Preventing Cardiovascular Complications of Acute Infection: A Missed Opportunity?

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The connections between infection and cardiovascular disease have been postulated for at least 125 years, when Gilbert and Lion observed that acute infection with the typhoid bacillus resulted in atherosclerotic changes to the rabbit aorta. In the last few decades, much work has investigated the role for chronic viral and atypical bacterial infections in progression of atherosclerosis; however trials of antibiotics as secondary prevention for cardiovascular events have been disappointing. More recently, epidemiological studies have demonstrated an association between acute infection and cardiovascular events such as acute myocardial infarction, stroke, cardiomyopathy or atrial fibrillation.

In this issue of Circulation, Dalager-Pedersen and colleagues explore the association between community-acquired bacteremia and acute myocardial infarction and ischemic stroke using a population-based cohort study of bacteremic patients from Northern Denmark. The authors compare rates of myocardial infarction and stroke among 4389 bacteremia patients to rates among 43,831 matched community-dwelling controls and 21,893 matched hospitalized controls. The use of a hospitalized control group allows for the assessment of excess cardiovascular risks associated with bacteremia as compared to age-, sex- and admission year-matched acutely ill, hospitalized patients, and reduces potential detection bias for cardiovascular events during a hospitalization. The community-dwelling cohort allows for assessment of excess...

“...This is an experimental verification of this medical concept, relatively new, suggesting that infections merit an important place in the etiology of human atheromatous arteritis...”

-Gilbert A and Lion G, Comptes Rendus Hebdomadaires des Séances et Mémoires de la Société de Biologie. Published 1889
cardiovascular risk as compared to matched general population controls. The authors found that patients with community-acquired bacteremia had higher rates of a composite endpoint of acute ischemic stroke or acute myocardial infarction (3.6% incidence) as compared with both hospitalized patients (1.7%) and a population-based cohort (0.2%). The time frame for increased stroke and myocardial infarction risk was mostly confined to the duration of the bacteremia hospitalization; risks declined precipitously after 30 days. Results were robust to multiple sensitivity analyses and adjustment for comorbidities.

Given that bacteremia and sepsis affected more than 1 million hospitalized patients in the United States in 2011, if Dalager-Pedersen and colleagues’ results are accurate and generalizable it is likely that 30-40 thousand new strokes or myocardial infarctions occur after bacteremia each year in the US. Adding in previously described risks of cardiovascular events following pneumonia or urinary tract infection, we estimate that 5-10% of acute myocardial infarctions or strokes may be associated with acute infection.

What does the study by Dalager-Pedersen and colleagues add to the literature? The authors were able to microbiologically confirm onset of bacteremia and validate temporality between infection and cardiovascular events, attenuating impact of potential misclassification of cardiovascular events as infections. The difficulty of discerning between infection and cardiovascular disease upon initial clinical evaluation is perhaps underappreciated; recent evidence suggests that 1 in 3 patients hospitalized with acute decompensated heart failure are initially treated with antibiotics. The authors linked multiple population-based databases with high levels of granularity - including access to comorbidities and medications - that allowed matching and adjustment for multiple potential confounders of the association between infection and cardiovascular disease. Patients with bacteremia had higher risks for myocardial infarction
and stroke in almost every subgroup analyzed, including among patients with a previous
diagnosis of cardiovascular disease.

In addition, Dalager-Pedersen and colleagues obtained data regarding pathogens and
biomarkers of inflammation (e.g., C-reactive protein, leukocyte count) to perform exploratory
analyses of potential mechanisms. Supporting an ‘inflammation hypothesis’, the incidence of
myocardial infarction and stroke appeared greater among bacteremic patients with higher
leukocyte counts and C-reactive protein levels. The ‘dose effect’ associations between markers
of inflammation and cardiovascular events were not obvious when bacteremic patients were
compared to hospitalized controls, who may have also had C-reactive protein and leukocyte
elevations. However, the increased risk of myocardial infarction and stroke after bacteremia as
compared to other hospitalized patients suggests that ‘being sick’ in general was not the only
mechanism for increased risk.

The study by Dalagar-Pedersen and colleagues also has significant limitations. The study
outcomes of myocardial infarction and stroke were identified using ICD-10 codes which may be
subject to misclassification bias. Prior studies showed that positive predictive values of ICD-10
codes for stroke (76%-87%)\textsuperscript{10} and myocardial infarction (82%)\textsuperscript{11} in the Danish National Registry
are fairly accurate in general. However, if differential misclassification bias occurred, where
patients with bacteremia were more likely to be recognized with stroke or myocardial infarction
than the controls due to closer monitoring, then associations between bacteremia and stroke or
myocardial infarction may be overestimated.

The potentially inflated classification of myocardial infarction diagnoses after bacteremia
deserves further discussion. Troponin elevations are observed in approximately half of patients
with bacteremia or sepsis.\textsuperscript{12} However, an acute coronary artery thrombotic plaque rupture
mechanism producing myocardial infarction (“Type I” Consensus definition) is probably the exception, rather than the rule for producing troponin elevations during acute infections. Myocardial supply-demand mismatch (Type II Consensus definition) is more likely to be the prevailing mechanism in patients with acute infection, though other reasons for troponin elevation during infection may include direct myocardial toxicity from endotoxin or cytokines, septic cardiomyopathy, bacterial myocarditis, or acute renal failure. We do not have information from Dalagar-Pedersen and colleagues as to how myocardial infarction diagnoses were determined, or granular data regarding timing of the events. However, two factors make diagnosis of myocardial infarction solely from mild troponin elevations during bacteremia less likely. First, the incidence of ‘myocardial infarction’ ICD-10 codes during bacteremia in the present study (1.7%) was almost 30-fold lower than the previously reported incidence of troponin elevations during bacteremia. Second, the incidence of myocardial infarction diagnoses did not substantially increase after introduction of the troponin assay into clinical practice. Interestingly, the risk of an acute ischemic stroke diagnosis following bacteremia was greater than the risk for a diagnosis of myocardial infarction. Concerns regarding accuracy of stroke diagnosis during infection are potentially as important as myocardial infarction diagnosis; acute delirium during infection can mimic stroke.

Many studies have now shown increased risk for myocardial injury or stroke during, or soon after, acute infection. Future studies should now focus on investigating questions that will more specifically inform our understanding of the mechanisms linking acute infection to cardiovascular disease. For example, what proportion of patients with sepsis have ischemic electrocardiographic changes combined with elevated troponins? What is the distribution of peak troponin levels after infection? How many patients undergo diagnostic angiography for
suspected acute myocardial infarction within 30 days after infection, and what are the findings? Does the timing of presentation of the cardiovascular event relative to the acute infection inform specific mechanisms of myocardial injury? Is the radiographic distribution of stroke following infection more consistent with watershed infarcts during episodes of hypotension, or embolic infarcts related to atrial fibrillation? To what extent is risk for poor outcomes following sepsis attributable to cardiovascular complications, as opposed to cardiovascular complications being merely a marker of more severe infection?

Due to a lack of understanding of prevailing mechanisms of cardiovascular complications following acute infection, optimal treatment strategies are currently unclear. Evidence supports a strong association between influenza vaccination and cardiovascular risk reduction. Increased efforts should be made to improve suboptimal vaccination rates among patients with cardiovascular disease. Early, goal-directed therapy of severe sepsis has been shown to reduce sudden cardiovascular collapse, yet its adoption into practice is unclear. Results of recent studies also suggest that aspirin, beta-blockers, or statins are associated with improved outcomes during sepsis. Further mechanistic studies and large randomized trials would be required to assess whether antiplatelet, beta-blocker, or statin therapies might result in lower cardiovascular complications, and possibly, better outcomes after acute infection. A conceptual model demonstrating how acute infection may result in cardiovascular complications, and potential future directions investigate strategies that may reduce the risk of cardiovascular complications after acute infection, is shown in Figure 1.

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References:


Figure Legend:

Figure 1. Acute infections may result in systemic inflammation to cause *sepsis*. Sepsis may produce cardiovascular complications through numerous mechanisms. These include direct cardiac injury from catecholamines and inflammation (*severe sepsis*), supply-demand mismatch, inflammation-induced plaque rupture, or secondary injury from other dysfunctional organ systems and organ replacement therapies. Development of one cardiovascular complication may lead to further cardiovascular injury (e.g., myocardial injury ➔ atrial fibrillation ➔ stroke). In addition to early, goal directed therapy of severe sepsis, further opportunities to prevent cardiovascular complications may exist. Currently, evidence is lacking as to which therapies may be most effective in preventing specific cardiovascular complications, or whether preventing cardiovascular complications improves patient-centered outcomes.
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