α], interleukin 1 beta [IL-1 β] and IL-6) demonstrated that acute release of pro-inflammatory cytokines play an important role in cardiomyocyte depression [12]. 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 [13]. In contrast, several clinical reports have shown no correlation between pro-inflammatory cytokines and functional measures such as echocardiography [12]. 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 myocardial infarction [14]. 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.

Limitations and implications for future studies

Most of studies reporting long-term cardiovascular disease incidence in sepsis survivors are limited by a cross-sectional and retrospective design. 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.

Most authors agree on the lack of long-term prospective studies to characterize cardiovascular dysfunction. An adequate infrastructure to follow sepsis survivors, especially in the first 12 months, would contribute to our understanding on the impact of acute sepsis incident on post-sepsis cardiovascular health status and could help design interventions to prevent cardiovascular disease, regardless the pre-sepsis health status. Non-invasive, reproducible and sensitive methods measuring 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 candidates 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. 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 anti-oxidant and anti-inflammatory nutraceutical agents and physical activity interventions to target the consequences of sepsis.

Finally, there is also a need for animal models due to complexity in obtaining cardiovascular specimen and manipulation of cardiovascular health status in humans. Longitudinal animal models of sepsis in older rodents of various phenotypes (e.g. healthy, atherosclerosis, cardiomyopathy, sarcopenia) could be helpful to better understand the interplay between health status before and cardiovascular disease after sepsis, and study effects of potential interventions to prevent and/or reduce cardiovascular burden of sepsis.

Conclusions

Cardiovascular disease incidence after sepsis is one of the emerging health issues, especially among vulnerable older adults. 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.

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Figure 1.

Conceptual mechanistic model of the long-term impact of a sepsis incident on cardiovascular disease development. 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 potential interactions between cardiovascular diseases such as development of atrial

fibrillation might contribute the development of stroke, myocardial infarction or heart failure.

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