REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Acute Infection and Myocardial Infarction

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Until the early 20th century, the human life expectancy was less than 50 years, and infections were often fatal. Only in the past century have humans, on average, lived long enough for cardiovascular disease to develop regularly and have antimicrobial therapies made survival from infection the norm. Furthermore, sophisticated techniques for assessing myocardial damage have evolved during the past 50 years. It is therefore not surprising that an association between acute infections and myocardial infarction has been appreciated only in the past few decades. We will review the evidence that acute bacterial and viral infections are associated with an increased risk of myocardial infarction in the short, intermediate, and long term, and we will then discuss mechanisms that might explain this association.

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Short-Term Risk of Myocardial Infarction Associated with Acute Infections

Excess mortality from cardiovascular disease during influenza epidemics was first recognized early in the 20th century, but the specific association of influenza and other infections with myocardial infarction was not characterized until decades later.[1] An increase in the short-term risk of myocardial infarction has been described in association with influenza, pneumonia, acute bronchitis, and other chest infections.[2-5] A recent study showed an increase in the risk of myocardial infarction during the week after laboratory-confirmed infection with influenza virus, respiratory syncytial virus, or other respiratory viruses, to a risk that was six, four, and three times higher, respectively, than the risk during the year before or after the onset of infection.[5]

In a retrospective case series[6] and, subsequently, in a prospective study,[7] Musher (one of the authors of this review article) and colleagues found a rate of myocardial infarction of 7 to 8% among patients who were hospitalized for pneumococcal pneumonia. The association between pneumonia and myocardial infarction was confirmed in patients with *Haemophilus influenzae* pneumonia and in those with pneumonia from any cause.[8-12] The risk of myocardial infarction associated with pneumonia peaks at the onset of infection and is proportional to the severity of illness.[9,11,12] A self-controlled case series involving U.S. veterans showed a remarkable increase in the risk of myocardial infarction during the first 15 days after hospitalization for acute bacterial pneumonia, to a risk that was 48 times higher than that in any 15-day period during the year before or after the onset of infection.[8] An increase in the short-term risk of myocardial infarction has also been described in association with urinary tract infection[2] and bacteremia.[13]

LONG-TERM RISK OF MYOCARDIAL INFARCTION AFTER ACUTE INFECTIONS

The association between acute infections and an increased risk of myocardial infarction persists beyond the short-term postinfection period. Among patients with mild respiratory infection or urinary tract infection, the risk of myocardial infarction returns to baseline within a few months after resolution of the infection. Among patients with pneumonia, the risk also decreases with time but still exceeds the baseline risk up to 10 years after the infection (Fig. 1).[12,16] The risk of myocardial infarction after bacteremia or sepsis also declines slowly during the years after the acute infection.[13,16-18] The increase in the risk of myocardial infarction, both in the short term and the long term, is more pronounced when the infection is more severe.[12,18]

POTENTIAL MECHANISMS

The strength and temporal pattern of the association between acute infections and an increased risk of myocardial infarction suggest a causal relationship. Because the association has been shown with a variety of pathogens (viral and bacterial) and sites of infection, and the association is stronger and lasts longer when the infection is more severe, it is likely that the infection and the host response to infection are major determinants in this relationship.

Type 1 myocardial infarction is defined as myocardial ischemia that is caused by acute coronary occlusion related to atherosclerotic-plaque disruption and superimposed thrombosis.[19] Atherosclerotic plaques contain inflammatory cells, and infection elsewhere in the body generates circulating inflammatory cytokines, such as interleukins 1, 6, and 8 and tumor necrosis factor α, that can activate inflammatory cells in atherosclerotic plaques (Fig. 2).[22] Studies in animals[23] and autopsy studies in humans[24] have shown that inflammatory activity in atheromatous plaques increases after an infectious stimulus. Activated intraplaque inflammatory cells up-regulate host response proteins, including metalloproteinases and peptidases, and promote an oxidative burst, all of which contribute to destabilization of the plaques (Fig. 3A).[19]

The prothrombotic, procoagulant state that is associated with acute infection further increases the risk of coronary thrombosis at sites of plaque disruption.[25,26] Factors that contribute to coronary thrombosis include the production of neutrophil extracellular traps from intraplaque and circulating neutrophils, increased platelet activity, increased generation of procoagulants such as tissue factor, impaired fibrinolysis, and overall impaired anticoagulant function of the endothelium.[25,27] Infection with influenza virus and other respiratory viruses is associated with expression of genes that have been linked to platelet activation and a risk of myocardial infarction.[26] Patients with pneumonia that is complicated by myocardial infarction have significantly higher levels of platelet activation and thromboxane synthesis than patients with pneumonia that is not complicated by myocardial infarction.[28] Increased systemic and intraplaque inflammatory activity, hypercoagulability, and platelet and endothelial dysfunction persist beyond clinical resolution of the acute infection.[23,29-31]

Type 2 myocardial infarction occurs when the metabolic demands of myocardial cells exceed the capacity of the blood to supply oxygen to the cells, a phenomenon commonly referred to as

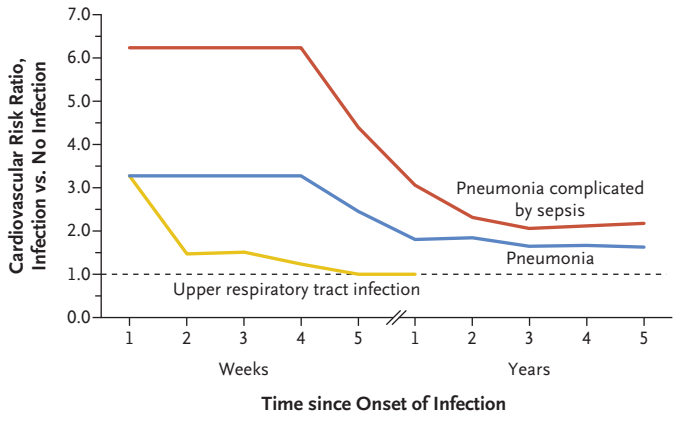

Figure 1. Temporal Pattern of Cardiovascular Risk after the Onset of Acute Infection.

The risk of a cardiovascular event is several times higher after the onset of respiratory infection than in the absence of infection. The risk of a cardiovascular event is proportional to the severity of the infection. The risk returns to baseline over a period of weeks after an upper respiratory tract infection. However, the time required for the risk to return to baseline is prolonged after a severe infection, such as pneumonia. Data are pooled from Smeeth et al.,[2] Kwong et al.,[5] Corrales-Medina et al.,[12] Warren-Gash et al.,[14] and Warren-Gash et al.[15]

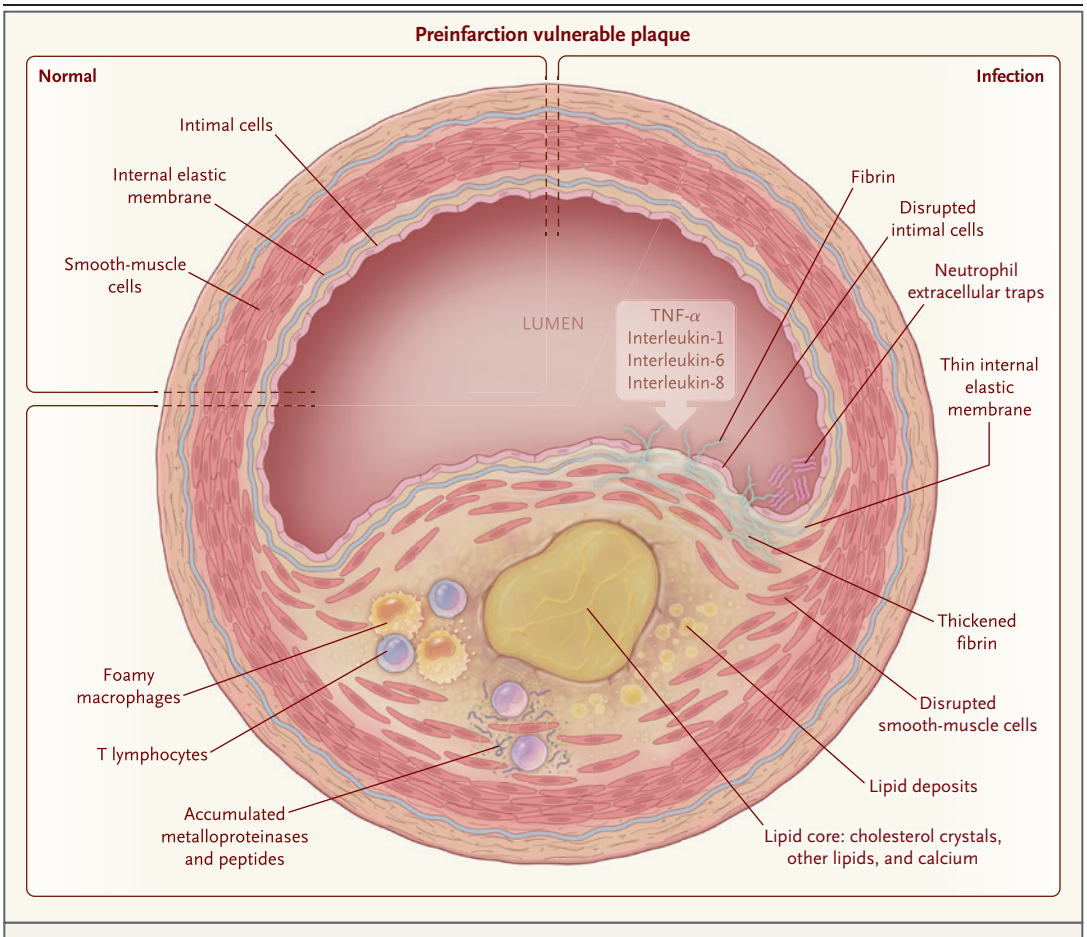

Figure 2. Features Present at the Time of Cardiac Involvement in Acute Infection.

Shown is a vulnerable plaque (thin-cap fibroatheroma) during early infection before the development of myocardial infarction. Lipids have already accumulated in the wall of the coronary artery, with thinning of the internal elastic membrane, disruption of intimal and smooth-muscle cells, and fibrin deposition. Also present are foamy macrophages, T lymphocytes, metalloproteinases, peptidases, and neutrophil extracellular traps. In the lumen are inflammatory cytokines, including tumor necrosis factor α (TNF-α) and interleukins 1, 6, and 8, that result from sepsis elsewhere in the body.[20]

"demand ischemia" (Fig. 3B). Inflammation and fever increase the metabolic needs of peripheral tissues and organs. The resulting increase in heart rate shortens the filling time during diastole, thereby compromising coronary perfusion, which occurs mainly in this part of the cardiac cycle.[32] In older adults, cardiac metabolic mismatch may be increased by coronary stenosis from chronic plaques and possibly by toxin-mediated vasoconstriction.[33] If pneumonia is the inciting infection, blood oxygen levels may fall because of ventilation–perfusion defects, thereby further limiting oxygen supply to the myocardium. Septic shock, if it occurs, has a substantial adverse effect on the coronary blood supply. Most studies of acute infection have not distinguished between type 1 and type 2 myocardial infarction, but demand ischemia should explain only a small proportion of infection-related myocardial infarction events that occur in the short-term postinfection period and none beyond that period.

Studies in animals have suggested a third possible mechanism by which infection might adversely affect cardiac function. Experimentally induced pneumococcal bacteremia has caused cardiac lesions that are characterized by vacuolization and loss of myocytes without accumulation of inflammatory cells; these changes are associated with elevated troponin levels, arrhythmias, and the presence of abnormalities on

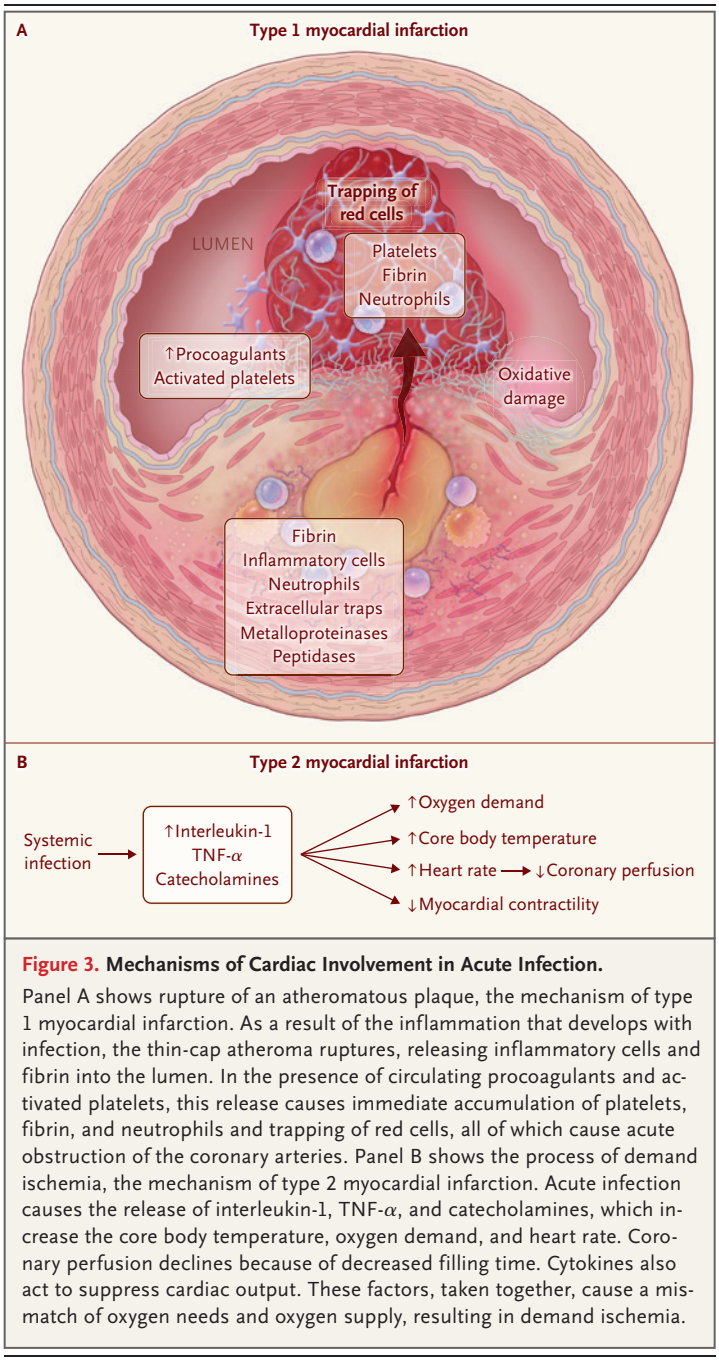

Figure 3. Mechanisms of Cardiac Involvement in Acute Infection.

Panel A shows rupture of an atheromatous plaque, the mechanism of type 1 myocardial infarction. As a result of the inflammation that develops with infection, the thin-cap atheroma ruptures, releasing inflammatory cells and fibrin into the lumen. In the presence of circulating procoagulants and activated platelets, this release causes immediate accumulation of platelets, fibrin, and neutrophils and trapping of red cells, all of which cause acute obstruction of the coronary arteries. Panel B shows the process of demand ischemia, the mechanism of type 2 myocardial infarction. Acute infection causes the release of interleukin-1, TNF-α, and catecholamines, which increase the core body temperature, oxygen demand, and heart rate. Coronary perfusion declines because of decreased filling time. Cytokines also act to suppress cardiac output. These factors, taken together, cause a mismatch of oxygen needs and oxygen supply, resulting in demand ischemia.

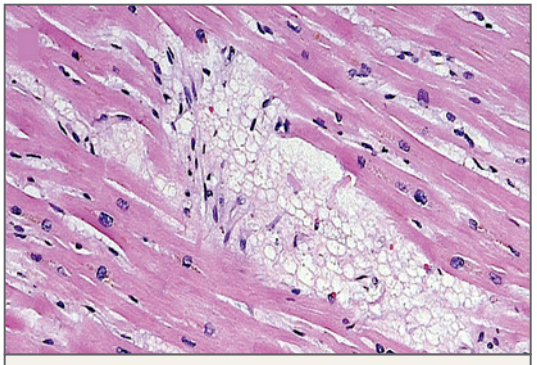

Figure 4. Features Present after Cardiac Involvement in Acute Infection.

Shown is an example of direct myocardial involvement in pneumococcal pneumonia. In the heart of a patient who was treated with antibiotic agents but still died from pneumococcal pneumonia, there are disrupted myocytes and there is a relative absence of neutrophil infiltration.[21] In addition, in experimentally induced infection and without treatment, microcolonies of *Streptococcus pneumoniae* were present.[21]

electrocardiography (Fig. 4).[21] Similar changes were observed at autopsy in two of nine patients who died of pneumococcal pneumonia.[21] In mice infected with influenza virus, cardiac lesions have been characterized by myocardial disruption rather than inflammation,[34] and similar lesions were described at autopsy in some patients who died of influenza.[35] Foci of myocardial injury do not involve coronary arteries, but they can exacerbate myocardial damage in the context of myocardial infarction and may contribute to arrhythmias and to new or worsened heart failure, events that are well documented in patients with pneumonia.[7,9,36,37] Finally, cytokine storm, which has widespread effects including inhibition of oxygen use by mitochondria, contributes to the occurrence of acute heart failure in patients with sepsis, even in young adults who have no cardiac risk factors or abnormalities of the coronary arteries.[38]

VACCINATION

A meta-analysis of five randomized trials showed a 36% lower risk of a composite of cardiovascular events among adults who had received influenza vaccine than among those who had not.[39] The benefit was even greater when the analysis was limited to persons with known coronary artery disease. In contrast, there are limited data from randomized trials regarding the effect of pneumococcal vaccination on cardiovascular risk. A meta-analysis of eight observational studies, all of which were published after 2000, showed a 17% lower risk of myocardial infarction among patients 65 years of age or older who had re-

ceived pneumococcal polysaccharide vaccine than among those who had not.[40] The lack of a more prominent effect may reflect the decline in the prevalence of pneumococcal pneumonia in recent decades.[41]

SUMMARY

Practitioners may be able to influence the risk of postinfection myocardial infarction if they remain mindful of the increased risk of myocardial infarction during and after acute infections and if they do not dismiss elevated troponin levels as "troponin leak." Among patients with acute infection who have clinical indications for statins and aspirin, these medications should be continued (if the patient is already receiving them) or may be initiated if no contraindications are present.

FUTURE DIRECTIONS

Whether statins and drugs that inhibit platelet activation offer a benefit to all patients with acute infection — even those who do not have known clinical indications for these treatments — is an issue worthy of clinical investigation. Observational studies have shown a lower risk of postpneumonia myocardial infarction among patients who were receiving glucocorticoids and drugs that block angiotensin than among patients who were not receiving these drugs.[42,43] A 7 to 8% risk of myocardial infarction among patients who are hospitalized for pneumonia certainly provides support for prospective testing of such agents for the prevention or mitigation of myocardial infarction. Likewise, the use of statins and other antiinflammatory agents, even in the absence of a specific indication, could be examined in patients who are considered to be at high risk by virtue of high Framingham risk scores or the presence of severe infection. The use of such prophylaxis might also be examined in patients who have severe sepsis of any cause.

Finally, because the risk of other cardiovascular events — such as heart failure, arrhythmias, and strokes — also increases after acute infection, the mechanisms that account for these associations need to be characterized. This is especially important in the case of heart failure, because after pneumonia the risk of worsening heart failure is even higher than the risk of myocardial infarction. An integrated understanding of the interplay between acute infections and the cardiovascular system should facilitate efforts to reduce the risk of myocardial infarction and other cardiovascular events after acute infections.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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