Introduction of a flexible polymeric heart valve prosthesis with special design for aortic position

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Received 27 January 2004; accepted 23 February 2004

Abstract

Objective: Current prosthetic heart valves necessitate permanent anticoagulation or have limited durability and impaired hemodynamic performance compared to natural valves. Recently a polymeric valve prostheses with special design for mitral position demonstrated excellent in vitro and in vivo results with improved durability and no need for permanent anticoagulation. In this study, a respective flexible polymeric aortic valve is presented and in vitro and in vivo results are reported.

Methods: The aortic prosthesis (ADIAM® lifescience AG, Erkelenz, Germany) is entirely made of polycarbonaurethane. The tri-leaflet flexible prosthesis mimicks the natural aortic valve and has a diminished pressure loss and reduced stress and strain peaks at the commissures. The valve underwent long-term in vitro testing and in vivo-testing in a growing calve animal model (20 weeks, 7 aortic valves) and was compared to two different commercial bioprostheses.

Results: The polymeric aortic heart valve substitute demonstrated excellent in vitro and in vivo hemodynamics. Five/seven animals with aortic PCU-prostheses had an excellent clinical long-term course. The explanted valves showed a variable degree of calcification. Two of the seven animals died at 27 and 77 days due to pannus overgrowth causing severe LVOTO without degeneration of the valve itself. Both animals with commercial bioprostheses had to be sacrificed because of congestive heart failure related to structural degeneration of the bioprosthesis after 10 and 30 days of implantation. There was no increased thrombogenity of the PCU valves compared to bioprostheses.

Conclusion: The new flexible polymeric aortic valve prosthesis is superior to current bioprostheses in animal testing.

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Keywords: Heart valve prosthesis; Aortic valve surgery; Polyurethane; Biodegradation

The first commercially available heart valve prosthesis was the Starr-Edwards mechanical valve designed for the aortic position [1]. Prior to that, at the end of the 1950s, sporadic implantation of aortic valve prostheses in humans had been performed with valves made of flexible polymers [2]. Thrombosis of the valves with thromboembolic complications and degeneration were the major problems leading to a high complication rate and to a cease of further clinical use particularly after the Starr Edwards prosthesis became the gold standard valve substitute [3,4]. Parallel to the introduction of optimized mechanical valves, i.e. tilting disc and bileaflet valves, and biological prostheses, the development of flexible polymeric heart valves went on. Polyurethanes turned out to be superior to other polymers such as silicone rubber, PTFE and collagen with regard to biocompatibility, resistance to thrombembolism and degeneration [5–7]. Despite various constructions and promising animal testing, none of the polymeric prostheses has so far proven long-term durability for clinical implantation. However, polyurethane valves are used effectively in assist devices (Abiomed®, Medos®, Berlin Heart®).

The development of polymeric heart valves casted light upon the impact of physiologic flow pattern on the durability
of valve prostheses: any energy loss on the valve is destructive energy for the valve. In addition, physiologic flow prevents from thromboembolism [8,9]. Therefore, major efforts were made to design a polymeric heart valve prosthesis specially for the mitral position. The result is an asymmetric polycarbonate-urethane mitral valve (ADIAM life science AG, Erkelenz, Germany) with optimized hemodynamics [10]. The prosthesis mimicks the natural flow pattern through the mitral orifice with a central, nonaxial flow forming two vortices in the ventricular cavity. The larger one fills the ventricle at the end of diastole and saves the kinetic energy for systolic ejection of the blood. The prosthesis is called a ‘biomechanical’ valve, because it is synthetic like a mechanical valve, but flexible like a bioprosthesis. The valve is supposed to combine the advantages of both currently available types of artificial heart valve prostheses: long-term durability without the necessity of permanent anticoagulation. In vivo testing results have demonstrated a durability superior to biological valves without the need for anticoagulation [10].

Accordingly, a special aortic valve prosthesis made of polycarbonateterethane (PCU) was designed and results of in vitro and in vivo testing are presented here. The excellent hemodynamics are expected to reflect in increased durability compared to biological valves and no necessity of permanent anticoagulation.

1. Material and methods

1.1. The PCU aortic valve

The ADIAM® (ADIAM® life science AG, Erkelenz, Germany) ‘biomechanical’ aortic valve prosthesis is made of a medical grade PCU specially developed for long-term implant needs (ADIAMat, ADIAM® life science AG, Erkelenz, Germany).

PCU is a material compound of hard segments and soft segments; the ratio of their mixture determines the degree of hardness. Stent, leaflets and sewing ring of the prosthesis consist of a multi-layered, cohesively bonded, not glued, single material of various degrees of hardness.

The valve design intends to mimic the natural aortic flow characteristics. According to aortic valve anatomy, the valve has three leaflets of a high profile to minimize stress and strain peaks at the commissures (Fig. 1). The steep configuration with almost complete opening of the leaflets leads to a circular orifice during systole providing an axial cylindrical flow-profile maintaining laminar, physiological flow pattern and, consequently, reduces energy losses. Stent profile is high to reduce alternating flexional stresses particularly at the commissures and the free margins of the leaflets. In addition, reduced leaflet thickness increases the flexibility of the leaflets. Thickness distribution of the leaflets is pre-defined to additionally reduce stress peaks at the commissures. To further minimize membrane stresses in diastolic and systolic position, the leaflets are shaped as flat as possible in an almost medium open position. This prevents the leaflets from being wrinkled in the middle position, when changing from open to closed. Stents and sewing ring are thin to provide a large effective orifice area in each valve size. Stent posts are flexible to some extent in order to ensure tight leaflet closing during diastole.

The manufacturing process starts with a mould dipped in dissolved PCU of higher hardness degree in order to obtain the stent form. The stent base holds an integrated stiffening ring of radiopaque MRI compatible titanium alloy. In a next step, biocompatible blood contact layers of softer PCU are applied by dropping techniques. They coat the whole valve and form the leaflets and, thus, provide a smooth transition between hard stent core material and soft leaflets. Accordingly, all surfaces are of soft hardness degree to provide high flexibility, thrombogenic resistance and hemodynamic compatibility as well as high mechanical resistance to alternating flexural movements. As the material...
takes up 2% water to get saturated, the leaflets become softer several hours after implantation. Pre-defined thickness distributions achieve lowest possible strains avoiding stress peaks at the commissures. The thickness of the leaflets varies between 80 and 200 μm. At the end of the manufacturing process the three leaflets are separated with a precision laser.

The sewing ring is made of dissolved PCU sprayed to fleece-like sheets, of which the sewing ring is punched out. The microfibrillar material of high elasticity is supposed to allow close fit to the natural annulus and rapid healing by neo-intima and fibroblast ingrowth without pannus formation. The sewing ring is cohesively bonded around the base of the stent.

The valve is kept in a specially designed holder.

1.2. In-vitro and in-vivo testing

In-vitro fatigue testing was performed in testing facilities with 700 working cycles/min. Thus, 38 million cycles represent one 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 by the Government of the State of Nordrhein Westfalen, Germany. This animal model was chosen because calves are considered an extreme calcification model [11]. 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, 3–5 months of age and 86 ± 8 kg (69–96 kg) of weight.

Surgery was performed in general anesthesia via a left thoracotomy. Anaesthesia was induced with atropin (0.5 mg i.v.), midazolam (10 mg i.m.), ketamin-hydrochloride (300–500 mg i.v.) and hypnotamide (10–30 mg i.v.) and was maintained with inhalative drugs (N₂O 30–50Vol.%, halothane 0.5–2Vol.%). Paralytic agents (alcuronium, initially 6 mg continuing with 4 mg/h) were administered.

Monitoring consisted of routine blood gas analysis according to human requirements for cardiopulmonary bypass (CPB) surgery. Arterial, central venous and pulmonary artery pressures were monitored continuously by an ear arterial line, a left jugular central venous line and a Swan Ganz thermodilution catheter, respectively. Cardiac output (CO) was measured every 30 min. ECG and heart rate were documented continuously.

The valves were implanted orthotopic in aortic position using cardiopлегic cardiac arrest with crystalloid or cold blood cardioplegia. Access to cardio-pulmonary bypass was gained via the descending aorta, the innominate artery, the right atrium and the pulmonary artery trunk. No blood was used for priming or postoperatively. Under mild hypothermia (28 °C) and full CPB flow (100 ml/kg body weight), the aorta was cross clamped and opened obliquely. Access to the aorta is complicated by the very proximal take-off of the innominate artery. In addition, the anatomy of the aortic root is special in calves; the root is extremely narrow and the deep sinuses lead to areas of dead space after implantation of heart valve prostheses with sewing rings.

The native valve was resected and the valve prostheses were implanted with 2-0 pledged mattress sutures. The aorta was closed with a 4-0 prolene running suture. After rewarming CPB was weaned and cannulae were removed. Epi-myocardial echocardiography was performed with assessment of morphology and function of the valves. After placement of chest drains, the wounds were closed in layers.

The animals were transferred into the intensive care unit and extubated after 2–6 h. Lines and drains were removed before the animals went into the barn on the next morning.

Perioperative medical treatment consisted of antibiotics (ciprofloxacin 2 × 200 mg i.v.d.) for 3 days beginning at the operation. Postoperative analgesia was achieved with opioids (piripramid 2 × 7.5 mg/d i.m.). The animals were fully heparinized perioperatively and received low molecular heparin for the first two weeks postoperatively to prevent from thromboembolic complications caused by the special anatomy of the aortic root. Additionally, Aspisol 100 mg i.v. was given once on the operative day followed by ASS 100 mg per os for two weeks. There was no permanent anticoagulation.

For long-term observation the calves were transferred to a farm. They were seen daily by veterinarians and examined weekly by cardiac surgeons. In case of development of congestive heart failure (CHF), anticoagent therapy with furosemide, digitoxin and ACE inhibitors was commenced.

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After the study period of 20.7 ± 0.5 (FDA requirement 20 weeks) [12] the animals were anaesthetized and the hearts dissected. For hemodynamic assessment Swan-Ganz catheters were placed and cardiac output was measured. 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 as well as hemodynamic performance was carried out. The animals were sacrificed with an i.v. overdose of phenobarbital and autopsy with macroscopical and histological examination of heart, lungs, liver, kidney and spleen was performed. The explanted valves underwent macroscopical, histological, radiographical and electron microscopical analysis including energy dispersive X-ray (EDX) spectroscopy and scanning electron microscopy.

Seven ADIAM® PCU-valves size 19 mm (1) and 21 mm (6) were implanted and compared to one size 23 mm Perimount® pericardial valve, Edwards lifesciences, Irvine,
CA, and one 21 mm Mosaic™ procine valve, Medtronic, Minneapolis, Minn, USA. The American Food and Drug Administration (FDA) requires comparison with two commercially available biological valves [12].

1.3. Statistical analysis

Statistical analysis was done with SPSS Version 11.0 (SPSS Inc., Chicago, IL, USA). Central tendency is expressed by mean, dispersion by standard deviation and range. Intraindividual differences were assessed using two tailed Wilcoxon test.

2. Results

2.1. In-vitro testing

In vitro fatigue testing of the PCU aortic valves has proved so far durability of up to 300 million cycles representing 7.9 years of average human function and fulfills FDA requirements for biological heart valves [12]. Testing is ongoing.

2.2. In-vivo testing

The perioperative course was uneventful. Epimyocardial echocardiography initially after implantation revealed the following systolic gradients across the aortic valve protheses at a CO of 6.4 ± 1.6; 4.8–9.4 l/min: PCU valves size 21: 9.7 ± 4.5; 4.5–15.2 mmHg, size 19: 20 mmHg; Medtronic Mosaic™ size 21: 61 mmHg (CO 7.0 l/min) and Edwards Perimount size 23: 10 mmHg (CO 4.6 l/min).

Five of the seven animals with PCU aortic valves including the animal with the size 19 valve reached the end of the study in good clinical condition without any medication and were sacrificed after 20.7 ± 0.5 weeks (Fig. 2). The other two animals with aortic PCU valve died suddenly after 4 and 11 weeks due to severe LVOT obstruction caused by subvalvular pannus growth without changes of the valve leaflets. The animals with the Mosaic™ and Perimount™ valve died suddenly after 10 and 30 days, respectively, due to severe valve degeneration with valve stenosis (Fig. 3).

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

Mean body weight of the five survivors reaching the study end was 157 ± 11 kg (140–170 kg). They underwent epimyocardial echocardiography and invasive assessment of hemodynamics except for one survivor who died at induction of anaesthesia.

Echocardiographic assessment showed mild thickening of the leaflets of all valves and restricted motion of the leaflet in two valves (size 19 and 21); one size 21 PCU valve had mild central aortic regurgitation. The mean systolic gradient across the size 21 PCU aortic valve was 65 ± 25 mmHg (40–90 mmHg) in echocardiography and 65 ± 24 mmHg (41–88 mmHg) invasively measured; CO was 12.6 ± 0.4 l/min (12.2–12.9 l/min). The respective systolic gradients across the size 19 PCU aortic valve were 145 and 170 mmHg at a CO of 11 l/min.

Gross examination did not reveal any paravalvular leaks in any prosthesis. The sewing rings of the PCU prostheses were completely covered with neointima. Pannus overgrowth below the sewing ring was found in three PCU aortic valves: In one it was mild-moderate and in two it was severe causing subtotal obstruction with early sudden death.

In gross examination the PCU valves of the long-term survivors showed mild calcification deposits preferably close to the commissures in two cases, and mild-to-moderate in one case (Fig. 3). One size 21 and the size 19 PCU aortic valves showed severe deposits leading to restricted leaflet motion. The size 21 PCU prosthesis with the mild central regurgitation showed a tear in the middle of the free margin of one leaflet directed to the middle of the cusp. There was mild thrombus formation in two PCU valves which was severe in the Mosaic™ and mild in the Perimount bioprosthesis. Both bioprostheses showed severe thickening and deformation of the leaflets.

Histology, radiography, and energy dispersive X-ray spectroscopy of the PCU valves revealed mild calcification in two, mild-to-moderate in one, and severe in two including the size 19 valve. Calcification was severe in both bioprostheses. The observed calcifications were exclusively extrinsic, i.e. on the surface of the leaflets of the polymeric and biological valves and not intrinsic. There was no destruction of the polymer integrity or the biological structure except for the described tear in one PCU leaflet. Microscopic analysis of the leaflet showed a reduced leaflet thickness of that cusp as a variation of the manual manufacturing of the prototype valve. Scanning electron microscopy showed a smooth surface of the PCU valve leaflets with differing calcification spots according to the degree of calcification predominantly at the commissures.
The surface of the biological valves was roughened demonstrating a degeneration of the 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 early deaths. 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 one animal with a PCU valve.

3. Discussion

More than forty years of heart valve replacement are characterized by the use of a universal prosthesis design irrespective of the implantation site—mitral or aortic. Both mostly used valve substitutes—mechanical and biological—carry a major disadvantage: either the necessity of lifelong anticoagulation or limited durability. This also applies to homografts.

In this study, we present a new aortic valve prosthesis, which is entirely made of polycarbonateurethane. The aim was to manufacture a so-called ‘biomechanical’ valve, a prosthesis which is totally made of artificial material, but which is flexible. The hypothesis is, that this concept combines the advantages of the currently available valve prostheses: long-term durability and no necessity for permanent anticoagulation.

The development of polymeric heart valve substitutes goes back to the end of the 1950s, when Roe implanted an aortic prosthesis made of silicone rubber in humans [2]. The clinical study was interrupted due to high morbidity and mortality caused by excessive embolisation; anticoagulation was not performed at that time. Braunwald implanted PTFE valves into aortic position in the early sixties [3]. Unfortunately, 13/33 patients developed severe aortic regurgitation due to stiffening and tearing of the leaflets. At that time, the Starr Edwards aortic prosthesis was introduced and became the gold standard of heart valve replacement. Therefore, the newly developed polymeric heart valves had to compete with the results of the Starr Edwards valve. Many polymeric valves were tested in vitro and in vivo, including valves made of silicone rubber, PTFE (Teflon®), PET (Dacron®), polyvinylchloride and polyurethane [2,4,5,6,13,14]. None of these valves, however, proved to be adequate for human implantation. Material degradation and thrombogenicity remained unsolved problems, which were multi-factorially caused by calcification, oxidation, hydrolysis, absorption of lipids and influence of mechanical factors [11,14].

In the 1980s and 1990s new insight was gained into the fact, that durability was not only depending on the polymer of the valve, but was mainly influenced by the manufacturing process and the design: the more physiologic the transvalvular flow pattern, the higher the durability of the valve or—translated to mechanical valves—the lower the thrombogenicity [15]. Any energy loss on the valve is energy, which works as destructive energy on the valve and the blood. Evolution provided heart valves with the best solutions adapted to their specific needs. What should be more obvious than mimicking the natural idol? Therefore, most of the new valve constructions were designed trying to optimize hemodynamics. However, the attempt to mimic the natural mitral and aortic flow characteristics with one prosthesis lead necessarily to compromises in both positions. Despite improvements in design and material, degeneration of the constructed polymeric valves remained a major problem in the 1980s [9,14,16,17,18,21].

In the 1990s trileaflet polyurethane valves showed good durability in growing valves [19,20]. One trileaflet polyurethane valve demonstrated good performance in growing sheep in comparison to mechanical and biological valves [19]. However, 3/8 valves were seriously thrombosed, which was of major concern, because sheep are less thrombogenic than human valve recipients [19]. Nevertheless, polyurethanes turned out to be superior to other polymers and newly developed polymeric heart valves proved efficacy in many assist devices, where their requirements to durability are limited [22]. Recently, the implementation of optimized hemodynamics in combination with the use of high performance polymers lead to the introduction of a PCU valve with special design for the mitral position (ADIAM® life science AG, Erkelenz, Germany) [10]. This prosthesis has proven superior durability in vivo compared to currently used bioprostheses without permanent anticoagulation. It is the first polymeric heart valve prosthesis since four decades, which is close to going into clinical studies for human long-term implantation.

According to this successful development, an aortic valve was designed mimicking the natural flow profile of the aortic valve as much as possible. Stresses and strains, particularly alternating flexional stresses at the edges of the leaflets, are minimized to achieve highest durability. This is achieved by steep configured leaflets and optimized distribution of leaflet thicknesses. The high profile of the valve with the almost circular orifice leads to an axial, cylindrical flow-profile. In addition, the thin stent and narrow sewing ring provide a large effective orifice area as well as very low transprosthetic gradients. Like the mitral PCU valve, the aortic prosthesis is completely made of the high performance PCU [10].

The in vitro testing and the development of a fully automated computer controlled manufacturing process of the PCU aortic valve is ongoing. For in vivo testing, we chose the hardest calcification model for heart valve degeneration: the growing calf [10]. In addition, calves are more thrombogenic than sheep, who even tolerate mechanical valves without anticoagulation [22]. This explains the extremely fast degeneration of biological mitral valves (both Perimount® Mosaic®) and the severe thrombosis of a Mosaic® valve in the PCU mitral valve study [10].
The body weight and the cardiac output of the calves at the end of our study period reached 150 kg and 12 l/min, respectively, representing significant hemodynamic stress to the valve prosthesis. A limiting factor of the reported animal study is the special anatomy of the aortic root in calves, which is characterized by a very narrow annulus and the creation of dead spaces after implantation of any ringed valve substitute. Therefore, only small valves can be implanted into a calf of 80 kg body weight. In addition, there is an increased risk of thromboembolism due to the dead spaces, which is not likely to be related to a special prosthesis, as we observed thrombus formation, though small, in all types of implanted valves. Particularly for the Perimount® valve, this has not been described in humans and we have not observed anything comparable in the mitral valve series [10,23,24]. A second limitation of our in vivo animal model is the development of pannus formation, which is well known after aortic valve replacement in children [25], but hardly ever occurs in adults. In our study, we saw severe, subvalvular pannus formation without calcification and without involvement of the valve leaflets in two animals with PCU valves; we did not see it in the two animals with biological prostheses. This, however, may be due to the small number and the fact, that the animals with the biological valves had very short survival times (1.5 and 4 weeks) because of degeneration of the prostheses. In summary, we prefer a growing animal model accepting the risk of pannus formation, because calcification of heart valves is undoubtedly related to the age of the recipient.

In our study, only animals with PCU aortic valves reached the end of the study period. Both animals with biological valves died after 1.5 and 4.1 weeks due to congestive heart failure. Accordingly, the explanted biological valves were severely degenerated and calcified already at 1.5 and 4.1 weeks after implantation. The PCU valves, explanted after 20.7 weeks, were also degenerated and showed minor to moderate calcification. However, the PCU valve with the highest grade of degeneration was only size 19 mm and the body weight of the animal at ascertainment was 160 kg. The other PCU valves also had a high discrepancy between valve size and body weight at explantation, whereas the animals with the biological valves reached only 87 and 105 kg body weight. In contrast to many polyurethane valves, which were developed in the 1980s and 1990s, we did not observe any intrinsic calcification; this confirms the integrity of the polymer and is according to the results of the ADIAM® PCU mitral valve [10]. In contrast to the mitral series, we found a tear in one aortic valve. This is a single observation, which occurs due to a reduced thickness in the manufacturing of this very valve. As long as the valves are manufactured manually and not in a fully automated process, a certain variability between the single valves in unavoidable.

In summary, the presented results of the aortic ADIAM® PCU valves are so far promising; they performed superior in vivo compared to biological aortic prostheses, which have proven excellent durability in clinical use [23,24]. The PCU valves demonstrated increased in vivo durability without increased thromboembolic complications without permanent anticoagulation. This is attributed to the use of biostable polycarbonateurethanes and the design with superior hemodynamic performance. The animal model has some restrictions due to anatomical reasons, which limit the conclusions inasmuch as they cause/increase some of the observed complications and blur the differences between the valves. In this setting, the PCU valves performed convincingly. Nevertheless, a second in vivo study may be useful to confirm the advantages of the aortic ADIAM® PCU valve, prior to controlled clinical studies.

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Appendix A. Conference Discussion

Dr M. Antunes (Coimbra, Portugal): Why did you decide not to use anticoagulation and do you really expect not to use anticoagulation in the clinical trials?

And another question. I am not sure about the characteristics of this material. Why do you think that it is less wearable, I mean more durable, than either the pericardium or the porcine valves?

Dr Daebritz: To the first question: the idea was to design a valve which combines the two advantages of currently available heart valves: long-term durability and no need for anticoagulation. However, we prefer to give anticoagulation for the first 6 to 12 weeks in the clinical studies as is mostly performed in biological valve recipients. To the second question: one major factor for durability is the material, the other major factor is related to the design of the prosthesis. By optimizing both, design and hemodynamics, we have maximally reduced energy loss on the valves, and any energy loss on the valves is destructive energy for the valves. Thus we expect prolonged durability.

In addition, polyurethanes have turned out to be superior materials for biological implants, compared to PTFE, silicone rubber and others tested in earlier devices, particularly in heart valve prostheses. However, polyurethanes comprise chemically a wide spectrum and this particular polyurethane used in the valves of our study has been refined by the company and has shown to be extremely durable in vitro and in vivo.

Dr T. Bottio (Padua, Italy): As you know, the calcification process is related to membrane phospholipids or to collagen fibers or to elastic fibers in the biologic tissue. In this PCU valve, the calcification after 20 weeks was related to what, to which one structure, since it is an all-synthetic valve?

Dr Daebritz: We did not see any intrinsic degeneration, particularly calcification; all changes were extrinsic, i.e. on the surface of the polymer. That means that the structure of the biopolymer stays stable even though there is some degeneration, but it is not destroying the chemical integrity of the polymer. Degeneration started on the surface. However, this process was very delayed compared to biological valves. Was that your question?

Dr Bottio: Yes. Was the pannus tissue overgrowth calcified?

Dr Daebritz: The pannus was not calcified. There was only additional fibrous tissue under the aortic valves causing subaortic stenosis. The valves were unremarkable.