51-Year-Old Man With Heart Murmur

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A 51-year-old man presented to the internal medicine clinic for a Department of Transportation medical examination to renew his commercial motor vehicle license. He denied any symptoms at the time of his visit. On detailed questioning, however, the patient reported progressive dyspnea on exertion of several months' duration. These symptoms were not particularly worrisome to the patient because he attributed them to deconditioning.

The patient's medical history was remarkable for hypertension, hyperlipidemia, diabetes mellitus type 2, and obesity. His medications, all of which he was taking on a long-term basis, included metoprolol, enalapril, simvastatin, glipizide, and metformin. He had a remote smoking history but had not smoked for nearly 5 years. He did not drink alcohol, had no history of intravenous drug use, and was in a monogamous relationship with his wife. Family history was remarkable for coronary artery disease and diabetes mellitus type 2 in his mother.

Physical examination revealed an obese man with a body mass index (calculated as weight in kilograms divided by height in meters squared) of 39.8, a blood pressure of 121/76 mm Hg, and a heart rate of 70 beats/min. Standard vision and hearing evaluations were normal. Cardiac examination revealed a regular rhythm and a soft 2/6 systolic crescendo-decrescendo murmur loudest at the right upper sternal border preceded by an ejection click. The murmur was softer with the strain phase of the Valsalva maneuver and with standing from a squatting position. On lung examination, breath sounds were diminished, but no adventitious breath sounds were appreciated. Findings on the remainder of his examination were unremarkable.

1. On the basis of the information provided, which <u>one</u> of the following is the <u>most likely</u> diagnosis in this patient?

a. *Coronary artery disease (CAD)*
b. *Chronic obstructive pulmonary disease*
c. *Hypertrophic cardiomyopathy (HCM)*
d. *Asthma*
e. *Aortic stenosis (AS)*

Dyspnea is the subjective awareness of breathlessness. The most common cause of dyspnea is cardiopulmonary dysfunction. A thorough medical history and physical examination are required to help differentiate the cause.

Patients with CAD may present with dyspnea even in the absence of chest pain, a condition known as an *anginal equivalent*. This shortness of breath is due to elevated left atrial pressures in the setting of myocardial ischemia. Atypical manifestations of angina are more common in women and people who are older or have diabetes. Atypical angina, however, would not account for this patient's murmur. Chronic obstructive pulmonary disease may present with exertional dyspnea but again would not account for his heart murmur. In HCM, the decrease in preload that occurs in the strain phase of the Valsalva maneuver or when standing from a squatting position results in increased outflow obstruction and a murmur of increased intensity. An ejection click is not typically present in HCM. The absence of features consistent with bronchial hyperresponsiveness or atopy makes the diagnosis of asthma less likely.

The patient's presentation is most consistent with bicuspid AS. Aortic stenosis is a disease in which progressive obstruction of left ventricular outflow results in pressure hypertrophy of the left ventricle; symptoms of exertional dyspnea, syncope, and angina; and, if left untreated, death.[1] The most common cause of AS since the 1990s has been senile degenerative changes; however, in patients who have symptomatic AS in their teens and early twenties, the cause is usually a congenitally unicuspid or fused bicuspid aortic valve (BAV). Patients who develop AS at age 40 to 60 years usually have a calcified BAV, or the stenosis may be the end result of rheumatic heart disease.[2,3] Aortic stenosis can be diagnosed by bedside physical examination, which usually reveals characteristic findings, including an ejection systolic murmur that becomes louder and peaks later with increasing severity and that radiates to the carotid arteries and the apex. The left ventricular systolic impulse may be localized and sustained. In progressive AS, A_2 may be diminished, delayed, or absent; in hemodynamically significant AS, the pulse is parvus (low volume) and tardus (delayed upstroke). The aortic ejection click occurs 20 to 40 ms after the onset of pressure increase in the central aorta, and it coincides with the sharp anacrotic notch on the upstroke of the aortic pressure curve. The aortic ejection click also coincides with the

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See end of article for correct answers to questions.

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maximal excursion of the domed valve. When the aortic valve is immobile because of severe calcification, no excursion or pistol-like ascent of the deformed valve is present.

This patient was advised to undergo further testing for valvular heart disease as the next step in his evaluation.

2. Which one of the following tests would provide the greatest amount of diagnostic information for this patient at this time?

a. *Plain chest radiography*
b. *Electrocardiography (ECG)*
c. *Transthoracic echocardiography*
d. *Cardiac catheterization*
e. *Pulmonary function test*

Plain chest radiography and ECG are appropriate tests in a patient presenting with dyspnea; however, in this case they do not provide adequate specific information. Radiography may reveal left ventricular predominance with dilatation of the ascending aorta. Although no specific radiographic features of AS may be present, radiography can be helpful in ruling out other common causes of dyspnea. In patients with AS, ECG may show left ventricular hypertrophy, but this finding is not highly sensitive.

Transthoracic echocardiography, the diagnostic modality of choice for diagnosing and evaluating the severity of AS, is indicated when there is a systolic murmur of grade 3/6 or greater, a single S_2, or symptoms that might be due to AS.[4] This patient underwent transthoracic echocardiography, which revealed a BAV, an aortic valve systolic mean Doppler gradient of 10 mm Hg (calculated valve area, 2.89 cm^2) without evidence of aortic regurgitation, severe sinus of Valsalva dilatation (diameter, 50 mm), and normal left ventricular size and systolic function (estimated ejection fraction, 65%). Moderate-to-severe dilatation of the ascending aorta (48 mm at mid level) was noted; however, further evaluation was recommended because the echocardiographic images were suboptimal in view of the patient's body habitus.

In patients whose clinical findings are inconsistent with the echocardiographic results or whose symptoms may be due to CAD, cardiac catheterization would be recommended for further hemodynamic assessment.[4] Pulmonary function tests can be used in the evaluation of dyspnea but are not helpful in the diagnosis of AS.

3. Which one of the following would be the most appropriate next step for diagnostic imaging evaluation of this patient?

a. *Cardiac catheterization and coronary angiography*
b. *Transesophageal echocardiography*
c. *Invasive contrast aortography*
d. *Magnetic resonance imaging (MRI)*
e. *No further imaging is indicated at this time*

In patients with AS, the indications for cardiac catheterization and angiography are to assess the coronary circulation and to confirm or clarify the clinical diagnosis. Coronary angiography before aortic valve replacement (AVR) in patients with AS at risk of CAD is a class I indication according to the American College of Cardiology/American Heart Association (ACC/AHA) Practice Guidelines.[4] Cardiac catheterization for hemodynamic measurements is recommended for assessment of the severity of AS in symptomatic patients when noninvasive tests are inconclusive or when a discrepancy exists between noninvasive test results and clinical findings regarding the severity of AS.[4] In fact, invasive measurement of atrioventricular hemodynamics has been shown to be potentially dangerous and should be reserved for patients in whom diagnostic questions remain after echocardiography.[5] Cardiac catheterization is not indicated in this patient.

Transesophageal echocardiography provides a good visualization of the aortic valve, the ascending aorta, the aortic arch, and the descending thoracic aorta and is widely used in unstable patients to rule out aortic dissection. Invasive contrast aortography is also not indicated in this case because noninvasive alternatives are available to assess the morphology of the aorta that are safer for the patient and provide accurate diagnostic information.

Awareness is growing that many patients with a BAV have disorders of vascular connective tissue that involve loss of elastic tissue, potentially resulting in dilatation of the aortic root or ascending aorta even in the absence of hemodynamically significant AS or aortic regurgitation (AR).[6-8] In many patients with a BAV, the histology of the aortic wall is similar to that in Marfan syndrome, with abnormalities of smooth muscle, extracellular matrix, elastin, and collagen.[9-11] Because the dilatation of either the aortic root or ascending aorta can progress with time, patients with a BAV have a risk of aortic dissection that is related to their severity of dilatation. Echocardiography remains the primary imaging technique for identifying patients in whom the aortic root or ascending aorta is enlarged.[4] In many cases, echocardiography provides all the information required to make management decisions. Either cardiac MRI or computed tomography, both of which can be used to more accurately quantify the diameter of the aortic root and ascending aorta and to fully assess the degree of enlargement, is indicated in patients with a BAV when morphology of the aortic root or ascending aorta cannot be assessed accurately by echocardiography.[4] Computed tomography may also enable the visualization of the coronary arteries, obviating the need for preoperative coronary angiography.

Because the patient's echocardiographic images were not entirely satisfactory, a cardiac MRI was subsequently performed, confirming a BAV with aortic root dilatation.

The aorta showed no signs of dissection and was measured to be 49 mm at the sinuses of Valsalva, 40 mm at the sinotubular junction, and 52 mm at the level of the right pulmonary artery approximately 6 cm above the valve.

4. On the basis of these findings on MRI and echocardiography, which <u>one</u> of the following would be the <u>recommended</u> plan of care for this patient?

a. *Follow-up outpatient echocardiography in 6 months*
b. *Follow-up outpatient echocardiography in 1 year*
c. *AVR*
d. *Aortic root repair*
e. *No follow-up or intervention necessary at this time*

The frequency of follow-up visits to the physician as well as serial echocardiograms depends on the severity of the valvular stenosis and the presence of comorbid conditions. Although an optimal schedule for follow-up medical examinations has not yet been defined, many physicians perform an annual history and physical examination in patients with asymptomatic AS of any degree. Patients should be counseled to look for the following symptoms: changes in exercise tolerance, exertional chest discomfort, dyspnea, light-headedness, or syncope. Serial echocardiography is also an important aspect of follow-up. According to the 2006 ACC/AHA Practice Guidelines, transthoracic echocardiography is recommended for reevaluation of asymptomatic patients according to the following schedule: every year for patients with severe AS, every 1 to 2 years for those with moderate AS, and every 3 to 5 years for those with mild AS.[4] For adults with severe, symptomatic, calcific AS, AVR is the only effective treatment and should be performed promptly after the onset of symptoms.[12] Because this patient does not have hemodynamically significant AS, neither outpatient follow-up nor AVR is indicated at this stage.

Aortic root or ascending aortic dilatation can progress with time in patients with a BAV, and so these patients have a risk of aortic dissection. According to the ACC/AHA Practice Guidelines, surgery to repair the aortic root or replace the ascending aorta is indicated in patients with a BAV if the diameter of the aortic root or ascending aorta is greater than 5.0 cm or if the rate of increase in diameter is 0.5 cm per year or more. Also, in patients with a BAV undergoing AVR because of severe AS or AR, repair of the aortic root or replacement of the ascending aorta is indicated if the diameter of the aortic root or ascending aorta is greater than 4.5 cm.[4]

On the basis of the assessment of the patient and all the aforementioned findings, arrangements were made for the patient to undergo an aortic root repair only. However, intraoperative inspection of the aortic valve revealed extensive calcification of the leaflets; thus, despite relatively normal valve function, the patient underwent an aortic valve and root replacement with a 27-mm graft (CarboMedics, Austin, TX), reconstruction of the proximal right coronary artery, as well as suture closure of a patent foramen ovale. The patient made an uncomplicated recovery and was discharged on hospital day 6.

5. If the patient asked whether any of his relatives should be screened for BAV, which <u>one</u> of the following would be the <u>most appropriate</u> recommendation?

a. *No screening of relatives is indicated because BAV is not an inherited condition*
b. *Screening is indicated in his children*
c. *Screening is indicated in his grandparents*
d. *Screening is indicated in his nieces and nephews*
e. *Screening is indicated in his half-siblings*

Evidence is accumulating for the familial clustering and the heritability of BAV. In a report of 30 consecutive patients with a BAV confirmed by echocardiography, all 210 first-degree relatives were contacted, and 190 agreed to undergo echocardiography. A BAV was present in 9.1% of first-degree relatives, and 37% of the families had at least 1 additional member with a BAV. The pattern of inheritance in these families was consistent with autosomal dominance.[13] Similar findings were noted in a review of 50 persons with a BAV and 259 first-degree relatives. A BAV was present in 9.3% of first-degree relatives, and 32% of the families had at least 1 additional member with a BAV. The heritability estimate of BAV using extended family analysis was 89%, suggesting that almost all cases had a genetic etiology.[14] Genetic heterogeneity has been a common finding in genetic studies of cardiovascular disease in the young, and thus sequence variations in diverse genes with dissimilar inheritance patterns may be responsible for the development of BAV in different families.[15]

Echocardiographic screening for the presence of a BAV is recommended for first-degree relatives of patients with a BAV.[16] Grandparents, grandchildren, uncles, aunts, nephews, nieces, and half-siblings all represent relatives who are 2 meioses away from the patient (ie, second-degree relatives), and therefore screening is not indicated.

DISCUSSION

The inherent mechanical advantage of a 3-cusp aortic valve was observed nearly 500 years ago by Leonardo da Vinci. By observing a glass model of the aortic valve and sinuses of Valsalva, he identified the mechanism of valve closure. He further deduced that 2 cusps would not allow a sufficient aperture for flux of the blood, that 4 cusps would be too weak in closure, and that the 3 cusps that nature provided were optimal. Patients with a BAV were first described as being prone to disease by Paget in 1844,

as having an increased tendency to develop stenosis and regurgitation by Peacock in 1868, and as having a tendency to develop infective endocarditis by Osler in 1886. Physical examination alone is unlikely to detect a BAV, particularly in young people, given the inconsistent systolic click and the difficulty of recognizing the low-frequency diastolic murmur associated with AR. As such, most patients with a BAV present between the ages of 40 and 60 years with calcific AS. Some patients, however, may present with symptomatic AS in their teens and early twenties as a result of a congenitally unicuspid or fused BAV.

With a prevalence of 1% to 2%, BAV is the most common congenital cardiac malformation. It is associated with other obstructive left heart lesions, such as those that constitute the Shone complex (supravalvular mitral membrane, valvular mitral stenosis by a parachute mitral valve, subaortic stenosis, and aortic coarctation). Among patients with a bicommissural aortic valve, coexisting coarctation of the aorta is seen in approximately 6% of cases.[17]

Patients with a BAV often develop AS and AR and have a tendency toward aortic dilatation that may result in aortic dissection. The risk of aortic dissection in patients with a BAV is 5 to 9 times higher than in the general population; however, some investigators hypothesize that this increased risk is limited to a certain subset of patients.[18,19] A more recent study indicated that the aortic root is functionally abnormal and that dilatation is common in about a third of first-degree relatives of patients with a BAV, even if they have normal tricuspid aortic valves.[20]

Therapeutic decisions regarding patients with a BAV are based largely on the presence or absence of complications such as AS, AR, aortic dilatation, and other coexisting abnormalities such as coarctation of the aorta or patent ductus arteriosus. The evidence-based clinical practice guidelines of the ACC/AHA suggest that AVR is a class I indication for symptomatic patients with severe AS and that, in patients with a BAV undergoing AVR as a result of severe AS or AR, repair of the aortic root or replacement of the ascending aorta is indicated if the diameter of the aortic root or ascending aorta is greater than 4.5 cm.[4] In a patient without AS or AR, replacement of the ascending aorta is indicated if the diameter of the aortic root or ascending aorta is greater than 5.0 cm.

Aortic stenosis in the setting of a calcified BAV should be considered in all middle-aged patients noted to have a characteristic heart murmur or click on physical examination. Echocardiographic screening is strongly recommended in these cases, and patients with a newly diagnosed BAV should also be screened for associated conditions, such as ascending aortic dilatation, patent ductus arteriosus, and coarctation of the aorta.

REFERENCES

1. Ross J Jr, Braunwald E. Aortic stenosis. *Circulation*. 1968;38(suppl 1):61-67.

2. Selzer A. Changing aspects of the natural history of valvular aortic stenosis. *N Engl J Med*. 1987;317:91-98.

3. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation*. 2005;111:920-925.

4. Bonow RO, Carabello BA, Chatterjee K, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2008 Focused update incorporated into the ACC/AHA 2006 Guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008;52(13):e1-e142.

5. Omran H, Schmidt H, Hackenbroch M, et al. Silent and apparent cerebral embolism after retrograde catheterisation of the aortic valve in valvular stenosis: a prospective, randomised study. *Lancet*. 2003;361:1241-1246.

6. Braverman AC, Guven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. *Curr Probl Cardiol*. 2005;30:470-522.

7. Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J. Clinical and pathophysiological implications of a bicuspid aortic valve. *Circulation*. 2002;106:900-904.

8. Ferencik M, Pape LA. Changes in size of ascending aorta and aortic valve function with time in patients with congenitally bicuspid aortic valves. *Am J Cardiol*. 2003;92:43-46.

9. Niwa K, Perloff JK, Bhuta SM, et al. Structural abnormalities of great arterial walls in congenital heart disease: light and electron microscopic analyses. *Circulation*. 2001;103:393-400.

10. de Sa M, Moshkovitz Y, Butany J, David TE. Histologic abnormalities of the ascending aorta and pulmonary trunk in patients with bicuspid aortic valve disease: clinical relevance to the Ross procedure. *J Thorac Cardiovasc Surg*. 1999;118:588-594.

11. Bauer M, Pasic M, Meyer R, et al. Morphometric analysis of aortic media in patients with bicuspid and tricuspid aortic valve. *Ann Thorac Surg*. 2002;74:58-62 Medline.

12. Kvidal P, Bergstrom R, Horte LG, Stahle E. Observed and relative survival after aortic valve replacement. *J Am Coll Cardiol*. 2000;35:747-756.

13. Huntington K, Hunter AG, Chan KL. A prospective study to assess the frequency of familial clustering of congenital bicuspid aortic valve. *J Am Coll Cardiol*. 1997;30(7):1809-1812.

14. Cripe L, Andelfinger G, Martin LJ, et al. Bicuspid aortic valve is heritable. *J Am Coll Cardiol*. 2004;44:138-143.

15. Benson DW. The genetics of congenital heart disease: a point in the revolution. *Cardiol Clin*. 2002;20:385-394.

16. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Adults With Congenital Heart Disease) Developed in Collaboration With the American Society of Echocardiography, Heart Rhythm Society, International Society for Adult Congenital Heart Disease, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008;52(23):e1-e121.

17. Roberts WC. The congenitally bicuspid aortic valve: a study of 85 autopsy cases. *Am J Cardiol*. 1970;26(1):72-83.

18. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. *J Am Coll Cardiol*. 1991;17:712-716.

19. Nistri S, Sorbo MD, Marin M, Palisi M, Scognamiglio R, Thiene G. Aortic root dilatation in young men with normally functioning bicuspid aortic valves. *Heart*. 1999;82:19-22.

20. Biner S, Rafique AM, Ray I, Cuk O, Siegel RJ, Tolstrup K. Aortopathy is prevalent in relatives of bicuspid aortic valve patients. *J Am Coll Cardiol*. 2009;53:2288-2295.

Correct answers: 1. *e*, 2. *c*, 3. *d*, 4. *d*, 5. *b*