The role of infection in cardiovascular disease: more support but many questions remain

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This editorial refers to 'Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34 892 subjects† by M. Majid et al., on page 1205.

The study by Majid et al. is a valuable addition to the evidence supporting a role for infections in cardiovascular disease. Capitalizing on the very high rate of autopsies that are routinely performed in St Petersburg and the availability of high quality data about circulating levels of influenza infection, a clear association between influenza epidemics and increased rates of deaths from coronary heart disease was demonstrated. The association may not, of course, be causal. Ambient cold temperatures are likely to have been closely associated with levels of influenza, and could well have contributed to the effect on coronary death observed, particularly given the setting of northern Russia. However, the study by Majid et al. does provide further support for a role of infection in triggering acute vascular events. A sharp increase in risk of both myocardial infarction and stroke following even relatively minor infections has previously been demonstrated. The mechanism of the effect of infections on acute vascular events is not clear but the increase in risk is seen for both arterial and venous events—deep vein thrombosis and pulmonary embolus. The increased risk is similar for respiratory and urinary tract infections, indicating the effect may be generic and not linked to specific types of infection or affected organ systems. Experimental studies in healthy volunteers have shown that transient inflammation produces a profound but reversible suppression of endothelial function and this would provide a plausible mechanism. The effect may be mediated by a range of inflammatory cytokines, whose circulating levels increase sharply during both infection and sterile inflammation and which are capable of producing endothelial dysfunction. However, factors such as dehydration, stasis, and increased coagulability could also all contribute.

While a causal role for acute infection as a trigger of vascular events is increasingly well established, many areas of uncertainty remain. Further research could help clarify the role more precisely, thus helping us design possible intervention strategies. The study by Majid et al. was an elegant demonstration of the clear insights that can be gained through large-scale epidemiological studies. Some of the remaining uncertainties about the role of infections or inflammation in cardiovascular disease could be usefully addressed through further population-based research. In the work on acute vascular events undertaken to date, the infectious exposure may have included a range of infecting organisms, both viral and bacterial. Numerous uncontrolled case reports have identified varicella-zoster virus infection as a precursor to stroke, but there have been no conclusive large-scale studies to assess this apparent association. The question is an intriguing one, because it provides an opportunity to study a specific viral exposure. The study of other infectious processes may also help in our attempts to understand the part played by infection in vascular disease. For example, low-grade dental infection, particularly periodontitis (a common chronic infection of the tissues surrounding the teeth) is associated with an increased risk of vascular disease. Reducing the burden of infection by treating the periodontal disease may therefore be expected to reduce the risk of vascular disease. Indeed, it has recently been established in a randomized controlled trial that, compared with standard therapy, more intensive therapy for periodontitis (a common chronic infection of the tissues surrounding the teeth) is associated with an increased risk of vascular disease. Reducing the burden of infection by treating the periodontal disease may therefore be expected to reduce the risk of vascular disease. Indeed, it has recently been established in a randomized controlled trial that, compared with standard therapy, more intensive therapy for periodontal disease improved markers of endothelial function at 6 months after treatment. However, factors such as dehydration, stasis, and increased coagulability could also all contribute.

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many features with atherosclerosis and also predicts future vascular risk. There is tantalizing but inconclusive evidence for an aetiological role of maternal infection in pre-eclampsia. Clarifying the role of infection in the risk of pre-eclampsia would be a major step forward in this important disorder for which trials of preventative interventions to date have been disappointing.

One area for which we may already have sufficient information to warrant an intervention trial is the major increase in cardiovascular events that occurs after the iatrogenic inflammatory insult of major surgery. The post-operative period represents a particularly high-risk period for a cardiovascular event, and thus should also represent a time during which prophylactic therapies, such as aspirin or statins, may have a disproportionately large absolute effect. However, the usual practice is to stop such therapies for the peri-operative period. A large simple randomized trial is needed to assess the risks and benefits of interventions such as statins in the peri-operative period. If the expected beneficial effect of statins in the peri-operative period were to be demonstrated in a large randomized trial, this would have major implications for patient management worldwide. Such a trial would also introduce a new paradigm for cardiovascular risk management based on identifying specific periods of enhanced risk. It would have practical benefit in terms of informing practice.

While the evidence supporting a role for acute infections in triggering vascular events is strong, in humans the evidence relating to chronic infections and cardiovascular disease is less compelling. Following the initial wave of studies reporting associations between serological markers of specific chronic infections and cardiovascular disease, recent large-scale work has been less consistent. However, the emerging evidence suggesting a generic role for infection rather than a key role for specific infections may lead to a re-appraisal of the part played by chronic infection in atherosclerosis. Moreover, the evidence of a higher than expected rate of vascular events in patients with long-term chronic inflammation, in the absence of infection, such as that seen in autoimmune disorders like rheumatoid arthritis accounts for the ongoing interest in inflammation as a novel risk factor for vascular disease. That said, there is also increasing doubt about the causal nature of the observed association between cardiovascular disease and downstream inflammatory biomarkers such as C-reactive protein and fibrinogen. The associations between circulating inflammatory biomarkers and disease risk may be due to reverse causality (because early disease affects inflammatory markers) or to residual confounding. Because of the randomization of alleles that occur at conception according to Mendel’s 2nd law, genetic variation might allow unbiased insight into the link between infectious exposures, the inflammatory response or specific inflammatory biomarkers, and vascular disease. For example, a common polymorphism in the C-reactive protein gene associated with higher C-reactive protein concentrations showed a less extreme risk of coronary heart disease than observational studies alone would have indicated, suggesting that the association between C-reactive protein and coronary disease in observational studies is likely to have been affected by reverse causation or confounding. Genetic variants in the innate immune response, such as the toll like receptor 4 gene, modify the risk of infection and the inflammatory response. There is emerging evidence that such variants may also affect susceptibility to cardiovascular disease. Exploring the role of this and other variants in the immune response provides an exciting research avenue well worth further exploration.

A growing body of evidence suggests inflammation plays an important role in the initiation and progression of atherosclerosis. Translating this evidence into strategies to prevent and treat disease requires a more precise understanding of the effect of inflammatory stimuli on hard disease endpoints in real world settings. The failure of antibiotics to prevent vascular events in recent clinical trials illustrates the need for further research in this area. In the meanwhile, while measures such as preventing influenza infections among high-risk populations through vaccination can be recommended, a role for more specific measures targeted at infection or inflammation to try and prevent vascular events is not yet supported by robust evidence.

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References