Functional Evaluation of the Medtronic Stentless Porcine Xenograft Mitral Valve in Sheep

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Background—Recently, renewed interest in allograft and stentless “freehand” bileaflet xenograft mitral valve replacement has arisen. The variability of human papillary tip anatomy and scarcity of donors limit allograft availability, making xenograft mitral valves an attractive alternative; however, these valves require new surgical implantation techniques, and assessment of their hemodynamics and functional geometry is lacking.

Methods—Seven sheep underwent implantation of a new stentless, glutaraldehyde-preserved porcine mitral valve (Physiological Mitral Valve [PMV], Medtronic) and were studied acutely under open-chest conditions. A new method of retrograde cardioplegia was developed. Hemodynamic valve function was assessed by epicardial Doppler echocardiography. 3D motion of miniature radiopaque markers sutured to the valve leaflets, annulus, and papillary tips was measured. Six other sheep with implanted markers served as controls.

Results—Both papillary muscle tips avulsed in the first animal, leaving 6 other animals. Mitral regurgitation was not observed in any xenograft valve. The peak and mean transvalvular gradients were 4.6±1.8 mm Hg and 2.6±1.5 mm Hg, respectively. The average mitral valve area was 5.7±1.6 cm². Valve closure in the xenograft group occurred later (30±11 ms, P<0.015) and at higher left-ventricular pressure (61±9 mm Hg, P<0.001) than in the control group; furthermore, leaflet coaptation was displaced more apically (5.6±2.2 mm, P<0.001) and septally (5.8±1.5 mm, P<0.001), and the anterolateral papillary tip underwent greater septal-lateral displacement (2.7±1.5 mm, P<0.001). Annular contraction during the cardiac cycle was similar in the 2 groups (xenograft 9.2±4.5% versus control 10.6±4.5% [mean±SD; 2-factor ANOVA model]).

Conclusions—Successful freehand stentless porcine mitral valve implantation is feasible in sheep and was associated with excellent early postoperative hemodynamics. Physiological mitral valve annular contraction and functional leaflet closure mechanics were preserved. Long-term valve durability, calcification, and hemodynamic performance remain to be determined in models. (Circulation. 1999;100[suppl II]:II-70–II-77.)

Key Words: mitral valve replacement ▪ unstented valve ▪ xenograft valves ▪ cardiac surgery

Stentless bioprosthetic valves promise to provide superior hemodynamic performance compared with stented tissue and mechanical valves and perhaps also offer the potential for enhanced durability when compared with stented bioprostheses. These potential advantages have led to an expansion of interest in the use of stentless porcine xenograft and pulmonary autograft (Ross procedure) valves in the aortic position. In contrast to the many options for aortic valve replacement, the only currently available alternatives for mitral valve replacement are mechanical valves and stented tissue bioprostheses (glutaraldehyde-preserved porcine aortic valve or bovine pericardial tissue). In comparison with stented tissue valves, the theoretical advantages of a stentless tissue valve in the mitral position include better hemodynamic performance and reduced mechanical stress on the valvular tissue, which may translate into better valve durability.1–4 Preservation of valvular-ventricular interaction, or papillary-annular continuity, also confers an additional advantage in terms of left ventricular (LV) systolic pump function.3,6

Allograft mitral valve replacement has a long history,7–9 but its use was abandoned early due to the lack of a reproducible implantation technique and difficulties with proper papillary muscle fixation. Subsequent attempts to replace the mitral valve with a xenograft mitral valve10,11 also failed because of papillary muscle avulsion, chordal rupture, and leaflet calcification and disruption.12 The development of improved techniques for mitral valve repair and superior methods of tissue fixation, however,
has recently prompted renewed interest in orthotopic, unstented allograft and xenograft mitral valve replacement\textsuperscript{13,14} and unstented, chordally supported mitral valve bioprostheses.\textsuperscript{15,16}

In contrast to the heterogeneous papillary muscle anatomy in human mitral valve allografts,\textsuperscript{17} with the attendant implantation difficulties, porcine xenografts offer a consistent anatomic preparation. This consistency makes them amenable to a well-defined and reproducible implantation technique with predictable functional outcome. The lack of anatomic homology across species of the mitral valve, particularly the papillary muscles, however, complicates xenograft mitral valve implantation. The anatomic discrepancies include porcine papillary muscles that lie \(\approx 180^\circ\) apart and porcine mitral leaflets that are approximately equal in size.

To define the implications of porcine xenograft anatomic differences for surgical technique and functional outcome, we investigated the surgical feasibility and immediate postoperative hemodynamic function of a new orthotopic, unstentless porcine mitral valve in sheep. Transvalvular hemodynamics were assessed by use of epicardial Doppler echocardiography. Miniature radiopaque markers on the valve were visualized with biplane cinefluoroscopy, which allowed precise characterization of 3D dynamic motion of the leaflets and subvalvular structures. We compared the valvular function and LV geometry of this unstented xenograft valve with that of the native mitral valve in sheep controls.

**Methods**

Seven adult castrated male sheep (73±8 kg) underwent implantation of a unstentless porcine xenograft mitral valve and insertion of miniature radiopaque markers on the mitral annulus, xenograft leaflets, papillary muscle tips, and the left ventricle. Both papillary tip implants avulsed in the first animal before data acquisition. The remaining 6 animals were taken to the experimental-animal cardiac catheterization laboratory for immediate study through use of an open-chest preparation. The control group, which consisted of 6 sheep (66±11 kg), underwent marker insertion only but were studied 7 to 10 days postoperatively under closed-chest conditions. The surgical preparation and cardiac catheterization of these animals were similar and have been reported previously.\textsuperscript{18}

**Stentless Porcine Xenograft Mitral Valve**

The PMV Bioprosthesis, a stentless porcine xenograft mitral valve, was provided by Medtronic Heart Valve Division. The valves were removed from pig hearts with the annulus, leaflets, chordae tendineae, and papillary heads intact and fixed in glutaraldehyde. Dacron sewing tubes were sutured to each papillary head, and a thin Dacron sewing ring was sutured to the annulus.

**Surgical Preparation**

The animals were intubated and ventilated mechanically (Servo Anesthesia Ventilator, Siemens-Elema AB). General anesthesia was maintained with inhalational isofluorane (1.0% to 2.2%). The mediastinum was exposed through a left thoracotomy at the fifth intercostal space. Pneumatic occluders (In Vivo Metric Systems) were placed around the superior and inferior vena cavae. The heart was suspended in a pericardial cradle, and 9 miniature radiopaque tantalum markers (ID 0.8 mm, OD 1.3 mm, length 1.5 to 3.0 mm) were inserted in the LV epicardium and septum for calculation of LV volume and load-independent measures of ventricular contractility. Markers were placed circumferentially on the anterior, lateral, posterior, and septal walls at 2 levels: LV apical and LV equatorial. An additional marker was placed at the LV apex.

Figure 1. Schematic illustration of the stentless porcine xenograft PMV. A Dacron ring was used for annular support, and Dacron sewing tubes were sutured to each papillary tip. Because the anterior and posterior leaflets in the porcine mitral valve are approximately equal in size, the papillary tips are oriented diometrically opposite each other and subtend an angle of \(180^\circ\) relative to the LV long axis. In contrast, ovine and human anterior leaflet size is approximately twice that of the posterior leaflet, and the papillary tips subtend an angle of \(120^\circ\). Miniature radiopaque markers were sutured to the annulus (markers 1 to 8), papillary muscle tips (markers 9 and 10), and the central meridian of the anterior and posterior xenograft leaflets (not shown). Given the relatively small size of the native ovine mitral valve, only 2 markers were sutured to the posterior leaflet (middle scallop).

The animals underwent cardiopulmonary bypass (CPB) with left carotid artery and right-atrial cannulation. The hemiazygos vein ("persistent left superior vena cava"), which consistently drains into the coronary sinus in sheep, was cannulated, and the heart was arrested by use of retrograde cold crystalloid cardioplegia solution; external finger pressure on the coronary sinus ostium was used to keep the cardioplegia from flowing into the right atrium. Through a left atriotomy, the mitral valve was sized, based on the intertrigonal distance and size of the anterior leaflet, by use of a Duran annuloplasty ring sizer. The native valve was completely excised; the chordae were sharply transected at papillary muscle insertion. Eight tantalum radiopaque markers were sutured circumferentially to the native mitral annulus in addition to the 10 markers that were sutured to the xenograft valve before implantation (4 markers along the central meridian of the anterior leaflet, 4 markers along the central meridian of the posterior leaflet, and 2 markers on each papillary tip. Figure 1).

The valve was oriented so that the xenograft anterior leaflet matched the orientation of the native anterior mitral valve leaflet. The resultant appropriate direction and position of the xenograft papillary tips were noted. Two or 3 Ethibond mattress sutures (2-0) with polytetrafluoroethylene pledgets were used to affix the papillary tips to the LV endocardial surface with deep mural sutures. The xenograft anterolateral papillary muscle sewing tube was implanted toward the septal side of the native anterolateral papillary muscle, and the posteromedial papillary sewing tube was secured near the native postero medial papillary muscle. The increased length of xenograft chordae and papillary muscle tips, compared with the native valve, required careful implantation of the papillary muscle sewing tubes apically far. Poor exposure deep inside the ventricle made this somewhat difficult in these normal-sized, naturally hypertrophic sheep hearts. The xenograft sewing ring was then sutured to the native mitral annulus with a continuous 5-0 polypropylene
suture. Coaptation of the mitral leaflets was assessed by injecting saline into the ventricle. The atriotomy was closed, the heart de-aired, the cross clamp removed, and the heart defibrillated into sinus rhythm. A micromanometer-tipped catheter (Millar MPC-500, Millar Instruments [previously zeroed in a 37°C water bath]) was positioned in the LV chamber through the apex.

**Experimental Design**

After 1 to 2 hours of recovery and stabilization, the isoflurane was stopped and sedation maintained with intravenous ketamine and diazepam. The animals were transported to the experimental-animal cardiac catheterization laboratory and ventilated mechanically (Veterinary Anesthesia Ventilator 2000, Hallowell EMC) with 100% oxygen. Simultaneous biplane videofluoroscopic and hemodynamic data were acquired with the animal in the right lateral decubitus position. The animals were studied in normal sinus rhythm after autonomic blockade and with ventilation arrested at end expiration during data acquisition runs to minimize the effects of respiratory variation. Data were acquired during control conditions after an intravenous bolus infusion of CaCl2 (15 mg/kg) to augment contractility and during a slow infusion of sodium nitroprusside to reduce maximum LV pressure by ~25%

All animals received humane care in compliance with the *Principles of Laboratory Animal Care* formulated by the National Society for Medical Research and the *Guide for Care and Use of Laboratory Animals* prepared by the National Academy of Sciences and published by the National Institutes of Health (DHEW[NIH] publication 85-23, revised 1985). This study was approved by the Stanford Medical Center Laboratory Research Animal Review Committee and conducted according to Stanford University policy.

**Data Acquisition**

A Philips Optimus 2000 biplane Lateral ARC 2/poly DIAGNOST C2 system (Philips Medical Systems, North America Company) was used to collect videofluoroscopic data at 60 Hz with the image intensifiers in the 9-inch mode. 2D images from each of the 2 x-ray views (45° right anterior oblique and 45° left anterior oblique) were digitized and merged to yield 3D coordinates for each radiopaque marker every 16.7 ms. Analog LV and left atrial pressures and ECG voltage were recorded on the video images during data acquisition and were digitized simultaneously. A Hewlett-Packard SONOS 1500 system was used for epicardial echocardiography. System software was used to calculate the velocity-time integral of Doppler signals across the implanted valves.

**Data Analysis**

End systole was defined as the videofluoroscopic frame preceding the maximum negative dP/dt (−dP/dt); end diastole was defined as the videofluoroscopic frame containing the peak of the ECG R wave.

**Echocardiography**

Epicardial echocardiography was used to study valve leaflet morphology and function. Pulse-wave (PW) Doppler was used to calculate flow velocities across the valve. The peak transvalvular pressure gradient, ΔP, was computed from the peak flow velocity V by using the modified Bernoulli equation ΔP=4V². The mean transvalvular pressure gradient was calculated from the velocity-time integral of the mitral valve Doppler signal by use of integrated Hewlett-Packard software. Mitral valve area (MVA) was estimated from the pressure half-time P1/2, the time required for velocity to drop to one half of peak velocity, using the empirically derived equation MVA=220P1/2. Satisfactory PW Doppler signals could not be acquired for the seventh animal.

**LV Systolic Function**

Preload recruitable stroke work (PRSW), calculated from stroke work and end-diastolic volume (EDV), was used to assess global LV systolic function.

**Mitral Valve Leaflets**

The height of each mitral valve leaflet was calculated from the sum of the distances between adjacent leaflet markers at end diastole (ED), the distance extended from the annular marker to the respective leaflet edge marker. The leaflet heights were computed at ED to minimize error introduced by possible leaflet folding at other times in the cardiac cycle. The time of mitral leaflet closure was defined as the first videofluoroscopic frame that showed a change of <10% between successive frames in the distance between the leaflet edge markers. The point of leaflet coaptation was defined as the midpoint of the 2 leaflet edge markers at the time of leaflet closure.

**Mitral Valve Annulus**

The area of the mitral valve annulus was computed from the 8 annular markers together with the geometric centroid of these 8 markers. Eight triangular regions were defined; the base of each triangle consisted of the annular length between adjacent pairs of markers, and the annular centroid was the apex of each triangle. The annular area was approximated by the sum of the areas of the 8 triangular components. The mitral annular area was computed for each videofluoroscopic frame during the cardiac cycle. The area reported for each frame was the average area for 3 consecutive steady-state cardiac cycles.

**Coordinate System**

Marker laboratory coordinates were transformed into a coordinate system fixed within the heart, with the origin being the midpoint of the septal and lateral annular markers (markers 1 and 5, respectively, Figure 1). The y axis was directed through the LV apex from the origin, the x axis was directed orthogonally to the y axis (in the plane of the apical-septal markers), and the z axis was directed orthogonally to both the x and y axes, toward the posterior commissure. Septal displacement was defined as displacement along the x axis toward the septal marker, apical displacement as motion along the y axis away from the origin and toward the apical marker, and commissural displacement as displacement along the z axis toward the posterior commissure. All distances, angles, and displacements were calculated relative to this internal coordinate system. Because the coordinate system is fixed in the heart, changes in these measurements during the cardiac cycle are not affected by rigid body rotation and translation artifacts that occur in the external fixed laboratory coordinate reference system.

**Statistical Analysis**

All data are reported as mean±1 SD. For each animal, data represent the average of 3 consecutive steady-state cardiac cycles. Comparisons between the control and the xenograft mitral valve groups were made by use of a 2-factor ANOVA model. Comparisons within each group were made with repeated-measures ANOVA. The level of significance for all statistical comparisons was P<0.05.

**Results**

Both papillary tips avulsed (1 completely and 1 partially) in the first sheep soon after it was weaned from CPB. A 27-mm xenograft PMV valve was implanted in that animal. The remaining 6 animals received 29-mm valves; all the remaining surgical valve implantations were successful, and data acquisition in those 6 animals was completed in the catheterization suite.

**Hemodynamics**

The hemodynamics of the 6 animals with PMV xenograft valves and the 6 animals in the control group are shown in Table 1. No significant difference was observed in PRSW,
which suggests that the LV systolic contractile state between the 2 groups was similar. Loading conditions, however, were significantly different: in the control group, LV preload (LV EDV) was higher, and in the PMV xenograft group, LV afterload (estimated as maximum systolic LVP) was lower. This difference in LV loading conditions may account for the higher stroke volume observed in the PMV animals.

**Echocardiography of the Xenograft PMV**

Epicardial 2D echocardiography of the implanted xenograft mitral valves revealed good leaflet-edge apposition during diastole, with no evidence of mitral incompetence (Figure 2a). During systole, the valve leaflets opened wide, allowing unimpeded LV filling (Figure 2b). Xenograft leaflet morphology during valve opening and closing, however, differed markedly from that of native valve leaflets. The xenograft mitral valve leaflets were markedly larger than the native leaflets. That increased leaflet redundancy may account for the increased leaflet coaptation noted during valve closure compared with the native valves. In addition, the glutaraldehyde-treated porcine xenograft leaflets appeared less compliant and relatively inflexible. In spite of the increased leaflet height, no evidence of systolic anterior leaflet motion or LV outflow tract (LVOT) obstruction, was observed in any animal. This finding may be due to the stiffer nature of the xenograft leaflets.

A short-axis view at the level of the native papillary muscle tips confirmed that the tips were oriented ~120° from each other relative to an axis through the centroid of the mitral annulus (Figure 3a). In contrast, the xenograft papillary tips were ~180° from each other, where they were sutured to the LV endocardium (Figure 3b).

Doppler echocardiography (PW Doppler) revealed relatively normal physiological flow patterns across the implanted xenograft mitral valves (Figure 4A). Early rapid ventricular filling across the valve was present, corresponding to the E wave in the PW Doppler tracing (Figure 4B). The A wave, or transvalvular flow generated by atrial contraction, was fused with the E wave on the PW tracing at these fast heart rates or significantly

<table>
<thead>
<tr>
<th>TABLE 1. Hemodynamic Profiles of Control and PMV Xenograft Valve Implantation Groups</th>
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<tbody>
<tr>
<td>Control</td>
</tr>
<tr>
<td>HR, min⁻¹</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
</tr>
<tr>
<td>EDV, mL</td>
</tr>
<tr>
<td>LVPmax, mm Hg</td>
</tr>
<tr>
<td>SV, mL</td>
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<tr>
<td>EF, %</td>
</tr>
<tr>
<td>DFT, ms</td>
</tr>
<tr>
<td>dP/dtmax, mm Hg/s</td>
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<tr>
<td>PRSW, mm Hg</td>
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</tbody>
</table>

HR indicates heart rate; EDP, end-diastolic pressure; SV, stroke volume; EF, ejection fraction; and DFT, diastolic filling time. Data are expressed as mean±SD. *The difference between the 2 groups was significant at P<0.005 by ANOVA. #The difference between the 2 groups was significant at P=0.01 (EDV) and P=0.02 (EF) by ANOVA.

![Figure 2. Epicardial 2D echocardiogram of an implanted stentless porcine PMV. Long-axis views of the implanted valve during (A) diastole and (B) systole showing leaflet morphology. Short-axis view (C) of implanted valve leaflets during diastole. LA indicates left atrium; and MVL, mitral valve leaflets.](image-url)
dampened in comparison with a normal A wave. The average peak and mean transvalvular pressure gradients across the PMV valves were 4.6±1.8 mm Hg and 2.6±1.5 mm Hg (Table 2). The average mitral valve area was 5.7±1.6 cm².

### Leaflet Motion During Mitral Valve Closure

The closure mechanics of the mitral valve leaflets were studied in both groups of sheep under steady-state conditions. In the control group, examination of the septal-lateral leaflet profile revealed that both leaflets began to move rapidly toward the closed configuration 17 ms before ED and had completed closure by 34 ms after ED (Figure 5A). The precise time of valve closure estimated from the distance between the leaflet-edge markers was 25±17 ms after ED. During valve closure, inspection of the motion of the markers along the central meridian showed that the leaflet was predominantly concave toward the atrium. Apposition of the leaflet-edge markers when closed indicated no leaflet redundancy at the point of leaflet coaptation.

Conversely, the mitral valve xenograft leaflets showed markedly different closing mechanics. In the PMV group, both leaflets began to move rapidly toward a closed configuration 17 ms after ED and completed closure by 67 ms after ED (Figure 5B). The time of valve closure was 55±14 ms after ED, which was significantly later than in the control group (P=0.015). In addition, a higher pressure gradient (P<0.001) was required to close the xenograft valve: the LV pressure gradient rose from 15±6 mm Hg at ED to 90±18 mm Hg at valve closure.

The septal-lateral leaflet profiles of the xenograft PMV leaflets during valve closure differed markedly from those of the control group. The leaflets were convex toward the atrium throughout valve closure and demonstrated increased convexity with increased leaflet apposition (Figure 5b).

The height of the anterior and posterior xenograft leaflets was 27.4±2.9 mm and 23.9±2.1 mm, respectively, versus 20.4±2.6 mm and 11.9±2.3 mm, respectively, for the native leaflets in the control group, based on the implanted leaflet.

### Table 2. Transvalvular Flow Velocities and Pressure Gradients across the Stentless Porcine Xenograft Mitral Valve Derived From Epicardial Doppler Echocardiography

<table>
<thead>
<tr>
<th></th>
<th>Peak Velocity, cm/s</th>
<th>Peak TVG, mm Hg</th>
<th>Mean TVG, mm Hg</th>
<th>MVA, cm²</th>
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</thead>
<tbody>
<tr>
<td>PMV 2</td>
<td>70</td>
<td>1.9</td>
<td>1.3</td>
<td>4.4</td>
</tr>
<tr>
<td>PMV 3</td>
<td>114</td>
<td>5.2</td>
<td>1.8</td>
<td>4.9</td>
</tr>
<tr>
<td>PMV 4</td>
<td>130</td>
<td>6.8</td>
<td>4.8</td>
<td>4.4</td>
</tr>
<tr>
<td>PMV 5</td>
<td>96</td>
<td>3.7</td>
<td>1.7</td>
<td>7.5</td>
</tr>
<tr>
<td>PMV 6</td>
<td>115</td>
<td>5.3</td>
<td>3.6</td>
<td>7.3</td>
</tr>
<tr>
<td>PMV 7</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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TVG indicates transvalvular pressure gradient; and N/A not available.
markers. The heights of the xenograft leaflets were significantly greater than those of the native leaflets (anterior \( P=0.002 \); posterior \( P<0.001 \)). During xenograft valve closure, this redundant tissue led to substantial leaflet overlap at the margin of coaptation, which extended to the markers adjacent to the leaflet-edge markers. Leaflet coaptation was also displaced more apically (xenograft 16.1±4.2 mm versus control 10.5±1.2 mm, \( P<0.001 \)) and septally toward the LVOT (xenograft 24.8±6.2 mm versus control 1.0±1.5 mm, \( P<0.001 \)), but clinical or echocardiographic signs of LVOT obstruction were not evident. Leaflet coaptation of the xenograft valve after a bolus of CaCl2 that increased maximum dP/dt (3027±532 mm Hg/s, \( P=0.025 \) versus steady state) and maximum LVP (127±16 mm Hg, \( P<0.005 \) versus steady state) did not change the position of the leaflet coaptation in the septal-lateral or apical direction (−4.9±2.8 mm and 15.2±4.3 mm, respectively). The position of leaflet coaptation in the xenograft valve was also unchanged in the septal-lateral and apical directions (−5.0±2.3 mm and 16.6±5.4 mm, respectively) after infusion of sodium nitroprusside, which decreased maximum LVP (80±18 mm Hg, \( P=0.028 \) versus control). Despite the convex shape, redundant leaflet tissue, and smaller LV chamber volumes, leaflet billowing was not observed.

**Figure 5.** Mitral valve closure in the (A) native and (B) implanted stentless xenograft PMV. These views show the apical and septal-lateral coordinates of the leaflet and papillary tip markers during valve closure. AMVL indicates anterior mitral valve leaflet; and PMVL, posterior mitral valve leaflet.

**Figure 6.** Papillary tip motion in the native and implanted stentless PMV. This view depicts the commissure-commissure and septal-lateral coordinates of the papillary muscle tips in each group during mitral valve closure.

### Papillary Motion During Mitral Valve Closure

The position and motion of the implanted xenograft papillary tips were compared with the native papillary muscle tips in the control group during valve closure (Figures 5 and 6). The apical position of the implanted and control papillary tips did not differ significantly. At ED, the apical coordinates of the xenograft and control papillary tips were 22.0±3.0 mm and 22.2±1.6 mm for the anterolateral papillary tip and 28.4±4.8 mm and 30.3±1.0 mm for the posteromedial papillary tips, respectively. Similarly, the commissure-commissure position did not differ significantly between the 2 groups. At ED, the commissure-commissure coordinates of xenograft and control papillary tips were −18.7±2.6 mm and −19.1±1.0 mm for the anterolateral papillary tip and 4.2±5.1 mm and 7.1±1.1 mm for the posteromedial papillary tip, respectively. Along the septal-lateral dimension, however, the 2 groups differed significantly (\( P<0.001 \)) at ED, the septal-lateral coordinates of implanted and control papillary tips were, respectively, 0.8±1.0 mm for the anterolateral papillary tip and 0.9±1.1 mm for the posteromedial papillary tip. During mitral valve closure, the control papillary tips did not move significantly from the ED positions. Similarly, the implanted papillary tips did not have significant motion in either the apical or commissure directions. Along the septal-lateral direction, however, the xenograft anterolateral papillary tip underwent a 2.7±1.5 mm displacement from its ED position during valve closure (\( P<0.001 \)).

### Mitral Annular Area

The stentless design of the xenograft PMV valve allowed the mitral annulus to change dimensions and shape normally during the cardiac cycle after valve implantation. The annuli in the animals with xenograft valves achieved a maximum area of 6.8±1.1 cm² during diastole. Similar to the control group, the xenograft valves demonstrated presystolic annular contraction, with a minimum area of 6.2±1.0 cm² noted 11.7±4.0 ms after ED. The annular contraction was 9.2±4.5% (\( P=0.017 \)) in the xenograft valves. In the control group, the maximum annular area was 7.8±0.8 cm² and the
Discussion

The resurgence of mitral valve allografts and unstented xenografts as a viable alternative to mechanical or stented bioprosthetic mitral valve replacement has prompted increased interest in the physiological and hemodynamic behavior of those valves, their durability, and mode of eventual failure. Mitral valve allografts or xenografts have several advantages over conventional rigid-tissue valve replacement alternatives. By preserving valvular-ventricular continuity, those valves help enhance LV systolic function. Furthermore, unstented mitral valves possibly offer superior hemodynamics and diminished risk of thromboembolism, endocarditis, and complications associated with anticoagulation.

The limited availability of suitable donors, the competing needs for the aortic valve, the larger sizes required for allograft implantation, and the heterogeneity of human papillary muscle anatomy limit the widespread availability of mitral valve allografts. Porcine xenograft mitral valves offer a solution to this shortage, and their relatively consistent configuration favors a standardized and reproducible surgical implantation technique. Although allograft mitral valve implantation has been repeatedly investigated in humans, sheep, and dogs, few clinical studies have been conducted on xenograft mitral valve implantation, and no animal studies have been performed. Because the ovine mitral anatomy shares substantial anatomic homology with human anatomy, sheep provide a suitable animal model for developing porcine xenograft implantation methods and investigating the effect of those techniques on xenograft valve function.

The porcine mitral valve differs from the ovine (and human) mitral valve in several key anatomic features. The 2 porcine mitral valve leaflets are approximately equal in height and area; in contrast, the anterior leaflet in sheep (and humans) is approximately twice the size of the posterior leaflet. That geometric difference in leaflet size leads to geometric divergence in the subvalvular structures. To balance chordal load distribution and ensure symmetric leaflet leads to geometric divergence in the subvalvular structures. To preserve the porcine papillary muscle configuration, the papillary tips were sutured directly to the ventricular endocardium and not the native (ovine) papillary muscles. Implantation of the papillary tips onto the ventricular wall, however, subjects them to the dynamic motion of the ventricle during the cardiac cycle. Thus, the site of papillary tip implantation balanced the risk of leaflet prolapse with the potential risk of papillary tip avulsion. The position of the implanted xenograft papillary tips did not differ significantly from the control group in the apical or commissural directions. Attachment of the xenograft papillary tips adjacent to the native papillary muscles, however, resulted in significant septal displacement of the xenograft papillary tips compared with the control group.

The greatest stress on the mitral subvalvular structures occurs during valve closure and isovolumic contraction, when the mitral valve undergoes a rapid increase in load. During that period, the implanted xenograft PMV papillary tips do not move in the apical or commissural directions, which is similar to the stability exhibited by the native papillary tips during the same period. The implanted anterolateral papillary tip, however, moved significantly along the septal-lateral direction during valve closure. That displacement was likely caused by the effect of ventricular contraction and wall thickening on the endocardially fixed anterolateral papillary tip. Although the increased motion of this papillary tip did not appear to affect valve competency (and, perhaps, even assisted in leaflet closure), the long-term implications of the dynamic stresses caused by this motion on subvalvular integrity need further study. The papillary-ventricular fixation site may remodel favorably over time to minimize motion and dissipate subvalvular stresses during valve closure.

The leaflet-closing mechanics of the xenograft valve differed markedly from the native valve. Leaflet closure in the xenograft valve occurred later and at higher LV pressures than did the native valve. The mechanism for this increased dependence on transvalvular pressure gradient to close the xenograft valve is probably related to the thicker, less compliant glutaraldehyde-treated xenograft leaflets, the denervated nature of this bioprosthesis, possible chordal restriction caused by the septally displaced papillary muscle tips, and, in this experimental preparation, higher left atrial pressures. In addition to closing later and over a longer period, the xenograft leaflets were convex toward the atrium during closure, whereas the native mitral leaflets are concave toward the atrium. The natural “sigmoid” or concave shape of the native leaflets is probably maintained by tension on the second-order chordae tendineae, which are inserted on the mid-portions of the leaflet at the junction of the rough and smooth zones. If that mechanistic hypothesis is operant, it would suggest that inadequate tension on the second-order chordae tendineae of the xenograft valve may explain the convex shape of the leaflets.

In comparison with the control group, the leaflet coaptation region in the xenograft valves was displaced septally and toward the LVOT. The most obvious explanation for that displacement is septal displacement of the implanted papillary tips relative to native papillary tip locations. In addition, the larger xenograft leaflets created an increased zone of coaptation. Despite the septal displacement and increased zone of coaptation, LVOT obstruction was not observed under control conditions nor after interventions that increased contractility or decreased afterload.

In summary, this study established the feasibility of a reproducible, albeit technically complex, surgical technique for mitral valve replacement with the Medtronic stentless porcine xenograft mitral valve. The implanted valves had excellent transvalvular hemodynamics. The larger and stiffer glutaraldehyde-treated xenograft leaflets did not compromise LV filling, and there was no appreciable regurgitation. The leaflets opened widely throughout diastole, allowing unimpeded filling of the ventricle with acceptable peak and mean pressure gradients.
transvalvular pressure gradients. In addition, the stentless design of the xenograft valve allowed the annulus to undergo normal physiological annular motion during the cardiac cycle. The ability of the xenograft annulus to respond in a physiological fashion may reduce peak loading and shearing stresses that are known to occur in stented bioprosthetic valves. 3,4 Clearly, long-term studies are needed to establish the fate of the papillary-ventricular fixation site and the effect of leaflet shape reversal on PMV valve durability.

Study Limitations

The closing and opening mechanics of the unstented PMV porcine xenograft valve were compared with those of native ovine mitral valves in the control sheep. Because of substantial anatomic differences in valve structure between the species, it is conceivable that the closing mechanics of a native in situ porcine mitral valve differ from those of the ovine mitral valve. Furthermore, in contrast to the open-chest preparation used to investigate the implanted PMV xenograft valves, the control group of animals was studied under closed-chest conditions 7 to 10 days after surgery. Hemodynamic differences between the 2 groups may also be attributed to the different postoperative times of investigation (immediate versus 7 to 10 days) and study conditions (immediate, anesthetized, open-chest preparation versus conscious-sedated, closed chest). Because CPB required the addition of 2 L of crystalloid volume, the intravascular volume status of the PMV xenograft valve animals was enhanced in the immediate post-CPB period compared with the recovered control animals, which had undergone diuresis. Varied levels of core rewarming and endogenous adrenergic stimulation may also have potentially accounted for the observed differences between the 2 groups. The extent to which those differences affected PMV valve function or masked potential systolic anterior motion of the valve leaflets is unknown; future long-term, closed-chest studies of the mitral apparatus in canine left ventricular systolic performance. 

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Functional Evaluation of the Medtronic Stentless Porcine Xenograft Mitral Valve in Sheep
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