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New Flexible Polymeric Heart Valve Prostheses for the Mitral and Aortic Positions

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ABSTRACT

Objective: Current prosthetic heart valves necessitate permanent anticoagulation or have limited durability and impaired hemodynamic performance compared with natural valves. We report in vivo and in vitro results with new polymeric valve prostheses that have a special design for the mitral and aortic positions. The aims are improved durability and elimination of the need for permanent anticoagulation.

Methods: The mitral and aortic prostheses (Adiam Life Science, Erkelenz, Germany) are made entirely of polycarbonate urethane (PCU). The bileaflet asymmetric mitral valve mimics natural, nonaxial inflow, which creates a left ventricular vortex, saving energy for systolic ejection of blood. The trileaflet aortic prosthesis has diminished pressure loss and reduced stress and strain peaks at the commissures. The valves were subjected to long-term in vitro testing and in vivo testing in a growing calf model (20 weeks; 7 mitral and 7 aortic valves) with comparison with 2 commercial bioprostheses (7 mitral, 2 aortic). Two-dimensional echocardiography was performed after implantation and prior to sacrifice with autopsy and valve examination.

Results: In vitro durability of the PCU valves was proved up to 20 years. In vivo durability and hemodynamics were superior to those of all bioprostheses. Survival of PCU valves versus bioprostheses was 7 versus 2 mitral valves and 5 versus 0 aortic valves, respectively. Two animals with PCU aortic valves died of pannus overgrowth that caused severe left ventricular outflow tract obstruction without changes in the valves. Degeneration and calcification were mild (mitral) and moderate (aortic) in PCU valves but were severe in biological valves. There was no increased thrombogenicity of the PCU valves compared with bioprostheses.

Conclusion: The new flexible polymeric aortic and mitral valve prostheses were superior to current bioprostheses in animal testing.

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INTRODUCTION

At the end of the 1950s, implantation of flexible polymeric heart valve prostheses in the aortic position had been performed sporadically [Roe 1958]. Thromboembolic complications and valve degeneration were the major problems with these valve substitutes, which caused high complication rates. Clinical use ceased, especially after the Starr-Edwards prosthesis became the standard valve substitute [Starr 1961, Braunwald 1965, Roe 1966]. However, the development of flexible polymeric heart valves went on. Among different polymers, polyurethanes turned out to be superior to silicone rubber, polytetrafluoroethylene (PTFE), and collagen in terms of biocompatibility and resistance to thromboembolism and degeneration [Imamura 1977, Nistal 1990, Zdrahala 1999]. Various constructions were developed, and promising results of animal testing were reported, but none of these polymeric prostheses had proven long-term durability for clinical implantation. However, polyurethane valves are used effectively in assist devices (Abiomed, Berlin Heart, Medos).

Over time, increasing insight was gained into the importance of optimal hemodynamic performance of valve substitutes for their durability and resistance to thromboembolism [Reul 1979, Edmunds 1996, Hyde 1999]. Yet most valves, including biological prostheses, are made for the aortic position, and the different requirements for the mitral position are not considered.

To optimize hemodynamics and thus increase durability and resistance to thromboembolism, we designed 2 flexible polymeric heart valve prostheses for the mitral and aortic positions. We called these prostheses biomechanical valves because they are flexible like bioprostheses but synthetic like mechanical valves.

Both prostheses were completely made of polycarbonate urethane (PCU). As in the respective natural valves, the mitral valve is bileaflet and asymmetric, and the aortic valve is trileaftlet and symmetric (Adiam Life Science, Erkelenz, Germany) [Daebritz 2003, 2004]. The prostheses were designed

to combine the advantages of both currently available types of artificial heart valves: long-term durability without the necessity for permanent anticoagulation. In vitro and in vivo results of animal testing are presented.

MATERIAL AND METHODS

The Adiam biomechanical heart valve prostheses are made of a medical-grade PCU especially developed for long-term implant needs (Adiamat; Adiam Life Science).

The sewing rings are made of dissolved PCU sprayed to fleece-like sheets, from which the sewing rings are punched out. This microporous material of high elasticity is supposed to allow close fit to the natural annulus and rapid healing by neointimal and fibroblast ingrowth. Stent, leaflets, and sewing rings consist of a multilayered, cohesively bonded, not glued, single material of various degrees of hardness. PCU is a material compound of hard and soft segments; the ratio of the mixture determines the degree of hardness.

The manufacturing process starts with a mold dipped in dissolved PCU of greater hardness to obtain the stent form. The stent base holds an integrated stiffening ring of radiopaque magnetic resonance imaging–compatible titanium alloy. In the next step, biocompatible blood-contact layers of softer PCU are applied by a dropping technique. These layers coat the entire valve and form the leaflets. Thus the core layer of the leaflet is of medium hardness to improve tensile strength during high systolic pressure. The upper and lower surfaces are soft to provide high flexibility, thrombogenic resistance, and hemodynamic compatibility as well as high mechanical resistance to alternating flexural movements. Because the material takes up 2% water to become saturated, the leaflets become softer several hours after implantation. Predefined thickness distribution achieves the lowest possible strain to avoid stress peaks at the commissures. At the end of the manufacturing process the leaflets are separated with a precision laser.

PCU Mitral Valve

The mitral valve is designed to mimic natural mitral flow characteristics with a central, nonaxial flow that forms 2 vortices in the ventricular cavity. The larger vortex fills the ventricle at the end of diastole and saves kinetic energy for systolic ejection of blood [Reul 1979]. According to mitral valve anatomy, the valve has a kidney-like stent with 2 asymmetric struts carrying a large anterior and a small posterior leaflet (Figure 1). The flat configuration of the leaflets maintains physiological vortices during the outflow phase and, consequently, reduces energy loss. The leaflets provide an oval orifice, which gives way for the typical mitral flow pattern. The thickness of the leaflets varies between 100 and 300 µm. Mimicking the chordae tendineae would have resulted in a complicated implantation technique. Therefore leaflet prolapse was avoided by a hanging-bridge construction in which the leaflets were connected saddle-like with the 2 stent struts. The stent profile is low to prevent interference with the ventricular wall. The valve size is defined by the smallest external stent diameter and corresponds to the diameter of round valves when the orifice area integral is calculated. The valve has a specially designed holder for preventing entrapment of the struts by sutures.

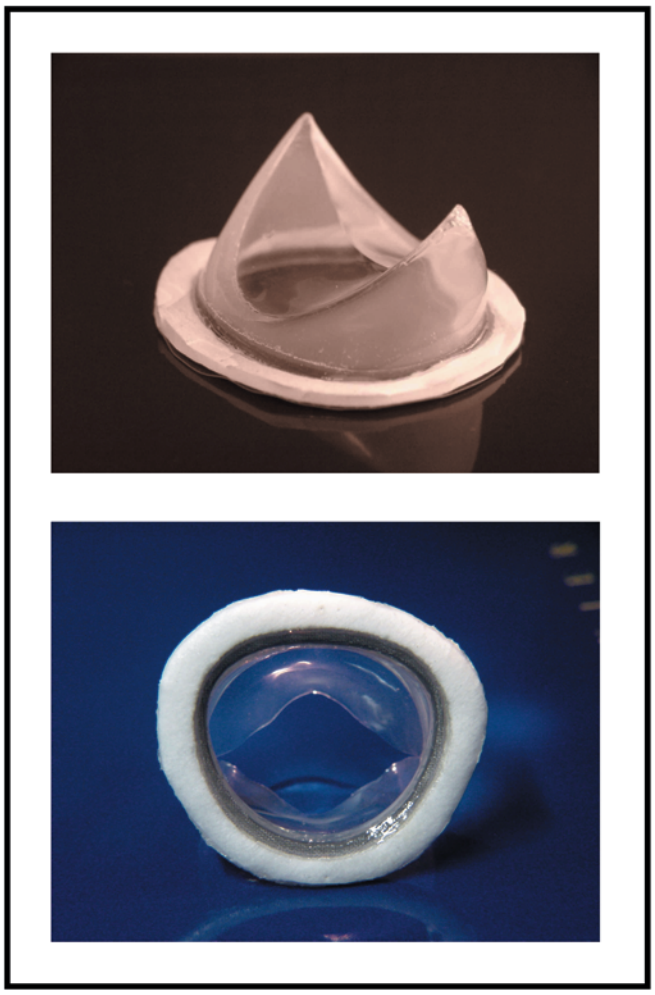

Figure 1. The Adiam polycarbonate urethane (PCU) valve with special design for the mitral position. Parts of this figure have been reprinted from Daebritz SH, Sachweh JS, Hermanns B, et al. 2003. Introduction of a flexible polymeric heart valve prosthesis with special design for mitral position. Circulation 108(suppl I):II-134-II-139, with permission from Lippincott Williams & Williams, Baltimore, Md, USA.

PCU Aortic Valve

The aortic valve is designed to mimic the natural aortic flow characteristics. According to aortic valve anatomy, the valve has 3 leaflets of a high profile for minimizing stress and strain peaks at the commissures (Figure 2). The steep configuration with almost complete opening of the leaflets produces a circular orifice during systole. This configuration provides an axial cylindrical flow profile that maintains a laminar, physiological flow pattern and, consequently, reduces energy losses. In addition, the high stent profile reduces alternating flexural stresses, particularly at the commissures and the free margins of the leaflets. Reduced leaflet thickness increases the flexibility of the leaflets. The thickness distribution of the leaflets is predefined to additionally reduce stress peaks at the

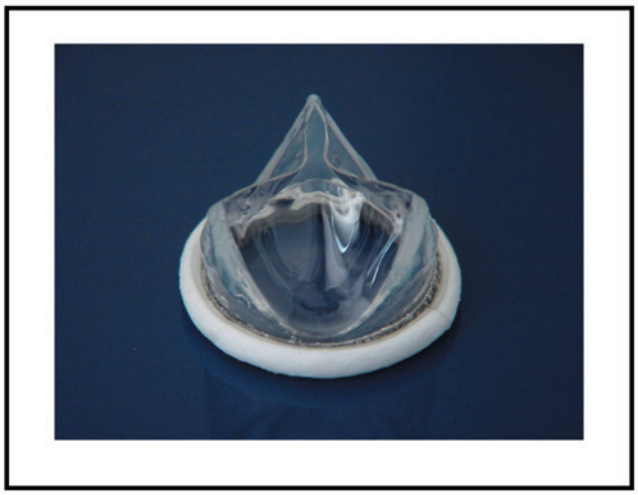

Figure 2. The Adiam polycarbonate urethane valve with special design for the aortic position. Parts of this figure have been reprinted from Daebritz SH, Bernd Fausten B, Hermanns B, et al. 2004. Introduction of a flexible polymeric heart valve prosthesis with special design for aortic position. Eur J Cardiothorac Surg 25:946-52, with permission from Elsevier BV.

commissures and varies between 80 and 200 μm. To further minimize membrane stresses in the diastolic and systolic positions, the leaflets are shaped as flat as possible in an almost medium open position. This configuration prevents the leaflets from being wrinkled during changes from the open to the closed position in the cardiac cycle. Stents and sewing ring are thin to provide a large effective orifice area in each valve size. Stent posts are flexible to some extent to ensure tight leaflet closing during diastole.

In Vitro and In Vivo Testing

In vitro fatigue testing was performed in testing facilities at 700 working cycles/minute. Thus 38 million cycles represented 1 year of average human function. The valves were checked once a week macroscopically for material degradation.

During in vivo testing, all animals received medical care according to the German guidelines for laboratory animal care. In vivo testing in juvenile Jersey calves was authorized by the government of the state of Nordrhein Westfalen, Germany. This animal model was chosen because calves are considered an extreme calcification model [Schoen 1988]. In addition, the fast growth of the animals, up to 170 kg after 5 months, represents an extreme hemodynamic workload for the valves. The animals were female 3 to 5 months of age and weighed 60 to 97 kg.

Mitral and aortic valve replacement was performed through a left thoracotomy with the calves under general anesthesia and has been described previously [Daebritz 2003, 2004]. Pressures were monitored continuously with an ear arterial line, a left jugular central venous line, and a Swan-Ganz thermodilution catheter. Cardiac output (CO) was measured every 30 minutes. Electrocardiographic findings and heart rate were documented continuously.

Animals with mitral valves received phenprocoumon (3 mg/day orally) for 6 weeks and aspirin (100 mg/day orally) for the entire study period. Animals with aortic valves received anticoagulation with heparin (fully heparinized postoperatively followed by low molecular weight heparin) and aspirin (100 mg intravenously postoperatively followed by 100 mg orally) for the first 2 weeks postoperatively to prevent thromboembolic complications potentially caused by the special anatomy of the narrow aortic root. There was no anticoagulation after 2 weeks.

For long-term observation the calves were transferred to a farm. In case of development of congestive heart failure (CHF), anticongestive therapy with furosemide, digitoxin, and angiotensin-converting enzyme inhibitors was begun.

Blood cell count, hemoglobin concentration, coagulation parameters, and levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase (LDH), bilirubin, and creatinine were checked once a week and compared with preoperative values.

After the study period of 21.3 ± 0.5 (US Food and Drug Administration [FDA] requirement, 20 weeks) [FDA 1994] the animals were anesthetized and the hearts dissected. For hemodynamic assessment, Swan-Ganz catheters were placed, and CO was measured. In the aortic series, left ventricular pressure was measured directly, and systolic gradients were calculated with the arterial pressure measured in the left carotid artery. Epicardial echocardiography with assessment of morphological changes and hemodynamic performance was carried out in both series. The animals were sacrificed with an intravenous overdose of phenobarbital, and autopsy with macroscopic and histologic examination of heart, lungs, liver, kidney, and spleen was performed. The explanted valves were subjected to macroscopic, histological, radiographic, and electron microscopic analysis, including energy dispersive x-ray (EDX) spectroscopy and scanning electron microscopy.

Seven 29-mm Adiam PCU mitral valves were implanted and compared with 7 widely used biological mitral heart valve prostheses. Four of the prostheses were Perimount pericardial valves (2, 29 mm; 2, 27 mm) (Edwards Lifesciences, Irvine, CA, USA), and 3 prostheses were 29-mm Mosaic porcine valves (Medtronic, Minneapolis, MN, USA).

Seven Adiam PCU aortic valves (1, 19 mm; 6, 21 mm) were implanted and compared with 1 23-mm Perimount pericardial valve and 1 21-mm Mosaic porcine valve. The FDA requires comparison with 2 commercially available biological valves [FDA 1994].

Statistical Analysis

Statistical analysis was done with SPSS version 11.0 (SPSS, Chicago, IL, USA). Central tendency was expressed by mean, dispersion by standard deviation and range. The 2-tailed Wilcoxon test and 2-tailed Mann-Whitney test were applied when appropriate.

RESULTS

In Vitro Testing

In vitro fatigue testing of the PCU mitral valves proved durability for 600 million to 1 billion cycles, representing 15.8 to 26 years of normal human function and fulfilling the

FDA requirements for mechanical heart valves (15 years) [FDA 1994]. The PCU aortic valves have so far proven durability for up to 450 million cycles, representing 11.8 years and fulfilling the FDA requirements for biological heart valves (5 years) [FDA 1994]. Testing is ongoing.

In Vivo Testing

Results of in vivo testing have been previously described [Daebritz 2003, 2004] and are summarized.

Mitral Series. Epimyocardial echocardiography immediately after implantation revealed the following mean gradients (CO, 6.7 ± 3.1 L/min): PCU valve, 5.1 ± 2.4 mm Hg; Perimount, 2.1 ± 0.7 mm Hg; Mosaic, 5.5 ± 2.3 mm Hg (mean gradients of PCU versus biological valves, $P = .276$).

All animals with PCU valves reached study end in good clinical condition without cardiac medication. One animal with a Perimount valve reached study end receiving triple anticongestive medication; the other 3 had to be sacrificed before the ninth week of testing because of severe CHF. One of the 3 animals with Mosaic valves reached study end in good clinical condition without cardiac medication; 1 died after 1 week because of acute thrombosis of the prosthesis; 1 had to be sacrificed after 4.4 weeks because of intractable CHF.

The mean body weight of the 9 animals reaching study end was 165 ± 5 kg. These calves underwent epimyocardial echocardiography, except for the survivor with the Perimount valve, which died at induction of anesthesia. Mean gradient across the PCU valves was 8.4 ± 5.3 mm Hg. In 6 of 7 valves, the gradient was between 3.6 and 9.7 mm Hg; in 1 valve, which turned out to be implanted in a malrotated position, the gradient was extraordinarily high (19.4 mm Hg). Morphologic assessment showed trivial to mild thickening of the leaflets except in the valve with the high gradient, which showed moderate changes close to the commissures. All PCU valves had normal function with trivial regurgitation. The Mosaic prosthesis had a mean gradient of 6.5 mm Hg and mild to moderate thickening of the leaflets with restricted motion causing grade 2 regurgitation. Mean left atrial pressure was 20.7 ± 2.9 mm Hg for the PCU valves and 26 mm Hg for the Mosaic valve.

There were no paravalvular leaks in any prosthesis. All suture rings were covered with neointima without pannus overgrowth. One PCU prosthesis was not implanted correctly, and it rotated.

The PCU valves showed minor deposits mainly close to the commissures, except in the malrotated prosthesis, in which the deposits were moderate. In addition, this valve revealed a tiny thrombus formation close to the stent, whereas the other PCU valves were free of any thrombus formation. All bioprostheses showed moderate to severe thickening and degeneration of the leaflets, except the Mosaic valve with acute massive thrombosis after only 1 week. Tiny thrombus formation was also observed on the Mosaic valve implanted for 22 weeks.

The results of gross examination (Figure 3) were confirmed by histologic, radiographic, and EDX spectroscopic examination. The PCU valves had mild calcification in 4 prostheses, mild to moderate calcification in 2 prostheses, and moderate calcification in the malrotated PCU prosthesis. Calcification was severe in all Perimount valves and was mild to moderate in 1 and severe in 1 of the Mosaic valves. The thrombosed Mosaic valve was not calcified. All calcifications were exclusively extrinsic, ie, not intrinsic inside the biological leaflet tissue or the polymer. Electron microscopy showed a smooth surface of the PCU valve leaflets with tiny calcification spots. The malrotated valve had a tiny tear on the edge of 1 leaflet close to the commissure. The other PCU valves were without any signs of destruction of the PCU polymer. The surface of the biological valves was roughened, suggesting destruction of surface integrity.

Laboratory studies of the long-term survivors did not show any significant changes in preoperative values in the animals with PCU valves or the Mosaic valve. LDH and γ-glutamyltransferase levels and platelet count were highly pathologic in the long-term survivor with the Perimount valve.

Autopsy revealed mild signs of chronic venous congestion in the liver, spleen, and lungs in the long-term survivors except for the animal with the Perimount valve, in which the changes were severe. Four of the 5 animals with valve-related deaths also had severe signs of chronic CHF in the inner organs. The animal with early thrombosis of the Mosaic valve had no chronic congestive changes. Peripheral emboli were not found in any animal.

Aortic Series. Initial epimyocardial echocardiography after implantation revealed the following systolic gradients across the valve prostheses (mean CO, 6.4 ± 1.6 L/min): 21-mm PCU valves, 9.7 ± 4.5 mmHg; 19-mm PCU valves, 20 mm Hg; 21-mm Medtronic Mosaic vales, 61 mm Hg; 23-mm Edwards Perimount valves, 10 mm Hg.

Five of 7 animals with PCU valves reached study end by in good clinical condition without any medication (mean body weight, 157 ± 11 kg). No animal with biological valves reached study end in this condition. The other 2 animals with aortic PCU valves died after 4 and 11 weeks of severe left ventricular outflow tract (LVOT) obstruction caused by subvalvular pannus formation without changes in the valve leaflets. The animals with the Mosaic and Perimount valves died of CHF after 10 and 30 days, respectively.

Blood parameters of all animals, including the long-term survivors, did not show any significant changes from preoperative values.

Echocardiography, performed on all survivors except for 1, which died at induction of anesthesia, revealed mild thickening of the leaflets of all valves and restricted motion of the leaflet in 2 valves (19 mm and 21 mm). One 21-mm PCU valve had mild central aortic regurgitation. The mean systolic gradient across the 21-mm PCU valves was 65 ± 25 mm Hg echocardiographically and invasively. Across the 19-mm PCU valve it was 145 mm Hg and 170 mm Hg, respectively (CO, 12.6 ± 0.4 L/min).

There were no paravalvular leaks in any prosthesis. The sewing rings of the PCU protheses were completely covered with neointima. Pannus overgrowth under the sewing ring was found in 3 PCU aortic valves. In 1 valve overgrowth was

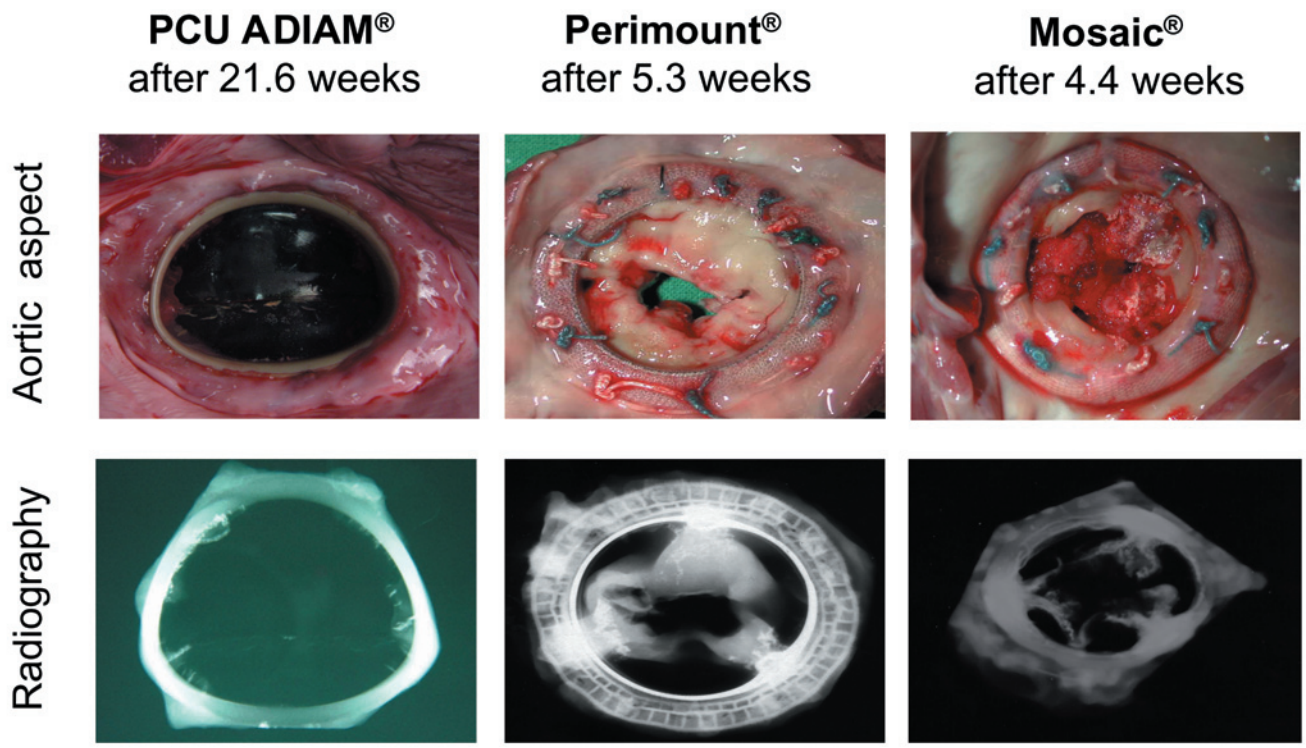

Figure 3. Gross and radiographic findings on an explanted polycarbonate urethane (PCU) mitral valve of a long-term survivor (20 weeks) and on explanted Perimount and Mosaic valves after 5.3 and 4.4 weeks, respectively. The PCU valve has no calcification, whereas both biological valves are clearly calcified. Parts of this figure have been reprinted from Daebritz SH, Sachweh JS, Hermanns B, et al. 2003. Introduction of a flexible polymeric heart valve prosthesis with special design for mitral position. Circulation 108(suppl I):II-134-II-139, with permission from Lippincott Williams & Williams, Baltimore, Md, USA.

mild to moderate, and in 2 it was severe, causing subtotal obstruction of the LVOT and early sudden death.

At gross examination the PCU valves of the long-term survivors showed mild calcification deposits mainly close to the commissures in 2 cases and mild to moderate calcification in 1 case. One 21-mm and the 19-mm PCU aortic valves showed severe deposits leading to restricted leaflet motion. The 21-mm PCU prosthesis with mild central regurgitation had a tear in the middle of the free margin of 1 leaflet directed to the middle of the cusp. There was mild thrombus formation in 2 PCU valves. Thrombus formation was severe in the Mosaic and mild in the Perimount bioprostheses. Both bioprostheses showed severe thickening and deformation of the leaflets (Figure 4).

Histologic, radiographic, and EDX spectroscopic examination of the PCU valves revealed mild calcification in 2 valves, mild to moderate calcification in 1 valve, and severe calcification in 2 valves, including the 19-mm valve. Calcification was severe in both bioprostheses. The observed calcifications were exclusively extrinsic. There was no destruction of polymer integrity or biological structure, except for the described tear in 1 PCU leaflet. Microscopic analysis of the leaflet showed reduced leaflet thickness of that cusp caused by variation of the manual manufacturing process of these prototype valves. Scanning electron microscopy showed a smooth surface of the PCU valve leaflets with differing calcification spots predominantly at the commissures. The surface of the biological valves was roughened, demonstrating destruction of surface integrity.

Autopsy revealed mild to moderate signs of chronic venous congestion of the liver, spleen, and lungs in all long-term survivors and signs of acute heart failure in the calves experiencing early death. Peripheral emboli were not found in any animal. However, there were signs of multiple myocardial infarctions in both animals with biological valves and an apical infarction area in 1 animal with a PCU valve.

DISCUSSION

Fifty years of development of heart valve prostheses are characterized by 2 major aspects: First, both currently used prostheses, biological and mechanical, have a major disadvantage, either limited durability or the necessity for lifelong anticoagulation. Second, valve replacement is characterized by the use of a universal prosthesis design irrespective of implantation site—mitral or aortic.

We present 2 newly developed so-called biomechanical heart valve prostheses made entirely of flexible PCU and specially designed for the mitral and aortic positions. The hypothesis was that optimizing material and hemodynamics for each position in the heart would combine the advantages of currently available valve substitutes: long-term durability and no necessity for permanent anticoagulation.

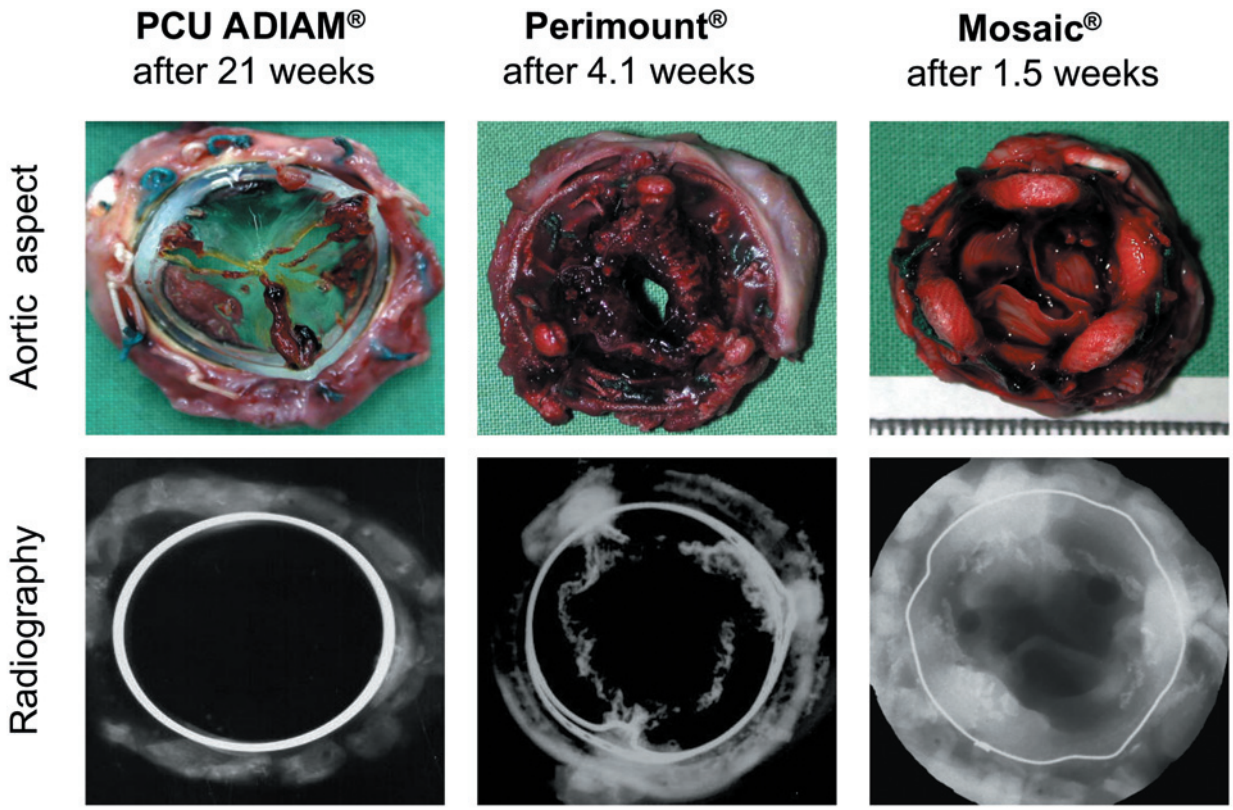

Figure 4. Gross and radiographic findings on an explanted polycarbonate urethane (PCU) aortic valve of a long-term survivor (20 weeks) and on the explanted Perimount and Mosaic valves after 4.1 and 1.5 weeks, respectively. The PCU valve has very little calcification, which is not visible radiographically. In contrast, both biological valves are clearly calcified. Parts of this figure have been reprinted from Daebritz SH, Bernd Fausten B, Hermanns B, et al. 2004. Introduction of a flexible polymeric heart valve prosthesis with special design for aortic position. Eur J Cardiothorac Surg 25:946-52, with permission from Elsevier BV.

The development of polymeric heart valves started in 1958, when Roe implanted into humans an aortic prosthesis made of silicone rubber [Roe 1958]. High morbidity and mortality caused by excessive embolization stopped clinical application. PTFE valves were also implanted into the aortic position [Braunwald 1965]. However, stiffening and tearing of the leaflets led to severe aortic regurgitation in many patients. Meanwhile, the Starr-Edwards prosthesis became the standard of heart valve replacement. Since then, many polymeric valve prostheses have been designed and tested in vitro and in vivo, including valves made of silicone rubber, PTFE (Teflon), polyethylene terephthalate (Dacron), polyvinyl chloride, and polyurethane [Roe 1958, 1966, Hufnagel 1977, Imamura 1977, Nistal 1990, Hyde 1999]. None of these valves, however, proved to be adequate for human implantation. Material degradation and thrombogenicity remained unsolved problems multifactorially caused by calcification, oxidation, hydrolysis, absorption of lipids, and the influence of mechanical factors [Hyde 1999].

In the 1980s and 1990s new insight was gained into the fact that durability not only depended on the polymer of the valve but also was mainly influenced by the manufacturing process and design. The more physiologic the transvalvular flow pattern, the higher was the durability of the valve or (translated to mechanical valves) the lower was the thrombogenicity [Chetta 1980]. Any energy loss on the valve is energy that works as destructive energy on the valve itself and the blood. This concept has been taken into consideration in most new valve constructions. However, the attempt to mimic natural mitral and aortic flow characteristics with a single prosthesis design led to compromises in both positions, and degeneration of the constructed polymeric valves remained a major problem, particularly in the early 1980s [Wisman 1982, Herold 1987, Hilbert 1987, Edmunds 1996, Hyde 1999].

Later, trileaflet polyurethane valves showed good durability in growing calves [Lo 1988, Jansen 1991]. In growing sheep one trileaflet polyurethane valve demonstrated good performance in comparison with mechanical and biological valves [Lo 1988]. However, 3 of 8 valves were seriously thrombosed, a major concern because sheep experience less thrombogenicity than human valve recipients [Lo 1988]. Nevertheless, polyurethanes turned out to be superior to other polymers, and newly developed polymeric heart valves proved efficacious in many assist devices, in which their requirements of durability are limited [Wheatley 2000].

In our study, we were able to demonstrate in vitro and in vivo that the newly developed biomechanical Adiam mitral PCU valve showed no degradation of the material, such as tearing, intrinsic calcification, or other signs of destruction of the integrity of the structure if implanted correctly. These findings were in contrast to those with prior polyurethane valve constructions and bioprostheses and most likely were due to the special asymmetric bileaflet design, which resembled a natural mitral valve, and the specific choice of polymer [Schoen 1988]. Degenerative changes were minor compared with those in the implanted biological valves but were increased, including minimal tearing on the ultrastructural level, if the PCU valve was implanted in a malrotated position. This finding emphasizes the importance of optimal hemodynamics for the durability of the valve. According to the pathological findings, the animals with PCU valves did better clinically than did those with either of the biological valves. Echocardiography proved the good function of the PCU valves, even under extreme hemodynamic stress at a weight of more than 160 kg.

The slightly higher gradients of the PCU valves soon after implantation were most likely due to the stiffness of the PCU, which decreases after a few hours owing to uptake of water by the polymer. This theory is supported by the low gradients prior to explantation. Except in the malrotated valve, no thrombus formation was observed on the PCU valves without permanent warfarin therapy.

If these results are extrapolated by the reported durability of the Perimount and Mosaic bioprostheses in humans [Marchand 2001, Dellgren 2002, Eichinger 2002], the mitral PCU valves are expected to have considerably longer freedom from valve-related reoperation.

The newly developed aortic PCU prosthesis was designed to mimic the natural flow profile of the aortic valve characterized by axial, cylindrical flow through an almost circular orifice of a high-profile valve. Stresses and strains, particularly alternating flexural stresses at the edges of the leaflets, are minimized to achieve highest durability. Thin stents and a narrow sewing ring provide a large effective orifice area with a very low transprosthetic gradient.

The results of our study demonstrated superior performance of the PCU aortic valves compared with biological prostheses. Only animals with PCU aortic valves reached the end of the study period. The animals with biological valves died as the result of severe degeneration of the prostheses with calcification after less than 5 weeks. The PCU valves, explanted at an average of 20.7 weeks, showed mild to moderate degenerative changes and minor to moderate calcification. However, the PCU valve with the highest grade of degeneration was only 19 mm, and the body weight of the animal at sacrifice was 160 kg. Translating these findings into performance of the PCU valves in humans anticipates increased durability without the need for anticoagulation.

There are some limitations of the growing calf animal model, particularly for aortic valve testing. The anatomy of the aortic root in calves is characterized by a very narrow annulus, which allows implantation of only small valves. In addition, creation of dead spaces after implantation of any ringed valve substitute in this anatomic situation increases the risk of thromboembolism. This problem is not likely to be related to a special prosthesis, because we observed thrombus formation, though small, in all types of implanted valves. This problem has not been described for biological prostheses in humans, particularly not for the Perimount valve, and we did not observe anything comparable in the mitral valve series [Dellgren 2002, Eichinger 2002, Daebritz 2003]. Another limitation of this growing animal model is pannus formation, which is well known after aortic valve replacement in children [Lupinetti 1999] but hardly ever seen in adults. In our study, we saw severe, subvalvular pannus formation without calcification and without involvement of the valves in 2 animals with PCU valves. We did not find it in the 2 animals with biological prostheses. However, these animals died after only 1.5 and 4 weeks because of degeneration of the prostheses.

We chose the growing calf animal model because it is the extreme calcification model for testing of tissue and polymeric valves [Schoen 1992]. In addition, calves are more thrombogenic than sheep, who even tolerate mechanical valves without anticoagulation [Wheatley 2000]. In addition, the growth of the animals to the end of the study period with a body weight of 150 to 170 kg and a CO of 12 L/min represented significant hemodynamic stress to the valve prostheses. In summary, this animal model is expected to point out the differences in performance of the tested prostheses and explains the severe calcification of the biological valves (both Perimount pericardial and Mosaic porcine) in the mitral and aortic positions and the severe thrombosis seen in a Mosaic valve in our series. Therefore the tested PCU valves performed convincingly in this animal model with minor degeneration and no thromboembolic complications. In contrast to many polyurethane valves developed in the 1980s and 1990s, the valves used in this study did not have intrinsic calcification. This finding confirmed the integrity of the polymer. We found 1 tear in an aortic valve leaflet in an area of reduced leaflet thickness of a prototype valve. As long as the valves are manufactured manually and not in a fully automated process, a certain variability between single valves in unavoidable.

In summary, the presented results with mitral and aortic Adiam PCU valves are promising. The performance of both prostheses in vivo was superior to that of biological mitral and aortic prostheses, which have proven excellent durability in clinical use [Marchand 2001, Dellgren 2002, Eichinger 2002]. The PCU valves demonstrated increased durability without thromboembolic complications and without permanent anticoagulation. This result was attributed to the use of biostable PCU and a design with superior hemodynamic performance. Restrictions of the animal model for the aortic position limit the conclusions inasmuch as they cause or increase some of the observed complications and blur the differences between the valves. However, even in this setting, the PCU valves performed convincingly. Nevertheless, a second in vivo study may be useful for confirming the advantages of the aortic Adiam PCU valve prior to clinical studies. Controlled clinical studies are planned for the Adiam PCU mitral valve.

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