Human Aortic Valve Calcification

To the Editor:

Rajamannan et al.1 addressed the problem of bone formation in calcified aortic valves, quoting the publication of actual bone formation by Mohler et al.2 Mohler et al had indicated that ossification in calcified aortic valves was relatively common, finding evidence of valve ossification in 36 of 323 patients.

Of historical interest, I reported ossification in the left ventricular wall of a patient who had died 3 years after a myocardial infarction.3 I could find no other example of human “myocarditis ossificans” in a literature search. In 1967, however, Selye et al4 reported on a rat model in which bone in the ventricular myocardium was produced. Were this a frequent occurrence, one would expect to find more reports of it in the literature. The fact that Selye et al4 could not produce myocarditis ossificans consistently before the 1967 method suggests that some unknown factor or factors must trigger bone formation in the aortic valve and ventricular wall aside from osteoblast phenotype (with its increased mRNA levels of osteopontin), bone sialoprotein, osteocalcin, and the osteoblast-specific transcription factor Cbfa1, as described by Rajamannan et al.1

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Response

Dr. Charles Grossman’s insightful letter addressing the study of ossification in the heart highlights an important aspect of our hypothesis. Our study was designed to determine whether there is evidence of bone formation in calcifying aortic valves.3 Our study further evaluated whether specific osteoblast markers critical in osteoblastogenesis, such as bone sialoprotein, osteopontin, osteocalcin and the osteoblast-specific transcription factor Cbfa1, are also present in the calcified aortic valve. Grossman2 and Selye et al3 have evaluated ossification in myocarditis ossificans and in an experimental model of ventricular banding. These studies do demonstrate other etiologies that may predispose to development of bone formation within the cardiovascular tissues. We have further addressed the issue of cardiac osteoblastogenesis in a study of hypercholesterolemia-induced cellular proliferation and bone matrix production in the rabbit aortic valve.4 We demonstrated that the osteoblast markers (Cbfa1, osteopontin, and alkaline phosphatase) are present in normal rabbit aortic valves and that Cbfa1 and osteopontin are upregulated in the presence of hypercholesterolemia. We also demonstrated by mRNA analysis that atorvastatin treatment decreased these bone markers. The evidence that cholesterol may have a role in the development of valvular heart disease is supported by the findings of Stewart et al5 that risk factors for atherosclerosis, including smoking, hypertension, male gender, and hyperlipidemia, are also risk factors for the development of aortic valve calcification. These epidemiologic data, combined with the findings in our experimental model4 and the data from our human aortic valve osteoblastogenesis study,1 provide a foundation for future studies of cardiac ossification. Models such as those of Grossman2 and Selye et al3 and our model provide links to the mechanisms of cardiac calcification, which for years was thought to be a degenerative process but now is evolving to be an active biological process within cardiac tissue.

Thank you for your consideration.

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