Hunting to Prevent Aortic Stenosis

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“A better to hunt in fields, for health unbought, Than fee the doctor for a nauseous draught, The wise, for cure, on exercise depend; God never made his work for man to mend.”

—John Dryden (1631–1700)

The advantages of exercise training in patients with atherosclerotic coronary artery disease are numerous and include the modification of traditional risk factors, improvement in myocardial and peripheral perfusion, enhancement of exercise tolerance, and reduction of cardiovascular morbidity and mortality.1 These salutary effects are thought to result from improvements in endothelial function and vascular inflammation. Although the precise mechanisms are not entirely clear, augmentation of nitric oxide bioavailability (by increasing expression and activity of endothelial nitric oxide synthase and reducing nitric oxide degradation), reduction of endothelial adhesiveness (by reducing expression of cellular adhesion molecules), enhancement of endothelial regenerative capacity (by stimulating endothelial progenitor cells), and reduction of vascular inflammation (by reducing proinflammatory cytokines and oxidative stress and increasing anti-inflammatory cytokines) by exercise-induced increases in blood flow and shear stress are responsible in large part for the beneficial effects of exercise on the pathogenesis and progression of atherosclerosis.1

Aortic stenosis, once considered an age-related degenerative disease, shares clinical risk factors and cellular and molecular pathways in its etiopathogenesis and progression with atherosclerosis. Thus, aortic stenosis and atherosclerosis share the risk factors of age, male sex, smoking, hypertension, diabetes, obesity, and hypercholesterolemia, and both are associated with an increased likelihood of clinical atherosclerotic events.2 Pathophysiological similarities include endothelial disruption, macrophage and lipoprotein accumulation, cytokine activation, and calcification; indeed, lesions in human stenotic aortic valves resemble histologically those in atherosclerotic plaques,3 and atherosclerotic-like lesions in the aortic valves that produce “stenosis” and increased valvular oxidative stress are noted in several animal models of atherosclerosis.1–6

Aortic stenosis is the most common valvular heart disease and the leading indication for valve replacement surgery in the United States. Despite this heavy burden of disease, medical therapy of aortic stenosis,2 primarily statins and, to a lesser extent, angiotensin-converting enzyme inhibitors, has been disappointing. Although retrospective studies of statin therapy were encouraging, randomized controlled trials have failed to support the hypothesis that lipid lowering would slow or halt the progression of aortic stenosis.7–8 Retrospective trials based on the observation that angiotensin-converting enzyme activity is increased in stenotic aortic valves have been conflicting,9,10 and prospective trials of angiotensin-converting enzyme pathway inhibition therapy on aortic stenosis progression have not materialized. Although failure of these therapies is most often ascribed to the severity of valvular disease at the time treatment is initiated, fundamental differences between atherosclerotic and aortic stenotic lesions may be culpable. For example, upregulation of the calcification signaling pathways, bone morphogenetic protein, Wnt3/β-catenin, and Runx2/Cba 1 (mediated by the bone matrix proteins osteopontin and osteocalcin) are prominent in aortic stenosis, and osteoclastic activity is greater in aortic stenosis than in atherosclerotic plaque.11 In addition, the clinical sequelae of the 2 lesions (ie, myocardial infarction due to plaque rupture in atherosclerosis and left ventricular outflow obstruction due to stiff leaflets in aortic stenosis) are pathophysiologically distinct. Thus, differences in the relative content of the lesions (ie, lipid-laden, fibrotic, and calcific lesions) may result in variable responses to interventions that are targeted to specific pathological processes. In this regard, normalization of cholesterol levels in a transgenic mouse model of aortic stenosis reversed osteogenic activity and valvular calcification but had no effect on valvular fibrosis.6 Another related but distinct factor to be considered is the timing of therapy relative to the prevailing histopathologic stage of aortic valve disease (ie, inflammation, matrix metalloproteinase–dependent matrix remodeling, myofibroblast transdifferentiation, angiogenesis, osteoblastic/osteoclastic activity, and calcium deposition). Finally, in the case of statins, pleiotropic effects may antagonize their lipid-lowering effect; for example, statins were shown to increase profibrotic signal transduction activating extracellular-regulated kinases (ERK 1/2) in human stenotic aortic valves.12

In view of the difficulties encountered with medical treatment of aortic stenosis, the similarities between atherosclerosis and aortic stenosis, and the favorable impact of exercise on atherosclerosis, it is reasonable to hypothesize that exercise training may have a salutary effect on the development and progression of aortic stenosis. In this issue of Circulation, Matsumoto and coworkers13 tested the effect of regular treadmill exercise (5 days per week for 16 weeks, 60 min/d,
15 m/min) on the increased aortic valve thickness, disrupted valvular endothelial integrity, enhanced inflammation and oxidative stress, osteoblastic phenotypic conversion, and mineralization that develop in a mutant mouse model of atherosclerosis fed a high-cholesterol diet. The model used in this study was the LDL-receptor–deficient mouse, which develops hypercholesterolemia, atherosclerosis, and aortic valve pathology in an age- and diet-dependent manner. The authors found that regular but not occasional exercise completely abrogated the abnormal responses to the high-fat diet and increased valvular and circulating levels of the inhibitors of calcification, osteoprotegerin and fetuin-A, respectively. Interestingly, serum cholesterol remained elevated, which indicates dissociation between lipid levels and aortic valve pathology. The latter finding is at odds with results from a different genetic mouse model of aortic valve disease, in which a rapid normalization of lipid levels normalized aortic valve superoxide, myofibroblast activation, and proosteogenic signaling and halted the progression of aortic valve disease. This suggests that exercise operates through lipid-independent mechanisms that may complement dietary manipulation and highlights the complexity of the disease process and the diverse signaling pathways affected. This is not altogether unexpected, because it was reported that exercise prevented and partially reversed pathology and not altogether unexpected, because it was reported that exercise prevented and partially reversed pathology and molecular changes in a mouse model of hypertrophic cardiomyopathy. The maintenance of endothelial integrity with exercise is another intriguing finding insofar as regulation of aortic valve mechanics by interactions between the valvular endothelium and valve interstitial cells is an area of emerging interest. The effect of exercise on the inhibitors of calcification is also noteworthy and consonant with a preliminary study that found a significant relation between maximal O2 consumption and fetuin-A levels and a negative correlation with coronary artery calcification in men.

Although Matsumoto and colleagues convincingly demonstrate that exercise training can prevent the increased valve thickening and the molecular and cellular changes that characterize aortic stenosis in a specific gene-targeted mouse model of hypercholesterolemia, the important shortcomings of a preclinical study in a small-animal model should be kept in mind. Species, model, and disease-stage dependency limit the ability to translate these results directly to aortic stenosis in humans. Although the molecular and cellular changes were similar to those seen in stenotic human aortic valves, the valve disease that developed in this study was early and mild, without a measurable valvular gradient. Whether regular exercise would effectively retard, halt, or reverse the progression of established aortic valve disease is unclear because both fat feeding and exercise began at 4 weeks of age. Indeed, whether the influence of exercise in humans with any degree of aortic stenosis and relatively normal cholesterol levels (even the mild disease seen in this study) would be similar to that seen in hypercholesterolemic mice with valvular stenosis of comparable severity is unresolved. Moreover, how the type (imposed versus voluntary), duration (acute versus chronic), and intensity of exercise used in this study can be translated to humans is unanswered. Finally, although the difficulties of extrapolating from mouse to human are well understood, mouse strain effects may be relevant and unappreciated. The CS7/BL6 background used in this study is relatively calcification resistant, which may have worked to the advantage of the investigators but may not reflect reality in humans with high calcium-phosphate products.

Despite these limitations, there is a critical need for animal models of aortic stenosis. Prospective randomized trials of aortic stenosis are constrained by the long natural history of the disease, limited follow-up intervals, insensitive methodology, coexisting atherosclerotic burden, a high prevalence of coronary disease, and comorbidities and medications that preclude detailed analysis of the relative contribution of various activating and inhibiting stimuli. Can the provocative data from this study be tested in a clinical trial? This will require the identification of individuals with early disease and/or those at risk for disease, coupled with sensitive methodology to detect stage-specific aortic valve pathology. Multimodality optical and magnetic resonance molecular imaging with probes to detect endothelial and macrophage activation and proteolytic and osteoblastic activity have shown promise in preclinical studies. Adaptation of these methods to a high-risk population identified by epidemiological and genetic means offers hope for the future. In the meantime, it is prudent to take the advice of the American College of Sports Medicine and the American Heart Association, which recommend “moderate-intensity aerobic physical activity for a minimum of 30 minutes on five days each week or vigorous intensity aerobic activity for a minimum of 20 minutes on three days each week,” or the counsel of a seventeenth century English poet.

Disclosures

None.

References


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