

Long-term Results after Carpentier-Edwards Pericardial Aortic Valve Implantation, with Attention to the Impact of Age

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ABSTRACT

Background: The purpose of this study was to determine long-term patient survival and valve durability for Carpentier-Edwards pericardial valves (Edwards Lifesciences) implanted in the aortic position, with specific attention to the impact of patient age.

Methods: We performed a retrospective cohort study of 2168 patients who underwent implantation of a Carpentier-Edwards pericardial aortic valve between 1991 and 2008. The mean follow-up time was 4.5 years. Primary outcomes of interest were mortality and valve explantation. Survival curves and event-free curves were obtained with the Kaplan-Meier method and compared with the log-rank test.

Results: Survival was 92% at 1 year, 73% at 5 years, 38% at 10 years, and 18% at 15 years. Although the mortality rate of younger patients was worse than in the general population, older patients had significantly better survival than their contemporaries. Age was the independent variable most significantly associated with explantation. There was an early hazard phase for patients between 21 and 49 years of age, such that the freedom from explantation was 89% at 3 years. By 10 years, the freedom from explantation was 58% for patients 21 to 49 years of age, compared with 68% for patients 50 to 64 years, 93% for patients 65 to 74 years, and 99% for patients 75 years of age and older.

Conclusion: We found good long-term survival and durability. Older patients had excellent freedom from explantation, whereas younger patients fared worse. As our population ages, this information becomes increasingly important. Assessing the durability of this pericardial aortic valve may aid in predicting the durability of the transcatheter aortic valves that share the same leaflets.

This work was presented at the 20th World Congress of the World Society of Cardio-Thoracic Surgeons, Chennai, India, October 20-23, 2010.

Received October 15, 2010; accepted November 29, 2010.

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INTRODUCTION

The Carpentier-Edwards (CE) pericardial valve (Edwards Lifesciences, Irvine, CA, USA) was introduced in 1981 and became available for commercial distribution in the United States following approval by the Food and Drug Administration in 1991. It has been a popular choice for aortic valve replacement, both in patients >65 years of age (for whom the American Heart Association/American College of Cardiology guidelines suggest biologic valves because of their low rates of structural deterioration and lack of need for anticoagulation) and in younger patients who want to avoid the lifestyle limitations and hemorrhagic risks associated with the lifelong anticoagulation recommended after mechanical-valve implantation [Bonow 2008]. Series from outside the United States and clinical investigations prior to commercial distribution demonstrated good mid- and longer-term durability for the CE pericardial valve in older populations [Cosgrove 1995; Pelletier 1995; Banbury 1998; Dellgren 2002; Aupart 2006]. A recent single-institution study of patients who received this valve after commercial release in the United States reported good long-term durability, with a low rate of structural valve deterioration [McClure 2010]. Higher rates of structural valve deterioration in younger patients have led some to limit use in this population [Aupart 1997; Banbury 2001; Biglioli 2004; Brown 2008].

Our center has had a long history of prosthetic valve placement and began implanting the CE pericardial valve upon its commercial release in the United States. The purpose of this study was to determine long-term patient survival and valve durability of CE pericardial valves placed in the aortic position, with specific attention to the impact of patient age. As options for valve replacement increase, this information becomes of particular importance as a baseline for comparison to percutaneously implanted valves that use similar bovine pericardial leaflets but lack the rigid geometry of a sewing ring.

MATERIALS AND METHODS

We performed a retrospective cohort study of all patients who underwent isolated aortic valve replacement with a CE pericardial valve from November 1991 to December 2008. Patients who underwent concomitant coronary artery bypass grafting were included in the cohort. Patients who underwent

simultaneous replacement or repair of another heart valve were excluded. Although the study design was retrospective, all data were collected prospectively. Patients were entered into a database at the time of surgery and were followed annually by either mailed questionnaire or telephone interview. Follow-up was 90% complete. Data collection and the present study were approved by the Providence Health and Services institutional review board.

At our institution, valves were implanted with contemporary surgical techniques that have evolved over time. In general, patients older than 65 years were offered biological valves, and patients younger than 60 years were offered mechanical valves. Patient preference played a major role in valve selection, however, especially in the age group 60 to 65 years. Valves were impacted in the aortic root, and downsizing was avoided. There was a low threshold for posterior aortic root enlargement, particularly in patients with aortic root diameters <21 mm. Pledgets were not used when the valves were implanted. Early in the series, patients were maintained on warfarin sodium while hospitalized. As the length of stay decreased in the early 1990s, this practice was abandoned. All patients were discharged on aspirin therapy unless it was contraindicated. Additional anticoagulation was reserved for patients with specific indications.

Table 1. Preoperative and Operative Characteristics of the Cohort (n = 2168)*

Age, y	73.1 ± 10.8
Male sex	62.5%
Body mass index, kg/m ²	27.9 ± 5.6
Chronic obstructive pulmonary disease	19.0%
Cerebrovascular disease	6.9%
Hypertension	62.7%
Pulmonary hypertension	11.4%
Peripheral vascular disease	13.5%
Renal failure	5.6%
Sinus rhythm	93%
Concomitant CABG	49.8%
Aortic valve pathology	
Stenosis	77.3%
Insufficiency	8.8%
Stenosis and insufficiency	2.7%
Valve size	
19 mm	3.1%
21 mm	18.0%
23 mm	31.8%
25 mm	27.0%
27 mm	13.3%
29 mm	6.8%

*Data are presented as the mean ± SD where indicated. CABG indicates coronary artery bypass grafting.

Valve-related deaths and complications were defined according to the Guidelines for Reporting Morbidity and Mortality after Cardiac Valvular Operations [Akins 2008]. Primary outcomes of interest were mortality, thromboembolic morbidity, and valve explantation. Causes of death were determined from hospital records or autopsy when available. Reasons for valve explantation were established from preoperative and intraoperative observations and from documentation. Early events were those that occurred in the hospital or within 30 days of valve placement, whichever was longer.

Continuous data are presented as the mean ± SD, and categorical data are presented as percentages. Survival curves and event-free curves were obtained with the Kaplan-Meier method and compared by means of the log-rank test. Cox regression was used to detect the risk factors for long-term survival. Statistical analysis was performed with PASW 17 (SPSS, Chicago, IL, USA) and R 2.9 (<http://www.R-project.org>).

RESULTS

Between 1991 and 2008, 2168 patients underwent implantation of a CE pericardial aortic valve (Table 1). The most common pathology was aortic stenosis (77% of patients). Fifty percent of patients underwent concomitant coronary artery bypass grafting. The mean age of the patients at the time of surgery was 73 years, with a downward trend in age over time (Figure 1). The mean follow-up period was 4.5 years, for a total of 9694 person-years. The longest follow-up was 17 years.

Survival

The mean survival incidence was 92% (95% confidence interval [CI], 91%-93%) at 1 year, 73% (95% CI, 70%-75%) at 5 years, 38% (95% CI, 35%-42%) at 10 years, and 18% (95% CI, 13%-25%) at 15 years (Figure 2). There were 86 early deaths (4%) and 658 late deaths (6.9% per patient-year;

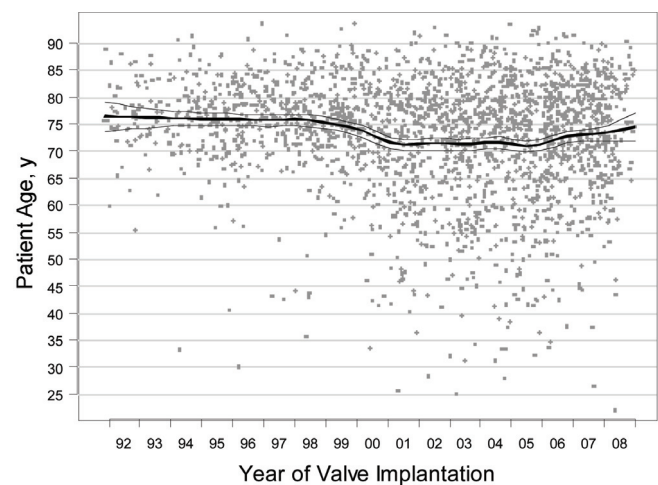


Figure 1. Patient age at valve implantation by year of valve implantation. The thick solid line and the 2 thin solid lines are the LOWESS curve and its 95% confidence intervals, respectively. There was a trend in more recent years toward placing Carpentier-Edwards pericardial valves in younger patients.

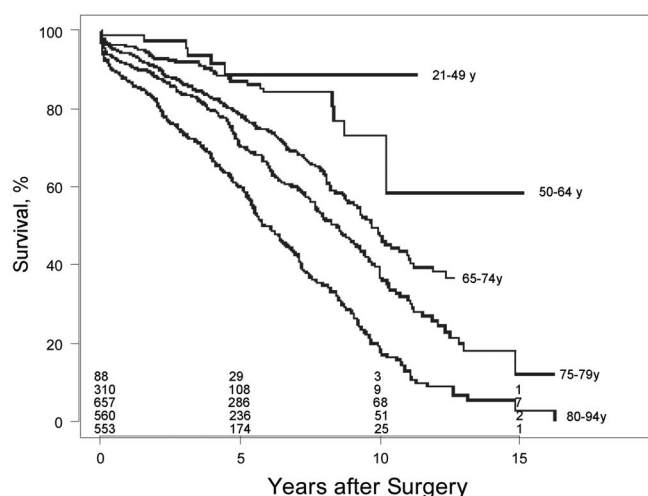


Figure 2. Long-term survival by age group. Numbers above the horizontal axis are the number of patients at risk at each 5-year time period.

Table 2. Causes of Death

Cause of Death	Time Period		
	Early, n	Late, n	Total, n
Cardiac (valve related)			
Thromboembolism	12	20	32
Hemorrhage	3	9	12
Spontaneous bacterial endocarditis	0	5	5
Perivalvular leak	1	0	1
Sudden death	0	148	148
Cardiac (not valve related)	30	122	152
Noncardiac	40	346	386
Unknown	0	8	8
Total	86	658	744

Table 2). Of the late deaths, 28% were valve related, 19% were due to a cardiac cause unrelated to a valve, 53% were not cardiac related, and 1% were of unknown cause. Risk factors associated with long-term survival were renal failure, chronic obstructive pulmonary disease, pulmonary hypertension, peripheral vascular disease, and congestive heart failure ($P < .01$ for all). As expected, a younger age at surgery was associated with greater survival during the study period (odds ratio, 1.06; 95% CI, 1.04-1.07; $P < .001$). Of note, however, was that although the mortality rate of younger patients was slightly worse than that for age- and sex-matched general populations, older patients showed significantly better survival than their peer populations (Figure 3).

Thromboembolic Events

We noted that 163 thromboembolic events occurred over the study period: 54 transient ischemic attacks, 10 reversible ischemic neurologic deficits, 66 strokes, and 33 deaths

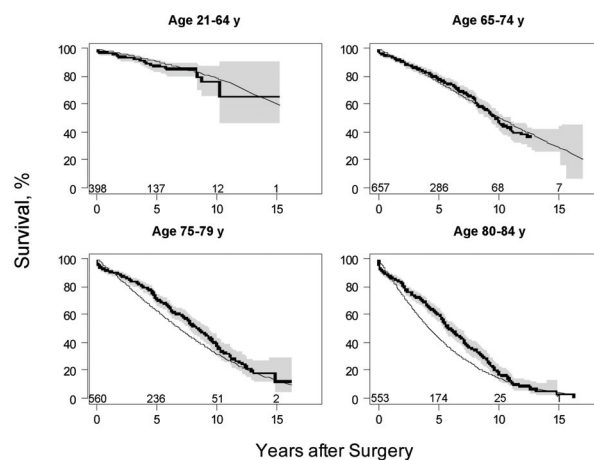


Figure 3. Probability of survival by age group, compared with age-, sex-, and surgery year-matched general populations. The numbers of patients are indicated above the horizontal axis. Indicated in each panel are the survival of the age group (dark line), the survival of the age-, sex-, and surgery year-matched general population (light line), and the 95% confidence interval around the line for the survival of the age group (shaded area).

Table 3. Types of Thromboembolic Events

Type of Event	Time Period		
	Early, n	Late, n	Total, n
Transient ischemic attack	11	43	54
Reversible ischemic neurologic deficits	10	0	10
Stroke	24	42	66
Fatal	12	21	33
Total	57	106	163

(Table 3). Of these events, 35% were within the early postoperative period, and 65% occurred late. Twenty percent were fatal. The frequency of freedom from a thromboembolic event was 92% (95% CI, 96%-97%) at 1 year, 93% (95% CI, 92%-94%) at 5 years, 88% (95% CI, 86%-91%) at 10 years, and 83% (95% CI, 76%-91%) at 15 years (Figure 4). The linearized rate of thromboembolism was 1.11% per valve-year and was highest in the older age groups (21-64 years of age, 0.44%; 65-74 years, 0.63%; 75-79 years, 1.61%; 80-94 years, 1.25%). Rates of fatal events were lower (65-74 years, 0.16%; 75-79 years, 0.26%; 80-94 years, 0.43%). No patient younger than 65 years had a fatal thromboembolic event.

Hemorrhagic Events

Forty-two patients had a total of 48 hemorrhagic events over the study period. Of these events, 12 were fatal. No deaths occurred among the 7 hemorrhagic events in patients <65 years of age. The incidence of freedom from hemorrhage was 99% (95% CI, 98.5%-99.4%) at 1 year, 98% (95% CI, 97%-99%) at 5 years, 96% (95% CI, 95%-98%) at 10 years, and 96% (95% CI, 95%-98%) at 15 years.

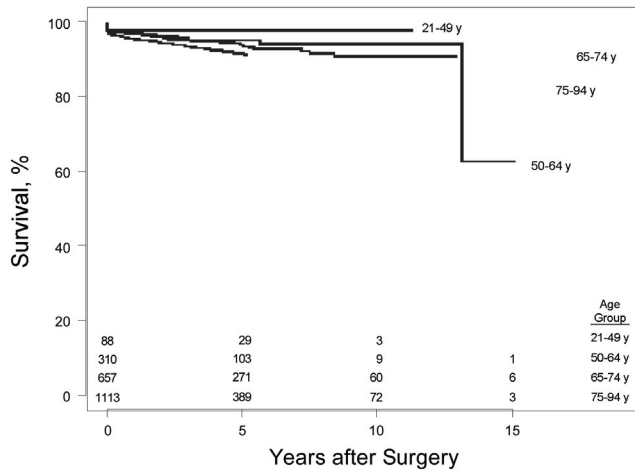


Figure 4. Freedom from thromboembolic events by age group. Numbers above the horizontal axis are the number of patients at risk at each 5-year time period.

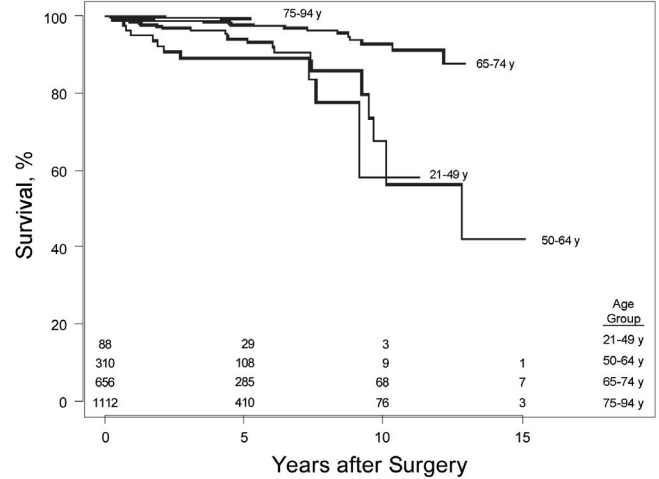


Figure 5. Freedom from valve explantation for all causes by age group. Numbers above the horizontal axis are the number of patients at risk at each 5-year time period.

Explantation

Fifty-seven valves were explanted over the study period. At 3, 5, 10, and 15 years, the incidence of freedom from explantation was 98% (95% CI, 98%-99%), 98% (95% CI, 97%-99%), 93% (95% CI, 90%-95%), and 83% (95% CI, 74%-93%), respectively. Structural valve deterioration was the most common reason for valve explantation (53%) (Table 4). Thirty-two percent of valves were explanted for endocarditis, and 9% of valves were removed for perivalvular leaks. The mortality rate at explantation was higher than at the initial operation: 8.8% (95% CI, 1.2%-16%) of 57 patients died within 30 days of valve explantation and replacement. Younger age was the only independent variable significantly associated with explantation ($P < .001$), with patients 49 years of age and younger being at the highest risk (Figure 5). There was an early-hazard phase for this group of patients, such that freedom from explantation was 84% (95% CI, 75%-93%) at 3 years; however, only 4 of 11 explantations in this age group were due to structural valve deterioration. The higher risk of early explantation was due to other causes (Table 4). Patients between 50 and 65 years of age were also at greater risk for earlier explantation than older patients. At 5 years, the incidence of freedom from explantation for this group was 94%

(95% CI, 91%-98%), compared with 98% (95% CI, 97%-99%) for patients between 65 and 74 years of age and 99% (95% CI, 99%-100%) for patients 75 years of age and older. By 10 years, the incidence of freedom from explantation was 58% (95% CI, 32%-100%) for patients between 21 and 49 years of age, compared with 68% (95% CI, 51%-90%) for patients between 50 and 64 years, 93% (95% CI, 89%-97%) for patients between 65 and 74 years, and 99% (95% CI, 99%-100%) for patients 75 years of age and older. Trends for freedom from explantation because of structural valve deterioration mirrored overall explantation trends, with the exception of the youngest age group (Figure 6). At 5, 10, and 15 years, the incidence of freedom from explantation due to structural valve deterioration for the entire cohort was 99% (95% CI, 98%-100%), 95% (95% CI, 92%-97%), and 86% (95% CI, 77%-95%), respectively. For patients from 21 to 49 years of age, the incidence of freedom from explantation was 97% (95% CI, 92%-100%) and 68% (95% CI, 38%-100%) at 5 and 10 years, respectively. The lower explantation rate due to structural valve deterioration compared with all causes reflects the influence of the higher rates of other indications for explantation in this age group. The rates for patients 50 to 65 years of age and patients 65 to 74 years of age were 96%

Table 4. Reasons for Valve Explantation by Age Group

Age Group	Reason for Explantation				
	Structural Valve Deterioration, n	Spontaneous Bacterial Endocarditis, n	Perivalvular Leak, n	Other, n	Total, n
21-49 y	4	3	2	2	11
50-64 y	14	6	1	1	22
65-74 y	12	5	2	1	20
75-79 y	0	3	0	0	3
80-94 y	0	1	0	0	1
Total	30	18	5	4	57

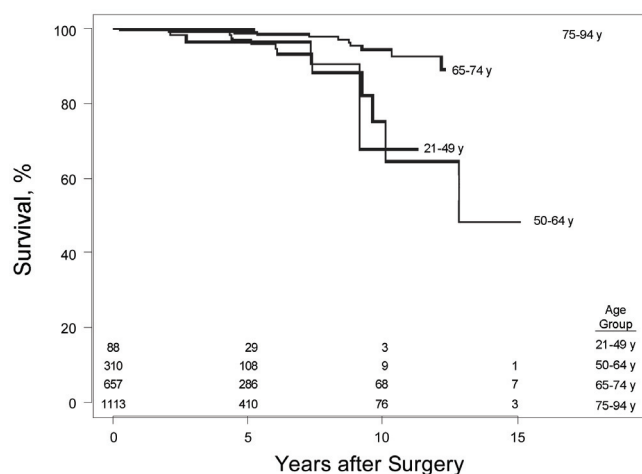


Figure 6. Freedom from valve explantation for structural valve deterioration only, by age group. Numbers above the horizontal axis are the number of patients at risk at each 5-year time period.

(95% CI, 93%-99%) and 75% (95% CI, 59%-96%), respectively, at 5 years, and 99% (95% CI, 98%-100%) and 95% (95% CI, 91%-98%), respectively, at 10 years. Only 1 patient 75 years of age or older had a valve explanted for structural valve deterioration.

DISCUSSION

In this single-institution, retrospective cohort study of patients who received CE pericardial aortic valves, we found good long-term outcomes. The survival of younger patients was worse than the population means, whereas the survival of older patients was superior to their contemporaries. Older patients had excellent freedom from explantation, and younger patients fared worse. Patients younger than 50 years of age were at the highest risk for explantation due to structural valve deterioration and demonstrated an early-hazard phase for explantation due to causes other than structural valve deterioration.

As patient age increased, the detrimental effect of aortic valve replacement on survival diminished. In fact, the long-term survival of patients 75 years of age and older was superior to their peers. This effect has been seen by previous investigators and is probably attributable to selection bias [Stoica 2006; Rizzoli 2010]. Older individuals who undergo valve replacement must be healthy enough to withstand the rigors of surgery and therefore may be more fit and less likely to die from other causes than many of their peers. Unfortunately, we were unable to provide data on patient-reported health status. It would be meaningful to know whether these patients experienced a postoperative quality of life equivalent to that of their peers who did not undergo operation. A significant advantage of a bioprosthetic valve over a mechanical valve is the ability of the patient to live life unencumbered by concerns about the risks of anticoagulation. Consequently, such patients may engage in a lifestyle more similar to individuals who do not undergo operation and may have an equivalent quality of life.

As previous authors have noted, we found a differential effect of age on the need for explantation [Aupart 1997; Banbury 2001; Biglioli 2004; Brown 2008]. The durability of the CE bovine pericardial valve was excellent in patients 65 years of age and older. Few patients in this age group will require a second valve replacement, and unless they require anticoagulation for other reasons, they will avoid the hemorrhagic risk associated with the lifelong anticoagulation necessary for patients with mechanical valves [van Geldorp 2009]. Patients younger than 65 years experienced higher rates of reoperation; however, the contrast between the low mortality risk of reoperative valve surgery and the increasing risk of anticoagulation-related hemorrhagic complications with age makes a bioprosthetic valve a rational choice for some younger patients [Potter 2005; Davierwala 2006; LaPar 2010]. In the future, this population may benefit from percutaneously placed valves. These valves can be placed inside failed bioprosthetic valves, thereby avoiding the need for a second open heart operation [Walther 2007; Walther 2009; Rodés-Cabau 2010; Ye 2010]. This alternative is not available to patients with mechanical valves.

Studies such as the present one provide a baseline with which the durability of transcatheter aortic valves (TAV) can be compared. Even though the surgically placed stented CE pericardial valve (PERIMOUNT; Edwards Lifesciences) and the CE TAV (SAPIEN; Edwards Lifesciences) both have bovine pericardial leaflets, their geometries differ. Unlike TAVs, surgically placed stented valves have shock-absorbing sewing rings that support the leaflets. The lack of a sewing-ring cushion could adversely affect the durability of the TAV. Thus, the durability of the PERIMOUNT valve may provide an upper limit for the durability of the TAV. If the former has excellent durability, then one can predict the latter to have acceptable durability. When patients are presented with a choice between a transcatheter and a surgically placed valve, they must be informed of not only the differences in procedural risks and recovery courses but also the potential discrepancies in long-term outcomes, such as structural valve deterioration, additional procedures, and functional status, specifically as affected by the area of the valve orifice. Further investigations are needed to define the magnitude and impact of these disparities.

Our study has several limitations. First, our cohort was derived from a single institution. The practice of medicine—from preoperative selection and evaluation through the perioperative period, to postoperative short- and long-term care—is likely to differ from that of other centers. Our practice, however, has been in line with contemporary literature and guideline recommendations. An additional effect of a single-institution study is that the study population is derived from a geographic region that may not be representative of the greater United States. In particular, the African American population of Oregon is smaller than in many other states (2.0% in Oregon versus 12.8% across the United States [U.S. Census Bureau 2000]). We did not have long-term echocardiographic or patient-reported health status data, the combination of which would have helped us determine whether patients who did not undergo reoperations experienced structural valve deterioration that limited the quality of life. Although our

study design was retrospective, all data were collected prospectively at the time of the initial operation or as part of scheduled yearly follow-ups. Despite these limitations, we were able to report long-term follow-up data for a large cohort restricted to isolated aortic valve replacement, with concomitant coronary bypass surgery being the only additional procedure.

When patients present for aortic valve replacement, they are concerned not only about perioperative mortality but also about long-term outcomes, such as mortality, thromboembolic events, and reoperation. Despite a body of literature and an expert consensus guideline endorsed by the American Heart Association and the American College of Cardiology to the contrary, many older patients continue to receive mechanical aortic valves [Schelbert 2005]. Our findings should reassure these patients that a bovine pericardial valve will provide excellent durability and survival, with a minimum of adverse events. Younger patients can use our data to inform their decision as to whether the reoperation risk of a bioprosthetic valve or the anticoagulation-related risk of a mechanical valve better fits their priorities and lifestyle. In addition, these data can serve as a baseline for comparison with percutaneously implanted valves that use the same leaflet material but have disparate geometries. As our population ages and more patients require aortic valve replacement, this information becomes increasingly important.

ACKNOWLEDGMENT

Writing of this article was partially supported by a nonrestricted educational grant from Edwards Lifesciences.

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