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EDITORIAL COMMENTARY

Inflammation: The classic double-edged sword

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See related article on pages 859-66.

Inflammation (from the Latin *inflammare*—*in-*, meaning *into*, plus *flamma*, meaning *flame*) is a complex protective response that is designed to respond to invading pathogens, to eliminate the initial cause of cellular injury, to remove necrotic tissues, and to initiate a process of repair. The role of the inflammatory response in the pathogenesis of coronary artery disease has become increasingly well recognized and defined (Figure 1).¹ Inflammation has not only been implicated in the potential pleomorphic benefits of statins but has been offered as an explanation for the association of cardiovascular disease with periodontal disease,² as well as for the reduced incidence of cardiac events after the receipt of influenza vaccine.³ The inflammatory process can be both pathogenic and protective. It is therefore highly appropriate to examine the potential interaction between inflammatory disease and cardiovascular disease. Such analyses may shed new light on pathogenesis while illuminating risks, alternatives, and novel therapeutic targets in treatment. It is in this arena that Lai and colleagues⁴ report their findings of coronary artery bypass grafting (CABG) in patients with inflammatory rheumatic diseases in this issue of the *Journal*. The source of data had several notable advantages: the National Health

Insurance Research Database of Taiwan essentially includes all the medical interactions in an entire population across time. Although the database is administrative in nature, the specific diagnoses of interest actually undergo particular scrutiny and validation because they are tied to governmental benefits. It would seem that a decade of data from such a compelling source, which includes more than 40,000 patients undergoing CABG, should certainly yield robust information regarding the diagnoses in question. Unfortunately, the actual numbers were quite small—101 patients with rheumatoid arthritis (RA), 56 with systemic lupus erythematosus (SLE), and 73 with ankylosing spondylitis. Because of the distinct natures of these syndromes, Lai and colleagues⁴ were wise to avoid the potential additional confusion of lumping them together to increase their numbers.

The prevalence of RA is estimated to be 0.5% to 1.0% of the general population, affecting women approximately twice as often as men.⁵ Given that 40% of deaths among patients with RA are from cardiovascular disease and that their risk of mortality is approximately double that of an age-matched population, it is somewhat surprising that there were not more patients with this syndrome in this sample who were submitted to CABG.⁶ Although mortality is more closely related to congestive heart failure, RA patients carry a 2-fold independent risk of myocardial infarction and stroke, a risk that rises to 3-fold with a disease duration exceeding 10 years.⁷ This apparent discrepancy may well reflect not only differing patterns of disease prevalence but also selection criteria among various therapeutic options. Obviously, without information regarding the patients with RA and coronary artery disease who did not undergo CABG, no inference can be drawn regarding the relative benefits of CABG in this population.

SLE, on the other hand, is a disease known to have wide variation depending on sex, ethnic, and cultural factors.

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FIGURE 1. Pathogenesis of atherosclerosis in inflammatory rheumatic diseases. Traditional risk factors play an important role in premature atherosclerosis and are typically more prevalent in patients with inflammatory rheumatic diseases. Both shared and disease-specific pathogenic mechanisms also contribute to accelerated atherogenesis, with rheumatoid arthritis, systemic lupus erythematosus, and the vasculitides shown as examples. *Ab*, Antibody; *ANCA*, antineutrophil cytoplasmic antibody; *dsDNA*, double-stranded DNA; *CCP*, cyclic citrullinated peptide; *EC*, endothelial cells; *IFN*, interferon; *Fc γ R*, Fc gamma receptor; *HOCl*, hypochlorite; *MPO*, myeloperoxidase; *ROS*, reactive oxygen species; *T reg*, regulatory T lymphocytes. Reprinted from Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions *Eur Heart J*. November 28, 2014 [Epub ahead of print]. Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2014. For permissions please E-mail: journals.permissions@oup.com.

Prevalence is reported to range from 20/100,000 to 50/100,000 population⁸⁻¹⁰ (roughly consistent with prevalence in this study of patients undergoing CABG). More common in urban than rural areas,⁹ SLE is more prevalent among African Americans⁹ but is rare among blacks in Africa.¹¹ The potential for the interaction of ethnicity, genetics, and environmental influences cannot be underestimated in the potential response to such end-stage interventions as CABG. SLE is an independent predictor of cardiovascular disease,¹² and the increased mortality after CABG surgery in this study, despite a significantly younger cohort, is worthy of note. The role of associated factors in these patients, however, such as clinically manifest renal disease and perhaps less clinically apparent vascular disease, likely cannot be adequately controlled for in this study.

The frequency of ankylosing spondylitis is estimated to be 0.5%, with cardiac manifestations in 2% to 10% of patients, mostly consisting of aortic, valvular, conduction, and cardiomyopathic disease.¹³ We are therefore not surprised to find a relatively small younger, highly male cohort of patients with a high incidence of associated valvular disease. The absence of demonstrable independent risk of mortality, despite the associated restrictive lung

disease and impaired mobility in these patients, may well be due to the limitations of sample size.

Absent from the data are markers of the stage and longevity of disease, the role of medications (both for the coronary artery disease and for the inflammatory rheumatic diseases), or the specifics of the patient and graft selection. Certain conclusions do, however seem warranted. First, CABG surgery can be accomplished in these patients with reasonable, albeit potentially higher, operative risk. Second, because of their relatively low prevalence yet high morbidity, these diseases are unlikely to yield significant results in prospective, randomized trials and therefore clearly warrant further study in large, comprehensive databases. The specific role that inflammation plays in outcomes remains to be determined.

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