EXPEDITED REVIEW

Treatment of Calcific Aortic Stenosis With the Percutaneous Heart Valve

Mid-Term Follow-Up From the Initial Feasibility Studies: The French Experience

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OBJECTIVES

The aim of this work was to study the feasibility, safety, efficacy, and durability of percutaneous heart valve (PHV) implantation in the aortic position.

BACKGROUND

We developed a PHV (equine pericardium valve in a balloon-expandable, stainless-steel stent) to treat patients with inoperable aortic stenosis (AS).

METHODS

Thirty-six patients (aortic valve area ≤0.7 cm², New York Heart Association [NYHA] functional class IV, and severe comorbidities), formally declined for surgery, were recruited on a compassionate basis. The PHV was implanted by retrograde or antegrade trans-septal approach. Clinical and echocardiographic outcomes were assessed serially.

RESULTS

Twenty-seven patients were implanted successfully (23 antegrade, 4 retrograde) in the subcoronary position with improvement in valve area (0.60 ± 0.11 cm² to 1.70 ± 0.10 cm², p < 0.0001) and transvalvular gradient (37 ± 13 mm Hg to 9 ± 2 mm Hg, p < 0.0001). Paravalvular aortic regurgitation was grade 0 to 1 (n = 10), grade 2 (n = 12), and grade 3 (n = 5). One week post-procedure, improvement in left ventricular function (45 ± 18% to 53 ± 14%, p = 0.02) was most pronounced in patients with ejection fraction <50% (35 ± 10% to 50 ± 16%, p < 0.0001). Thirty-day major adverse events after successful implantation were device-related.

CONCLUSIONS

Percutaneous heart valve implantation is feasible in inoperable patients with end-stage AS leading to hemodynamic and clinical improvement. Continued advances and improved patient selection should decrease adverse events in the near future. (J Am Coll Cardiol 2006;47:1214–23) © 2006 by the American College of Cardiology Foundation

Aortic stenosis, the most common form of valvular heart disease in adults (1), affects thousands of patients every year, causing significant morbidity and mortality in those with advanced disease. To date, surgical valve replacement is the only effective therapy for these patients, improving survival and ameliorating symptoms (2). However, almost one-third of patients with severe valvular lesions who could benefit most from intervention are declined for operative treatment because of end-stage disease, advanced age, and multiple comorbidities with subsequent short life expectancy (1). The size of this untreated cohort is expected to increase in the next several years reflecting the aging population and improving therapeutic options in patients with multiple and advanced medical conditions.

The initial attempts to treat non-surgical patients with advanced aortic stenosis began with balloon aortic valvuloplasty (BAV) in 1985 (3). This technique, initially met with enthusiasm, was largely abandoned by clinicians as the benefits of valvuloplasty rarely lasted more than one year (4). The problem of valve restenosis after balloon dilation was finally addressed in 1999 with the development of a bioprosthetic heart valve, which was sutured onto a balloon expandable stent (Percutaneous Valve Technologies, Edwards Lifesciences, Irvine, California) (Fig. 1). Though previous attempts at percutaneous valve replacement in the aortic position had been limited by the applicability to humans (5,6), this percutaneous heart valve (PHV) was successfully implanted on April 16, 2002, in a patient with inoperable aortic stenosis and life-threatening comorbidities (7).

Since then, improvements in technique and a more complete comprehension of percutaneous aortic valve re-
placement have been developed and partially reported in six patients (four patients before the onset of the protocol-driven study, two patients included in the current analysis) (8). In August 2003, we started a single-center pilot trial to study the feasibility and safety of compassionate percutaneous valve implantation in patients with end-stage aortic stenosis and no surgical options (the Initial Registry of EndoVascular Implantation of Valves in Europe [I-REVIVE] trial). With the acquisition of Percutaneous Valve Technologies (Fort Lee, New Jersey) by Edwards Lifesciences, the protocol continued with minor amendments as the Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST) trial. In the following text we describe our experience with the initial 36 patients enrolled in our institution for percutaneous aortic valve implantation.

METHODS

Thirty-six elderly patients that were able to give informed and signed consent were recruited for percutaneous valve implantation at Charles Nicolle Hospital, University of Rouen, France. Eligibility for entry into the study required the presence of severe aortic valve stenosis ($\leq 0.7 \text{ cm}^2$) with associated symptoms (by New York Heart Association [NYHA] functional class IV dyspnea) that were expected to benefit from isolated valve replacement. Patients had to be refused for standard aortic valve replacement by two independent cardiac surgeons on the basis of their high risk for surgery (Parsonnet's score $\geq 30$) (9). Exclusion criteria included the following: vascular disease that precluded access, severe deformation of the chest, intracardiac thrombus, unprotected stenosis of the left main coronary artery not amenable to percutaneous intervention, myocardial infarction (MI) within seven days, prosthetic heart valves, active infection, leukopenia ($<3,000$ white blood cells/mm$^3$), coagulopathy, active bleeding, or acute anemia (hemoglobin $<9$ mg/dl). Patients that could not be fully dilated with a 23-mm aortic valvuloplasty balloon (notable waist) and patients with a native aortic valve annulus size $\geq 24 \text{ mm}$ or $<19 \text{ mm}$ were also excluded. The study was approved and performed in accordance with the regulations of our institutional ethics committee (CCPPRB, Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) and the French government (AFSSAPS, Agence Francaise de Sécurité Sanitaire des Produits de Santé).

Definitions and baseline measurements. The primary objectives of this study were to evaluate the feasibility and safety of PHV implantation. Feasibility was evaluated by procedural success defined as accurate placement of the PHV in the subcoronary position with associated improvement of hemodynamic parameters (at least $30\%$ reduction in mean transvalvular aortic gradient) and absence of severe aortic regurgitation (grade $4$) (10). Safety was evaluated by the occurrence of major adverse cardiac and cerebrovascular events (MACCE) or other valve-related adverse events. Major adverse cardiac and cerebrovascular events were defined as death, MI, emergent cardiac surgery, and cerebrovascular accident. Any MACCE that occurred either during or within 30 days of PHV implantation was considered a procedure-related complication. Any adverse event that was secondary to PHV malfunction after implantation was considered a device-related complication. Safety was

Figure 1. (A) Top view of the percutaneous heart valve in the closed position showing the three pericardial leaflets sutured to the stainless-steel stent. (B) Side view of the percutaneous heart valve crimped over a 3-cm $\times$ 22-mm balloon catheter. (C) Side view of the percutaneous heart valve after being expanded by the delivery balloon.
assessed at 1, 3, 6, and 12 months; after 1 year, patients were followed every 6 months.

The secondary objectives of the study were to obtain data regarding the efficacy and durability of the PHV. Efficacy and durability were assessed by NYHA functional classification and hemodynamic improvement (measured by echocardiography). Hemodynamic variables, such as native and prosthetic aortic valve gradient, area, and regurgitation (valvular or paravalvular, graded from 0 to 4) (10), were evaluated by standard methods of echocardiographic measurement. Clinical evaluation and echocardiographic examination were performed immediately post-procedure, on day 1, day 7, 1 month, 3 months, 6 months, and 12 months; afterwards, patients were followed every 6 months.

Valve anatomy and function were determined in all patients by transesophageal echocardiography and transthoracic echocardiography (TTE) pre-procedure; coronary anatomy was also evaluated pre-procedure. In addition to echocardiographic measurements, right-sided heart pressures, cardiac output, oxygen saturations, and aortic transvalvular pressure gradient were measured on the day of implantation by invasive methods. Valve calcification was assessed qualitatively by fluoroscopic evaluation.

Procedure. The materials and technique for implantation have been previously described in detail (7,8,11). Briefly, each procedure was performed under mild sedation and local anesthesia. All patients received aspirin (160 mg) and clopidogrel (300 mg) 24 h before valve placement; antibiotics for procedural prophylaxis (first generation cephalosporin) were given 1 h before. After measurement of baseline hemodynamics, supra-aortic angiography and placement of a right ventricular pacing lead were performed. Heparin 5,000 IU was given intravenously before retrograde catheterization of the aortic valve. Retrograde pre-dilation of the aortic valve was done in all patients (except two who were dilated antegrade) with a 23-mm Z-MED balloon (NuMED Inc., Hopkinton, New York) during rapid ventricular pacing (200 to 220 stimulations/min) (Fig. 2). Delivery of the valve was performed by an antegrade trans-septal or retrograde approach.

In the antegrade approach, atrial trans-septal catheterization was performed, and a 7-F Swan-Ganz catheter (Edwards LifeSciences, Irvine, California) was used to cross the mitral valve and direct a guidewire across the aortic valve (Fig. 3A). Using the pigtail catheter as a conduit, this guidewire was exchanged for an extra stiff guidewire, which was snared and externalized through the left femoral artery sheath. The septum was then dilated with a 10-mm septostomy balloon. The PHV was advanced over the guidewire through a 24-F sheath (COOK, Bjaeverskov, Denmark) in the right femoral vein. A 7-F Sones catheter (Cordis, Miami, Florida) was advanced over the same guidewire from the left femoral artery to facilitate valve placement (Fig. 3B).

In the retrograde approach, pre-closure of the common femoral artery puncture site was done before introduction of the 24-F sheath (four patients) using two 10-F Prostar XL devices (Abbott Vascular Devices, Redwood City, California) (12). After retrograde catheterization of the aortic valve, the crossing catheter was exchanged for an extra stiff guidewire, and pre-dilation of the aortic valve was done as described previously. The femoral artery was then predilated with a series of dilators of increasing size (18-, 20-, and 22-F) in order to facilitate entry of the 24-F sheath.

Regardless of the approach used, the final steps of PHV implantation were similar for both methods. The PHV was mounted onto a 22-mm Z-MED II balloon (NuMed Canada Inc., Cornwall, Ontario, Canada) using a specially designed crimper. The supra-aortic angiogram and native valve calcifications were used as anatomical

Figure 2. Electrocardiogram and aortic pressure curve depicting the effect of rapid stimulation (arrows) of the right ventricle (200 to 220 stimulations/min).
landmarks for valve placement in the anteroposterior projection (mid-line of the stent frame was placed at the level of the calcifications). All valves were deployed (Figs. 3C and 3D) during rapid pacing except two patients that were implanted during cardiac arrest. Hemodynamic improvement was measured immediately afterwards, and a supra-aortic angiogram was performed in patients without renal insufficiency to verify placement as well as the presence of aortic regurgitation (Fig. 3E). A cranial view of the stent-valve was used to evaluate uniform expansion of the PHV (Fig. 3F). Arterial access was managed using closure devices and/or surgical repair before device use or in cases of device failure. Venous access was managed by manual compression. Antibiotics were given up to 48 h after the procedure. Subcutaneous enoxaparin (40 mg/day) was administered until the day of discharge. Clopidogrel (75 mg/day) was continued for one month, and aspirin (160 mg/day) was continued indefinitely.

Statistical analysis. Comparison of clinical and echocardiographic variables with baseline values was performed using the non-parametric Wilcoxon rank sum test. Comparison of procedural times was done by the Mann-Whitney U test. Differences were considered statistically significant for p < 0.05. All values were expressed as mean ± SD.

Figure 3. (A) Swan-Ganz (SG) catheter is used to direct a guidewire (GW) across the native aortic valve in the antegrade approach. (B) Guidewire loop in the left ventricle is tracked by the percutaneous heart valve from the right femoral vein (antegrade approach). Sones catheter (SC) from the left femoral artery is used to help position the percutaneous heart valve. Native aortic valve calcifications (arrows) in the anteroposterior projection transect the mid-line of the length of the stent valve. (C) Deployment of the percutaneous heart valve using the antegrade approach. (D) Valve deployment via the retrograde method. (E) Supra-aortic angiogram showing no aortic regurgitation and the subcoronary position of the percutaneous heart valve (arrow: filling of the left coronary artery). (F) Cranial view of the percutaneous heart valve showing symmetrical and complete expansion of the stent frame. MS = Mullins sheath; PL = pacing lead.
RESULTS

Patient characteristics. Characteristics of the patients recruited are shown in Table 1. In addition to their age and end-stage aortic stenosis, these patients had extensive and multiple comorbid conditions (≥3 per patient). Other significant comorbid conditions not detailed in the table included severe kyphoscoliosis, severe osteoporosis, hepatic cirrhosis, systemic sclerosis, angiodysplasia of the colon with chronic anemia (hematocrit <30%), myelodysplastic syndrome with chronic anemia, chronic steroid use, antiphospholipid syndrome with previous thrombotic history, peripheral neuropathy, severe obesity, severe right heart failure, and Parkinson’s disease. One patient was a Jehovah’s Witness. All native aortic valves were tricuspid and calcified (12 heavy, 17 moderate, 7 mild).

Procedural success. Of the 36 patients enrolled, 35 patients were taken to the catheterization laboratory (Fig. 4): 1 patient died of sudden cardiac death while awaiting his procedure. After pre-dilation, one procedure was cancelled because the annulus size was inappropriately large for a 23-mm PHV (the 23-mm balloon could not be stabilized in the native valve during valvuloplasty). One patient in cardiogenic shock arrested during pre-dilation of the aortic valve and had an unsuccessful resuscitation. Among 33 patients, the antegrade trans-septal approach was used in 26 cases, and retrograde implantation was attempted in the remaining 7 cases. Twenty-two of the antegrade implantations were performed successfully with four technical failures. Two of these patients could not hemodynamically tolerate the guidewire across the mitral valve, and the procedure was aborted before proceeding to valve implantation. In one case of migration, the PHV was positioned too high, and in the other case, the native valve was only mildly calcified with a large annulus.

Table 1. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Age, yrs</td>
<td>80 ± 7 (range 62–91)</td>
</tr>
<tr>
<td>≥ 85 yrs</td>
<td>9 (24)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>21 (57)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>11 (30)</td>
</tr>
<tr>
<td>31%–50%</td>
<td>15 (42)</td>
</tr>
<tr>
<td>≤30%</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>28 (76)</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (70)</td>
</tr>
<tr>
<td>Renal failure*</td>
<td>14 (38)</td>
</tr>
<tr>
<td>Severe lung disease</td>
<td>15 (41)</td>
</tr>
<tr>
<td>Pulmonary hypertension†</td>
<td>14 (38)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Porcelain aorta</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>12 (32)</td>
</tr>
<tr>
<td>≥ grade 3 regurgitation</td>
<td>10 (27)</td>
</tr>
<tr>
<td>≥ moderate stenosis</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Active cancer</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Previous chest irradiation</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Other comorbidity</td>
<td>22 (59)</td>
</tr>
<tr>
<td>Parsonnet’s score</td>
<td>47 ± 9</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>12 ± 2</td>
</tr>
</tbody>
</table>

*Serum creatinine >2 mg/dl or creatinine clearance ≤30 ml/min. †Mean pulmonary artery pressure >30 mm Hg or systolic pulmonary artery pressure >60 mm Hg.

CABG = coronary artery bypass grafting.

Figure 4. Schematic representation of patient enrollment and procedural success (*Patient #16 was implanted successfully by the antegrade approach after initial retrograde failure). PHV = percutaneous heart valve.
In both situations, the PHV was deployed in the aorta (thoracic descending aorta in one, and between the left common carotid and left subclavian artery in the other) without sequelae. In all cases of technical failure, the patients were discharged from the catheterization laboratory in stable condition.

Four of seven patients were successfully implanted using the retrograde method. Of the three technical failures, one patient could not be implanted because the stent-mounted catheter was too short to reach the aortic valve (PHV removed surgically from the femoral artery). Two of the patients’ valves could not be crossed retrograde with the delivery system because of extensive calcification, and the PHV was implanted in the descending aorta without sequelae. In one of these cases, the PHV was successfully implanted by the antegrade approach in the same session. A total of 27 (75%) patients were implanted successfully.

The procedural time for the antegrade approach was 164/11006 38 min in the I-REVIVE trial and 130/11006 30 min in the RECAST trial (p 0.047). No detectable atrial shunt could be measured by oximetry at the end of the procedure. Procedural time for the retrograde approach (only I-REVIVE patients) was 96/11006 23 min.

Echocardiographic data. A statistically significant increase in aortic valve area (AVA) was seen in the group of patients with successful implantation. Twenty-four hours after the procedure, the AVA, measured by TTE, increased from 0.60 ± 0.09 cm² to 1.70 ± 0.11 cm² (p < 0.0001, n = 25 surviving patients). At 1, 3, 6, 12, and 24 months, the AVA remained stable at 1.68 ± 0.11 cm² (n = 16), 1.66 ± 0.09 cm² (n = 12), 1.63 ± 0.07 cm² (n = 7), 1.75 ± 0.18 cm² (n = 3), and 1.64 ± 0.04 cm² (n = 2), respectively (p = NS) (Fig. 5A). Similarly, the mean aortic gradient decreased from 37 ± 13 mm Hg to 9 ± 2 mm Hg post-procedure (p < 0.0001, n = 25), and remained 10 ± 2 mm Hg, 11 ± 2 mm Hg, 11 ± 2 mm Hg, 10 ± 1 mm Hg, and 12 ± 1 mm Hg (1, 3, 6, 12, and 24 months, respectively) during follow-up (p = NS) (Fig. 5B). Peak velocity across the aortic valve decreased from 4.01 ± 0.60 m/s to 2.25 ± 0.40 m/s post-implantation (p < 0.0001), and was 2.36 ± 0.25 m/s, 2.45 ± 0.25 m/s, 2.42 ± 0.31 m/s, 2.33 ± 0.11 m/s, and 2.36 ± 0.17 m/s upon follow-up (p = NS).

The ejection fraction also improved significantly in the patient group with a successful implantation. Left ventricular function was 45 ± 18% pre-procedure and 53 ± 14% (Fig. 6A) one week post-procedure (n = 22, p = 0.02). The most dramatic improvements were seen in patients that had depressed function at baseline (Fig. 6B). In these 15 patients, the ejection fraction (35 ± 10%) increased to 50 ± 16% (p < 0.0001) at one week.

Aortic regurgitation in patients after implantation was always paravalvular in origin. In 10 patients, the regurgitation was mild (grade 0 to 1). In 10 patients, moderate (grade 2) paravalvular leak was observed, and in 5, moderate-to-severe regurgitation was noted (grade 3). In the two patients without post-procedure echocardiography, aortic insuffi-

Figure 5. (A) Improvements in aortic valve area in patients 24 h, 1, 3, 6, 12, and 24 months after successful implantation. (B) Decrease in mean aortic gradient in patients 24 h, 1, 3, 6, 12, and 24 months after successful implantation.
ciency was grade 2 by angiography. The amount of para-valvular leak was unchanged in most patients during follow-up. In two patients, an improvement of paravalvular leak by one grade was seen three months after the procedure. In two patients, an increase of paravalvular leak by one grade was seen after one week. No atrial shunt was visualized by TTE at three-month follow-up.

Clinical follow-up. Six of the 27 patients with PHV implantation had a complication during the procedure. Two patients died as a consequence of cardiac tamponade. One of these patients, with severe dextrorotation of the heart, had a complicated trans-septal puncture. The other patient, on chronic steroid therapy for pulmonary fibrosis, had a slow bleeding perforation of the right ventricle from the pacing lead; infection and subsequent sepsis developed after surgical repair. Another patient on chronic steroids for treatment of rheumatologic disease developed urosepsis three days after the procedure and died two days later. Complete heart block with temporary loss of pacing lead contact occurred in one case; despite successful PHV implantation, prolonged resuscitation lead to irreversible brain damage. One patient developed a stroke during retrograde catheterization of the aortic valve. She expired at 33 days secondary to multi-organ failure. Intractable hypotension in the procedure room after removal of the 24-F sheath from the femoral artery was the cause of another death. No etiology was found at autopsy; the PHV appeared normal and appropriately positioned (Table 2).

The remaining 21 patients with successful PHV implantation experienced remarkable amelioration of symptoms with improvements in functional class. Five patients improved to NYHA functional class I; 14 improved to NYHA class II, and 2 improved to NYHA class III (limited by severe lung disease). Despite their improvements, however, their advanced comorbid conditions limited the extent of their survival. One patient with severe right and left ventricular dysfunction died of a ventricular arrhythmia at day 18 post-procedure. Three patients died of progressive renal failure at two months. Three patients died of a non-cardiac cause during a prolonged and complicated postoperative course (toe amputation at 2 months, revascularization of the lower extremities at 3 months, and orthopedic surgery at 5.5 months). Third-degree heart block developed in one patient three months after the procedure. Pacemaker implantation was complicated by pulmonary embolus, sepsis, and death. Another patient expired at three months secondary to pneumonia. One patient with underlying metastatic breast cancer, died with a morphine overdose (3.5 months), (Table 2).

Figure 6. (A) Improvement in ejection fraction one week after successful implantation (n = 22). (B) Improvement in ejection fraction comparing baseline values with values one week after successful implantation in patients with left ventricular function <50% (n = 15).
Device-related complications (0% occurrence in this study) were not a cause of death in any of these cases.

To date, 11 patients are alive (3 from the I-REVIVE trial, 8 from the RECAST trial) and have returned to a normal life, limited only by their previous medical conditions (NYHA functional class I in 4 patients, class II in 6 patients, class III in 1 patient). Their follow-up is 9 months (n = 2), 10 months (n = 3), 11 months (n = 1), 12 months (n = 2), 23 months (n = 1), and 26 months (n = 2). The valve function by the most recent echocardiographic exam (valve area 1.69 ± 0.10 cm², mean transvalvular gradient 11 ± 3 mm Hg, measured at 3 to 24 months post-procedure) is unchanged compared to the day of implantation (valve area 1.72 ± 0.13 cm², mean transvalvular gradient 9 ± 3 mm Hg, p = NS). The amount of paravalvular leak in these patients is grade 0 to 1 (n = 3, 11 months; n = 4, 26 months). Ejection fraction in this group is 53 ± 12% (baseline 51 ± 15%, p = NS). One patient has not returned for repeat TTE, but remains clinically improved.

Seven patients who underwent BAV without a successful valve implantation or attempted valve implantation, survived several months after their procedure. One patient survived 19 months but suffered from recurrent heart failure, multiple strokes, and, eventually, a neurovegetative state. One patient died 10 months after dilation, spending most of her remaining life hospitalized for heart failure. Another patient died of heart failure (three months), and one succumbed to pancreatic cancer (two months). Three patients are alive at eight, six, and four months post-procedure. One (month 8) had return of NYHA functional class IV dyspnea.

### Table 2. Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 Days and 6 Months After Successful Implantation

<table>
<thead>
<tr>
<th>MACCE at 30 days</th>
<th>Count</th>
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<tbody>
<tr>
<td>Death</td>
<td>6</td>
</tr>
<tr>
<td>Tamponade</td>
<td>2</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
</tr>
<tr>
<td>Brain death post resuscitation</td>
<td>1</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
</tr>
<tr>
<td>Emergent cardiac surgery</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>7 (26)</td>
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<table>
<thead>
<tr>
<th>MACCE at 6 months*</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10</td>
</tr>
<tr>
<td>Renal failure</td>
<td>3</td>
</tr>
<tr>
<td>Postoperative</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Multi-organ failure†</td>
<td>1</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
</tr>
<tr>
<td>Emergent cardiac surgery</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>10 (37)</td>
</tr>
</tbody>
</table>

Values are n (%). *MACCE <30 days not included. †Multi-organ failure death occurred at 33 days in the patient who suffered a procedural stroke.

### DISCUSSION

During this phase I trial, we had to develop criteria for appropriate patient selection and the optimal technique for PHV implantation, utilizing our experience from animal models and previous cases of BAV. The inclusion criteria imposed for this study resulted in a selection of patients that were among the toughest we have intervened upon. Knowingly, the learning curve for an innovative procedure such as this one is steep and is only partly reflected by improvements in procedural times.

**Feasibility and technique.** Twenty-seven patients (82% of the 33 patients attempted) with debilitating and life-threatening aortic stenosis were successfully implanted with a PHV in the subcoronary position without coronary occlusion or interference of the mitral valve apparatus. Both the antegrade and retrograde approach were used in the I-REVIVE part of the trial; only the antegrade approach was used in the RECAST part of the trial (per protocol amendment). With the antegrade approach, the success rate was very high (85%), and the problems associated with introducing a 24-F sheath into the femoral artery were avoided (two cases of closure device failure of four attempted). It was easier to cross the native valve with the PHV in the antegrade rather than the retrograde direction, especially in patients with excessive calcification. This approach, however, was technically more demanding and required more case experience. Hemodynamic collapse used to occur during implantation until we learned that the stiff guidewire could exert traction on the anterior leaflet of the mitral valve. Straightening of this guidewire loop in the left ventricle caused massive mitral regurgitation and hemodynamic collapse that recovered only when the loop shape was resumed. The problems of the guidewire loop were markedly improved by pushing the Sones catheter retrogradely into the left ventricle, maintaining the guidewire shape during passage of the PHV in the left heart. Guidewire-induced hemodynamic collapse, consequently, did not occur during PHV implantation in the RECAST trial. In the I-REVIVE trial, however, five patients experienced this problem during implantation.

The success of retrograde implantation (57%, four of seven patients) was lower than that of the antegrade approach. The procedure, however, was quicker and less technically demanding without the problem of guidewire loops. Many patients were not candidates for this method because of diseased or tortuous femoral arteries that could not accommodate such a large sheath size. In some patients with heavily calcified valves, we were unable to retrogradely cross the native valve with the PHV because of wire bias into a commissure (the three failures). In this situation, we continued the procedure by the antegrade route in one patient. When the valve could not be implanted in the heart, the PHV was surgically removed from the femoral artery (one patient) or safely deployed above the bifurcation of the iliac arteries to avoid the complications of vascular surgery,
mechanical ventilation, and general anesthesia (two patients). In one of the patients with a valve in the descending aorta, angiographic and clinical follow-up (10 months) confirmed the valve in the open position without impedance to flow. In the other patient, autopsy evaluation revealed the valve also in the open position without evidence of migration (12 h). Likewise, in two patients with a failed procedure secondary to migration, implantation of the PHV in the thoracic aorta was without sequelae (up to six months follow-up). In our previous animal experience (A. Cribier and S. Eltchaninoff, unpublished data, 2001), the PHV implanted in the aorta remains in the open position and is of no clinical consequence.

In both the antegrade and the retrograde approach, rapid ventricular pacing was fundamental for the success of the procedure. At a rate of 200 to 220 beats/min, rapid pacing causes an immediate and predictable decrease in stroke volume, preventing the ejection of the PHV-mounted balloon catheter by the left ventricle. Rapidly pacing the heart for <10 s during PHV deployment or BAV is well tolerated and has not provoked malignant ventricular arrhythmias in our series. The pacemaker lead is also helpful to prevent episodes of significant bradycardia that can occur during the procedure.

Safety. Thirty-day MACCE was 26% in those with a successful implantation. Though none of these patients expired because of prosthetic valve dysfunction, these deaths were related to complications from the procedure. Obviously, this group was also at an extremely high risk for surgical valve replacement. A Parsonnet’s surgical risk score of 47 and a EuroSCORE of 12 has been respectively associated with a >25% and >20% mortality within 30 days of cardiac surgery (9,13). The high mortality reflects the nature of intervening on this precarious group. The rate of stroke in our series (including patients who underwent PHV implantation or just BAV with a failed implantation) was 2.8% (1 of 35 patients), which is similar to the incidence reported with surgical valve replacement (14).

The six-month MACCE was also very high (37% excluding MACCE at one month). Even after successful implantation with improvement in functional status, many of our patients (n = 10) remained fragile, unable to tolerate non-cardiac surgery or succumbing to conditions such as stroke, pneumonia, progressive renal failure, cancer, and pulmonary embolism. None of the mortality that occurred after 30 days was related to the PHV or to the procedure.

Efficacy and durability. The AVA increased to 1.7 cm² consistently after PHV implantation and did not significantly change even up to two years. Similarly, the mean transvalvular gradient decreased to 10 mm Hg post-procedure and remained at this value throughout the follow-up. Left ventricular function improved as early as one week with the most significant increase seen in patients with depressed myocardial function (15). This phenomenon is well described in the surgical literature after appropriate selection of patients with depressed ejection fraction for valve replacement (16). And though our patients were not pre-selected by dobutamine echocardiography, recovery of left ventricular dysfunction was seen in several cases, consistent with afterload mismatch pathophysiology.

Improvements in echocardiographic variables correlated with clinical improvement as well. All patients had symptomatic relief after the procedure, with the majority improving from NYHA functional class IV to class II. Obviously, the largest amelioration of symptoms was seen in patients without comorbidities that limited functional status such as severe lung disease. In patients without PHV implantation, improvement in symptoms after only BAV were short lived. Patients either died of heart failure or had the return of class IV dyspnea by six months, which is consistent with previously published data on BAV (4).

Future directions. Future improvements in technique and hardware will be directed at two different issues: improved deliverability of the PHV via the retrograde approach and resolution of adverse events that are related to PHV size. Currently, a new, lower-profile system with a steerable delivery catheter has been developed to revive the retrograde approach. The results of this new technology and the concomitant implantation of a larger PHV (26 mm) in a series of less severely ill patients are promising and should soon be reported. In our series, we have been implanting patients that have different size aortic annuli with one size PHV (23 mm). Keeping this limitation in mind, grade 3 paravalvular leak occurred in five patients (four in I-REVIVE, one in RECAST). The regurgitation was well tolerated, and all patients maintained an improved functional class post-procedure (one patient has 10 months follow-up and paravalvular leak is now grade 2). In these cases, however, a larger size prosthesis could have been better apposed to the native leaflets, resulting in less regurgitation. Similarly, a larger PHV may have been important in decreasing the risk of migration. Although this problem is less common than paravalvular leak, patients with a larger annulus and mild aortic valve calcification seem to be at increased risk. Currently, we believe that patients with an aortic annulus >21 mm would benefit from a larger size PHV.

With increasing experience, complications related to the procedure should decrease, and innovations in hardware should make PHV implantation technically less demanding, with less risk to the patient. Soon, multicenter trials will begin in Europe to study the feasibility, safety, and efficacy of PHV implantation in patients at high surgical risk with less severe comorbidity. In this cohort, we hope to study the long-term performance of the PHV and the continuing clinical benefits of this technique. With continued advances in this field, percutaneous aortic valve implantation should become a very realistic way of treating a select population of patients with degenerative aortic stenosis in the near future.
REFERENCES


APPENDIX

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