Echocardiographic Changes in the Thickness of Porcine Valves with Time*

Mohsin Alam, M.D., F.C.C.P.; Sidney Goldstein, M.D.; and Jeffrey B. Lakier, M.D.

To assess the ability of M-mode echocardiography to detect the incidence and frequency of porcine xenograft valve thickening, echocardiograms were obtained in 147 mitral and aortic porcine xenograft valves implanted in 131 patients. The patients were divided into an early group in whom the echocardiograms were performed within two months of valve replacement, an intermediate group studied two to 48 months after surgery, and a late group 48 months or longer after surgery. The porcine cusp echoes were visualized with proper gain settings, enlarged, and then recorded on a strip chart. The mean thickness of both the mitral and the aortic cusps was measured with the valve in the coapted position. The mean thickness of the porcine mitral valve increased from 1.23 ± 0.12 in the early group to 2.3 mm ± 0.19 in the late group (P < .02). Aortic valve thickness increased from 0.91 mm ± 0.07 in the early group to 2.1 mm ± 0.37 (P < .05) in the late group. A significant change in valve thickness was not observed in the intermediate group. In the late group of valves, 21/82 (27 percent) had a thickness greater than 3 mm. Nine of these valves (43 percent) have required replacement because of clinical dysfunction. Only 1.6 percent (1/61) of the valves in the late group with a thickness of less than 3 mm had or developed severe porcine valve insufficiency (P < 0.001). In all ten instances, the echocardiographic assessment of valve thickness was validated on gross examination of the valve removed at surgery. This study indicates that the thickness of both mitral and aortic porcine valves can be measured by M-mode echocardiography. Valve thickness increases after 48 months and those valves with thickening of 3 mm or more are at a higher risk of developing clinical evidence of valve dysfunction.

The porcine valve xenograft, although providing an important advance in prosthetic heart valve replacement, has recently been shown to undergo late degeneration in some patients. These studies indicate that clinically significant degeneration of the valve begins to occur at four to five years and is characterized by valve thickening associated with either destruction and tearing or rigidity of the valve cusps. Clinically, significant valvular insufficiency or stenosis occurs depending on the pathology of the valve. We have previously described the echocardiographic features of this late degenerative process. Electron microscopic studies of the valve by Ferrans and associates have shown that early degenerative changes in the cusp tissue can be identified within months of implantation. This study is designed to evaluate the capability of M-mode echocardiography to detect the incidence of valve thickening in patients with xenograft implantation and to establish a time course for this degenerative process.

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MATERIALS AND METHODS

One hundred sixty-four glutaraldehyde-fixed porcine xenograft (Hancock) valves implanted in the mitral and the aortic positions were evaluated by M-mode echocardiography. Adequate cusp echoes obtained in 147 of the 164 porcine valves. The 17 valves that were not adequately demonstrated were excluded from the study. These 147 porcine valves were implanted in 131 patients who were divided into three groups. An early group consisted of those patients in whom echocardiographic studies were performed within two months of valve replacement, an intermediate group in whom the echocardiographic studies were performed two to 48 months after implantation, and a late group in whom the patients were studied 48 months or longer after surgery.

The early group consisted of 30 consecutive valves studied in the immediate postoperative period. As all these valves were studied before discharge from hospital or at the time of first outpatient clinic visit, the cut-off point between early and intermediate groups was two months. Eighty-five percent of valves in the intermediate and 90 percent in late groups (which were randomly selected) had the echocardiographic study performed in response to our telephone request. The remaining valves in these two groups were studied at the request of their physicians. In this study, therefore, the valves were not studied sequentially.

Of the 147 adequately visualized valves, 98 were implanted in the mitral position, 16 of which were in the early group, 21 in the intermediate, and 61 in the late group. Of the 49 valves implanted in the aortic position, 10 were in the early
group, 18 in the intermediate, and 31 in the late group. The age of the patients ranged from 9 to 81 years, with a mean of 51 years. Sixteen patients were under 35 years of age, and only one was under 17 years at the time of echo study. There were 88 females and 43 males in the total group, and none had evidence of active bacterial endocarditis at the time of the study.

The echocardiograms were performed with a Smith-Kline Ekoline 20-A instrument with the patients either in the supine or 30° to 40° left lateral position. The tracings were recorded on an Ekoline 21 strip chart recorder at a paper speed of 50 to 100 mm/sec. The porcine cusps were recorded using gain and reject settings, which reliably visualized other cardiac structures such as aortic root and interventricular septum. Great care was observed so as not to influence the thickness of the porcine cusps by gain settings that were too high. The scale of the echocardiographic strip was expanded so that the porcine valve occupied the whole width of the echocardiographic strip (Fig 1). In some valves this magnification led to loss of resolution. In those situations the cusp measurements were made from somewhat smaller echocardiographic strips where high resolution of the cusp margin was retained. The cusps of both mitral and the aortic porcine valves in its coapted position were identified from the prominent stent echoes and its reverberations by the fibrous continuity of the cusp with the opening motion of the valve (Fig 1). The thickness of both the mitral and the aortic porcine valves was measured from at least three different segments of the magnified porcine cusps in the coapted position, and the mean thickness was then recorded. In addition to the mean cusp thickness, the cusp thickness at its maximal point was also measured in all patients. The mitral valve thickness was measured in systole, and the aortic valve was measured in diastole. In view of the importance of obtaining good cusp echoes with proper gain settings, all the echocardiographic studies were performed by one of us (M.A.) without knowledge of the duration of the valve implantation.

Cardiac catheterization and angiography were performed in six patients with dysfunctioning mitral valves, two with dysfunctioning aortic valves, and one with a thickened but normally functioning porcine aortic valve. The cardiac catheterization was performed within two weeks of the echocardiographic study.

RESULTS

Echocardiographic porcine valve thickness in the three groups is summarized in Table 1. The individual measurements of valve thickness for all the mitral (Fig 2) and the aortic (Fig 3) xenografts are plotted against duration of implantation. During the first 48 months, none of the valves was thicker than 2 mm. Although some early thickening possibly occurred after implantation and before the measurements were obtained, this seems unlikely, since valve thickness remained constant through the first 48 months. Only after 48 months was the mitral (P<.02) and the aortic (P<.05) valve coapted thickness significantly greater than that in the early and intermediate periods. In the late group, 21/82 (27 percent) porcine valves were thicker than 3 mm; 14 were in the mitral position, and seven in the aortic position. In Table 2, the valve thickness in the late group is related to clinical evidence of valve dysfunction. Nine of 21 valves (43 percent) 3 mm or more thick and only 1.6 percent (1/61) of the valves less than 3 mm thick had developed severe porcine valve insufficiency (P<.001). The maximal thickness of the porcine cusps

Table 1—Echocardiographic Measured Porcine Valve Thickness

<table>
<thead>
<tr>
<th>Valve Position</th>
<th>Duration of Implantation*</th>
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<tbody>
<tr>
<td></td>
<td>&lt;2 Mos</td>
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<tr>
<td>Mitral</td>
<td>1.23 mm ± 0.12</td>
</tr>
<tr>
<td>Aortic</td>
<td>0.91 mm ± 0.07</td>
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* ± SD.
was within 0.2 mm of the mean thickness in all instances and therefore did not change our results when maximal cusp thickness was substituted for the mean valves.

Cardiac catheterization and angiography were performed in 8/10 patients with dysfunctioning valves and revealed severe valvular insufficiency. All ten patients with dysfunctioning valves under-
went valve replacement surgery within two weeks of the echo study. The valves which were echocardiographically thickened (Fig 4) had evidence of thickened cusps with calcific nodules on gross examination (Fig 5). The one dysfunctioning valve not thickened echocardiographically was thin, with a tear in one of the cusps at surgery.

The thickness of 9/10 dysfunctioning valves on gross examination were not uniform, but varied from cusp to cusp and also in the same cusp (Fig 5). In view of this and our inability to predict the path of the echo beam in a given valve, only qualitative comparison could be made between the thickness obtained by echo and on gross examination. The echo thickness (1.1 mm) of one dysfunctioning mitral valve (which was uniformly thin on
gross examination) was within 0.1 mm of that obtained on measurement of the valve following surgical removal. Similarly the thickness of a aortic porcine valve at autopsy was the same (0.8 mm) as that obtained by M-mode echocardiography in another patient who died of metastatic carcinoma a month after the echo study.

It is important to note that not all valves thicken with time. Many remain less than 2 mm thick. Conversely, many valves (14/21) thicker than 3 mm appeared to function normally. However, two of 14 patients with thickened valves who were initially asymptomatic developed evidence of congestive heart failure within nine months of echocardiographic examination. These valves became severely regurgitant, requiring surgical replacement. There was no clinical or laboratory evidence of infective endocarditis in either of these patients.

DISCUSSION

The glutaraldehyde-fixed porcine xenograft is one of the common prosthetic valves in use today. Long-term follow-up has revealed that these valves have good hemodynamic characteristics and a low incidence of thromboembolism.6,9,10 However, valve dysfunction due to degenerative changes has been reported as a late complication1,8 in a relatively small percentage of patients. Spray and associates have noted histologic changes of cellular infiltration of the cusps within two months of valve implantation; however, gross anatomic evidence of valve degeneration in the mitral position was not noted until late.11 M-mode echocardiography and sector echocardiography have been reported by our group and others to be of value in the detection of porcine

![Table 2—Relationship of Valve Thickness to Clinical Dysfunction in the Late Mitral and Aortic Groups](image)

<table>
<thead>
<tr>
<th></th>
<th>&lt;3 mm</th>
<th>&gt;3 mm</th>
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<tr>
<td>No. of valves</td>
<td>61</td>
<td>21</td>
</tr>
<tr>
<td>Dysfunctioning valves</td>
<td>1 (1.6%)</td>
<td>9 (43%)</td>
</tr>
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valve thickening and dysfunction\textsuperscript{5,12} once it has become clinically important.

There have been other attempts at assessing porcine valve function which have depended on the measurements of the mobility and the initial diastolic slope of the valve stents.\textsuperscript{10-15} In our experience, these features have been unreliable because of their associated dependence on cardiac function. In the setting of decreased cardiac output, a marked decrease in stent mobility can occur with a normal valve. Similarly, a poorly compliant left ventricle by itself could reduce the diastolic slope of the valve stents.\textsuperscript{9} We have recently reported an increase in the dominant frequency of the aortic closure sound in patients who have had the porcine xenograft implantation in the aortic position for longer than five years suggesting possible stiffening of valve cusps.\textsuperscript{16} The thickness of native as well as porcine valves has been qualitatively assessed in the past. However, quantification of valve thickness and calcification has just recently been reported with the stenotic native mitral valve.\textsuperscript{17}

The results reported previously indicate that valve thickening as measured by M-mode echocardiography begins to appear 48 months after implantation and supports our recent observations in the long-term follow-up of patients with porcine valve implantation. In that study, with a follow-up of 60 to 89 months, 23 percent of the aortic and 7.8 percent of the mitral porcine valves required replacement. Aortic valve failure began to occur at about 24 months, and mitral valve failure began somewhat later. There is no evidence in the present investigation to indicate that the aortic valve becomes thicker any earlier than the mitral valve, although further observations are needed in this area before firm conclusions can be made. It is also important to note that not all valves become thicker. It is not clear if the thickening that occurred is a feature unique to the recipient patient or to the valve itself.

There have been recent reports of accelerated porcine valve degeneration and calcification in children.\textsuperscript{18,19} Since we had only one patient under 15 years old in our study (who had thickened and dysfunctioning porcine mitral valve), no firm conclusion can be drawn about the time framework of valve thickening in this age group.

The validation of echo valve thickness with gross anatomy in two uniformly thin valves indicates that the axial resolution of a single-dimension echo instrument is adequate in measuring the thin porcine cusps. One of the drawbacks of our study is that each valve was not studied sequentially and therefore did not serve as their control. The results of sequential valve thickening with time in these patients will be of great interest.

Ten patients developed symptoms of cardiac failure necessitating valve replacement. All of these patients with echocardiographic cusp thickening of 3 mm or more had gross anatomic evidence of severe valve degeneration. Other patients with 3 mm or more of thickening have no clinical evidence of valve dysfunction at present, and their exercise tolerance has remained stable for many years. Although valve dysfunction is usually associated with thickening, thin valves may spontaneously rupture, as we observed in one patient. We do not recommend replacement based only upon thickening, since the clinical syndrome of valve dysfunction leading to regurgitation or stenosis, in contrast to other prosthetic valves, occurs relatively slowly and permits time for elective replacement. On the other hand, when hemodynamic decompensation occurs associated with a new murmur and echocardiographic evidence of valvular thickening, valve replacement is indicated.

In conclusion, we have observed that the thickness of the porcine valve can be quantitated by M-mode echocardiography. It appears that the valve thickness increases with time and can be correlated well with the gross anatomic finding of valve degeneration. Patients with “late” porcine valves (longer than 48 months) more than 3 mm thickened on M-mode echocardiography are at a significantly higher risk of developing valve dysfunction and should, therefore, be closely followed up.

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III World Conference on Lung Cancer

The International Association for the Study of Lung Cancer will present the III World Conference on Lung Cancer in Tokyo, Japan, May 17-20, 1982. For information, contact the Japan Organizing Committee for the III World Conference on Lung Cancer, National Cancer Center, Tsukiji, Tokyo 104, Japan.

Pulmonary Gas Exchange Group

The next meeting of the Pulmonary Gas Exchange Group of the Societas Europaea Physiologiae Clinicae Respiratoriae will be held in Brussels, Belgium, September 15-16, 1981. The topic of discussion will be "Single and Multiple Inert Gas Washout." For further information, contact Dr. J. C. Yernault, Chest Service, Hopital Erasme, Route de Lennick 808, B1070 Brussels, Belgium.