Spark That Lights the Fire: Infection Triggers Cardiovascular Events

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Atherosclerosis is a complex pathology resulting from a dysfunctional endothelium, activated leukocytes, macrophages, and lipid-laden foam cells, implying a wealth of different actors driving plaque disruption. Classically, all of these actors have been considered acting chronically (ie, the so-called cardiovascular risk factors such as hypertension, diabetes mellitus, etc.)[1]; however, acute triggers have also been identified recently. Among these, infections have been associated with cardiovascular events.[2,3] In this issue of the *Journal of the American Heart Association* (*JAHA*), Cowan et al[4] shed more light on this relationship.

Inflammation has been described as a causal link between traditional cardiovascular risk factors and modification of the arterial wall, which leads to atherosclerosis and cardiovascular events such as myocardial infarction (MI) and stroke.[1] Clinically, autoimmune diseases characterized by a hyperinflammatory status such as systemic lupus erythematosus,[5] rheumatoid arthritis,[6] and psoriasis[7] are also associated with increased cardiovascular risk. Mechanistically, this association has indeed been confirmed by elegant experimental approaches with various other inflammatory insults. The boosted inflammation in the immediate post-MI period causes progression of atherosclerosis lesions (enlarged necrotic core size, increased protease activity, and enhanced inflammatory cell infiltration) in apolipoprotein E knock-out mice subjected to experimental MI[8] mediated via augmented inflammation and increased sympathetic activity. Enhanced inflammation is also the central mechanism of atherosclerotic progression after other insults, both acute (orthopedic surgery)[9] or chronic (prolonged stress).[10] The necessary role of inflammation in the worsening of atherosclerosis after MI has been mechanistically corroborated by several studies showing mitigation of atherosclerosis progression by the inhibition of essential inflammatory pathways such as adhesion molecules[11] and NLRP3 inflammasome.[12] This hypothesis has also been clinically confirmed because the clinical trial CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) demonstrated that anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering.[13]

Infections, both acute and chronic, are one of the main triggers of inflammation, thus it is not far-fetched to hypothesize that infections could also elicit cardiovascular events. This has been demonstrated in the clinical setting given that patients with chronic infections such as *Helicobacter pylori*[14] also experienced more cardiovascular events. The role of acute infections as triggers for cardiovascular events has been recently investigated. While several recent retrospective clinical observations found an increased incidence of MI after community-acquired pneumonia (CAP), this was further confirmed by a prospective multicenter cohort of 2344 unselected patients with CAP[2] showing that the 30-day incidence of heart failure, arrhythmia, and MI was 21%, 10% and 3%, respectively, with this risk peaking in the first 2 days of hospitalization. Additional prospective data in hospitalized CAP patients[15,16] found even higher MI rates, with half of CAP patients showing high levels of hs-TnT (High-sensitivity cardiac Troponin T) while 11% of CAP patients additionally showed electrocardiographic signs of MI and clinical symptoms on top of the high hs-TnT levels. Of note, this MI incidence of 11%[17] was higher than in previous reports (3% as reported by Corrales-Medina[2]), which is probably explained by the use of hs-TnT (a more sensitive marker of myocardial injury than the CK (Creatine Kinase) that was used in previous studies[2]) and by the fact that the levels of hs-TnT were measured not only at hospital baseline but also every 12 hours during hospital admission.[2] An analysis of even larger populations (5888 patients in the Cardiovascular Health Study and 15 792 in the ARIC (Atherosclerosis Risk in Communities) study confirmed that CAP was associated with increased risk of cardiovascular events.[17] Increased MI risk is not circumscribed to CAP, but it also extends to other types of

respiratory infections. Large retrospective epidemiological studies involving >33 000 patients found an increase in MI risk after acute respiratory infections.[18–20] This link is further supported because influenza vaccination is associated with a reduced risk of MI and stroke, both in retrospective studies[21] and in clinical trials,[22] and because early treatment of influenza in patients with established CVD was associated with a 60% decrease in the MI risk.[23] Furthermore, the authors of the present article[4] have previously expanded this field by demonstrating that infections do not only increase the risk of MI but also the risk of stroke.[3] Of the utmost importance, infections also increase the risk for heart failure[2,24] and not only for MI.

The main hypothesis to explain this association is the infection-triggered enhancement in inflammation that boosts atherosclerosis and prompts plaque rupture. Atherosclerosis is an inflammatory disease; acute infections not only elicit systemic inflammatory responses but can also have direct inflammatory effects on atherosclerotic plaques, increasing their vulnerability. In atherosclerotic apolipoprotein E knock-out mice, influenza virus infection promotes acute inflammation in the atheromata (infiltration of plaques with macrophages and T lymphocytes) and superimposed fibrin deposition, similar to unstable plaques after MI.[25] Coronary artery tone abnormalities may also be involved, as increased vasoconstrictive responses were observed in animals injected with staphylococcal alpha-toxins.[15] Other factors may likely contribute: tachycardia shortens diastole (when coronary perfusion occurs); decreased central blood pressure (as in severe sepsis) impairs myocardial perfusion through stenotic coronary segments; hypoxemia and increased cardiac metabolic demands (secondary to tachycardia and catecholamine release) can contribute to development of myocardial ischemia.[15] Furthermore, infections increase platelet aggregation[15] and higher in vivo markers of platelet activation (soluble CD40L, soluble P-selectin, and TxB2 levels) in CAP patients,[16] thus suggesting that CAP may increase platelet activation which in turn may be the cause of MI. This platelet hyper-reactivity may be explained because Gram-positive bacteria induce platelet aggregation and formation of platelet-neutrophil complexes and, in response to lipopolysaccharide from Gram-negative bacteria, platelets bind more avidly to fibrinogen under flow conditions in a Toll-like receptor-4-dependent manner.[15] The main mechanisms responsible for triggering an episode of CVD after infections are summarized in Table.

In this issue of *JAHA*, Cowan et al[4] expands these results by showing high incidence of both MI and stroke after infection and that all infections (whether respiratory or not, whether inpatient or outpatient) increase the risk of cardiovascular events. The authors perform a case-crossover study design nested within the population-based cohort of ARIC

Table. Mechanism Involved in Triggering Cardiovascular Events After Acute Infections

Direct-boost atheroma plaque vulnerability and rupture
Coronary artery tone abnormalities (ie, vasospasm)
Catecholamine release
Tachycardia
Increased cardiac metabolic demands
Hypoxemia
Decreased central blood pressure
Impaired myocardial perfusion
Increased platelet activity and aggregation

study which comprises a perfectly characterized population with a follow-up of up to 30 years. The occurrence of infection immediately before cardiovascular events was compared with preceding time intervals 1 and 2 years before the cardiovascular event, so the same patient serves as its own control. A total of 1312 incident MI cases and 727 incident stroke cases were analyzed. The authors demonstrated that the risk of both MI and stroke is higher after both inpatient and outpatient infection up to 90 days after infection compared with equivalent periods 1 and 2 years before the event. Given the role of infection as a trigger for cardiovascular events, the authors suggest that infection may be considered a "treatable moment" which may prompt more aggressive treatment with standard preventive strategies (statins and perhaps antiplatelets given the role of platelet hyper-reactivity). As a consequence, this study endorses and urges the use of vaccination (for influenza and pneumonia) to reduce infections that may likely trigger cardiovascular events and impair prognosis.

There are 4 novelties and major points of this study. The first novel discovery is that all type of infections and not merely respiratory infections cause cardiovascular events; in fact, respiratory infections accounted for <30% of the trigger events for MI and 15% for stroke, while urinary infections accounted for 30%, skin infections for 11% and blood infections for 5% to 10%. The second novelty is the fact that association is stronger for infections diagnosed in inpatient settings compared with infections diagnosed in outpatient settings; for instance, odds ratio (OR) of cardiovascular events at 14 days post-infection was 12.8 for inpatients but only 3.29 for outpatients, while the OR for cardiovascular events at 30 days was 8.39 for inpatients and only 2.69 for outpatients. This association may be partially explained by the fact that infections requiring hospitalization are likely to be severe and thus to trigger a stronger inflammatory response, resulting in higher cardiovascular risk. In addition, the "hospitalization effect" with prolonged immobilization and changes in

medication may be also playing a role in triggering cardiovascular events. The third novelty is the time association between infection and MI/stroke given that the influence of infection with cardiovascular events wanes overtime and is less important the longer the time after infection (OR 12.8 for MI at 14 days, 8.39 for 30 days, 6.24 for 42 days, and 4.48 at 90 days for inpatients) as the inflammatory response is mitigated overtime. This contrasts with previous studies[17] that suggest that the risk of cardiovascular events remained elevated into the 10th year after the original infection; further studies are needed to clarify this temporal association. Finally, most of the previous literature focuses on MI as a consequence of infection while neglecting the study of stroke; the authors report that infections are also a trigger for stroke, which confirms their preliminary results.[3] Importantly, infection seemed to be a stronger trigger for MI than for stroke (OR at 14 days 12.83 versus 5.93, and OR at 30 days 8.39 versus 3.06 for MI and stroke, respectively). An obvious corollary of the study with clinical implications in everyday practice is the urge for vaccinations in at-risk population, which will reduce the severity of the inflammatory reaction and thus greatly diminish the risk of cardiovascular events.

This study has a clear number of strengths, among which we find a large sample size from a real-life community (ARIC study) that is perfectly characterized and studied. Another methodologic asset is the case-crossover study design on which each patient is its own control, which adjusts for potential confounding. The main limitation is the confounding for age, as patients with an MI (cases) are compared not exactly with themselves but with the same patient 1 and 2 years younger ("controls"), thus these "controls" will have lower cardiovascular risk as they are younger, and age is an important risk factor for cardiovascular events. An interesting question not answered in this study is whether bacterial or viral infections are more potent to cause cardiovascular events. Furthermore, if we consider infection a "treatable moment" for cardiovascular prevention, it would be highly interesting to know whether the severity of inflammation (eg, using biomarkers such as C-reactive protein, white blood cell count, or other acute-phase reactants) are correlated with the risk for cardiovascular events. All these questions remain unanswered and warrant further investigations.

In summary, the article by Cowan et al[4] confirms the high incidence of cardiovascular events after infections, particularly after inpatient infections. The inflammatory theory mechanistically supports the role infections as trigger for cardiovascular events. Importantly, all types of infections and not only respiratory show this causal role, the mechanistic role of infection withers over time, and all types of cardiovascular events (both MI and stroke) are increased. As a corollary, vaccinations should be enforced to reduce this cardiovascular risk and perhaps we should consider infection as a "treatable moment" during which cardiovascular preventive strategies should be implemented.

Disclosures

None.

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