Aortic stenosis (AS) is the most common valvular heart disease in the elderly, affecting 2–4% of adults older than 65 years. The number of aortic valve replacements performed over the past decade has doubled, and the prevalence of AS is likely to double again in the next 20 years with an increasing elderly population. With recent advances in new therapeutic devices, such as transcatheter valve implantation, cardiologists have paid more attention to AS. This technique has given hope to patients who were unable to benefit from surgical treatment because of their high surgical risk, especially elderly patients. Broadening the indication for interventional treatment to elderly patients has focused on the effect of multiple comorbid conditions on progression of AS. However, its underlying etiology is still poorly understood.

Valvular calcific degeneration has been thought to be age-associated, but recent evidence suggests that it is rather the result of an active inflammatory process (Figure). Injury of the endothelium of the aortic valve from mechanical stress is the initial process, which is in many ways similar to that of atherosclerosis. Such injury may allow lipids to penetrate the

Figure. Pathologic pathways to valvular calcification in aortic stenosis. IL, interleukin; LDL, low-density lipoprotein; TGF, transforming growth factor; TNF, tumor necrosis factor.
endothelium and accumulate in areas of inflammation and undergo oxidative modification.\textsuperscript{4} Oxidized lipoproteins stimulate inflammatory activity and subsequent mineralization. The endothelial damage and subsequent lipid deposition trigger inflammation within the valve. Recent evidence suggests that inflammation contributes to the development and progression of atherosclerosis.\textsuperscript{5} The question arises whether these focal inflammatory processes in a valvular lesion are stimulated by systemic inflammation.

\textbf{Article p 867}

In this issue of the Journal, Mizuno et al\textsuperscript{6} evaluate the change in severity of AS after major noncardiac surgery. They retrospectively enrolled 218 patients with nonrheumatic AS who underwent echocardiography at least twice, 6 months apart. They divided the patients into 2 groups: those who underwent major noncardiac surgery and those who did not. They demonstrated that the progression of severity of AS was more rapid in the major noncardiac surgery group than in the control group.

The underlying mechanism of the rapid progression of severity of AS following major noncardiac surgery is unknown, as stated by the current authors. A number of studies have demonstrated that C-reactive protein (CRP), a sensitive marker of systemic inflammation, is associated with an increased risk of cardiovascular events.\textsuperscript{7} There have also been reports of a positive association between CRP and aortic valve calcification in both symptomatic\textsuperscript{8} and advanced\textsuperscript{9} AS patients. On the other hand, a recent study by Novaro et al followed 3,917 subjects in a population-based observational study and found that baseline CRP was not associated with progression of AS.\textsuperscript{10} However, their report did not investigate the effect of major inflammatory events during the follow-up time course. Moreover, CRP was localized in valve tissue of both calcific stenotic aortic valves and degenerative aortic-valve bioprostheses,\textsuperscript{11} with a positive correlation between serum CRP level and valvular CRP expression. In another experimental animal model, preexisting atherosclerosis was aggravated by acute myocardial infarction, representing a major systemic inflammatory condition that stimulates the atherosclerotic process at a distance.\textsuperscript{12} It was related to abundant monocyte recruitment by increased supply of hematopoietic stem and progenitor cells from bone marrow via activation of sympathetic activity. These reports support the hypothesis that systemic inflammation accelerates the progression of AS.

Is it possible to prevent the progression of AS severity in patients undergoing major noncardiac surgery? Atherosclerosis and AS share many common risk factors, associated with endothelial damage, lipid deposition, angioneogenesis, and inflammation. Statin therapy has proved effective for preventing the progression of coronary and carotid atherosclerosis.\textsuperscript{13} with the expectation that statin therapy will reduce the progression of AS. However, recent major prospective randomized controlled trials failed to demonstrate any effect on disease progression or clinical outcomes of AS.\textsuperscript{14,15} It is a matter of speculation, but there may be effective medical therapies for AS patients before major noncardiac surgery that will prevent AS progression.

In view of the limitations of medical therapy for AS progression, predicting the rate of progression of AS has become clinically important for cardiologists when determining the timing of any interventions. Although Mizuno et al’s work is a retrospective study and further study is required, we should be aware that major noncardiac surgery might exacerbate AS progression, and patients should be carefully followed up with echocardiography after surgery.

\textbf{References}