TOBIAS PEIKERT, MD
Department of Internal Medicine, Cleveland Clinic

CRAIG R. ASHER, MD
Department of Cardiovascular Medicine, Cleveland Clinic

BRIAN P. GRIFFIN
Department of Cardiovascular Medicine, Cleveland Clinic

A SELF-TEST ON A CLINICAL CASE

Systolic ejection murmur presenting with dyspnea on exertion

A 43-YEAR-OLD WOMAN was referred to the cardiology outpatient clinic for evaluation of a systolic ejection murmur. Her symptoms at presentation consisted of dyspnea on exertion, decreased exercise tolerance, generalized fatigue, and intermittent palpitations. Her functional impairment was consistent with New York Heart Association (NYHA) class 2 to class 3. She had a known cardiac murmur since childhood. In the past she experienced presyncopal episodes and, on one occasion, syncope.

She admits to the social use of cigarettes and alcohol. Her father had coronary artery disease and diabetes mellitus, and an uncle had died suddenly of an unknown cause.

Physical examination

Her vital signs were within normal limits. She had no carotid bruits or jugular venous distention. The carotid upstroke was slightly delayed, with normal volume and without pulsus bisferiens (a midsystolic dip). The point of maximum impulse was nondisplaced and sustained. Cardiac auscultation revealed a normal S_1 and S_2 (P_2) and no S_3 or S_4. A 3/6 systolic ejection murmur with early onset and harsh crescendo was noted throughout the precordium, with no radiation to the axilla or the neck. The murmur did not change with standing, hand-gripping, and the Valsalva maneuver. Her pulses were symmetric, and she had no peripheral edema.

Initial studies

Chest radiography revealed slight cardiomegaly. Baseline electrocardiography showed sinus rhythm and left ventricular hypertrophy with repolarization abnormalities.

DIFFERENTIAL DIAGNOSIS OF SYSTOLIC EJECTION MURMUR

1 Which of the following conditions should *not* be included in the differential diagnosis of a systolic ejection murmur?

- ❑ Aortic valve stenosis
- ❑ Mitral valve regurgitation
- ❑ Aortic valve sclerosis
- ❑ Hypertrophic cardiomyopathy
- ❑ Subaortic membrane

Mitral valve regurgitation is the only one of the above conditions that does not present with a systolic ejection murmur.

Systolic murmurs are characterized as "ejection" (TABLE 1) or "regurgitant". Systolic ejection murmurs are audible only during part of systole, that is, they begin after S_1 and end before S_2. However, regurgitant murmurs, such those caused by mitral valve prolapse, are holosystolic, ie, they are audible throughout all of systole: they generally start with S_1 and end with S_2.

The proper evaluation of any systolic murmur requires consideration of such factors as the location, intensity, timing, configuration, character, radiation, change of characteristics with certain maneuvers, and associated findings and symptoms (TABLE 2). To differentiate aortic valve stenosis from aortic valve sclerosis it is important to know that patients with aortic valve sclerosis usually have no symptoms and that there is no radiation of the murmur, no change in pulse character, and no delay or decreased intensity of the aortic component of S_2. The murmur is usually brief and soft.

To distinguish a fixed stenosis (as in aor-

Keep an open mind when evaluating patients with preexisting diagnoses

TABLE 1

Differential diagnosis of systolic ejection murmurs

Aortic systolic ejection murmurs
- Left ventricular outflow tract (LVOT) obstruction
  - Valvular aortic stenosis
    - Rheumatic fever
    - Degenerative (tricuspid valve)
    - Degenerative (bicuspid valve)
  - Subvalvular aortic stenosis
    - Hypertrophic obstructive cardiomyopathy
    - Fixed (discrete) subvalvular stenosis
  - Supravalvular aortic stenosis
- Aortic dilation
  - Hypertension
  - Aneurysms
  - Coarctation of the aorta
- Aortic valve sclerosis
- Increased aortic flow
  - Aortic regurgitation
  - Anemia
  - Thyrotoxicosis
  - Fever
  - Pregnancy
  - Exercise
  - Bradycardia

Pulmonic systolic ejection murmurs
- Right ventricular outflow tract (RVOT) obstruction
  - Pulmonic valvular stenosis
  - Infundibular stenosis
  - Supravalvular pulmonic stenosis
- Pulmonary artery dilation
  - Idiopathic
  - Pulmonary hypertension

tic valve stenosis) from a dynamic left ventricular outflow tract (LVOT) obstruction (as in hypertrophic cardiomyopathy), it is important to evaluate changes of the murmur during certain functional maneuvers that produce changes in cardiac preload, afterload, and contractility (TABLE 2).[1] For example, standing and the Valsalva maneuver decrease the intensity of the murmur in patients with aortic valve stenosis, whereas they accentuate the murmur in patients with hypertrophic cardiomyopathy. Patients with a fixed subvalvular stenosis have a preserved S_2 and carotid upstroke, and the murmur may decrease in intensity with the Valsalva maneuver and standing.

CASE CONTINUED

Prior evaluation and treatment at other institutions

The patient had been evaluated in different hospitals before presenting to our institution. Echocardiography and cardiac catheterization had detected a pressure gradient of 100 mm Hg within the LVOT (the normal pressure gradient is zero). The aortic valve was deemed morphologically normal with regular excursion, and no evidence of coronary artery disease had been seen.

The patient had been given a diagnosis of hypertrophic cardiomyopathy, but treatment with beta-blockers, calcium channel blockers, and disopyramide and the implantation of a DDDR (dual-chamber, adaptive-rate) pacemaker had failed. Holter monitoring prompted by the syncopal episode had shown frequent premature ventricular contractions and runs of nonsustained ventricular tachycardia.

LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

On the basis of the patient's clinical presentation and the prior echocardiographic and arteriographic findings, especially the presence of a pressure gradient between the left ventricular cavity and the LVOT, a diagnosis of LVOT obstruction can be made.

2 What would be the most likely cause of LVOT obstruction in this patient?

- ❑ Hypertrophic cardiomyopathy
- ❑ Valvular aortic stenosis
- ❑ Supravalvular (ie, supra-aortic valve) stenosis
- ❑ Fixed subvalvular stenosis
- ❑ Aortic coarctation

For reasons discussed below, a subvalvular cause is the most likely in this patient, based on the history, symptoms, and physical findings.

The differential diagnosis of LVOT obstruction can be divided into three major categories on the basis of the location of the obstructing lesion (TABLE 2): supravalvular, valvular, and subvalvular.

TABLE 2

Features of the physical examination that help to differentiate the causes of left ventricular outflow tract obstruction

FEATURE	VALVULAR	SUPRAVALVULAR	SUBVALVULAR	
			DISCRETE SUBVALVULAR STENOSIS	HYPERTROPHIC CARDIOMYOPATHY
Pulse pressure after ventricular premature beat	Increased	Increased	Increased	Decreased
Effect of Valsalva maneuver on systolic murmur	Decreases	Decreases	Decreases	Increases
Murmur of aortic regurgitation	Common	Rare	Sometimes	Rare
Fourth heart sound	If severe	Uncommon	Uncommon	Common
Paradoxic splitting	Sometimes	Absent	Absent	Common
Ejection click	Most, except in cases of calcified valve	Absent	Absent	Absent
Maximal thrill and murmur	Second right intercostal space	First right intercostal space	Second right intercostal space	Fourth left intercostal space
Carotid pulse	Reduced upstroke	Unequal	Normal to reduced upstroke	Brisk, jerky upstroke, systolic rebound

ADAPTED FROM MARRIOTT HJL. BEDSIDE CARDIAC DIAGNOSIS. PHILADELPHIA: J.B. LIPPINCOTT, 1993:116.

Supravalvular causes of LVOT obstruction

Supravalvular causes of LVOT obstruction are aortic coarctation, fixed supravalvular stenosis, fibrous membranes, and fibromuscular ridges.

Aortic coarctation and fixed supravalvular stenosis are congenital conditions that usually become symptomatic and are diagnosed earlier in life. Aortic coarctation is caused by a fibromuscular ridge in the location of the former ductus arteriosus distal to the origin of the left subclavian artery. Symptoms at presentation usually include hypertension involving the upper extremities and delayed and decreased pulses in the lower extremities. Aortic coarctation is a cause of secondary hypertension. In this particular case, aortic coarctation is very unlikely since hypertension is absent and the peripheral pulses are normal on physical examination.

Fibrous membranes and fibromuscular ridges can also occur immediately above the aortic sinuses and often lead to hypoplasia of the ascending aorta. However, these forms of aortic stenosis are rare. They generally become symptomatic and subsequently require surgical intervention early in childhood, which makes them an unlikely diagnosis in our patient.[2,3] Occasionally, severe familial hyperlipidemia leads to fatty deposition above the aortic valve and to stenosis at that point.

Valvular causes of LVOT obstruction

The most frequent valvular abnormality resulting in aortic stenosis is degenerative disease. Depending on the underlying anatomy, aortic stenosis becomes hemodynamically significant in different age groups. The most common cause of aortic stenosis in people under age 55 is a congenitally abnormal aortic valve. Often, the valve is still pliable at the time of presentation, resulting in an ejection click preceding the systolic ejection murmur.

The most common congenital valvular cause of LVOT obstruction is a bicuspid aortic valve caused by congenital commissural fusion. This condition may lead to significant hemodynamic compromise, with severe fusion and calcification that causes valvular aortic stenosis requiring early surgical intervention.

Rheumatic aortic stenosis is now uncommon. Rheumatic fever results in thickening and fusion of the aortic cusps and commissures leading to aortic stenosis, regurgitation, or both. In this setting aortic disease is almost always associated with mitral valve abnormalities. The typical age of onset of symptoms is the fourth through sixth decades of life, usually 10 to 20 years after an episode of acute rheumatic fever. In our patient, the presence of the murmur early in life and the echocardiographic findings make this diagnosis very unlikely.

In people age 55 and older, aortic stenosis is usually caused by degenerative changes involving a tricuspid aortic valve, resulting in progressive calcification and restriction. Risk factors contributing to the progression of disease are similar to risk factors for coronary artery disease and include hyperlipidemia and hypertension.[2–7]

In our patient a problem with the valve itself appears to be very unlikely, since the aortic valve appeared normal on echocardiography. The most likely type of stenosis in our patient is subvalvular.

Valsalva and other maneuvers caused no change in the murmur

Subvalvular causes of LVOT obstruction

Two subvalvular conditions are known to cause subaortic LVOT obstruction: hypertrophic cardiomyopathy and discrete subaortic stenosis.

Hypertrophic cardiomyopathy is a genetic cardiac disorder with a prevalence estimated at 1:500. It is caused by several distinct genetic mutations resulting in hypertrophy and myocardial disarrangement. Involvement of the interventricular septum is predominant. The myocytes are of bizarre shapes and are arranged in a chaotic pattern oriented in oblique and perpendicular angles. These cellular abnormalities are thought to be the substrate for cardiac arrhythmias. Ventricular arrhythmias constitute the major cause of death in patients with hypertrophic cardiomyopathy.

Dynamic LVOT obstruction. In a subgroup of patients with hypertrophic cardiomyopathy, signs and symptoms of LVOT obstruction dominate the clinical picture. In these patients the LVOT compromise appears to be due to septal hypertrophy resulting in systolic anterior motion of the mitral valve and causing contact of the valve with the interventricular septum. A distinct feature of this particular form of LVOT obstruction is its dynamic character: ie, the severity of the LVOT obstruction changes in response to variation in hemodynamic variables such as cardiac preload, afterload, and inotropic stimulation.

In many patients, medical treatment with negative inotropes such as beta-blockers, calcium channel blockers, or disopyramide may improve or alleviate the symptoms. In some patients, however, the dynamic LVOT obstruction responds only to ablation of the septal muscle at surgery (myectomy) or with alcohol injection of a septal coronary artery (alcohol septal ablation).[8,9]

Discrete subvalvular stenosis (fixed LVOT obstruction). In patients with a fixed LVOT obstruction, severe ventricular hypertrophy may result and may simulate the clinical and echocardiographic picture of hypertrophic cardiomyopathy. Careful two-dimensional and Doppler echocardiography is essential to distinguish hypertrophic cardiomyopathy from a fixed LVOT obstruction. Often transesophageal echocardiography (TEE) is necessary to adequately exclude a membrane in the LVOT as the cause of a fixed obstruction (as in fixed subaortic stenosis).[10]

Fixed subaortic stenosis may occur as long-segment (tunnel) stenosis or short-segment (fibromuscular ring or membrane) stenosis.

Pathophysiology of discrete subaortic stenosis

The pathophysiology of discrete subaortic stenosis is not completely understood. On one hand, a genetic component is reflected by the familial incidence of the disease and the presence of a similar condition in Newfoundland dogs. In addition, more than 50% of patients have an association with other congenital heart lesions, including coarctation, bicuspid aortic valve, mitral valve abnormalities, and ventricular septal defects. On the other hand, subaortic stenosis is rarely seen in infancy, as would be expected. Current thinking favors an acquired lesion that develops based on a genetic predisposition. Gewillig et al[11] suggested that an abnormal flow pattern, in conjunction with endothelial damage and a coexistent genetic predisposition, likely results in the development of the typical fibromuscular

obstruction. Further evidence that the condition is acquired is the significant recurrence rate after surgical resection of the lesion. The lower recurrence rate seen after combined resection of the subaortic membrane and myectomy is thought by some to be due to an alteration in the intraventricular flow pattern by the myectomy.

Associated complications include an increased risk of endocarditis (enough to warrant antibiotic prophylaxis), severe left ventricular hypertrophy, and damage to the aortic valve by the high-velocity jet in the LVOT, resulting in aortic insufficiency. This is thought to be caused by mechanical damage due to the stenotic jet.

CASE CONTINUED

Consideration of a fixed subaortic obstruction

Our patient's prior diagnosis of hypertrophic cardiomyopathy had been based on her clinical presentation and echocardiographic and arteriographic findings. Since therapeutic attempts including medical therapy and implantation of a dual-chamber pacemaker had been unsuccessful, the possibility of a fixed subaortic obstruction needs to be considered.

SELECTING THE APPROPRIATE DIAGNOSTIC TEST

3 Which of the following diagnostic tests would be appropriate to clarify the patient's diagnosis?

- ❑ Transesophageal echocardiography (TEE)
- ❑ Cardiac catheterization
- ❑ Cardiac magnetic resonance imaging (MRI)
- ❑ All of the above

All of the above listed tests could contribute to the clarification of the diagnosis in this particular patient. However, the most appropriate next step would be TEE.

TEE allows both anatomic and physiologic evaluation of an LVOT obstruction regardless of the patient's body habitus. For the physiologic evaluation it provides the opportunity to perform maneuvers such as the Valsalva maneuver, to use vasodilators such as amyl nitrate, or to apply positive inotropic agents such as isoproterenol to assess the dynamic character of the LVOT obstruction. TEE also provides information regarding the attachment of subaortic lesions (mitral valve, septum), the degree of obstruction of the aortic valve, and the amount of aortic regurgitation, and aids the identification of associated cardiac abnormalities.

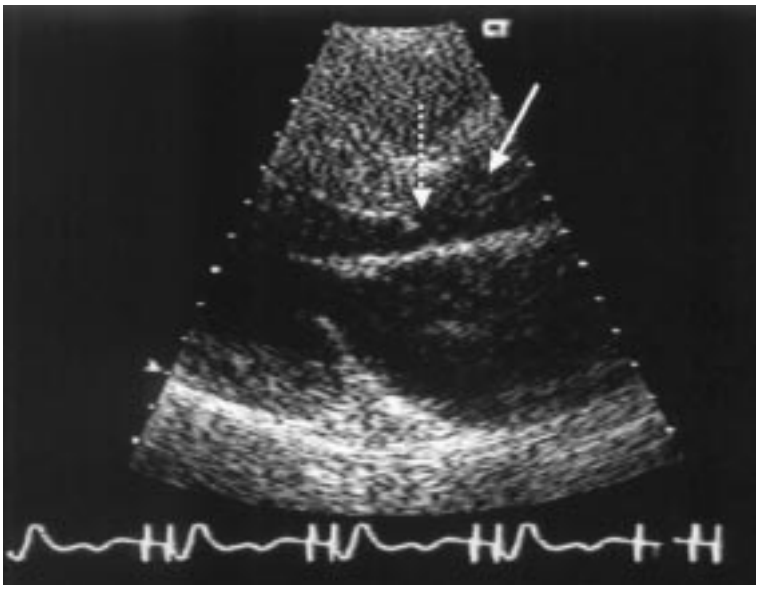

FIGURE 1. Transthoracic echocardiogram, parasternal long-axis view. Dotted arrow points to LVOT subaortic membrane. Solid arrow identifies the position of the normal aortic valve.

Cardiac catheterization is an invasive procedure capable of defining the area of obstruction angiographically and of measuring the severity of the pressure gradient; however, it provides less anatomic detail than TEE. Still, it is helpful in the preoperative evaluation of the coronary arteries and can be combined with functional maneuvers.

Cardiac MRI is a very helpful noninvasive test for the delineation of cardiac anatomy, but it provides less information about the severity of the pressure gradient and its response to maneuvers.

Failure of drug and pacemaker therapy hint at a fixed LVOT obstruction

CASE CONTINUED

Findings on echocardiography

The patient underwent two-dimensional transthoracic echocardiography at our institution. This suggested an LVOT obstruction (peak gradient 93 mm Hg; mean gradient 55 mm Hg), 3+ aortic regurgitation, left ventricular hypertrophy resulting in thickening of

the interventricular septum, and normal global left and right ventricular function. TEE detected a subaortic membrane and confirmed the other transthoracic echocardiographic findings (FIGURE 1). On cardiac catheterization, no evidence of coronary artery disease was found.

WHEN IS SURGICAL INTERVENTION APPROPRIATE?

4 Based on current knowledge, when is surgical intervention appropriate?

- ❑ Immediately after diagnosis of the stenosis
- ❑ When the LVOT mean pressure gradient is more than 50 mm Hg in a patient with no symptoms
- ❑ When symptoms develop
- ❑ When complications occur, such as aortic insufficiency or bacterial endocarditis

The timing of surgical correction is still controversial. Given the risk of recurrence, early intervention in this condition might be associated with multiple reoperations. Certain experts propose surgery immediately after the diagnosis of the stenosis,[12,13] whereas others establish specific cut-off points for the LVOT gradient for surgical intervention in asymptomatic patients.[14,15] Experts agree that surgery is required in patients who have symptoms.[16] Current thinking favors an early approach to surgery if the patient has a high pressure gradient (> 50 mm Hg mean), evidence of damage to the aortic valve (such as aortic regurgitation), or symptoms.

CASE CONTINUED

Results of surgical treatment

The patient underwent surgical resection of the subaortic membrane and septal myectomy. Postoperative transthoracic echocardiography revealed resolution of the LVOT obstruction with a dynamic gradient of 18 mm Hg and 2+ aortic regurgitation. The histologic evaluation of the resected tissue revealed hypertrophied myocardium but no myocardial disarray indicative of hypertrophic cardiomyopathy.

LESSONS LEARNED

It is very important to keep an open mind when evaluating patients carrying preexisting diagnoses who are referred for treatment questions. A poor response to the standard therapeutic regimens in a patient with presumed hypertrophic obstructive cardiomyopathy should always raise suspicion of an incorrect diagnosis. In the case of our patient, a fixed LVOT obstruction needed to be excluded.

It is also important to remember that hypertrophic cardiomyopathy is not the only disease process resulting in a dynamic LVOT obstruction: it may also occur after mitral valve repair or in patients who have left ventricular hypertrophy and a small ventricular cavity who are dehydrated, eg, after a surgical procedure.

REFERENCES

1. **Marriott HJL.** Bedside cardiac diagnosis. Philadelphia: JB Lippincott Company, 1993:116.
2. **Friedman WF, Child JS.** Congenital heart disease in adults. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, editors. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill, 1998:1300–1309.
3. **Carabello BA, Crawford FA Jr.** Medical progress: valvular heart disease. N Engl J Med 1997; 337:32–41.
4. **Braunwald E.** Aortic stenosis. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, editors. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill, 1998:1317–1320.
5. **Wilmshurst PT, Stevenson RN, Griffiths H, Lord JR.** A case-control investigation of the relation between hyperlipidemia and calcific aortic valve stenosis. Heart 1997; 78:475–479.
6. **Brickner ME, Hillis LD, Lange RA.** Medical progress: congenital heart disease in adults. First of two parts. N Engl J Med 2000; 342:256–276.
7. **Lester SJ, Heilbron B, Gin K, Dodek A, Jue J.** The natural progression of aortic stenosis. Chest 1998; 113:1109–1114.
8. **Maron BJ.** Hypertrophic cardiomyopathy. Lancet 1997; 350:127–133.
9. **Spirito P, Seidman CE, McKenna WJ, Maron BJ.** Medical progress: the management of hypertrophic cardiomyopathy. N Engl J Med 1997; 336:775–785.
10. **Bruce CJ, Nishimura RA, Tajik J, Schaff HV, Danielson GK.** Fixed left ventricular outflow tract obstruction in presumed hypertrophic obstructive cardiomyopathy: implications for therapy. Ann Thorac Surg 1999; 68:100–104.
11. **Gewillig M, Deanen W, Dumoulin M, et al.** Rheologic genesis of discrete subvalvular aortic stenosis: a Doppler echocardiographic study. J Am Coll Cardiol 1992; 19:818–824.
12. **Wright GB, Keane JF, Nadas AS, et al.** Fixed subaortic stenosis in the young: medical and surgical course in 83 patients. Am J Cardiol 1983;52:830–835.
13. **Coleman DM, Smallhorn JF, McCrindle BW, et al.** Post-operative follow-up of fibromuscular subaortic stenosis. J Am Coll Cardiol 1994; 24:1558–1564.
14. **Sommerville J, Stone S, Ross D.** Fate of patients with fixed subaortic stenosis after surgical removal. Br Heart J 1980; 43:629–647.
15. **Brauner R, Laks H, Drinkwater DC, et al.** Benefits of early surgical repair in fixed subaortic stenosis. J Am Coll Cardiol 1997; 30:1835–1842.
16. **Kitcher D.** Subaortic stenosis: still more questions than answers. Heart 1999; 82: 647–648.

ADDRESS: *Brian P. Griffin, MD, Department of Cardiology, F15, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail griffib@ccf.org.*