16. Hughes H, Tipton LS, Feuchuk D, Prabhakar G, Aboul-Enen HY, Duran CMG: Glutaraldehyde γ carboxyglutamic acid and calcium in explanted bioprosthetic heart valves. *J Heart Valve Dis* 3: 111–116, 1994.
17. Lee MJ, Boughner DR: Tissue mechanics of canine pericardium in different test environment: evidence for time dependent accommodation, absence of plasticity and new roles for collagen and elastin. *Circ Res* 49: 533–544, 1981.
18. Scott M, Vesely I: Aortic valve cusp microstructure: the role of elastin. *Ann Thorac Surg* 60: S391–S394, 1995.

Transluminal Aortic Valve Placement

A Feasibility Study With a Newly Designed Collapsible Aortic Valve

NADER MOAZAMI, MARC BESSLER, MICHAEL ARGENZIANO, ASIM F. CHOUDHRI, SANTOS E. CABRERIZA, JOHN D. F. ALLENDORF, ERIC A. ROSE, AND MEHMET C. OZ

Percutaneous stents are used in vascular applications in conjunction with angioplasty and in combination with graft material for repair of abdominal aneurysms. The authors have designed a collapsible bioprosthetic aortic valve for placement by a transluminal catheter technique. This trileaflet stent valve is composed of stainless steel and bovine pericardium. Stent valves, 23 and 29 mm, were tested in a pulse duplicator system with rigid rings from 21 to 31 mm in 2 mm increments. At a mean flow of 3.1 L/min (±0.7), normal systemic aortic pressure was generated with a transvalvular gradient of 14.9 ± 7 mmHg (mean ± SD). Regurgitation fraction ranged from 10 to 18% (mean 13.8 ± 3%) in the best ring size. Valves with the best hemodynamic profile were used for implantation in three 70 kg pigs in an open chest model. The valve was collapsed in a 24 Fr catheter designed to allow slow, controlled release. After resection of the native leaflets, the new valve was placed in the subcoronary position. No additional sutures were used for securing the valve. Two animals were successfully weaned from cardiopulmonary bypass and maintained systemic pressures of 100/45 (±10) and 116/70 (±15) mmHg, respectively. Intraoperative color echocardiography revealed minimal regurgitation, central flow, full apposition of all leaflets, and no interference with coronary blood flow. Both animals were sacrificed after being off bypass for 2 hr. Postmortem examination revealed the valves to be securely anchored. The third animal was weaned from cardiopulmonary bypass but developed refractory ventricular fibrillation because of valve dislodgment due to structural failure. Although long term survival data are needed, development of a hemodynamically acceptable prosthetic aortic valve for transluminal placement is feasible. *ASAIO Journal* 1996;42:M381–M385.

Intravascular stents have gradually obtained acceptance for peripheral and coronary vascular occlusive disease.[1–3] Combinations of stents with grafts have allowed for intraluminal bypass of aneurysms and long segment atherosclerotic lesions.[4] Transfemoral percutaneous aortic valve replacement is an extended application of this new technology that offers several new challenges. First, the valve needs to be accurately positioned without the benefit of direct open visualization. Second, the valve must remain firmly in the annulus under physiologic conditions. Finally, in the absence of sutures, the valve must provide a sufficient seal to minimize perivalvular regurgitation.

We have developed a novel sutureless bovine pericardial bioprosthetic aortic valve mounted on a collapsible stent. This prosthetic valve can be collapsed in a 24 Fr catheter for delivery. This report represents our initial characterization of this valve in a pulse duplicator system and in an open chest porcine model.

From the Department of Surgery, Columbia-Presbyterian Medical Center, New York, New York.
Reprint requests: Nader Moazami, MD, Columbia-Presbyterian Medical Center, PO Box 383, 630 W 168 St., New York, NY 10032.

Methods

Stent Valve Construction

Stainless steel wire, size 0.020″, was used to construct all stents, and size 0.022″ was soldered on the ring to serve as the anchoring fixation point in the aortic annulus. For constructing the stent valves at different sizes, because of the collapsible nature of the design, all valves were placed in a ring of predetermined size. Subsequently, bovine pericardium stabilized by a photooxidation process[5] was sewn on the stent from a single sheet to construct trileaflet valves constrained to different sizes.

In Vitro Measurements

A total of 16 stent valves were constructed. The four that were acceptable in terms of overall symmetry were subjected to further studies. A pulse duplicator similar to a previously described mock circulatory system[6] was constructed

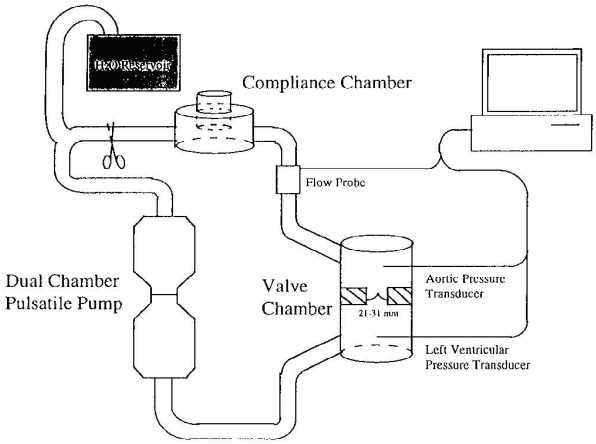

Figure 1. Diagram of the mock circulatory loop used for *in vitro* testing of valves. The chamber allows for adjustment of compliance and resistance.

(Figure 1). This system uses an Abiomed BVS 5000 dual chamber (Abiomed, Inc., Danvers, MA) to generate pulsatile flow. Each stroke ejects 80–85 ml of saline into the circuit. The system possesses an open reservoir to simulate the venous and atrial systems. In addition, a piston–cylinder–spring arrangement functions as an adjustable compliance chamber. Peripheral vascular resistance could be adjusted by application of a clamp to the circuit partially to impede forward flow. The valve was placed on a ring in a rigid chamber made of Plexiglas. The ring size in the chamber could be changed to a diameter ranging from 21 to 31 mm in 2 mm increments. A 5 Fr Millar catheter (Millar Instruments, Houston, TX) was placed on the ventricular side and the aortic side of the valve to measure transvalvular pressures gradients. An ultrasonic flow probe (Transonics, Ithaca, NY) was placed on the outflow tubing to monitor forward and backward flow. All data were digitized at 200 Hz using a 12 bit A-D board (AD Instruments, Milford, MA) recorded with the MacLab system and stored on the hard drive for subsequent analysis. Regurgitant fraction was calculated by the ratio of the integral of backward flow to the integral of total flow (forward and backward) using customized wave analysis software (IGOR; Wavemetrics, Inc., Lake Oswego, OR).

Animal Care

Animals received humane care in compliance with the *Principles of Laboratory Animal Care* formulated by the Institute of Laboratory Animal Resources and the *Guide for the Care and Use of Laboratory Animals* published by the National Institutes of Health (NIH Publication No. 86-23, revised 1985).

Experimental Procedure

Pigs weighing 60–70 kg were anesthetized with ketamine (20 mg/kg) and thiamylal sodium (4.5 mg/kg). After endotracheal intubation, anesthesia was maintained with isoflurane (1.5–2.5%) mixed with 100% oxygen. Lidocaine 2 mg/kg and bretyllium 5 mg/kg were given as a loading dose, and a continuous drip of 1 mg/kg/hr for each was maintained throughout the experiment. Standard concentrations of phenylephrine (Neo-Synephrine; Winthrop Pharmaceuticals, New York, NY), norepinephrine bitartrate (Levophed; Winthrop Pharmaceuticals), and epinephrine drips were used as needed to maintain a mean blood pressure of 60 while on cardiopulmonary bypass (CPB). Internal paddles charged up to 50 V were used for defibrillation as needed.

Surgical Procedure

Sternotomy was performed, and the pericardium was opened. Heparin (300 μg/kg) was administered and adequate anticoagulation was verified by an activated clotting time of greater than 400 sec. A 14 Fr cannula was inserted in the aorta and a 36 Fr dual stage venous cannula was inserted in the right atrium for CPB. The aorta was dissected proxi-

Table 1. Hemodynamic Characterization of the Stent Valves in the Mock Circulatory System

Valve Size (mm)	Ring Size (mm)	VP (mmHg)	AoP (mmHg)	Regurgitant Fx (%)	Flow (L/min)
Empty chamber (no valve)	25	177	167	100	3.3
	27	158	149	100	3.3
	29	165	156	100	3.3
	31	157	152	100	3.3
23	21	173/20	163/70	10	2.7
	23	188/23	178/70	14	3.2
	25	160/25	150/33	26	2.2
	27	193/35	184/36	50	2.1
23	21	130/15	120/60	14	2
	23	174/9	169/52	18	2.1
	25	153/25	145/37	27	2.1
29	27	161/10	146/63	13	3.71
	29	163/12	149/52	15	3.67
	31	169/18	147/46	20	4.5
29	27	137/9	122/60	10	3.24
	29	145/18	120/42	17	3.46
	31	144/25	114/30	27	3.28

VP, ventricular pressure; AoP, aortic pressure; Fx, fraction.

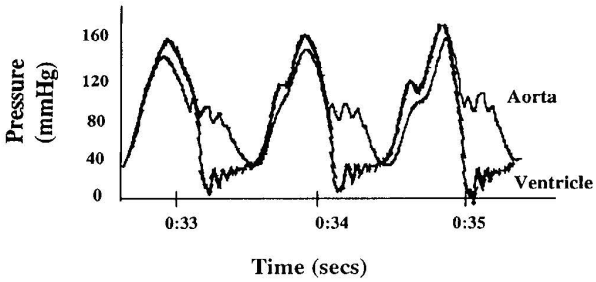

Figure 2. Representative *in vitro* aortic and ventricular pressure tracing for a 23 mm stent valve in a 21 mm ring.

mally until the origin of the left main coronary artery could be visualized. Subsequently, the animal was placed on CPB and cooled to 32°C. After placement of a left ventricular vent through the apex of the heart, the proximal aorta was cross-clamped. One liter of 4°C standard crystalloid cardioplegia solution was delivered to the aortic root to arrest the heart. A partial transverse aortotomy was performed as close to the coronary artery as technically feasible. The deep aortic root in this animal model necessitated the use of three traction sutures placed at each commissure to pull the native leaflets into view. After sizing the annulus with standard sizers, the appropriate stent valve, collapsed in a 24 Fr catheter, was delivered under direct vision and secured in placed. No sutures were used for fixation of the stent valve. All traction sutures were removed and the aortotomy was closed with a double layer of running 4-0 polypropylene suture. After removing the cross-clamp, deairing the left ventricle, and rewarming, the animal was slowly weaned from CPB.

Hemodynamic Measurements

Pressure was measured with a 5 Fr Millar micromanometer placed in the left ventricle through the apex, and a second catheter guided to the proximal aorta through the left carotid artery. All hemodynamic data were recorded off CPB on the MacLab system. All data are reported as mean ± standard deviation.

Echocardiography

Two dimensional and m-mode echocardiograms were obtained using a hand held 5 MHz ultrasound transducer (Vingmed CFM 750; Vingmed Sound, Inc., Salt Lake City, UT). Color flow Doppler was obtained to assess valvular regurgitation.

Table 2. Size of the Aortic Annulus After Cardiac Arrest Relative to the Size of the Stent Valve Implanted

Animal	Annulus Size (mm)	Valve Size (mm)
1	18	23
2	25	29
3	20	23

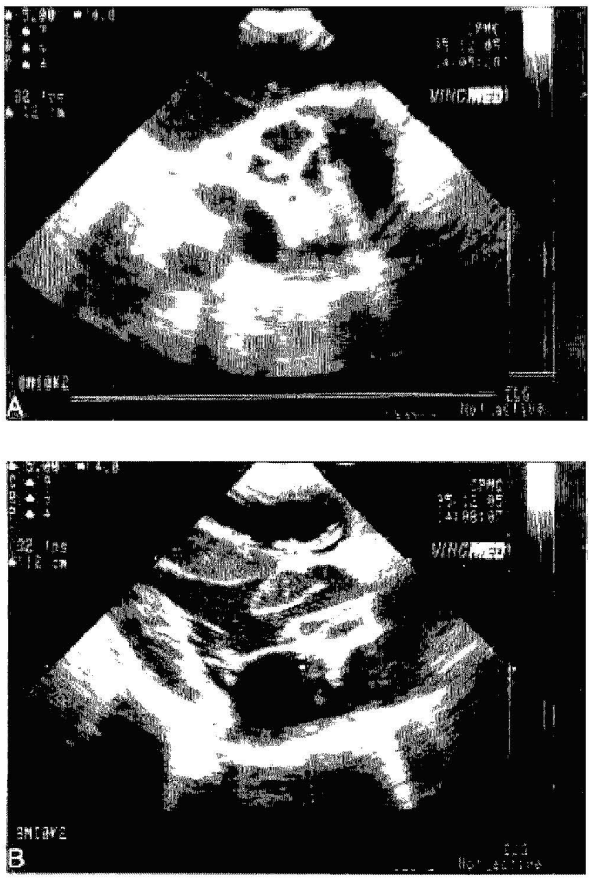

Figure 3. (A) Short axis echocardiogram demonstrates the three leaflets to be fully apposed during diastole. One of the leaflets is slightly redundant. **(B)** Long axis view demonstrates opening of the leaflets. The lower, redundant leaflet does not open completely.

Results

In Vitro Studies

Table 1 shows the results obtained from studying valves of different sizes in our pulse duplicator system. Flow generated ranged from 2.0 to 4.5 L/min with a mean of 3.1 L/min (±0.7). The lowest regurgitation fractions were obtained by placing the valves in rings 2 mm smaller than the stent valve. Placing the valve in smaller chambers caused too much leaflet redundancy and interference with proper valve opening. The valves were considered adequate for animal implantation if the regurgitant fraction was less than 15% at a given annulus size and a diastolic pressure of 60 mmHg could be maintained. Calibration of the pulse duplicator in absence of any valve shows that the system has a transvalvular gradient of 5–10 mmHg. The stent valves had a mean transvalvular gradient of 14.9 (±7.4) mmHg. In **Figure 2,** representative pressure and flow curves generated in our mock circulatory loop are shown.

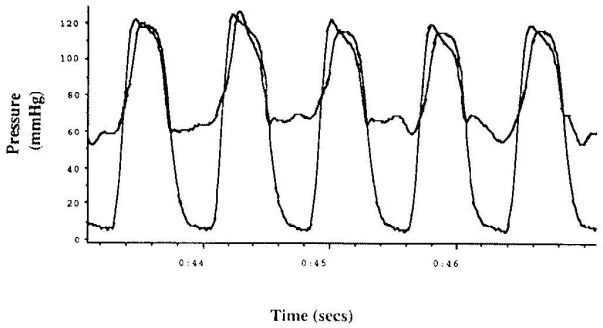

Figure 4. Representative *in vivo* aortic and ventricular pressure tracings. Mean aortic root pressure was 116/70 mmHg, with maintenance of a diastolic gradient of 66 mmHg between the aorta and left ventricle.

In Vivo Studies

Table 2 demonstrates the size of the porcine annulus and the most appropriately sized valve that was available for implantation. Engagement of the valve required approximately 5 min. Cross-clamp time was approximately 20 min in animals 1 and 3 and 40 min in animal 2 because of inadvertent dislodgment of the aortic cannula. All animals were successfully weaned from CPB.

Animal 1 maintained a systemic pressure of 100/45 (±10) mmHg over a period of 2 hr. Intraoperative echocardiography revealed complete opening of two leaflets, with the third leaflet redundant and relatively immobile. All leaflets were fully apposed during diastole **(Figure 3).** The stent valve was in the subcoronary position without any obstruction to coronary blood flow. Color Doppler studies showed mild regurgitation at the level of the non mobile posterior leaflet. Postmortem examination revealed complete fixation of the valve at the annulus without any displacement. Because of the small size of the annulus, one of the leaflets appeared redundant, as had been observed during echocardiography.

Animal 2 was successfully weaned from bypass, but within 5 min refractory ventricular fibrillation developed. Postmortem examination revealed dislodgment of the valve secondary to structural failure.

Animal 3 had an annulus sized at 20 mm and received a 23 mm stent valve. This animal maintained a systemic blood pressure of 116/70 (±15) mmHg. Pressure recordings at the aortic root and left ventricle revealed an asystolic gradient of 2 (±1) mmHg. The mean diastolic gradient was 66 (±3) mmHg with the left ventricular diastolic pressure at 4.9 (±1) mmHg, suggesting absence of significant regurgitation **(Figure 4).** Two dimensional echocardiography revealed no turbulence during systole, with maintenance of central flow. Color Doppler flow showed trace central regurgitation. No perivalvular leak could be identified. m-Mode echocardiography showed full opening of the leaflets with complete apposition during diastole **(Figure 5).**

Discussion

Development of a percutaneously implantable aortic valve poses many challenging considerations. Two investigators have recently described aortic stent valves for percutaneous aortic valve replacement: a ball–cage and a balloon expandable porcine valve.[7,8] This study presents a new design for a collapsible, sutureless bioprosthetic valve for transluminal application. The acute study was undertaken to evaluate several features of this design.

First, the stability of a sutureless stent in the aortic annulus needed to be determined. In all *in vitro* studies, the valve remained firmly anchored in the ring with no displacement. This was confirmed in the animal studies, with the exception of animal 2. In this animal, valve dislodgment occurred secondary to structural failure of the stent at the weld point. This was probably caused by excessive manipulation and wear of the stent during the multiple *in vitro* studies that were performed. Previous prosthetic valves have also been plagued with this problem, and design changes have included making the strut from a single sheet of metal to eliminate weld sites.[9,10]

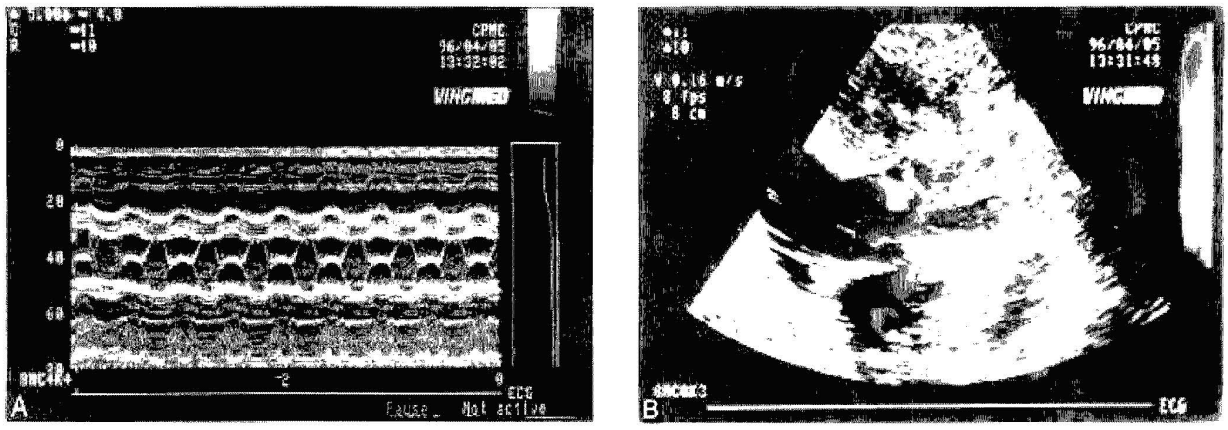

Figure 5. (A) m-Mode echocardiogram demonstrates full opening and closing of the leaflets. **(B)** Long axis view with trace regurgitation during diastole represented by the mosaic pattern at the center of the valve. No perivalvular leak is observed.

Second, an effective watertight seal to prevent perivalvular leakage is of paramount importance. Our studies have demonstrated that the stent valve mechanism effectively prevents regurgitation when the valve is anchored properly. The dynamic nature of the aortic root during the cardiac cycle that causes the aorta to decrease in size[11] is probably another feature in favor of effective sealing. We postulate that this dynamic interaction between the stent valve and aorta is the reason that minimal to trace regurgitation was observed in the animal studies, as opposed to the *in vitro* data, which were collected in a rigid system and resulted in 10–18% regurgitation.

Finally, we have shown that when an appropriately sized valve is implanted in the subcoronary position, flow is unidirectional, with no turbulence and minimal transvalvular gradient and central flow. These factors are important to the design of a prosthetic valve with good hemodynamic performance.[12]

Conclusion

We have developed a collapsible bioprosthetic aortic valve for implantation in the subcoronary position at the level of the aortic annulus. This report summarizes the preliminary evaluation of this stent valve in terms of secure anchoring, prevention of regurgitation, and adequate flow properties. The study is limited in that long term analyses were not performed, and many questions regarding durability of the stent and leaflets remain open. In addition, chronic studies are needed to assess valve thrombogenicity, thromboembolism, and absence of stent migration. This preliminary study establishes that a sutureless prosthetic stent valve is functional in the aortic position, and is a step toward development of a percutaneous approach in the foreseeable future.

Acknowledgments

The authors thank Carbomedics, Inc. (Austin, TX) for preparation of bovine pericardium and assistance with construction of the valves on the stents.

References

1. Parodi JC: Endovascular repair of abdominal aortic aneurysms and other arterial lesions. *J Vasc Surg* 21: 549–557, 1995.
2. Fischman DL, Leon MB, Baim DS, *et al*: A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 331: 496–501, 1994.
3. Serruys PW, Jaegere P, Kiemeneij F, *et al*: A comparison of balloon-expandable stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 331: 489–495, 1994.
4. Chuter TAM, Green RM, Ouriel K, *et al*: Transfemoral endovascular aortic graft placement. *J Vasc Surg* 18: 185–197, 1993.
5. Moore MA, Bohachevsky IK, Cheung DT, *et al*: Stabilization of pericardial tissue by dye-mediated photooxidation. *J Biomed Mater Res* 28: 611–618, 1994.
6. Rosenberg G, Phillips WM, Landis DL, Pierce WS: Design and evaluation of the Pennsylvania State University Mock Circulatory System. *ASAIO J* 4(2): 41–49, 1981.
7. Pavcnik D, Wright KC, Wallace S: Development and initial experimental evaluation of a prosthetic aortic valve for transcatheter placement. *Radiology* 183: 151–154, 1992.
8. Andersen HR, Knudsen LL, Hasenkam JM: Transluminal implantation of artificial heart valves: description of a new expandable aortic valve and initial results with implantation by catheter technique in closed chest pigs. *Eur Heart J* 13: 704–708, 1992.
9. Bjork VO: The Bjork-Shiley tilting disc valve: past, present and future. *Cardiac Surgery: State of the Art Reviews* 1987, 183–000.
10. Starek PJK, Beaudet RL, Hall KV: The Medtronic-Hall valve: development and clinical experience. *Cardiac Surgery: State of the Art Reviews* 1987, 223–000.
11. Tindale WB, Black MM, Martin TR: In vitro evaluation of prosthetic heart valves: anomalies and limitations. *Clin Phys Physiol Meas* 3: 115–130, 1982.
12. Arom KV: Choice of mechanical aortic prosthetic valve, in Emery RW, Arom KV (eds), *The Aortic Valve*, Philadelphia, Hanley & Belfus, 1991, pp. 187–201.