EDITORIAL COMMENT

Is Ventricular Arrhythmia a Possible Mediator of the Association Between Aortic Stenosis-Related Midwall Fibrosis and Mortality?*

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In 1954, Mitchell et al. (1) reported on 40 years of experience with clinical features of 533 cases of aortic stenosis managed at the Peter Bent Brigham Hospital of Boston, Massachusetts. This patient series spanned the development of mercurial diuretics, surgical cure for aortic stenosis, and penicillin, advances that have transformed the epidemiology and prognosis of aortic stenosis. Several remarkable observations of this study remain central to the findings reported in this issue of the *Journal*. Mitchell et al. (1) noted significantly shorter expected survival after the onset of symptoms. The average lifespan was 4 years after the onset of angina, 3.5 years after the onset of congestive heart failure, and 3 years after syncope. Among patients with witnessed deaths, 35% died of congestive failure, 20.1% of subacute bacterial endocarditis, 2.3% of myocardial infarction, and 18.7% of sudden death; the remaining causes of death were noncardiac. Sudden death tended to occur in the later stages of disease and was associated with history of angina. However, autopsy examinations revealed that sudden death frequently occurred in the absence of

significant coronary disease. Examination of the coronary arteries in patients with aortic stenosis and angina revealed coronary atherosclerosis in some cases. However, in patients younger than 50 years, 28% had normal coronary arteries and 56% had only up to moderate atherosclerosis. Even among those older than 50 years, 22% had normal coronary arteries and 32% had only up to moderate atherosclerosis.

Examination of the myocardium of patients with angina revealed that no one younger than 50 years, and only 19% of those older than 50 years, had prior myocardial infarction. When comparing aortic stenosis patients with and without angina, there was no significant difference in the degree of aortic stenosis, but the average cardiac weight was significantly higher in those with angina. The observations of Mitchell et al. (1) thus suggested that in aortic stenosis: 1) sudden death was associated with history of angina; and 2) angina was associated with left ventricular hypertrophy.

Since the publication of the observations by Mitchell et al. (1), significant advances have been made in medical therapy for congestive heart failure, prophylaxis of bacterial endocarditis, and treatment of associated coronary occlusions. Despite these medical advances, for a patient with aortic stenosis, the advent of symptoms today heralds as adverse a prognosis as that in 1954, unless the patient undergoes surgery (2). Sudden death remains a major contributor to mortality and occurs in up to 5% of patients with asymptomatic, and 35% of patients with symptomatic aortic stenosis (3–8). Multiple mechanisms have been implicated to explain sudden death in the setting of aortic stenosis. These mechanisms include myocardial ischemia and elevated levels of catecholamines leading to ventricular tachyarrhythmia, and/or an abnormal Bezold-Jarisch reflex resulting in hypotension or bradyarrhythmias (8–10). The risk of cardiac death is mitigated with valve replacement, consistent with the idea that bradyarrhythmias or tachyarrhythmias, without a fixed substrate and secondary to primary valvular pathology, are responsible for a significant proportion of sudden deaths in the setting of aortic stenosis. However, even after corrective surgery, patients exhibit an elevated risk of sudden death (11). In fact, sudden death is reportedly the most frequent mode of death after aortic valve surgery and seems to be associated with greater left ventricular hypertrophy (12). Some of these sudden deaths are likely due to causes other than arrhythmia, such as embolism or valvular dehiscence. However, Blackstone and Kirklin (13) found normal prosthetic valve and periprosthetic myocardium in 8 of 15 autopsies conducted in subjects with sudden death after valve replacement. It seems, therefore, that even after corrective surgery for aortic stenosis, some patients remain predisposed to sudden death.

In this issue of the *Journal*, Dweck et al. (14) report their findings on cardiac magnetic resonance imaging examinations of 143 patients with moderate (40% of patients, 1.0 to 1.5 cm^2) or severe (60% of patients, <1.0 cm^2) aortic stenosis. Before enrollment, all patients underwent evaluation for ischemia, and 57% were found to have concomitant coronary artery disease. Using the late gadolinium enhancement technique, the investigators found evidence for myocardial fibrosis in 66% of patients with aortic stenosis. It is possible that techniques with greater sensitivity for detection of diffuse myocardial fibrosis, such as T1 mapping (15), may modify these results. However, the investigators have

reliably described the extent of macroscopic fibrosis using validated methods (16–18). Overall, patients with evidence of macroscopic fibrosis were older and more likely to be male. A fibrotic pattern consistent with prior myocardial infarction was seen in 28% of patients, whereas a pattern of midwall fibrosis was seen in 38% of patients. Those patients with evidence of myocardial infarction had more severe coronary artery disease on angiography and lower ejection fractions than those with midwall fibrosis or no evidence of fibrosis. Patients with midwall fibrosis had higher left ventricular mass and lower ejection fraction compared with those with no fibrosis.

During a mean follow-up of 2 years after imaging, 72 patients underwent aortic valve replacement and 27 died. On univariate analysis, patients with midwall fibrosis had 8-fold higher risk of all-cause mortality, and those with myocardial infarction had 6-fold higher risk of all-cause mortality compared with those without fibrosis. It is worth noting that midwall fibrosis remained predictive of mortality even after adjustment for left ventricular function. As noted by the investigators, this finding suggests that midwall fibrosis is associated with mortality through mechanisms other than pump failure. Only 3 of 27 deaths were sudden (11%), precluding statistical assessments of any association with fibrotic patterns. However, all 3 sudden deaths occurred in patients with midwall fibrosis. Despite lowering the overall risk for mortality, aortic valve replacement did not completely remove the adverse prognosis associated with midwall fibrosis. Even after aortic valve replacement, those with midwall fibrosis had higher mortality than patients without fibrosis (14).

Due to limited information about the immediate cause of death and paucity of events, the present study cannot assess the mechanism by which midwall fibrosis is associated with increased mortality. Ventricular arrhythmia, a possible mediator of this association, has been documented as a cause of sudden death before (9) and after aortic valve surgery (19). Narasimhan et al. (20) studied 9 patients who presented with ventricular tachycardia after valve replacement for aortic stenosis. Of these 9 patients, 2 had bundle branch re-entry, 5 had myocardial fibrosis–related ventricular tachycardia, and 2 had both myocardial fibrosis–related and bundle branch re-entrant ventricular tachycardia. It is notable that 3 of those with myocardial fibrosis–related ventricular tachycardia had no associated coronary artery disease. A more recent report by Eckart et al. (21), which excluded patients with coronary artery disease, also found that ventricular tachycardia after valve surgery is most often due to re-entry around myocardial fibrosis. As noted by Marchlinski (22) in an editorial that followed the latter study, the perivalvular distribution of fibrosis in patients after valve surgery mimics the location of fibrosis in a variety of other nonischemic cardiomyopathies. The study by Dweck et al. (14) expands on prior findings and shares this theme. The midwall fibrosis pattern visualized in 38% of participants mimics the pattern seen in approximately one-third of patients with nonischemic cardiomyopathy (17). The "scattered streaky fibrosis" in excess of that expected from coronary disease has been previously noted on autopsy studies of patients with aortic stenosis (23). In his observations at autopsy of 7 cases with aortic stenosis in 1957, Wigle (24) noted that "the various types of macroscopic fibrosis were greatest in the mid-portion of the left ventricular wall," and predominantly affected the posterobasal region of the left ventricle. Midwall fibrosis of the basal left ventricle seems to be a common fibrotic pattern among patients with aortic stenosis and those with nonischemic cardiomyopathy. In nonischemic cardiomyopathy, midwall fibrosis is associated with ventricular arrhythmia and adverse outcomes (25,26). The etiology of midwall fibrosis is not yet known. As Dweck et al. (14) suggest, the association of midwall fibrosis with left ventricular hypertrophy points to ischemia and/or mechanical stress, as possible etiologies for apoptosis and scar formation. Conversely, midwall fibrosis has been observed in nonischemic cardiomyopathies without prior evidence of left ventricular hypertrophy. Further investigation regarding the etiology and mechanical and electrophysiological effects of midwall fibrosis, and the factors that mediate its association with mortality, may lead to improved management strategies in aortic stenosis and other nonischemic causes of myopathy.

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REFERENCES

1. Mitchell AM, Sackett CH, Hunzicker WJ, Levine SA. The clinical features of aortic stenosis. Am Heart J 1954;48:684–720.
2. Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation 1997;95:2262–70.
3. Ross J Jr., Braunwald E. Aortic stenosis. Circulation 1968;38:61–7.
4. Matthews AW, Barritt DW, Keen GE, Belsey RH. Preoperative mortality in aortic stenosis. Br Heart J 1974;36:101–3.
5. Chizner MA, Pearle DL, deLeon AC Jr. The natural history of aortic stenosis in adults. Am Heart J 1980;99:419–24.
6. Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. Am J Cardiol 1988;61:123–30.
7. Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. J Am Coll Cardiol 1990;15:1012–7.
8. Sorgato A, Faggiano P, Aurigemma GP, Rusconi C, Gaasch WH. Ventricular arrhythmias in adult aortic stenosis: prevalence, mechanisms, and clinical relevance. Chest 1998;113:482–91.
9. von Olshausen K, Witt T, Schmidt G, Meyer J. Ventricular tachycardia as a cause of sudden death in patients with aortic valve disease. Am J Cardiol 1987;59:1214–5.
10. Janse MJ. Possible mechanisms of arrhythmias in valvular heart disease. Acta Cardiol 1992;47:93–8.
11. Bloomfield P, Wheatley DJ, Prescott RJ, Miller HC. Twelve-year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. N Engl J Med 1991;324:573–9.
12. Foppl M, Hoffmann A, Amann FW, et al. Sudden cardiac death after aortic valve surgery: incidence and concomitant factors. Clin Cardiol 1989;12:202–7.

13. Blackstone EH, Kirklin JW. Death and other time-related events after valve replacement. Circulation 1985;72:753–67.
14. Dweck MR, Joshi S, Murigu T, et al. Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis. J Am Coll Cardiol 2011;58:1271–9.
15. Iles L, Pfluger H, Phrommintikul A, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. J Am Coll Cardiol 2008;52:1574–80.
16. Simonetti OP, Kim RJ, Fieno DS, et al. An improved MR imaging technique for the visualization of myocardial infarction. Radiology 2001;218:215–23.
17. McCrohon JA, Moon JC, Prasad SK, et al. Differentiation of heart failure related to dilated cardiomyopathy and coronary artery disease using gadolinium-enhanced cardiovascular magnetic resonance. Circulation 2003;108:54–9.
18. Debl K, Djavidani B, Buchner S, et al. Delayed hyperenhancement in magnetic resonance imaging of left ventricular hypertrophy caused by aortic stenosis and hypertrophic cardiomyopathy: visualisation of focal fibrosis. Heart 2006;92:1447–51.
19. Wolfe RR, Driscoll DJ, Gersony WM, et al. Arrhythmias in patients with valvar aortic stenosis, valvar pulmonary stenosis, and ventricular septal defect. Results of 24-hour ECG monitoring. Circulation 1993;87:I89–101.
20. Narasimhan C, Jazayeri MR, Sra J, et al. Ventricular tachycardia in valvular heart disease: facilitation of sustained bundle-branch reentry by valve surgery. Circulation 1997;96:4307–13.
21. Eckart RE, Hruczkowski TW, Tedrow UB, Koplan BA, Epstein LM, Stevenson WG. Sustained ventricular tachycardia associated with corrective valve surgery. Circulation 2007;116:2005–11.
22. Marchlinski FE. Perivalvular fibrosis and monomorphic ventricular tachycardia: toward a unifying hypothesis in nonischemic cardiomyopathy. Circulation 2007;116:1998–2001.
23. Lund O, Larsen KE. Cardiac pathology after isolated valve replacement for aortic stenosis in relation to preoperative patient status. Early and late autopsy findings. Scand J Thorac Cardiovasc Surg 1989;23:263–70.
24. Wigle ED. Myocardial fibrosis and calcareous emboli in valvular heart disease. Br Heart J 1957;19:539–49.
25. Nazarian S, Bluemke DA, Lardo AC, et al. Magnetic resonance assessment of the substrate for inducible ventricular tachycardia in nonischemic cardiomyopathy. Circulation 2005;112:2821–5.
26. Wu KC, Weiss RG, Thiemann DR, et al. Late gadolinium enhancement by cardiovascular magnetic resonance heralds an adverse prognosis in nonischemic cardiomyopathy. J Am Coll Cardiol 2008;51:2414–21.