Percutaneous approaches to aortic valve replacement

Adam M. Brodsky, MD

Aortic valvular disease is a common disorder often affecting elderly patients with multiple comorbidities. A percutaneous approach to aortic valve replacement would allow treatment of high-risk patients without exposing them to the risks associated with surgery and cardiopulmonary bypass. Percutaneous aortic valve replacement presents several challenges due to the valve's proximity to the coronary ostia and mitral valve. To date, 20 patients have received percutaneous aortic valve implants with follow-up periods ranging from 2 weeks to 8 months. Further trials are ongoing.

The most common type of aortic valvular disease today is senile calcific aortic disease and may result in either stenosis, regurgitation, or a mixture of these. A study in 2000 by Otto and colleagues[1] documented calcific aortic stenosis by echocardiography in 2.9% of adults older than 65 years. Rheumatic disease continues to account for a large proportion of acquired valvular disease, though its incidence is declining.[2] Congenital malformations, such as bicuspid aortic valve, as well as acquired insults, such as endocarditis, myxomatous proliferation, and trauma, also contribute to the spectrum of aortic valvular disease.

Medical therapy is helpful but unlikely to modify the course of the disease, especially once symptoms or left ventricular dysfunction become manifest. Percutaneous balloon aortic valvotomy has only a limited role in the treatment of aortic stenosis, as the results are not durable. Surgical valve replacement or repair remains the mainstay of definitive treatment for both aortic stenosis and aortic regurgitation. While surgical therapy is effective, it entails the risks and morbidity associated with cardiopulmonary bypass and median sternotomy.

In 1999, the Society of Thoracic Surgeons reported an operative mortality rate from isolated aortic valve replacement (AVR) of 4.3% in >26,000 patients and up to 8% in >22,000 patients undergoing combined AVR with coronary artery bypass grafting.[3] A recent study of 2359 patients undergoing surgical aortic valve replacement in Sweden documented a 5.9% mortality rate at 30 days.[4] Higher operative mortality rates of 8% to 20% are observed in patients with concomitant left ventricular failure.[5] The elderly have also been shown to have higher operative mortality from surgical aortic valve replacement.[4,6] Because aortic stenosis and regurgitation are diseases of the elderly, comorbidities are a frequent concern that may render patients inoperable due to the attendant comorbid risks. A percutaneous approach to aortic valve replacement would, therefore, be a welcome option for many patients.

Percutaneous valve replacement was first performed in the pulmonary circulation of pediatric patients with congential heart defects, such as tetralogy of Fallot or pulmonary atresia. Several years after initial surgical therapy, these patients developed either obstruction of the right ventricle (RV) to pulmonary artery (PA) conduit and/or severe pulmonary regurgitation. In October 2000, Bonhoeffer and coworkers[7] reported the first percutaneously implanted valved stent in the pulmonic position in a 12-year-old boy with stenosis and insufficiency of an RV-to-PA conduit. In May 2002, Bonhoeffer and colleagues[8] published a series of 8 patients with RV-to-PA conduit obstruction and/or incompetence in whom a similar valved stent was inserted percutaneously into the pulmonic position. At a mean follow-up of 10 months, echocardiography documented that all the implanted valves were competent.

Challenges

This early experience with percutaneous pulmonary valve replacement proved the concept of transcatheter valve insertion to be technically feasible. However, the anatomy of the aortic valve presents several unique challenges. The positioning of any implanted valve must be extremely precise, as the aortic valve lies in close proximity to both the mitral valve and the coronary ostia. If the valve is to be placed in the anatomic position, malposition of the prosthesis in either direction could result in severe acute mitral dysfunction or severe acute ischemia. One must also decide, therefore, if placement in the anatomic position is indeed the most practical approach. An alternative strategy would be to place the valve in the ascending aorta, distal to the coronary ostia. This would avoid both the mitral valve and the coronaries but might decrease coronary perfusion if the aortic pressure contiguous

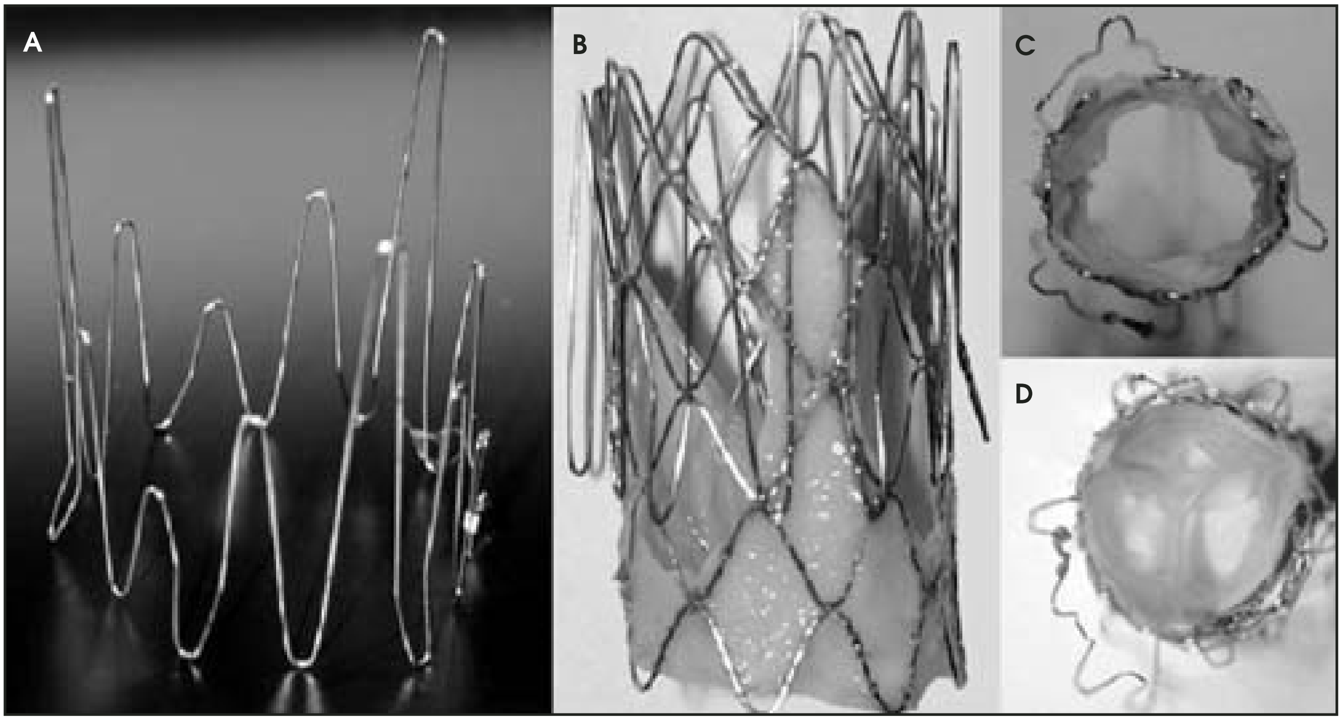

FIGURE 1. The bovine jugular valve is sewn inside the inner, platinum stent that is fastened along the valve commissures to the outer, self-expanding nitinol stent. (A) The outer, self-expanding nitinol stent; (B) the entire valved-stent assembly; (C) longitudinal view of the valved-stent assembly with the valve open; and (D) longitudinal view of the valved-stent assembly with the valve closed. (From Boudjemline Y, Bonhoeffer P: Percutaneous valve implantation: Past, present, and future. Heart Views. *2002;3(2):55-60. By permission of Gulf Heart Association, Qatar.[13])*

with the coronary ostia (and proximal to the valve prosthesis) were too low. If the prosthesis is not placed in the native position, it may be hemodynamically possible to leave a regurgitant native aortic valve in place; however, a stenotic native aortic valve would still require dilation, ablation, or explantation. The stent must be adequately fixed in place such that stent migration or embolization does not occur despite high systemic pressures. The risk of periprocedural emboli must be addressed as well.

Delivery of the prosthesis to the aortic position is challenging, and appropriate vascular access must be established. Venous access would allow easier passage of large-profile valved stents but would entail a transseptal approach with passage through (and possible damage to) the native mitral valve. A transseptal approach would, however, allow antegrade crossing of the native aortic valve, which, compared with retrograde crossing, may allow easier and more precise placement of the prosthesis due to less motion of the large delivery system during the cardiac cycle. Arterial access would allow direct retrograde crossing of the native aortic valve without the need for transseptal puncture and would avoid potential damage to the mitral valve; however, it would require a low-profile system if surgical vascular access and repair is to be avoided.

Animal models

In 1992, Anderson and colleagues[9] published the first reports of percutaneously implanted aortic valves in animal models using porcine valves in a porcine model; and Pavcnik and colleagues[10] reported using artificial ball-in-cage valves in a canine model. The porcine valves were sutured inside stainless steel stents that were placed successfully in all cases; however, in 3 out of 7 pigs, the coronary arteries were obstructed. The ball-in-cage valves were placed successfully in all cases; although in 3 of 12 cases, the ball embolized through the cage into the ascending aorta.

In 2001, Boudjemline and Bonhoeffer[11] described the implantation of a prosthetic aortic valve into a lamb. The valve prosthesis, initially used for percutaneous pulmonic valve replacement, was composed of a section of bovine jugular vein containing a native venous valve that was sewn into a platinum stent. A section of the venous wall was excised between each of the commissures on the aortic side of the valve to allow room for coronary perfusion. The stent was fashioned with hooks to assure stability once in place and to decrease the risk of stent migration. The valved stent was placed retrograde from the carotid artery into the native position using a 20F delivery system. The implanted valve continued to function normally as documented by transesophageal echocardiography at 2 weeks, and the lamb remained healthy throughout the 4-week follow-up period.

In February 2002, Boudjemline and Bonhoeffer[12] described their technique in more detail in a series of 12 lambs. This was a short-term study in which the lambs were killed and the valves explanted 1 hour after implantation. The lambs were divided into 3 groups with a different technique used in each group. In the first group, the valved stent was placed in the descending aorta after creating severe aortic insufficiency by piercing one of the native aortic valve leaflets with a transeptal needle and then dilating the leaflet with an 18-mm balloon. Valve placement and function was uniformly successful in this group, with normal pressures distal to the valve and a 40 mm Hg gradient across the valve during diastole. In the second group, the valve was implanted in the native position. All lambs died suddenly in this group due to malposition of the valve, which caused coronary ischemia or severe mitral regurgitation, or, in one case, valve embolization into the ascending aorta. In the third group, the valve was also implanted in the native position, but a self-centering technique was used to assure proper alignment of the new valve commissures with the native commissures, thus avoiding coronary obstruction and assuring proper valve placement. This was accomplished by placing the valved stent inside a self-expanding nitinol stent while securing the 2 stents together only along the prosthetic valve's commissures and not along its leaflets. Thus, when the self-expanding nitinol stent was uncovered in vivo, the sections along the leaflets expanded while leaving the sections along the commissures tethered to the unexpanded platinum stent containing the valve prosthesis. The sections of expanded nitinol stent were then positioned within the sinuses of Valsalva, assuring that the new leaflets were exactly aligned with the native leaflets. Then the inner valve-containing stent was expanded, deploying the stent in the native position. The excised sections of venous wall would then lie exactly in line with the coronary ostia. The native aortic valve leaflets were thus sandwiched between the 2 stents and fixed against the aortic side wall (Figure 1[13]). In this group, all valves were deployed successfully and angiography documented no mitral impingement and no coronary obstruction. The correct positioning of the nitinol outer stent and the platinum inner stent with respect to the native aortic valve and coronary arteries was verified grossly after the lambs were killed and the valves were explanted.

In April 2002, Lutter and colleagues[14] described 14 pigs into which either cadaveric porcine aortic valves or porcine pericardial valves were placed percutaneously. The valves were sewn inside self-expanding nitinol stents, and hooks were used to anchor the stents in position. The stents ranged in length from 21 to 28 mm. To preserve coronary perfusion, the valved stents were not positioned in the native aortic position, but rather were implanted in either a subcoronary position in the left ventricular outflow tract, a supracoronary position in the ascending aorta, or in the proximal descending aorta. Technical failure occurred in 2 pigs due to twisting of the delivery assembly in the ascending aorta. Another pig died from ventricular fibrillation during the procedure. The remaining 11 pigs had successful implantations. The pigs were observed for approximately 2.5 hours and were then killed and the valves explanted. Minor paravalvular leakage was documented by echocardiography in 1 animal in each group. One valve in the supracoronary position was placed too cranial and was found to obstruct brachiocephalic outflow; another migrated 2 to 3 mm toward the aortic arch after implantation. One valve in the subcoronary position was found at explantation to have thrombus present between the stent and the left ventricular outflow tract. All valves were competent with normal pressures documented by angiographic and echocardiographic measurements. This study highlighted the limitations of nonanatomic positioning, including brachiocephalic obstruction, stent migration, and stent malapposition leading to thrombus formation.

In July 2002, Boudjemline and Bonhoeffer[15] reported their results after they placed a bovine jugular valved stent into the descending aortas of 8 lambs. The lambs had aortic regurgitation induced by transseptal puncture of a native aortic valve leaflet followed by balloon dilation. Half the group had severe regurgitation induced using an 18-mm balloon and half had mild regurgitation induced using a 10-mm balloon. All the animals with severe aortic regurgitation died within the first 24 hours. All valves were implanted successfully and were found to be competent in early evaluation. The explanted valves from the animals with severe aortic regurgitation were also all found to function normally. Because the implanted valves were functional, but located distal to the coronaries, the coronary perfusion pressure, which was initially low due to the severe aortic insufficiency, likely remained quite low even after the competent prosthetic valve was implanted. This acute and persistent drop in coronary perfusion pressure, while not measured in this study, likely contributed to these early deaths. The animals with mild regurgitation survived for the entire 3-month study period and were noted to be asymptomatic. Prosthetic valvular function was normal at 1 and 2 months, as documented by angiography. However, at 3 months, the native aortic valve leaflet had healed in all of the lambs with initially mild regurgitation, and the prosthetic valves had all become incompetent. The explanted prostheses from these animals showed intimal proliferation that had impeded their function. The authors noted that they had obtained similar results in the pulmonary circulation.[16] They concluded that prosthetic valves that are hemodynamically unnecessary and in which there is not at least minimal back flow during diastole will become covered in neointimal tissue, eventually rendering them incompetent.[13,15]

Human trials

In December 2002, Cribier and colleagues[17] described the first human implantation of a prosthetic aortic valve. The patient was a 57-year-old man with a history of chronic pancreatitis, lung cancer, asbestosis, and severe peripheral arterial disease who had presented in cardiogenic shock due to severe calcific aortic stenosis with a bicuspid aortic valve. Balloon aortic valvuloplasty was performed initially with transient improvement; however, the patient deteriorated over the next week. The reported ejection fraction was <20%, and the systolic blood pressure remained approximately 70 mm Hg, despite multiple vasopressors. A prosthetic aortic valve fashioned from bovine pericardium and sewn into a stainless steel stent was placed in the native position. In

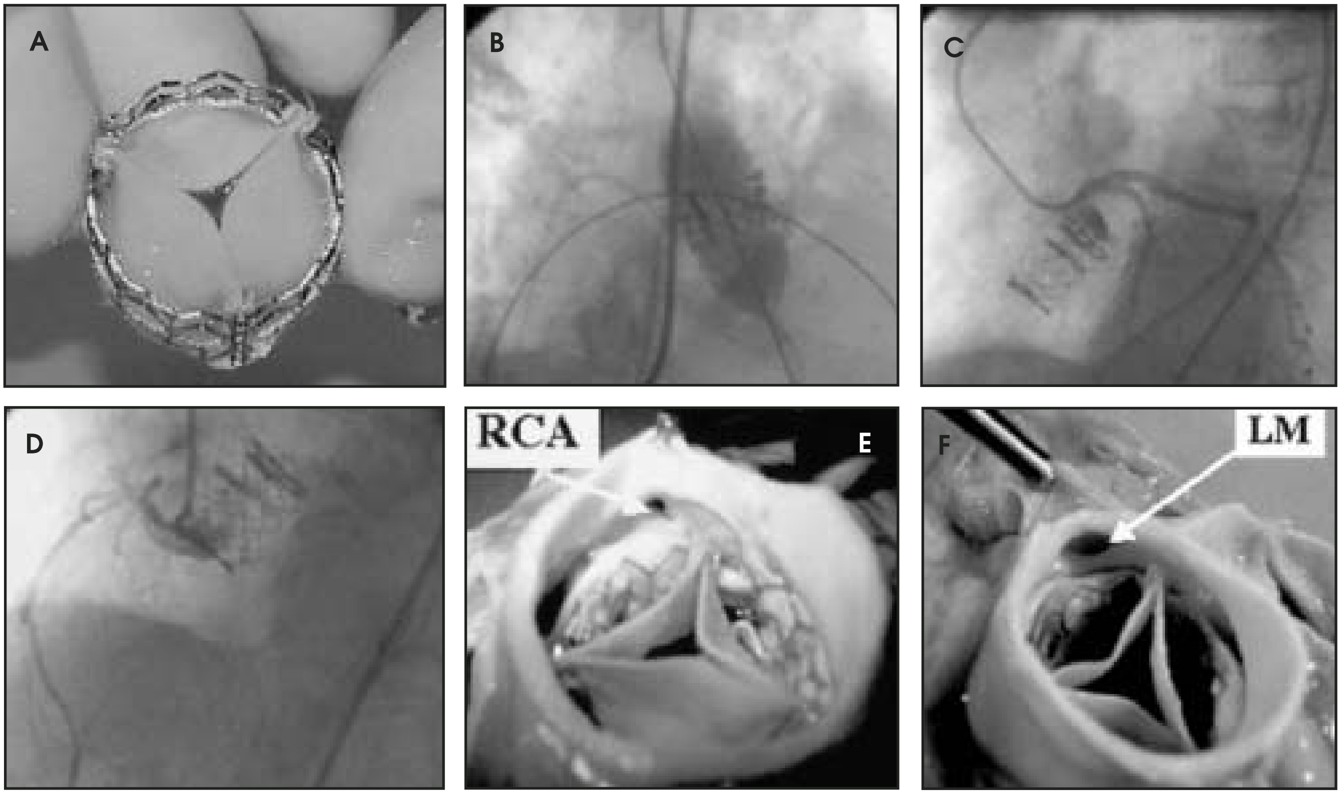

FIGURE 2. *(A) Equine pericardial valve sewn inside stainless steel stent. (B) Deployment of the valved stent into native position. (C and D) Angiography shows unobstructed coronaries. (E and F) Valve at autopsy showing unobstructed coronary ostia. Areas of stent wall nonapposition causing perivalvular regurgitation may also be seen. RCA = right coronary artery; LM = left main coronary artery. (Images reprinted with permission from Cribier A, Eltchaninoff H, Tron C, et al. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis.* J Am Coll Cardiol. *2004;43:698-703.[18])*

contrast to the study by Lutter and colleagues[14] in which stents ranging in length from 21 to 28 mm were used, Cribier and colleagues[17] used a shorter 14-mm stent to minimize the risk of coronary obstruction while allowing placement of the valved stent in the native position. The patient's severe peripheral arterial disease precluded passage of the large delivery system arterially, therefore femoral venous access was established using a 24F sheath. A guidewire was placed across the interatrial septum, which was then dilated with a 10-mm balloon, allowing antegrade crossing of the native aortic valve. Femoral arterial access was also established, and the guidewire was snared and externalized through the arterial sheath. Angiography documented normal function of the prosthesis and no coronary obstruction. Transesophageal echocardiography revealed moderate perivalvular regurgitation through an area of nonapposition between the stent and one of the heavily calcified native aortic commissures. Follow-up transesophageal echocardiograms obtained at weeks 1, 4, 7, and 9 documented normal valve function with stable paravalvular regurgitation. The patient died 17 weeks after valve implantation due to sepsis after an above-the-knee amputation necessitated by progressive peripheral ischemia.

In February 2004, Cribier and colleagues[18] reported a series of 6 additional patients in whom percutaneous aortic valve replacement was performed. The patients ranged in age from 57 to 91 years, had severe calcific aortic stenosis, had been declined surgery due to multiple comorbidities, and had New York Heart Association functional class IV congestive heart failure. As in the patient from the December 2002 report, the valve prostheses were implanted using a venous, transseptal approach. Right ventricular pacing was performed briefly at rates up to 220 beats per minute during balloon inflation to temporarily reduce cardiac output and allow for more stable and precise positioning of the valved stent. The valve used in these patients was composed of equine pericardium sewn into a stainless steel stent (Figure 2[18]). There was 1 procedural death due to premature dislodgement of the valved stent from the delivery system with embolization into the ascending aorta. This patient had undergone prior balloon valvuloplasty, which was complicated by a valve tear that caused severe aortic regurgitation. In 2 other patients, the guidewire was unintentionally straightened as it passed through the mitral valve toward the left ventricular outflow tract, causing damage to the mitral valve and severe mitral regurgitation. In all cases, angiography showed unobstructed coronaries and revealed an average mean gradient across the prosthesis of only 5.6 mm Hg. Two patients required transient cardiopulmonary resus-

Table 1. Patient outcomes in Cribier study[18]

Patient	Age (y)	Sex	Comorbidities	Mean gradient (mm Hg)* Pre/postimplant	Aortic regurgitation† Pre/postimplant	Ejection fraction (%)* Preimplant/ Follow-up	Outcome
1	57	M	Severe PAD, lung cancer s/p left lobectomy, silicosis, chronic pancreatitis	35/8	0/1	10/22	Died at 18 weeks, after leg amputation
2	80	M	Severe AR, recent stroke, CRI, asbestosis, prostate cancer	—	—	—	Died during procedure
3	91	M	Pacemaker, decubitus ulcers	56/6	2/3	29/40	Died at 4 weeks of acute abdominal syndrome
4	63	M	Rectal adeno-carcinoma, severe COPD, CRF	30/4	0/1	28/42	Died at 2 weeks of rectal hemorrhage
5	80	F	HTN, breast cancer with lung and bone metastases, COPD, kyphoscoliosis	38/6	1/1	34/53	Alive
6	77	M	IMI, stroke, CRF	31/13	2/3	19/48	Alive

Table data from Cribier A, Eltchaninoff H, Tron C, et al. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. *J Am Coll Cardiol.* 2004;43:698-703.[18]
* Follow-up measurement of mean gradient and ejection fraction performed at 2 weeks in patient 3 and at 4 weeks in patients 1, 4, 5, and 6.
† Post-implant assessment of AR performed immediately after implantation.
AR = aortic regurgitation; PAD = peripheral arterial disease; CRI = chronic renal insufficiency; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; HTN = hypertension; IMI = inferior myocardial infarction.

citation during balloon inflation. Three patients died of noncardiac causes at weeks 2, 4, and 18. The remaining 2 patients were reported to be alive and clinically stable at 8 weeks. In all cases, follow-up echocardiography showed normally functioning valve prostheses and only mild interatrial shunting. Varying degrees of perivalvular regurgitation were observed in all cases (Table 1[18]). The anticoagulation regimen consisted only of aspirin and Plavix (Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, New York, NY); heparin or low-molecular-weight heparin were only used briefly while patients were in the hospital.

To date, a reported total of 20 patients have undergone percutaneous aortic valve replacement with the equine pericardial valved stent. Thirteen valves have been implanted using the transseptal, antegrade approach, and 7 have been performed using an arterial, retrograde approach. There have been 3 technical failures utilizing the retrograde approach. Two procedure-related deaths have been reported in addition to the 1 death reported in the February 2004 article. All reported nonprocedural deaths have been due to noncardiac causes at times ranging from 1 to 4 months. The longest follow-up to date is 8 months.[19]

Future directions

Further trials are ongoing, including the single-center I-REVIVE trial, which hopes to study short- and long-term clinical outcomes of percutaneous aortic valve replacement in patients who are not surgical candidates.[18] Bonhoeffer and colleagues[20] hope to begin human trials in the United States in May 2005. In addition, several companies are developing valves for percutaneous placement in the aortic position, including NuMed Inc. and Palmaz/Bailey.[21] Core Valve is also developing a percutaneously delivered valve for the aortic position that will be mounted inside a self-expanding stent. Core Valve has deployed this stent in 21 animals and hopes to begin an initial feasibility trial in humans.[22] Percutaneous Valve Technologies, the company that initially developed the equine pericardial valve used in the studies by Cribier and coworkers,[17-19] was recently acquired by Edwards Lifesciences (Irvine, CA). They are continuing development and hope to have a Humanitarian Device Exemption from the Food and Drug Administration (FDA) by the end of 2005 and FDA approval by late 2007.

Conclusion

Several important lessons can be learned from the first reported patients and from the preceding animal studies. First, with a short stent and with proper positioning, it is possible to avoid coronary and mitral impingement. Second, the transseptal antegrade approach and the arterial retrograde approach are both feasible, though each has its own risks and limitations. Third, full apposition of the stent within the native aortic annulus is difficult, if not impossible, to achieve in a severely stenotic aortic valve; therefore, some degree of perivalvular regurgitation should be expected. Fourth, native valves with both severe stenosis and severe regurgitation may carry a high risk of embolization of the stent prior to balloon inflation due to the turbulent flow-reversal seen in severe aortic regurgitation. Fifth, reduced coronary perfusion pressure may mandate the placement of valved stents in the native position below the coronary arteries, even in cases of pure aortic regurgitation when placing the implant in an alternate location and leaving the native regurgitant valve intact might not otherwise interfere hemodynamically with systemic perfusion. Long-term follow-up data regarding the durability of the valved stent, the optimal antithrombotic regimen, and the possibility of late migration or embolization have yet to be published.

While still far from mainstream practice, percutaneous aortic valve replacement appears to be a promising new treatment that may offer new hope to patients who otherwise might have few options.

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THE AUTHOR

Adam M. Brodsky, MD

Dr. Brodsky is an Interventional Cardiology Fellow at Northwestern University in Chicago, IL. He graduated from Northwestern University Medical School in 1998. He completed his Internal Medicine Residency at Beth Israel Deaconess Medical Center, Boston, MA, in 2001 and his Cardiology Fellowship at Northwestern University in 2004.