Transcatheter Aortic Valve Replacement
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Case History: A 77-year-old man presents with fatigue and shortness of breath with minimal exertion. He is brought into the examination room in a wheelchair due to shortness of breath with ambulation. He has a history of hypertension, diabetes mellitus, and coronary artery disease with prior stent to left anterior descending artery. Examination is notable for a harsh III/VI late-peaking systolic murmur in the right upper sternal border that radiates to the carotid arteries. EKG shows left ventricular hypertrophy with strain. Laboratory results are notable for serum creatinine of 2.0 mg/dL. Echocardiography is notable for an ejection fraction of 35%, with global hypokinesis in a hypertrophied ventricle. The aortic valve is calcified and stenotic with a peak velocity of 4.2 m/s, a mean gradient of 45 mm Hg, and a calculated aortic valve area of 0.7 cm². Computed tomography scan of the thorax reveals a densely calcified aorta (Figure 1).

Overview
Calcific aortic stenosis is a disease most commonly found in the elderly, with an estimated incidence of 2% to 4% in people >65 years of age, making it the most common acquired valvular disease seen in the developed world. Aortic stenosis may affect younger patients who have either congenitally bicuspid aortic valves or, less commonly in the developed world, a history of rheumatic fever as a child. The pathophysiology of calcific aortic stenosis is not completely understood, but the disease is thought to be secondary to leaflet stress and shares some features histopathologically with atherosclerosis; inflammatory-rich plaques develop on the leaflets and subsequently become mineralized. The immobility of the aortic leaflets leads to attenuation of cardiac output, especially with increased physiological demand, and places the ventricle under a pressure load. This leads to concentric hypertrophy and diastolic dysfunction and, in late stages, dilatation and systolic failure.

The symptoms of aortic stenosis are typically related to a fixed cardiac output with little reserve. This leads to shortness of breath with exertion and, eventually, to frank heart failure. In advanced cases, syncope can also occur. Angina, even in the absence of epicardial coronary artery disease, is also common due to the inability to sufficiently perfuse the larger mass of hypertrophied myocardium under high wall tension. Although associated with a long latent period, the prognosis for patients with critical aortic stenosis who develop symptoms is poor, with average survival of 1 to 2 years after the development of congestive heart failure.

Early pioneering work of Gorlin and Gorlin established hemodynamic measurements in the catheterization laboratory as a highly reliable method of quantifying the severity of aortic stenosis. Doppler echocardiography has largely supplanted invasive studies as the gold standard for diagnosis, showing very reproducible results compared with catheterization. The most problematic population for accurate diagnosis is patients with low cardiac output. Differentiation of those with pseudo-stenosis from true stenosis often requires the addition of dobutamine to assess contractile reserve and augmentation of gradients.

It has been 50 years since the initial implantation of an artificial cardiac...
valve in a human. Early data showed incontrovertibly that surgical aortic valve replacement in the patient with critical aortic stenosis improved symptoms and dramatically improved survival. Balloon aortic valvuloplasty is a technique that, although often leading to early salutary results, has not been shown to alter survival compared with medical therapy. It is therefore relegated to use as a bridge to more definitive therapy or palliation.

The High-Risk Patient
Epidemiological evidence suggests that there is a large population with critical aortic stenosis who are not offered surgical valve replacement. Given that the disease is associated with advanced age, patients often present with comorbid conditions that increase the risk of cardiac surgery. Interestingly, even though ACC/AHA guidelines specifically state that age and reduced left ventricular function are not contraindications to surgical aortic valve replacement, these are common reasons cited by both surgeons and referring clinicians for deferring surgical therapy.

Transcatheter Development
Early development of transcatheter valves focused largely on temporary devices inserted in either the ascending or descending aorta to relieve aortic insufficiency for the purpose of allowing patients to recover from acute hemodynamic instability and become acceptable surgical candidates. In the early 1990s, Andersen et al conceived of and tested the first percutaneous transcatheter heart valve for permanent implantation in a porcine model. Subsequent development resulted in several designs, with the common themes being bioprosthetic valve material mounted on a stent-like support frame and deployed either through balloon expansion or with the aid of self-expanding superelastic metals (Figure 2).

Clinical Trials
In 2002, Cribier and others performed the first transcatheter aortic valve implantation (TAVI) in a human. Since then, numerous registries and small-scale randomized trials have been performed that have led to approval in the European Union (CE Mark 2007) and elsewhere for two devices, the balloon-expandable Edwards Sapien valve (Edwards Lifesciences Inc., Irvine, CA) and the self-expanding CoreValve system (Medtronic Inc., Minneapolis, MN). By some estimates, >20 000 of these procedures have now been performed in Europe, with registry studies and small randomized trials suggesting reasonable outcomes. Within the United States, both devices have active clinical trial programs. Whereas the clinical trial involving CoreValve has just been initiated, the Edwards Sapien valve has been tested extensively via the PARTNER (Placement of AoRTic TranScatheter Valve) trial, and data has already been released.

Trials for both devices follow a similar design, with 2 patient populations being represented. The first population is the high-risk surgical group, a group of patients identified by a Society of Thoracic Surgery (STS) score of ~10, which in this patient population predicts a perioperative mortality of ~15%. The STS database was established in 1989 and now represents ~94% of all cardiac surgical programs in the United States. As of 2004, data were available for >2.4 million patients. Risk factors considered in the model are numerous, but include advanced age, depressed left ventricular function, renal insufficiency, pulmonary disease, cerebrovascular disease, and redo operative status. An online website is available for performing individual calculations of risk. The second group represents the so-called inoperable or extreme-risk patient, identified

Figure 1. Computed tomography scan of thoracic aorta of patient with critical aortic stenosis. Left panel shows a transverse section and a densely and circumferentially calcified aorta (arrow). The right panel shows the calcified segment (arrow) in a 3D reconstructed view.

Figure 2. Left panel shows the Medtronic CoreValve, which consists of porcine tissue supported on a self-expanding nitinol stent (image courtesy of Medtronic Inc.). The right panel shows the Edwards Sapien valve, which consists of bovine tissue supported on a balloon-expandable stainless steel stent (image courtesy of Edwards Lifesciences Inc.).
by a cardiologist and 2 cardiac surgeons as having a risk of either death or irreversible morbidity of at $\geq 50\%$. This latter group consists of patients with risks such as porcelain aorta preventing cross-clamping during surgery, extensive mantle irradiation in the past, pulmonary disease prohibiting surgery, and multiple serious comorbidities. For both trials, patients must have symptomatic aortic stenosis with a valve area calculated by echocardiography of $\leq 0.8$ cm$^2$ with a mean gradient of $\geq 40$ mm Hg or a peak velocity across the valve of $\geq 4.0$ cm/s. For the balloon-expandable Sapien valve, the aortic valve annulus diameter must be 18–25 mm. For the self-expanding CoreValve, annular measurements must be 20 to 27 mm. In addition, for the CoreValve, the ascending aorta must be $< 45$ mm in diameter. This is reflective of the fact that, as opposed to the Sapien valve, which relies on expansion into the calcified mass of the diseased aortic valve, the CoreValve also depends on anchoring well below and above the level of the annulus. Severe aortic insufficiency, severe mitral valve disease (regurgitation or stenosis), and severe tricuspid regurgitation are contraindications. In addition, any prior surgical valve repair or replacement is an exclusion criterion.

Results of the PARTNER trial for inoperable patients have been released.$^{13}$ These patients were randomized to transfemoral placement of a percutaneous valve versus best standard therapy, which often included palliative balloon valvuloplasty. The trial enrolled 358 patients from 21 centers. The intraprocedure course is remarkable for almost complete abolition of transaortic gradients. The primary outcome of all-cause death at 1 year was 30.7% with TAVI compared with 50.7% with standard therapy ($P<0.001$). In addition, among survivors, quantitative and qualitative measures of symptoms were markedly improved. At 30 days post implantation, patients receiving TAVI were more likely to have suffered stroke (5.0% versus 1.1%, $P=0.06$) or major vascular complications (16.2% versus 11.1%, $P<0.001$). These results are remarkable not only for the dramatic reduction in mortality seen with TAVI, but also for the high morbidity associated with this disease in this very sick cohort of patients, with an average age in the mid 80s.

Data from the high surgical risk cohort in the PARTNER trial have also been released.$^{14}$ Designed as a noninferiority trial, 699 patients were randomized to either TAVI or standard surgical therapy. In addition, for those patients who had poor femoral access, an option for transapical access via a left thoracotomy was available, in which a sheath was placed into the beating left ventricle via the apex. At 1 year, the primary end point of all-cause mortality was 24.2% for TAVI and 26.8% in the standard surgical arm (noninferiority $P=0.001$). The stroke or TIA rate was 8.3% for TAVI and 4.3% in the standard surgical arm at 1 year ($P=0.04$).

The PARTNER 2 trial has recently been initiated with a newer device (Edwards Sapien XT valve) that allows for a smaller diameter access sheath. The Medtronic CoreValve trial will follow a similar design, with a high-risk cohort being randomized to TAVI versus standard surgery and an extreme risk group that will receive the TAVI via a registry. No transapical approach is planned for the CoreValve, but for those with poor femoral access, axillary or subclavian approaches may be utilized.

**Procedural Details [please click here for the embedded movie video of TAVI]**

The procedure can be thought of in 3 distinct stages: (1) obtaining appropriate vascular access; (2) placement of the valve; and (3) safely removing the large-caliber arterial sheath. The procedure is generally performed utilizing both general anesthesia and transesophageal echocardiography for guidance. Transfemoral cases can take place in either the catheterization laboratory or hybrid operating room catheterization laboratory suites. It is important to note that, given the large access sheaths required, even cases performed in a percutaneous fashion are at risk of requiring open surgical closure. Therefore, a thoroughly sterile environment and appropriate surgical equipment are imperative. Transapical cases require an appropriately sterile environment including operating room level ventilation systems. All procedures are currently performed with both an interventional cardiologist and cardiac surgeon participating.

Access for the sheath necessary for delivery of the prosthesis is a critical portion of the case, given the large size necessary. For the PARTNER trial, 2 sheaths are provided for the 2 valve sizes: 25-French outer diameter sheath for the 23-mm valve and 28-French outer diameter for the 26-mm valve. For the CoreValve, the outer diameter sheath size is 22 French. Access is obtained from either the right or left femoral artery. Some operators perform surgical cut downs to gain arterial access, whereas others use purely percutaneous techniques with use of suture-based closure devices to ensure hemostasis. The arteriotomy is serially dilated with increasing size dilators, culminating with placement of the delivery sheath. If the sheath cannot be safely advanced, it is sometimes necessary to perform a more extensive dissection and placement of a conduit graft on a larger caliber segment of the iliac artery to allow placement. In the PARTNER trial, there is the additional option of a transapical approach via left thoracotomy and apical puncture.

The prosthetic aortic valve is then advanced and negotiated around the aortic arch across the diseased valve. Care is taken to visualize the aortic valve with both fluoroscopy and transesophageal echocardiography to allow proper placement of the valve. Rapid right ventricular pacing is employed during the actual dilation of the balloon-expandable valve to limit cardiac motion and inadvertent shifting of the valve.

At procedure end, the sheath is removed and arterial hemostasis achieved.
either through surgical closure of the arteriotomy or through percutaneous-based closure devices. The latter is a suture-based closure device (Perclose or Prostar; Abbott Inc, Abbott Park, IL) placed at the beginning of the procedure and activated at procedure end.

Patients are generally awakened and extubated immediately after the procedure. Ambulation is encouraged at day 1, and the general hospital course is 3 to 5 days. Anticoagulation is achieved with 6 months of a thienopyridine (Clopidogrel 75 mg/d) and aspirin (75–100 mg/d).

Using data from the PARTNER trial,11 the most common complications of the procedure are ≈16% incidence of major vascular access complications and a ≈5% risk of stroke. A small degree of paravalvar regurgitation is commonly seen. More significant aortic insufficiency (moderate or severe) is seen in ≈13% of cases. Valve embolization either into the ventricle or into the aorta is very rare. Complete heart block is uncommon with the balloon-expandable valve. However, it may be more common with the self-expanding valve due to the deeper seating of the valve in the outflow tract with proximity to the His bundle.

Who Should Be Referred?

The process of identifying patients who are potential candidates for these trials can be somewhat complicated. Full details of inclusion and exclusion criteria can be obtained for either trial via the web.15 Briefly, the process can be broken down into 3 questions: (1) Is the patient high risk enough? (2) Does the patient meet echocardiographic criteria? (3) What is the state of the patient’s vascular anatomy? Figure 3 provides a decision tree analysis.

As discussed above, a simple and quick way to judge surgical risk is to use the online STS risk calculator. An STS risk score of ≈10% is the barrier for entry into the high-risk cohort of the PARTNER trial. For the CoreValve trial, the wording states that 1 cardiologist and 2 cardiac surgeons must agree that perioperative mortality is ≈15%. The barrier to entry into the inoperable or extreme-risk category for either trial is that the risk of death or serious irreversible morbidity is ≈50%.

Iliofemoral access is generally assessed by both angiography at the time of cardiac catheterization (a necessary study for all patients considered) and computed tomographic angiography. For the PARTNER trial, minimal vessel diameter is 7 mm for the 23-mm valve and 8 mm for the 26-mm valve. The newer PARTNER 2 Sapien XT valve is deliverable through arteries ≥6 mm. Similarly, the CoreValve requires a minimal diameter of 6 mm. In addition, vessels are assessed for excessive tortuosity and calcification, which may impede safe sheath placement. Extensive aortic tortuosity or bulky atherosclerotic disease may also preclude transfemoral access and indicate the need for a transapical or transaxillary approach.

Case Follow-Up

On the basis of overall risk and porcelain aorta, the patient was deemed inoperable. Evaluation of his lower extremity vasculature revealed large-caliber femoral and iliac arteries bilaterally. He was enrolled in the inoperable cohort of the PARTNER trial and received a 26-mm Edwards Sapien valve. He is alive 2 years after his procedure and has had marked improvement in his symptoms (now NYHA class 1–2). He is able to walk moderate distances with little shortness of breath and arrives for clinic visits without the aid of a wheelchair.

Disclosures

Dr Welt serves on the Scientific Advisory Board for Medtronic Inc. Drs Davidson and Eisenhauer have accepted honoraria from Edwards Lifesciences Inc. Dr Leon serves on the Scientific Advisory Board for Edwards Lifesciences Inc.

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