Introduction of a Flexible Polymeric Heart Valve Prosthesis With Special Design for Mitral Position

Sabine H. Daebritz,* MD; Jörg S. Sachweh,* MD; Benita Hermanns MD; Bernd Fausten MD; Andreas Franke MD; Jan Groetzner MD; Bernd Klosterhalfen MD; Bruno J. Messmer, MD

Background—Current heart valve prostheses are constructed mimicking the native aortic valve. Special hemodynamic characteristics of the mitral valve such as a nonaxial central inflow with creation of a left ventricular vortex have so far not been taken into account. A new polycarbonatethane (PCU) bileaflet heart valve prosthesis with special design for the mitral position is introduced, and results of animal testing are presented.

Methods and Results—After in vitro testing, 7 PCU-prostheses and 7 commercial bioprostheses (Perimount, n=4; Mosaic, n=3) were implanted in mitral position into growing Jersey calves (age 3–5 months, weight 60–97 kg) for 20 weeks. 2-Dimensional echocardiography was performed after implantation and before sacrifice. Autopsy included histologic, radiographic, and electron microscopic examination of the valves. In vitro durability was proven for >15 years. After implantation 2-dimensional-echocardiography showed no relevant gradient or regurgitation of any prosthesis. Clinical course of the animals with PCU valves was excellent. In contrast, 5 of 7 calves with bioprostheses were sacrificed after 1–9 weeks because of congestive heart failure. 2-Dimensional echocardiography of the PCU valves after 20 weeks showed mild leaflet thickening with trivial regurgitation; mean gradient was 8.1±5.0 mm Hg (weight: 160–170 kg). The explanted PCU prostheses revealed mild calcification and no structural degeneration. All of the Perimount bioprostheses were severely calcified and degenerated after 11±7 weeks. One Mosaic bioprosthesis was thrombosed after 1 week, and 2 showed severe and mild-to-moderate degeneration after 4 and 22 weeks, respectively.

Conclusions—Polycarbonatethane valve prostheses with special design for mitral position show excellent hemodynamic performance and durability in vivo. Calcification and structural changes are mild compared with bioprostheses. Controlled clinical studies are planned. (Circulation. 2003;108[suppl II]:II-134-II-139.)

Key Words: heart valve prosthesis ■ mitral valve surgery ■ polyurethane ■ biodegradation

Despite 5 decades of research, the ‘ideal’ heart valve prosthesis has not been found. The currently available devices have a number of unsolved problems. The major disadvantage of mechanical heart valves is the necessity of life-long anticoagulation; biological valve prostheses as well as homografts have limited durability particularly in the young.

Heart valve prostheses made of flexible polymers have been designed for more than four decades and were among the first valves undergoing human implantation.1,2 Of all the materials tested, including collagen, silicone rubber, polytetrafluoroethylene (PTFE), and polyurethane, polyurethanes turned out to have the best biocompatibility, durability, and thrombogenic resistance.3–5

In the last 2 decades increasing insight was gained into the importance of optimal hemodynamic performance of elastomeric valves in their durability.6,7 Any energy loss on the valve is destructive energy for the valve. Therefore, more concerns were given to the design of the stent and leaflets in addition to the selection of the polymer. Despite this understanding, almost all prostheses, including mechanical, biological, and biomechanical valves have so far been designed for the aortic position or are mimicking the aortic valve. However, the hemodynamic characteristics of the natural mitral valve are completely different. It is asymmetric with a central, nonaxial inflow directed to the apex of the ventricle creating a smaller and a larger vortex. At the end of diastole, the larger vortex fills the ventricle completely and, thus, saves the energy for systolic ejection of the blood (Figure 1).7 The advantage of a physiological mitral inflow is difficult to measure in current testing facilities, which generally assess energy loss as pressure loss, turbulences, leakage, and cavitation in axial flow. However, optimal hemodynamics are expected to reflect in increased durability of polymeric as well as biological heart valves.

Currently, some polymeric valves have shown their efficacy in assist devices (Abiomed, Medos, and Berlin Heart). However, so far no flexible polymeric heart valve has proven durability for long-term implantation.

From the Department of Cardiac Surgery, Ludwig-Maximilians-University, Munich, Germany; and Department of Thoracic- and Cardiovascular Surgery, Department of Pathology, and Department of Cardiology, University Hospital, 52057 Aachen, Germany

Correspondence to Sabine Daebritz, MD, Department of Cardiac Surgery, LMU, University Hospital Grosshadern, Marchioninistr. 15, D-81377 Munich, Germany. Phone: 49-89-7095-3451, Fax: 49-89-7095-3943, E-mail: sabine.daebritz@hch.med.uni-muenchen.de

*These authors contributed equally to the manuscript.

© 2003 American Heart Association, Inc.

Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.cir.0000087655.41288.dc

II-134
The ADIAM polyurethane valve with special design for the mitral position. Computer design and picture.

Figure 2. The ADIAM polyurethane valve with special design for the mitral position. Computer design and picture.

In this study, we introduce a bileaflet PCU heart valve prosthesis with special design for the mitral position. We call this prosthesis a “biomechanical” valve, because it is completely synthetical, but flexible. The prosthesis is supposed 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 are presented.

Materials and Methods

The PCU Mitral Valve

The ADIAM (ADIAM Life Science AG) biomechanical mitral valve prosthesis is made of a medical PCU specifically developed for long-term implant needs (ADIAMat, ADIAM Life Science AG). Stent, leaflets, and sewing ring consist of a multilayered, cohesively bonded, not glued, single material of various degrees of hardness. PCU is a material compound of hard segments and soft segments; the ratio of their mixture determines the degree of hardness.

The valve design intends to mimic the natural mitral flow characteristics. 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 2). Their flat configuration maintains physiological vortices during the outflow phase and, consequently, reduces energy losses. The leaflets provide an oval orifice, giving way for the typical mitral flow pattern. Mimicking the chordae tendineae would result in a complicated implantation technique. Therefore, leaflet prolapse is avoided by a hanging bridge construction in which the leaflets are connected saddle-like with the 2 stent struts. Stent profile is low so that there is no interference with the ventricular wall. The valve size is defined by the smallest external stent diameter and corresponds to the same diameter of round valves if orifice area integral is calculated.

The manufacturing process starts with a mold dipped in dissolved PCU of higher hardness degree in order to obtain the stent form. The stent head holds an integrated stiffening ring of radiopaque magnetic resonance imaging 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. Thus, the core layer of the leaflet is of medium hardness degree in order to improve tensile strength during high systolic pressures. The upper and lower 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. Predefined thickness distribution achieves lowest possible strains avoiding stress peaks at the commissures. The thickness of the leaflets varies between 100 and 300 μm. At the end of the manufacturing process the 2 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 microporous material of high elasticity is supposed to allow close fit to the natural annulus and rapid healing by neointima and fibroblast ingrowth without pannus formation. The sewing ring is cohesively bonded around the base of the stent.

The valve has a specially designed holder to prevent it from strut entrapment by sutures, which has been observed in prior series.

In Vitro and in Vivo Testing

In vitro fatigue testing was performed in a testing facility with 700 working cycles/minute. Thus, 38 million cycles represent 1 year of normal human function. The valves were checked once a week macroscopically for material degradation.

All of the animals received human care according to the German guidelines for laboratory animal care. In vivo testing was performed with the permission of the Government of the State of Nordrhein Westfalen, Germany, in a growing Jersey calf animal model. This animal model was chosen because calves are considered an extreme calcification model. In addition, the 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 60–97 kg (79±9 kg).

Surgery was performed in general anesthesia via a left thoracotomy. Anesthesia was induced with atropin (0.5 mg i.v.), midazolam (10 mg i.m.), ketamin-hydrochloride (300–300 mg i.v.), and hypnomidate (10–30 mg i.v.), and was maintained with inhalative drugs (N₂O 30–50 Vol.%, halothane 0.5–2 Vol.%). 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 was measured every 30 minutes. ECG and heart rate were documented continuously.

The valves were implanted into mitral position in a beating heart technique without cardioplegic cardiac arrest. Access to cardiopulmonary bypass was gained via the descending aorta, the left jugular vein, and the pulmonary artery trunk. No blood was used for priming or postoperatively. Under mild hypothermia (32 °C) and full CPB flow (100 mL/kg body weight), the left atrium was opened, and the mitral valve was immediately opened with a sucker to avoid ejection...
of blood and, thus, prevent from air embolism. The native valve and the chordae were resected to prevent from any interference with the prostheses despite the negative effect on ventricular function. The valves were implanted with 2–0 pledged mattress sutures. It was of major concern to insert particularly the PCU valves in correctly rotated position. Just before completion of the left atrial suture line, the valves were allowed to close. After short rewarming CPB was stopped, and cannulae were removed. Epimyocardial 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 hours. 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/day) for 3 days starting at the operation. Postoperative analgesia was achieved with opiates (pirorhamid 2×7.5 mg/day i.m.). The animals received phenprocoumon for 6 weeks (3 mg/day p.o.) and aspirin (100 mg/day p.o.) for the whole study period.

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

Blood cell count, coagulation, and hepatic and hemolysis parameters were controlled once a week and compared with preoperative values.

After the study period of 21.8±0.4 weeks (Food and Drug Administration requirement 20 weeks),9 the animals were anesthetized and the heart dissected. Hemodynamics were assessed, Swan-Ganz Catheters could not be placed accurately for measurement of cardiac output because of the size of the animals. Therefore, left atrial pressure was measured directly. 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 spectroscopy and scanning electron microscopy.

Seven ADIAM PCU-valves size 29 mm were implanted and compared with 7 widely used biological mitral heart valve prostheses (4 Perimount pericardial valves, Edwards Lifesciences, size 29 mm [2] and 27 mm [2], and 3 Mosaic proicine valves, size 29 mm). Two additional animals with bioprostheses were sacrificed after 21.8 weeks. One of the 4 animals with Perimount valves reached the study end under triple anticoagulative medication. Three animals had to be sacrificed after 5.3, 6.7, and 8.4 weeks because of severe CHF despite anticoagulative therapy.

One of the 3 animals with Mosaic valves reached the study end in good clinical condition without cardiac medication. One animal died 1 week postoperatively because of fulminant thrombosis of the valve prosthesis. The third animal had to be sacrificed after 4.4 weeks because of intractable CHF.

Mean body weight of the 9 survivors reaching the study end was 165±5 kg (160–172 kg). They underwent epimycocardial echocardiography except the survivor with the Perimount valve, who was in bad clinical condition and died at induction of anesthesia. Mean gradient across the PCU-valves was 8.4±5.3 mm Hg (3.6–19.4 mm Hg; Figure 3). In 6 of 7 valves, the gradient was between 3.6 and 9.7 mm Hg; in 1 it was extraordinary high (19.4 mm Hg). Morphological assessment showed trivial to mild thickening of the leaflets except in the valve with the high gradient, which had moderate changes close to the commissures. All of the PCU valves had normal function with trivial regurgitation. The Mosaic prosthesis revealed a mean gradient of 6.5 mm Hg and mild to moderate thickening with restricted leaflet motion causing grade 2 regurgitation (Figure 4). Mean left atrial pressure for the PCU valves was 20.7±2.9 mm Hg (15–24 mm Hg) and 26 mm Hg for the Mosaic valve.

Gross examination did not reveal any paravalvular leaks in any prosthesis. The suture rings were all covered with neointima without pannus overgrowth. One PCU valve prosthesis was not rotated correctly with respect to physiological hemodynamics. This was the PCU valve with the exceptionally high transvalvar gradient at the end of the study.

In gross examination the PCU valves showed minor deposits preferably close to the commissures except in the malrotated prosthesis, in which the deposits were moderate. In addition, this valve revealed a tiny thrombus formation following mean gradients across the valve prostheses: PCU valve 5.1±2.4 mm Hg (2.0–7.4 mm Hg), Perimount 2.1±0.7 mm Hg (1.4–3.0 mm Hg), and Mosaic® 5.5±2.3 mm Hg (3.8–4.6 mm Hg) measured under a cardiac output of 6.7±3.1 l/min. There was no significant difference between the mean gradients of the PCU valves and the 7 biological prostheses (P=0.276).

All of the animals with PCU valves reached the study end in good clinical condition without cardiac medication and were sacrificed after 21.8±0.4 weeks. One of the 4 animals with Perimount valves reached the study end under triple anticoagulative medication. Three animals had to be sacrificed after 5.3, 6.7, and 8.4 weeks because of severe CHF despite anticoagulative therapy.

Of the animals with PCU valves reached the study end in good clinical condition without cardiac medication. One animal died 1 week postoperatively because of fulminant thrombosis of the valve prosthesis. The third animal had to be sacrificed after 4.4 weeks because of intractable CHF.

Mean body weight of the 9 survivors reaching the study end was 165±5 kg (160–172 kg). They underwent epimycocardial echocardiography except the survivor with the Perimount valve, who was in bad clinical condition and died at induction of anesthesia. Mean gradient across the PCU-valves was 8.4±5.3 mm Hg (3.6–19.4 mm Hg; Figure 3). In 6 of 7 valves, the gradient was between 3.6 and 9.7 mm Hg; in 1 it was extraordinary high (19.4 mm Hg). Morphological assessment showed trivial to mild thickening of the leaflets except in the valve with the high gradient, which had moderate changes close to the commissures. All of the PCU valves had normal function with trivial regurgitation. The Mosaic prosthesis revealed a mean gradient of 6.5 mm Hg and mild to moderate thickening with restricted leaflet motion causing grade 2 regurgitation (Figure 4). Mean left atrial pressure for the PCU valves was 20.7±2.9 mm Hg (15–24 mm Hg) and 26 mm Hg for the Mosaic valve.

Gross examination did not reveal any paravalvular leaks in any prosthesis. The suture rings were all covered with neointima without pannus overgrowth. One PCU valve prosthesis was not rotated correctly with respect to physiological hemodynamics. This was the PCU valve with the exceptionally high transvalvar gradient at the end of the study.

In gross examination the PCU valves showed minor deposits preferably close to the commissures except in the malrotated prosthesis, in which the deposits were moderate. In addition, this valve revealed a tiny thrombus formation following mean gradients across the valve prostheses: PCU valve 5.1±2.4 mm Hg (2.0–7.4 mm Hg), Perimount 2.1±0.7 mm Hg (1.4–3.0 mm Hg), and Mosaic® 5.5±2.3 mm Hg (3.8–4.6 mm Hg) measured under a cardiac output of 6.7±3.1 l/min. There was no significant difference between the mean gradients of the PCU valves and the 7 biological prostheses (P=0.276).

All of the animals with PCU valves reached the study end in good clinical condition without cardiac medication and were sacrificed after 21.8±0.4 weeks. One of the 4 animals with Perimount valves reached the study end under triple anticoagulative medication. Three animals had to be sacrificed after 5.3, 6.7, and 8.4 weeks because of severe CHF despite anticoagulative therapy.

Of the 3 animals with Mosaic valves reached the study end in good clinical condition without cardiac medication. One animal died 1 week postoperatively because of fulminant thrombosis of the valve prosthesis. The third animal had to be sacrificed after 4.4 weeks because of intractable CHF.
close to the stent, whereas the other PCU valves were free of any thrombus formation. All of the bioprostheses showed moderate to severe thickening and deformation of the leaflets except the Mosaic valve with the peracute thrombosis. This valve was completely covered by a huge thrombus. Tiny thrombus formation was additionally observed on the Mosaic valve implanted for 22 weeks.

Histology, radiography, and energy dispersive x-ray spectroscopy of the PCU valves revealed mild calcification in 4, mild-to-moderate in 2, and moderate calcification in the malrotated PCU-prosthesis (Figure 5). Calcification was severe in all of the Perimount valves, and mild-to-moderate and severe each in 1 of the Mosaic valves; the thrombosed Mosaic valve was not calcified. The observed calcifications were exclusively extrinsic, ie, on the surface of the valves and not intrinsic, ie, with destruction of the polymer integrity or the biological structure.

Scanning electron microscopy showed a smooth surface of the PCU valve leaflets with tiny calcification spots (Figure 6). 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 hinting at a destruction of the surface integrity.

Laboratory studies of the long-term survivors did not show any significant changes to preoperative values in the animals with PCU valves and the Mosaic valve. Lactate dehydrogenase, y glutamyl transferase, and thrombocytes 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 valve had no chronic congestive changes. Peripheral emboli were not found in any animal.

**Discussion**

The first artificial heart valve prosthesis for routine clinical use was the Starr-Edwards mechanical valve, which was introduced in the 1960s. The problem of life-long anticoagulation therapy with warfarin in mechanical heart valves was solved with the introduction of biological valves in the 1970s–porcine or pericardial. However, their durability turned out to be limited and age dependent with faster degeneration at younger age. Homografts have the same disadvantage and are widely used only in aortic position.

The development of flexible polymeric heart valves started as early as in 1958, when Roe performed human implantation of a flexible polymeric valve made of silicone rubber. The clinical study had to be interrupted because of high mortality and morbidity due to massive embolization. Between 1961...
and 1963, 23 patients underwent aortic valve replacement with a tricuspid PTFE-prosthesis by Braunwald et al. Again, mortality was high, and the explanted valves showed severe thickening and rupture of the leaflets. Another aortic prosthesis made of Dacron and silicone was implanted into 18 patients by Roe in 1966; only 4 patients survived the operation and lived 33–61 months. In 1977 Hufnagel implanted a single leaflet aortic prosthesis made of Dacron into aortic position. Most valves failed, but some patients survived up to 15 years. Thereafter, a number of other constructions underwent animal testing without proving durability for long-term implantation. Embolic complications and fatigue failure were observed frequently in silastic, collagen, and PTFE valves; the latter showed shrinking in addition. Calcification was also observed frequently, either extrinsic on the surface of the polymer or intrinsic insight the polymer hinting at a destruction of the chemical integrity of the polymer. Polyurethanes have demonstrated the best biocompatibility, durability, and resistance to thromboembolism among all polymers and are, therefore, also used for a variety of medical devices.

Human implantation of flexible polymeric heart valves ceased in the 1980s, but valves made of polyurethanes are widely used in external assist devices. Based on their good performance, research for long-term valve replacement with polyurethane valves is continuing. In the 1990s a trileaflet polyurethane valve showed good durability in growing calves. Recently, a trileaflet polyurethane valve demonstrated good performance in growing sheep in comparison with mechanical and biological valves. However, 3 of 8 valves were seriously thrombosed and had fibrous attachments to the leaflets. Thromboembolic complications in this study were of major concern, because sheep are less thrombogenic than human valve recipients.

Almost all available heart valve prostheses do not take into account the hemodynamic characteristics of the mitral valve, although improved hemodynamics add to durability (biological and flexible polymeric valves) and resistance to thromboembolism (mechanical valves).

The aim of this study was to design a flexible polymeric heart valve prosthesis for the mitral position, which does not necessitate lifelong anticoagulation and has improved durability compared with current biological mitral valve prostheses.

Implanted correctly, the biomechanical ADIAM mitral PCU valve showed no degradation of the material in vitro and in vivo, such as tearing, intrinsic calcification, or other signs of destruction of the integrity of the structure as observed in many prior polyurethane valve constructions and bioprostheses. Degenerative changes were of minor degree compared with the implanted biological valves, but were increased including minimal tearing on ultrastructural level, if the PCU valve was implanted in malrotated position. This emphasizes the importance of optimal hemodynamics for the durability of the valve. According to the pathological findings, the animals with the PCU valves did clinically better than those with either of the biological valves. Echocardiography proved the good function of the PCU valves even under hemodynamic stress at a weight of >160 kg. The slightly higher gradients of the PCU valves shortly after implantation are most likely because of the stiffness of the PCU, which reduces after few hours by uptake of water by the polymer. This theory is supported by the low gradients before explantation. Except in the malrotated valve, no thrombus formation was observed on the PCU valves without permanent warfarin therapy.

The growing calf model is considered an extreme calcification model. In addition, calves are more thrombogenic than sheep, who even tolerate mechanical valves without anticoagulation. This explains the severe calcification of the biological valves (both Perimount pericardial and Mosaic porcine) after 21 weeks and the severe thrombosis seen in a Mosaic valve. Therefore, the tested PCU valves performed convincingly in this animal model with little biological degradation and no thromboembolic complications.

Extrapolating the results of this in vivo study by the reported durability of the Perimount and Mosaic bioprostheses in humans, the PCU valves are expected to have a considerably longer freedom from valve related reoperation.

The good results are because of the selection of the biostable polycarbonatethane, the exceptional manufacturing process, and the design with superior hemodynamic performance in mitral position.

So far, the biomechanical ADIAM mitral PCU valve seems to combine the advantages of the current available heart valve substitutes: long-term duration and no need for permanent anticoagulation. In a next step, controlled, multi-institutional studies are planned.

References

14. Ghista DN, Reul H. Optimal prosthetic aortic leaflet valve: design para-
metric and longevity analyses: development of the Avothane-51 leaflet
valve based on the optimum design analysis. J Biomechanics. 1977;10:
313–324.
15. Chetta GE, Lloyd JR. The design, fabrication and evaluation of a trileaflet
cardiac valve prosthesis: in vitro and in vivo studies. Transactions – Am
1987;94:419–429.
assessment of polytetrafluoroethylene trileaflet heart valve prosthesis.
an alternative to mechanical prostheses or bioprostheses. ASAIO Trans-
tri-leaflet polyurethane heart valve prosthesis: design, manufacture, and first
22. Wheatley DJ, Raco L, Bernacca GM, et al. Polyurethane: material for the
fluid dynamics of a flexible polymeric heart valve. ASAIO Transactions.
cation: Pathology, mechanisms, and strategy of prevention. J Biomed
25. Jones M, Barnhart GR, Chavez AM, et al. Experimental evaluation of
bioprosthetic valves implanted in sheep. In: Cohn LH, Gallucci V (eds).
Cardiac Bios prostheses. New York, Yorke Medical Books, 1982:
275–292.
with the Mosaic bioprosthesis. J Thorac Cardiovasc Surg. 2002;124:
333–339.
the mitral Carpentier-Edwards PERIMOUNT pericardial bioprosthesis.
Introduction of a Flexible Polymeric Heart Valve Prosthesis With Special Design for Mitral Position
Sabine H. Daebritz, Jörg S. Sachweh, Benita Hermanns, Bernd Fausten, Andreas Franke, Jan Groetzner, Bernd Klosterhalfen and Bruno J. Messmer

Circulation. 2003;108:II-134-II-139
doi: 10.1161/01.cir.0000087655.41288.dc

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/108/10_suppl_1/II-134

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/