AMAR KRISHNASWAMY, MD
Department of Cardiovascular Medicine, Cleveland Clinic

BRIAN P. GRIFFIN, MD
Department of Cardiovascular Medicine, Cleveland Clinic

Challenges in the management of aortic stenosis

THE CLASSIC CASE OF AORTIC STENOSIS is in an otherwise healthy middle-aged patient with symptomatic severe disease who is referred to a cardiac surgeon for surgical aortic valve replacement. Unfortunately, physicians who manage valvular heart disease do not encounter this straightforward scenario on a regular basis. Rather, patients come with comorbidities such as advanced age, pulmonary disease, renal dysfunction, coronary artery disease, and significant left ventricular dysfunction. They also come with severe aortic stenosis without symptoms.

See related article, page 487

In this issue of the *Cleveland Clinic Journal of Medicine*, Sawaya and colleagues[1] review the management of aortic stenosis, focusing on clinically challenging scenarios such as low-flow, low-gradient aortic stenosis, low-gradient severe aortic stenosis with a normal ejection fraction, aortic stenosis in elderly patients, moderate aortic stenosis in patients undergoing other cardiac surgery, and transcatheter aortic valve replacement, according to the guidelines from the American College of Cardiology and American Heart Association.[2]

In addition to the situations covered in their review, a few other complicated situations in patients with severe aortic stenosis also merit discussion. We discuss these below.

ASYMPTOMATIC SEVERE AORTIC STENOSIS AND A NORMAL EJECTION FRACTION

Patients with aortic stenosis may be unaware of their decline in functional capacity, since the illness is gradually progressive. In these patients, exercise testing is often done, as it can uncover limitations and determine the need for aortic valve replacement. Another group of patients with asymptomatic severe aortic stenosis who need aortic valve replacement are those whose ejection fraction is less than 50%.

However, many patients with asymptomatic aortic stenosis pass the stress test with flying colors—no symptoms, no blood pressure changes, no arrhythmias—and have a normal ejection fraction. Managing these patients can be more complicated.

Lancellotti et al[3] described a group of patients with asymptomatic severe aortic stenosis, a normal ejection fraction, an aortic valve area smaller than 1 cm^2, and normal results on exercise testing. Rates of the primary end point (cardiovascular death or need for aortic valve replacement due to symptoms or left ventricular dysfunction) were assessed in subsets of patients grouped on the basis of two variables:

- Left ventricular stroke volume index (flow)—either normal or low (< 35 mL/m^2) and
- Mean gradient—either high or low (< 40 mm Hg).

The prevalence rates and 2-year event rates (which were substantial) were as follows:

- Normal flow, high gradient—51% of patients; event rate 56%
- Normal flow, low gradient—31% of patients; event rate 17%
- Low flow, high gradient—10% of patients; event rate 70%
- Low flow, low gradient—7% of patients; event rate 73%.

Mihaljevic et al[4] at our institution found that left ventricular hypertrophy at the time

Managing severe aortic stenosis requires patient-by-patient analysis of clinical, echocardiographic, and hemodynamic data

doi:10.3949/ccjm.79a.12059

of surgery for aortic stenosis may have lasting negative consequences. In an observational study of 3,049 patients who underwent aortic valve replacement, severe left ventricular hypertrophy preceded symptoms in 17%. Additionally, the survival rate at 10 years in the group whose left ventricular mass was greater than 185 g/m^2 was 45% at 10 years, compared with 65% in patients whose left ventricular mass was less than 100 g/m^2. Left ventricular hypertrophy may, therefore, eventually become another factor that we use in defining the appropriateness of surgery in patients with severe but asymptomatic aortic stenosis.

Comment. Not all patients who have severe aortic stenosis, no symptoms, and a "normal" ejection fraction are the same. Our view of what constitutes appropriate left ventricular function in aortic stenosis has changed and now encompasses diastolic filling values, myocardial velocity, and patterns of hypertrophy in addition to ejection fraction. Surgery is already considered reasonable for patients with asymptomatic but "extremely severe" aortic stenosis (aortic valve area < 0.6 cm^2, jet velocity > 5 m/sec, mean gradient > 60 mm Hg), and it may improve long-term survival.[2,5]

Not all patients who have severe aortic stenosis, no symptoms, and a 'normal' ejection fraction are the same

However, closer inspection of left ventricular mechanics may also identify another group of patients whose prognosis is worse than in the rest. It is possible that a more thorough evaluation of left ventricular mechanics, including strain imaging, will provide a more elegant way to risk-stratify patients and help clinicians decide when to intervene in this difficult group of patients.[6]

While these factors are not yet a part of the diagnostic algorithm, the work by Lancellotti et al[3] and Mihaljevic et al[4] sheds light on the idea that evaluation of advanced echocardiographic variables may provide clinical insights into whether patients should undergo aortic valve replacement.

PCI FOR CONCOMITANT SEVERE CORONARY ARTERY DISEASE

The risk factors for aortic stenosis are similar to those for coronary artery disease, and many patients with moderate or severe aortic stenosis also have significant coronary disease. These patients are traditionally referred for combined surgical aortic valve replacement and coronary artery bypass grafting.

Patients who have the combination of both diseases have a worse prognosis, and adding coronary artery bypass grafting to surgical aortic valve replacement increases the perioperative mortality rate.[7]

With advances in transcatheter aortic valve replacement, attention has turned to managing concomitant coronary artery disease percutaneously as well. Until recently, however, there were few data on the safety of percutaneous coronary intervention (PCI) in patients with severe aortic stenosis.

Goel et al[8] analyzed the outcomes of 254 patients with severe aortic stenosis who underwent PCI at our institution, compared with a propensity-matched group of 508 patients without aortic stenosis undergoing PCI. Overall, the 30-day mortality rate did not differ significantly between the two groups (4.3% vs 4.7%, $P = .20$), nor did the rate of complications such as contrast nephropathy, periprocedural myocardial infarction, and hemodynamic compromise during the procedure. In subgroup analysis, patients who had severe aortic stenosis and ejection fractions of 30% or less had a significantly higher risk of death than those with ejection fractions greater than 30% (15.4% vs 1.2%, $P < .001$).

Comment. This information is important, since many patients with severe aortic stenosis also have coronary artery disease. Certainly, for patients with significant coronary artery disease and severe aortic stenosis who cannot undergo surgery, the findings are especially encouraging with respect to the safety of PCI.

The findings also suggest that in patients for whom transcatheter aortic valve replacement can be performed in a timely fashion, a completely percutaneous approach to treating aortic stenosis and coronary artery disease may be reasonable. This hypothesis must be further investigated, but the preliminary data are encouraging.

TRANSCATHETER AORTIC VALVE REPLACEMENT IN LOWER-RISK PATIENTS

The PARTNER (Placement of Aortic Transcatheter Valves) trial showed that transcatheter aortic valve replacement was superior to medical therapy alone for patients who cannot

undergo surgery, and not inferior to surgical aortic valve replacement for patients at high surgical risk, ie, a Society of Thoracic Surgeons (STS) mortality risk score greater than 10%.[9]

Given these encouraging results, the PARTNER II trial is now randomizing patients who are at moderate surgical risk (STS score > 4%) to surgical vs transcatheter aortic valve replacement.

Since transcatheter aortic valve replacement has been performed in Europe under the Conformité Européenne (CE) marking since 2007, diffusion of the procedure there has occurred in a more rapid fashion than in the United States. As a result, a number of patients with low or moderate surgical risk have undergone this procedure.

Lange et al[10] summarized their experience at a single center in Munich, Germany, with an eye toward patient selection and surgical risk. Between 2007 and 2010, 420 patients underwent transcatheter aortic valve replacement. When the authors divided the cases into quartiles according to the sequence in which they were seen, they found a statistically significant decline in the STS score over time, from 7.1% in the earliest quartile to 4.8% in the latest quartile ($P < .001$), indicating the procedure was diffusing into lower-risk groups. With respect to outcome, the 6-month mortality rate declined from 23.5% to 12.4%; this was likely due to a combination of patient-related factors (more patients at lower risk over time), device advances, and greater operator experience. Also of note, only 70% of patients in the latest quartile were intubated for the procedure.

Comment. Diffusion of transcatheter aortic valve replacement in the United States is following a thoughtful path, with patients being assessed by "heart teams" of clinical cardiologists, interventional cardiologists, imaging cardiologists, and cardiac surgeons, and with strict criteria for site approval to perform commercial placement of the Edwards Sapien valve. In keeping with this controlled process, future randomized studies (such as PARTNER II) of transcatheter aortic valve replacement in lower-risk patients will be necessary before this procedure can be widely applied to this patient group. The results are, therefore, eagerly anticipated, but preliminary experience from Europe is encouraging.

BALLOON AORTIC VALVULOPLASTY IS SEEING A RESURGENCE

In large part due to rising interest in managing aortic stenosis and to the anticipated diffusion of transcatheter aortic valve replacement, balloon aortic valvuloplasty has seen a resurgence in recent years.

This procedure can be considered in a number of situations. In patients with severe aortic stenosis who are hemodynamically unstable and for whom urgent aortic valve replacement is not feasible, balloon valvuloplasty may serve as a "bridge" to valve replacement. Similarly, we have seen significant functional improvement in patients after balloon aortic valvuloplasty, so that some who initially were unable to undergo aortic valve replacement have improved to a point that either transcatheter or surgical replacement could be performed safely. In patients who need urgent noncardiac surgery, balloon valvuloplasty may be considered as a temporizing measure in the hope of reducing the risks of perioperative hemodynamic changes associated with anesthesia.

Many patients with severe aortic stenosis have comorbidities such as chronic obstructive pulmonary disease or liver or kidney disease that make it difficult to discern the degree to which aortic stenosis contributes to their symptoms. In such cases, the balloon procedure may provide a therapeutic answer; improvement of symptoms points to aortic stenosis as the driver of symptoms and may push for a more definitive valve replacement option.

A completely percutaneous approach to treating aortic stenosis and coronary artery disease is reasonable hypothetically

Finally, in patients with no option for either transcatheter or surgical aortic valve replacement, balloon aortic valvuloplasty may be considered as a palliative measure.

The benefit of this procedure is only temporary, and restenosis generally occurs within 6 months. Therefore, its value as a stand-alone procedure is limited, and the overall survival rate is significantly improved only when it is used as a bridge to valve replacement.

It should be noted that balloon aortic valvuloplasty carries significant risk. The 30-day mortality rate may be as high as 10%, usually due to either aortic regurgitation (as a complication of the procedure) or persistent heart fail-

ure. Other complications occur in up to 15% of cases and include stroke, peripheral vascular complications (due to the size of the devices used and concomitant incidence of peripheral arterial disease), coronary occlusion, need for permanent pacemaker implantation, cardiac tamponade, and cardiac arrest. In patients who require a repeat procedure, it entails similar risks and outcomes as the first procedure.

Comment. Balloon aortic valvuloplasty holds an important place in the treatment of patients with severe aortic stenosis. In our experience, it is most often performed to bridge severely symptomatic patients to transcatheter or surgical aortic valve replacement, or to better understand the contribution of aortic stenosis to functional limitation in patients with multiple comorbidities. It has tremendous potential to alleviate symptoms and provide an opportunity for functional improvement, in turn allowing definitive treatment with aortic valve replacement and improved quality and quantity of life in patients with severe aortic stenosis.

Diffusion of transcatheter aortic valve replacement in the United States is following a thoughtful path

MANAGING SEVERE STENOSIS IS FULFILLING, BUT CHALLENGING

Managing patients with severe aortic stenosis is very fulfilling but at the same time can be extraordinarily challenging. It requires a patient-by-patient analysis of clinical, echocardiographic, and hemodynamic data. In some cases, the relationship between aortic stenosis and current symptoms or future outcomes may be in doubt, and provocative testing or balloon aortic valvuloplasty may be necessary to provide further direction. A meticulous assessment, requiring the expertise of clinicians, imagers, interventionalists, and surgeons is often necessary to deliver optimal care to this group of patients.

REFERENCES

1. **Sawaya F, Stewart J, Babaliaros V**. Aortic stenosis: who should undergo surgery, transcatheter valve replacement? Cleve Clin J Med 2012; 79:487–497.
2. **Bonow RO, Carabello BA, Chatterjee K, et al; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force**. 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. Circulation 2008; 118:e523–e661
3. **Lancellotti P, Magne J, Donal E, et al**. Clinical outcome in asymptomatic severe aortic stenosis: insights from the new proposed aortic stenosis grading classification. J Am Coll Cardiol 2012; 59:235–243.
4. **Mihaljevic T, Nowicki ER, Rajeswaran J, et al**. Survival after valve replacement for aortic stenosis: implications for decision making. J Thorac Cardiovasc Surg 2008; 135:1270–1278; discussion 1278–1279.
5. **Kang DH, Park SJ, Rim JH, et al**. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. Circulation 2010; 121:1502–1509.
6. **Ozkan A, Kapadia S, Tuzcu M, Marwick TH**. Assessment of left ventricular function in aortic stenosis. Nat Rev Cardiol 2011; 8:494–501.
7. **Nowicki ER, Birkmeyer NJ, Weintraub RW, et al; Northern New England Cardiovascular Disease Study Group and the Center for Evaluative Clinical Sciences, Dartmouth Medical School**. Multivariable prediction of in-hospital mortality associated with aortic and mitral valve surgery in Northern New England. Ann Thorac Surg 2004; 77:1966–1977.
8. **Goel SS, Agarwal S, Tuzcu EM, et al**. Percutaneous coronary intervention in patients with severe aortic stenosis: implications for transcatheter aortic valve replacement. Circulation 2012; 125:1005–1013.
9. **Smith CR, Leon MB, Mack MJ, et al; PARTNER Trial Investigators**. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011; 364:2187–2198.
10. **Lange R, Bleiziffer S, Mazzitelli D, et al**. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. J Am Coll Cardiol 2012; 59:280–287.

***ADDRESS**: Amar Krishnaswamy, MD, Department of Cardiovascular Medicine, J2-3, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail krishna2@ccf.org.*