CARDIOVASCULAR

Transapical Aortic Valve Implantation: An Animal Feasibility Study

Todd M. Dewey, MD, Thomas Walther, MD, PhD, Mirko Doss, MD, David Brown, MD, William H. Ryan, MD, Lars Svensson, MD, PhD, Tomislav Mihaljevic, MD, Rainer Hambrecht, MD, Gerhard Schuler, MD, Gerhard Wimmer-Greinecker, MD, Friedrich W. Mohr, MD, PhD, and Michael J. Mack, MD

Cardiopulmonary Research Science and Technology Institute, Dallas, Texas, Heart Center Leipzig, Leipzig, Germany, Department for Thoracic and Cardiovascular Surgery, JW-Goethe University, Frankfurt, Germany, and Cleveland Clinic Foundation, Cleveland, Ohio

Background. **Percutaneous aortic valve implantation has recently been performed in nonsurgical patients with severe aortic stenosis. Retrograde valve delivery has been problematic because of the size of the delivery system and concomitant peripheral vascular disease. We investigated a minimally invasive approach through the left ventricular apex for antegrade placement of a device-deliverable valve.**

Methods. **Transapical aortic valve implantation was performed using a 23-mm equine valve mounted on a stainless steel stent in 24 swine (weight range, 35 to 45 kg). A limited or full sternotomy approach was used to access the apex of the heart. The crimped valve was introduced through a sheath in the left ventricular apex. Fluoroscopy and echocardiography were used for guidance. Deployments were performed on the beating heart either with ventricular unloading using femoral extracorporeal circulation or rapid ventricular pacing.**

Results. **All valves were successfully delivered at the selected target site with acceptable visualization of the noncalcified aortic annulus. Valve migration occurred during eight deployments (two distal and six retrograde) secondary to persistent cardiac output, unfavorable annular anatomy, and dislodgement by the delivery catheter. Exact positioning of the nonmigrated valves at the aortic annulus was examined by necropsy of all animals at the end of the procedures. Paravalvular leak was noted in 14 of 18 (77.8%) valves remaining in situ.**

Conclusions. **The transapical approach was used for the successful antegrade placement of a stented valve, obviating the technical problems associated with a large delivery system transiting the peripheral vascular system. Stent design contributing to paravalvular leak remains problematic.**

(Ann Thorac Surg 2006;82:110–6)

Aortic valve replacement using cardiopulmonary bypass and cardioplegic arrest has been the standard approach for the treatment of severe aortic stenosis for decades. Increases in overall life expectancy combined with a rapidly growing elderly population have increased the numbers of patients presenting with calcific degenerative aortic stenosis. Patients now routinely present with comorbid illnesses that increase their operative risk with standard valve surgery. Although most surgeons believe that the preponderance of patients with critical aortic stenosis are referred for surgery, there likely exists a sizable subset of patients with critical aortic stenosis that are never referred for surgical evaluation. Reasons identified for nonreferral include an apparent lack of patient symptoms, a wish to avoid major surgery on the part of the patient, or a perceived prohibitive operative risk by the referring cardiologist. Balloon valvuloplasty has been used selectively in some patients considered nonoperative candidates. Valvuloplasty achieves an increase in aortic valve area by the fracturing of calcific deposits, separation of commissural fusion, and stretching of the aortic root. Unfortunately, widespread adoption of this technique remains low because of a high return of symptoms and restenosis within months of the procedure [1–3].

Recent advances in the field of aortic valve replacement have focused on avoiding a sternotomy and minimizing the incision size required to reach the valve. Comparative reports have demonstrated equivalent perioperative outcomes with corresponding reduced length of hospital stay using these minimally invasive techniques. Unfortunately, the greatest source of potential complications in a high-risk population, ie, the use of extracorporeal circulation with cardioplegic arrest, remains unchanged.

Advances in the integration of bioprosthetic valve

Accepted for publication Feb 13, 2006.

Presented at the Basic Science Forum of the Fifty-second Annual Meeting of the Southern Thoracic Surgical Association, Orlando, FL, Nov 10–12, 2005.

Address correspondence to Dr Dewey, 7777 Forest Lane, Suite A323, Dallas, TX 75230; e-mail: tdewey@csant.com.

Drs Dewey, Doss, and Wimmer-Greinecker disclose that they have a financial relationship with Edwards Lifesciences.

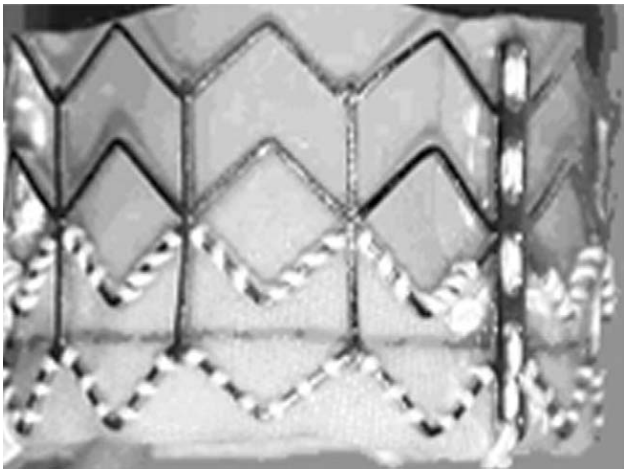


Fig 1. Cribier-Edwards Aortic Bioprosthesis Model 9000.

technology and balloon-expandable stainless steel stents have made intervention of the nonoperative patient with severe aortic stenosis feasible [4]. Once successfully delivered, the stent valves have demonstrated a significant reduction in transvalvular gradients [5]. Additionally, valve fixation in the annulus has been stable as evidenced by no reports of migration or embolization of the devices. Unfortunately, actual delivery of the device to the aortic annulus has been extremely problematic. Retrograde delivery of this prosthesis has been difficult because of the obligatory size of the delivery system and anatomic factors such as the diameter of the patients' peripheral arterial tree and concomitant occlusive disease. Thus, the majority of the procedures to date have been performed antegrade using a challenging transseptal approach to the aortic valve. Although possible, this approach places a premium on the individual practitioners' experience and skill level with transseptal puncture and may not be widely applicable to the average operator.

Previous reports have described the use of the left ventricular apex as a reproducible route for minimally invasively accessing the aortic annulus [6]. We performed a series of animal studies validating this approach as a valuable technique for facilitating the placement of a catheter-deliverable aortic stent valve in the aortic annulus.

Material and Methods

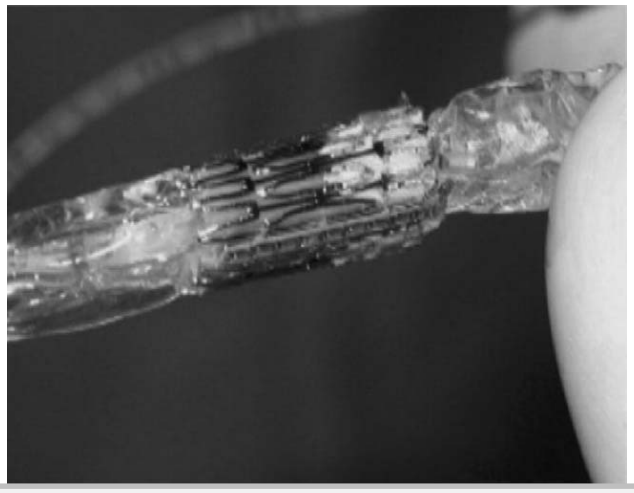
Experimental Group and Protocol

Transapical aortic valve implantation of twenty-six 23-mm Cribier-Edwards Aortic Bioprosthesis (Edwards Lifesciences, Irvine, CA; Fig 1) equine valves mounted on a stainless steel stent was performed in twenty-four 35- to 46-kg juvenile swine. Ten procedures were performed at the Edwards Lifesciences Biological Resource Center, (Irvine, CA), and 14 animals were operated on in the compliance with the NIH "Guide for the Care and Use of Laboratory Animals" (revised 1996). All components of the transapical animal work that were performed at the Edwards Lifesciences facility in Irvine were conducted in an American Association for Accreditation of Laboratory Animal Care–accredited facility and reviewed by the Edwards Institutional Animal Care and Use Committee. Experiments in Leipzig had been approved by the local government offices.

Device preparation was completed just before implantation for an antegrade delivery through the left ventricular apex. The delivery catheter was first flushed and primed using a heparinized saline solution. The deployment balloon was then inflated with a 4:1 mixture of saline and contrast and purged of air. The balloon was then reinflated and compared with a sizing ring to obtain the exact amount of saline and contrast to expand the balloon to 22 mm. The balloon was then deflated, and a partially crimped valve was placed over the balloon between two radiopaque markers. The valve is then fully crimped to just under 24F to permit passage through the delivery sheath (Fig 2). Confirmation of adequate crimping was obtained by passing the catheter with the valve through a 24F sizing bushing. All valve deployments were performed using volumetric inflation of the balloon owing to the variability of balloon expansion with pressure inflation.

Procedure

The animals were anesthetized, intubated, and placed in the dorsal recumbent position. Anesthesia was maintained with inhaled anesthetics and narcotic agents. An introducer sheath was placed in the right external jugular vein for volume and drug administration. A surgical cutdown was performed to cannulate the right internal carotid artery for placement of a calibrated pigtail catheter in preparation for preimplant and postimplant angiography. Intracardiac or epicardial echocardiography was performed on all pigs to aid with annular sizing, implantation, and evaluation of valve performance after



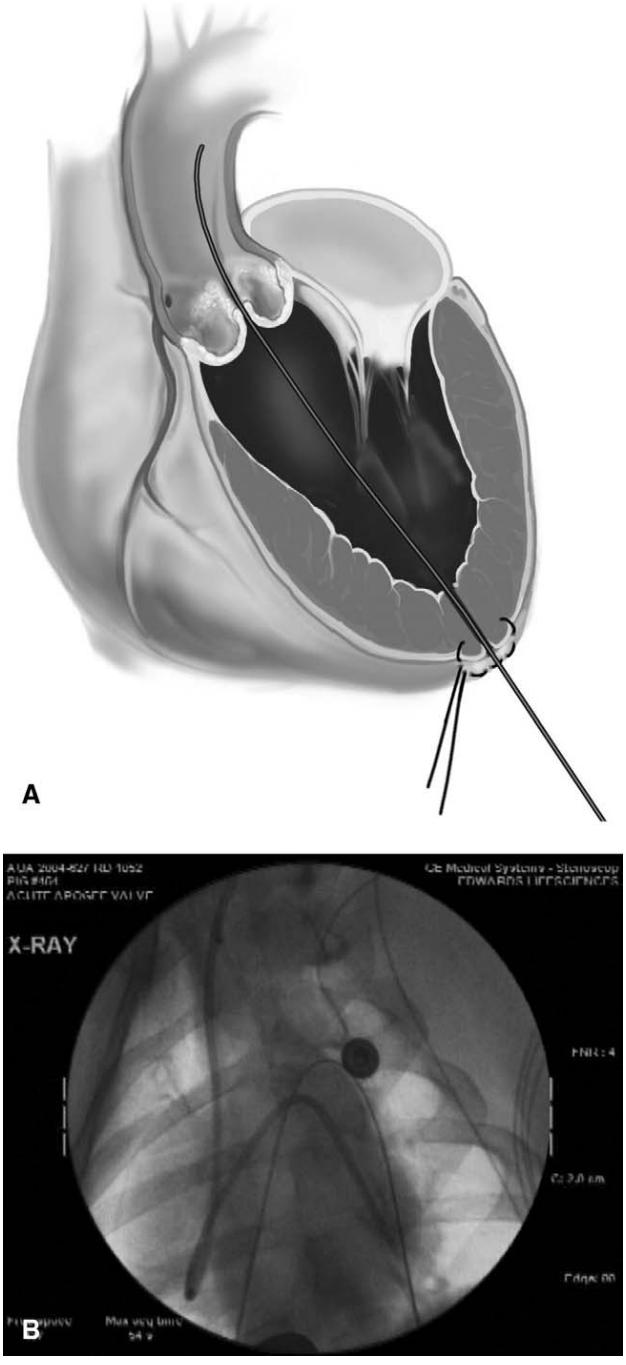


Fig 3. (A) Illustration of guidewire crossing the left ventricular cavity and into the descending thoracic aorta. (B) Fluoroscopic image of guidewire crossing the left ventricular cavity and into the descending thoracic aorta.

placement. Femoral cutdowns were performed to access the femoral vessels for cannulation in all 11 animals placed on cardiopulmonary bypass.

The apex of the heart was exposed either through a ministernotomy that extended from the subxiphoid cised and tacked to the chest wall. A double pursestring suture of 3-0 polypropylene was placed in the apex of the heart to provide hemostasis. The animals were then anticoagulated with 300 IU/kg of heparin. Activated clotting times were measured every 15 to 20 minutes to maintain adequate anticoagulation. Cineangiography of the aortic root with a calibrated catheter was then performed to size the aortic annulus. Confirmation of the measured annular size was achieved by echocardiogra-

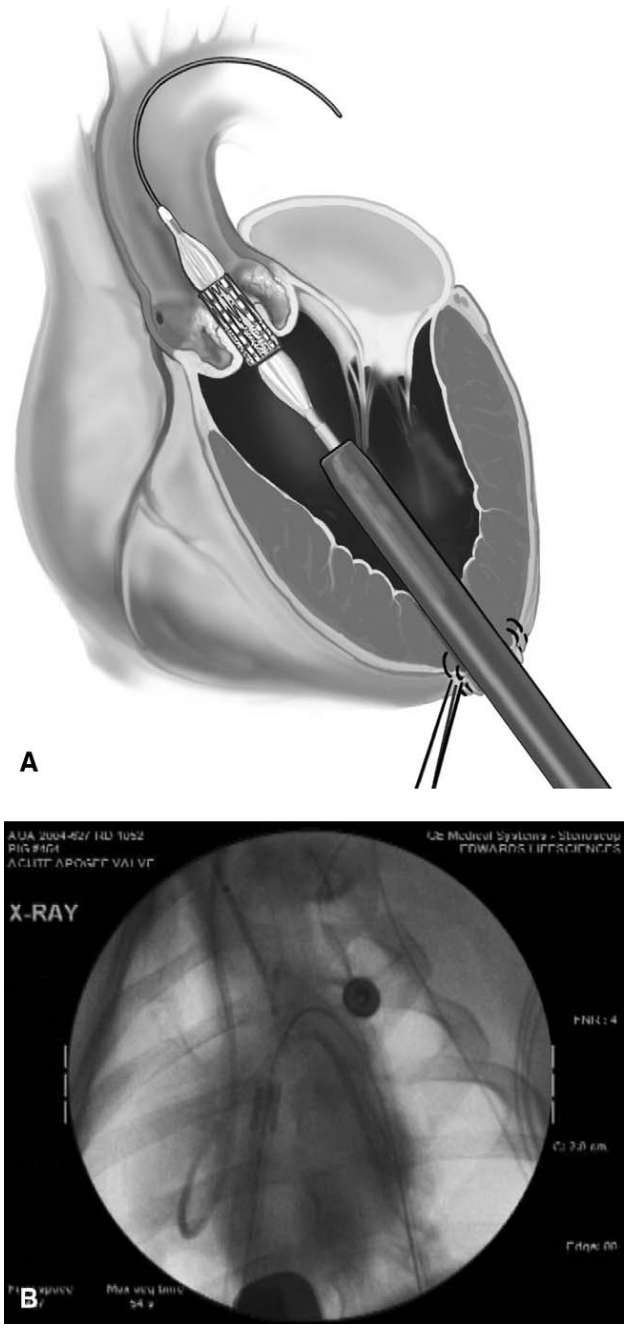


Fig 4. (A) Illustration of valve on the delivery catheter crossing the

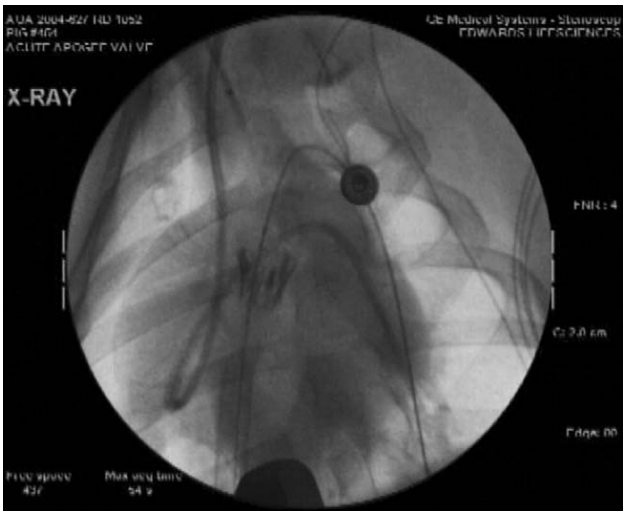


Fig 5. Fluoroscopic image of valve during deployment.

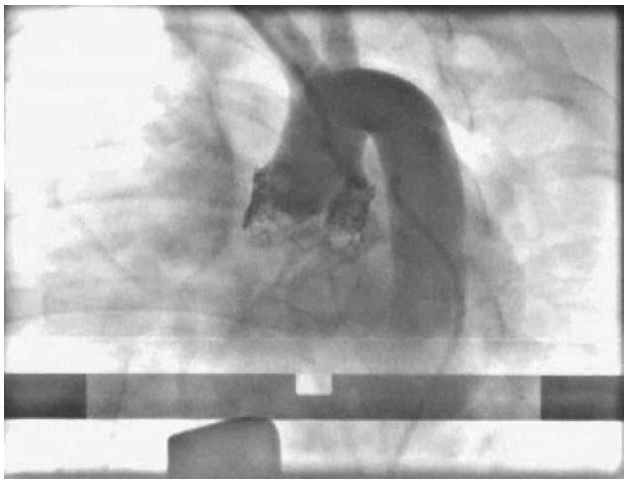


Fig 6. Completion angiogram after valve deployment.

phy. The animals were selected by weight to provide an aortic annulus of between 15 and 21 mm in size. Landmarks from the cineangiogram were used to identify the noncalcified porcine annulus. Additionally, small puffs of contrast were given during implantation to locate the annulus for deployment.

The left ventricle was accessed with an 18-gauge needle through the pursestring sutures. A 5F introducer sheath was inserted over a small guide wire into the left ventricle and secured with snares. This introducer was then used to place a 0.035-inch superstiff guidewire across the aortic valve and down the descending thoracic aorta (Fig 3). Once the stiff wire was positioned, the small introducer sheath was then removed. A cruciate incision was then made in the apex, and the 24F introducer sheath was placed into the left ventricle below the aortic valve under fluoroscopic guidance (Fig 4). The crimped valve on the delivery catheter was then introduced through the delivery sheath and into the left ventricle. The catheter has two radiopaque markers to identify the margins of the deployment balloon. Cardiac output was then reduced, either by initiating cardiopulmonary bypass or by instituting rapid ventricular pacing. Once transaortic valve flow had been reduced, as confirmed by loss of systolic pressure spike on arterial monitoring, the valve was positioned so that the annulus bisected the stent. Small boluses of contrast were given to aid in identifying the noncalcified porcine annulus and coronary ostia. Once positioned, the valve was deployed by inflating the delivery balloon with saline mixed with contrast to achieve full expansion of the stent (Fig 5). Once deployed, the balloon was deflated and rapid ventricular pacing discontinued. The stent-valve sits within the confines of the native porcine annulus and leaflets. The delivery catheter, sheath, and guidewire are then completely removed. Pigs on cardiopulmonary bypass are then weaned from extracorporeal support. A completion cineraphy was used to evaluate valve function, leaflet motion, and regurgitation. The animals were then sacrificed, and an examination of the heart was performed to evaluate the positioning of the valve and to identify any damage to the annulus or adjacent structures.

Results

The average diameter of the aortic annulus in the juvenile swine was 19.7 ± 1.3 mm as measured using a calibrated catheter and cineangiography of the aortic root (Table 1). All valves were deployed successfully at the intended target site primarily using fluoroscopy. Intracardiac echocardiography was available for 10 animals but did not provide the necessary discrimination of the aortic annulus and the delivery catheter to be the primary imaging modality for implantation. The first 2 animals had the valves deployed without maneuvers to decrease cardiac output. Of the remaining valve deployments, 11 were performed using cardiopulmonary bypass, and 11 were done using rapid ventricular pacing to decrease cardiac output and forward flow across the aortic annulus. Three animals had ventricular fibrillation

Table 1. Results of Animal Experiments[a]

Characteristics	Results
Mean weight (kg)	40.0 ± 3.1
Mean annular size (mm)	19.7 ± 1.3
None	2/24 (8.3%)
CPB	11/24 (45.8%)
RVP	11/24 (45.8%)
Distal embolization	2/26 (7.7%)
LV embolization	6/26 (23.1%)
Regurgitation (yes/no)	14/18 (77.8%)
Mean regurgitation Value	1.8 ± 1.4

[a] Twenty-six valves were deployed in 24 animals.

shortly after valve placement and completion aortogram, and before intended sacrifice, secondary to ostial coronary artery impingement. A third animal experienced fibrillation after the valve migrated proximally into the left ventricular cavity.

Eight of 26 valves (31%) migrated (two distally into the ascending aorta, and six proximally into the left ventricle) after being deployed in the aortic annulus. The two distal migrations were in the first 2 experimental animals in which ventricular unloading either with rapid ventricular pacing or cardiopulmonary bypass was not used. One of the proximal migrations occurred as a result of the delivery balloon sticking to the stent and subsequently dragging the valve back into the left ventricle as the catheter was being removed. The remaining valves were pushed back into the left ventricle by systemic pressure once the animal was weaned from cardiopulmonary bypass or rapid ventricular pacing discontinued. A second valve was subsequently successfully deployed into the aortic annulus in 2 animals without removing the initial valve from the heart. These animals account for 26 valves being deployed into 24 swine. One animal experienced fibrillation when the valve migrated proximally into the left ventricle; the other migrations were not associated with any adverse hemodynamic consequences.

Paravalvular leak or aortic regurgitation was noted in 14 of the 18 (77.8%) valves that remained intraannular and did not migrate. The degree of regurgitation was visually estimated from the completion aortogram performed after implantation and retention of the valve in the annulus. A scale was derived in which mild regurgitation was denoted as 1+, moderate 2+, moderate to severe 3+, and wide open reflux of contrast into the ventricle as 4+. The mean degree of regurgitation was 1.8 ± 1.4. Only two valves showed severe (4+) regurgitation secondary to nonfunction of one of the leaflets that became trapped by a fold of aorta at the sinotubular junction. This occurred in 2 animals with smaller than average ascending aortas. The remaining animals exhibited lesser degrees of paravalvular leak across the annulus into the left ventricle on completion angiogram. The leak primarily appeared to be caused by regurgitation of blood back through the stent interstices, thereby going around the leaflets in an area not covered by cloth. Central leak through the valve was not noted in the majority of animals.

Comment

Percutaneous implantation of a stent type aortic valve became a clinical reality with the first reported successful human case by Cribier and colleagues in 2002 [4]. Subsequently, intense interest has formed toward the development of a catheter-delivered valve for use in patients with critical aortic stenosis declined for surgery. These first-generation devices have now been implanted in selected patients worldwide. As with any new device, significant questions regarding patient selection, implant-what constitutes an acceptable result remain to be answered.

This study was initiated to validate the transapical technique as a viable alternative to either an antegrade transseptal or a retrograde approach to the aortic valve. The majority of cases documented in the literature have been performed antegrade, in which the valve travels over a superstiff guidewire across the atrial septum, through the mitral valve, and ultimately across the aortic valve [7]. The wire by necessity forms a loop in the left ventricle so that the guidewire becomes coaxial with the ventricular outflow tract and the valve is not angulated across the annulus. Dramatic hemodynamic deterioration has been documented when the loop of wire in the ventricle becomes too large and places traction on the anterior leaflet of the mitral valve, causing severe mitral regurgitation [7]. Another limitation of the transseptal technique is that the operator has reduced fine motor control over the valve as the intervening loop provides significant "play" in the system. Most of the described morbidity and mortality of the procedure can be traced to the technical difficulty of this challenging approach. Likewise, the retrograde approach can be problematic because of the obligatory size of the 24F delivery sheath. Many of these elderly patients have coexisting peripheral vascular disease that precludes passing large size sheaths or catheters from the groin, around the arch of the thoracic aorta, and across the aortic valve annulus. Moreover, this technique also runs the risk of embolizing atherosclerotic material from the aorta into the distal circulation. However, in patients with adequate vessel size and without peripheral vascular disease, a retrograde approach would be the easiest and most direct of the percutaneous routes. We believe that the transapical approach provides a reliable alternative to either of these techniques. The distance of the aortic valve from the left ventricular apex is straight and relatively short, which provides good control over the delivery catheter. Additionally, in this animal series, control over the placement of the valve was believed to be optimal, and all valves were deployed at the intended target site.

Valve migration after deployment was seen in eight valves for clearly identifiable reasons. The two distal embolizations were in animals in which no attempt was made to decrease cardiac output during deployment. It became quickly obvious that with maintained blood flow across the aortic valve, the deployment balloon acts like a sail and carries the valve distally into the ascending aorta. Once measures such as cardiopulmonary bypass or rapid ventricular pacing were instituted to decrease cardiac output during deployment, no further distal embolizations were noted. Likewise, the six episodes in which the valve migrated into the ventricle could primarily be attributed to the animal model. On one occasion, early in the experience, a valve was crimped too tightly to the delivery catheter, so that on deployment the valve stuck to the balloon and was pulled back into the ventricle on removal of the catheter. The rest of the valve migrations

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