Marked Thrombosis and Calcification of Porcine Heterograft Valves

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SUMMARY Prosthetic valvular dysfunction resulting in clinically significant complications occurred in six patients with Hancock porcine heterografts. In one patient with a prosthetic valve in the aortic position, massive prosthetic thrombosis resulted in death. In two patients who had a mitral prosthesis, thrombosis resulted in congestive heart failure and systemic embolization; in one of the latter patients, the thrombi were infected with Candida sp. Calcification of organizing thrombi and cusp tissue resulted in valvular stenosis and congestive heart failure in one patient with an aortic prosthesis and in two patients with mitral prostheses. Four of the six patients died. The prosthetic valves had been in place for 6 months to 3 years before onset of complications. During the same 4-year interval, over 400 porcine prostheses were inserted. This report provides further clarification of the nature and frequency of clinical complications related to degeneration and thrombosis of Hancock porcine heterograft valves.

THE PORCINE HETEROGRaFT has become the prosthetic valve of first choice in many medical centers. After insertion of the porcine heterograft, anticoagulation is generally not necessary because the frequency of embolic phenomena is small. During the past 4 years, we have observed six patients who developed significant clinical complications associated with gross and histopathologic evidence of thrombosis or calcification of porcine heterografts. Five patients exhibited various manifestations of clinical deterioration and valvular dysfunction, and one patient died suddenly after complete obstruction of his aortic valve heterograft. In this report, we describe the clinical details and morphologic correlations in these patients.

Materials and Methods

Patients

Over the past 48 months, approximately 400 porcine heterografts have been implanted at Parkland Memorial Hospital and the Veteran's Administration Hospital in Dallas, Texas. Six adult patients (each with a Hancock porcine heterograft) have had significant thrombosis or calcification of their porcine heterografts (table 1). The porcine prostheses were obtained for detailed morphologic evaluation after surgical replacement in four patients and at postmortem examination in two. Rheumatic fever and consequent valvular damage were responsible for the initial valvular abnormalities in four patients; one had congenital aortic stenosis and a bicuspid aortic valve, whereas the other had traumatically induced aortic insufficiency. None had clinically significant renal insufficiency or elevated levels of serum calcium-phosphorus product.

Morphologic Examination

The porcine heterografts from these patients were fixed in phosphate-buffered 10% formalin, inspected grossly and photographed. Blocks from each valve were embedded in paraffin, with or without prior decalcification. Sections from the blocks were stained with hematoxylin and eosin and, in some instances, with Masson's trichrome stain, the periodic acid-Schiff technique or the Brown and Brenn variant of the Gram stain. Frozen sections from two valves were stained with the oil-red-O method for neutral lipids. Small blocks from one valve were embedded in epoxy resin and sectioned for electron microscopy.

For comparison, four porcine heterografts were obtained from three patients who died of causes unrelated to prosthetic valve dysfunction 1–15 days after valve implantation. These valves were fixed in formalin and histologic sections were prepared as described above.

Results

Five of the six patients in whom thrombus developed on their porcine heterografts were males. The ages of these patients ranged from 22–59 years (mean 40 years). Rheumatic heart disease caused the initial valvular abnormality in four. Initial valvular abnormalities were mitral stenosis in three, aortic insufficiency in one, valvular aortic stenosis in two and mitral insufficiency in one. In the patients with valvular aortic stenosis, one had previous rheumatic heart disease and the other had a congenitally bicuspid aortic valve.

The length of implantation of the porcine heterografts ranged from 6 months to 3 years (mean 24 months). Clinical complications are summarized in table 1. Patient 2 was asymptomatic until sudden...
Table 1. Clinicopathologic Findings in Six Patients with Porcine Heterograft Valves

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Race/sex</th>
<th>Initial lesions</th>
<th>Prosthesis</th>
<th>Implant time</th>
<th>Clinical findings</th>
<th>Pathologic changes of valves (other major autopsy findings)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>B/M</td>
<td>PAPVD; RHD-MS (SBE)</td>
<td>Hancock MV</td>
<td>6 mos.</td>
<td>Grade 3/6 systolic murmur, pulmonary edema, painful right thumb, quadriplegia terminally</td>
<td>Thrombus; perivalvular leak; cusps intact</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hancock MV</td>
<td>6 mos.</td>
<td></td>
<td>Thrombus with Candida sp.; perivalvular leak; cusps intact; mycotic emboli with infarcts of right hand, kidney and brain)</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>W/M</td>
<td>Traumatic AI*</td>
<td>Hancock AV</td>
<td>9 mos.</td>
<td>Asymptomatic before sudden collapse. Grade 2/6 systolic murmur before collapse and disappearance of this murmur immediately before this collapse</td>
<td>Acute thrombus; degenerative change of cusps</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>B/M</td>
<td>RHD-AS, MS</td>
<td>Hancock MV</td>
<td>2 yrs.</td>
<td>Grade 3/6 systolic murmur, pulmonary edema, flank pain, renal and splenic artery emboli (angiogram)</td>
<td>Acute and organizing thrombus; degenerative change of cusps</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>W/M</td>
<td>Cong. AS, (bicuspid AV) CAD</td>
<td>Hancock AV</td>
<td>2 2/3 yrs.</td>
<td>Grade 3/6 systolic and 1/6 diastolic murmurs, chest pain, pulmonary edema, ST and T changes on ECG, abnormal Te-99m pyrophosphate myocardial scintigram</td>
<td>Grossly normal at operation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Carpentier AV</td>
<td>2 yrs.</td>
<td></td>
<td>Organizing thrombus with calcification; degeneration with calcification of cusps</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>B/F</td>
<td>RHD-MS</td>
<td>Hancock MV</td>
<td>3 yrs.</td>
<td>Grade 1/6 apical diastolic rumble, pulmonary edema, 14-mm Hg mean gradient at cardiac catheterization</td>
<td>Organizing thrombus with calcification; degeneration with lipid accumulation and calcification of cusps</td>
</tr>
<tr>
<td>6†</td>
<td>20</td>
<td>B/M</td>
<td>RHD-MR</td>
<td>Hancock MV</td>
<td>3 yrs.</td>
<td>Grade 1/6 apical diastolic rumble, pulmonary edema, 16-mm Hg mean gradient at cardiac catheterization</td>
<td>Organizing thrombus with calcification; degeneration with lipid accumulation and marked calcification of cusps; focal tears of cusps</td>
</tr>
</tbody>
</table>

*Previous aortic valve replacement with Braunwald-Cutler prosthesis in place for 3 years.
†Patient was 17 years old at original implant, an age that may be associated with earlier degeneration of porcine valves.17

Abbreviations: AI = aortic insufficiency; AV = aortic valve prosthesis; CAD = coronary artery disease; Cong. AS = congenital aortic stenosis (bicuspid valve); ECG = electrocardiogram; MR = mitral insufficiency; MS = mitral stenosis; MV = mitral valve prosthesis; PAPVD = partial anomalous pulmonary venous drainage; RHD = rheumatic heart disease; SBE = subendocardial myocardial infarct; B = black; W = white; F = female; M = male.

collapse and death. In the other five patients, a clinical diagnosis of valvular dysfunction was made, but one (patient 4) died before surgical intervention. The other four patients underwent valve replacement, but two died — patient 1 of severe heart failure and patient 2 of embolic complications.

Morphologic Findings

The four porcine heterografts removed from patients who died without prosthetic valve malfunction were grossly normal. On histologic examination, the valve cusps exhibited a fibrosa composed of dense collagen, a spongiosa composed of more loosely arranged collagen, and a thin compact ventricularis. Focal small fibrin deposits and aggregates of lymphocytes were observed occasionally on the valve cusps.

The porcine mitral heterograft from patient 1, who had recurrent perivalvular leakage, showed large thrombi attached to the cusps and prosthetic rings...
Gross and histopathologic findings in patient 2, who died suddenly 9 months after a porcine heterograft was implanted in the aortic valve position. (A) View of the prosthesis from the outflow (aortic) side shows a large thrombus ($T$) completely filling one of the cusps. The other two cusps also were filled with thrombus, which was removed for microbiological studies at autopsy. (B) The thrombus consists of fibrin, platelets and leukocytes and is free of microorganisms. Cultures were negative (hematoxylin and eosin stain, magnification ×148). (C) Histologically, the valve cusps exhibited a fibrosa ($F$) on the outflow side and a spongiosa ($S$) and ventricularis ($V$) on the inflow side. The collagen of the cusps is focally disrupted, especially in the spongiosa, which also contains pools of amorphous proteinaceous material (hematoxylin and eosin stain, magnification ×148). (D) Higher magnification view shows the very loose collagen and pools of proteinaceous material in the spongiosa (top) and denser collagen and elastic fibers in the ventricularis (bottom) (hematoxylin and eosin stain, magnification ×370).

The thrombus from the first valve did not have identifiable microorganisms, whereas the thrombus from the second valve had large numbers of fungi (Candida sp.). The cusps from both valves were histologically unremarkable.

In the porcine aortic heterograft from patient 2, who died suddenly, large thrombi filled each of the cusps (table 1, fig. 1). The aortic valve prosthesis appeared completely obstructed by the massive thrombus, which was presumably responsible for his
sudden death. The thrombus was not organized and was devoid of stainable microorganisms. The cusps showed foci of degeneration characterized by disruption and fraying of collagen and accumulation of amorphous proteinaceous material. Focal calcification was not identified. The presence of the proteinaceous material was helpful in distinguishing degenerative changes from separation and spreading of tissue due to processing and cutting of the sections. Similar light and/or electron microscopic evidence of this type of degenerative change was observed in other patients (fig. 2).

The prosthetic valves from the other patients (table 1) also showed more chronic degenerative changes. These prostheses showed multifocal, firm, granular, friable deposits that were present on both surfaces but were particularly prominent adjacent to the commissures near the base of the cusps (figs. 3–5). These deposits had the histologic appearance of organizing thrombi containing abundant calcium (figs. 3 and 4). Microorganisms were not identified. The cusps showed multifocal degeneration characterized in some areas by a decrease in collagen and accumulation of amorphous proteinaceous material and in other areas by extensive calcification of the degenerated tissue. The cusps frequently had a gross yellowish appearance suggestive of lipid accumulation. Lipid accumulation in two valves was confirmed in frozen sections stained with oil-red-O (fig. 4). The focally calcified cusps exhibited increased rigidity (figs. 3–5). These findings appeared to correspond to the functional stenosis observed clinically (table 1).

**Discussion**

The glutaraldehyde-preserved porcine heterograft is widely used as a prosthetic cardiac valve. Acceptable clinical and hemodynamic results have been reported by several groups in patients with porcine heterografts for up to 5 years. Previous studies have emphasized the low incidence of thromboembolism and the general lack of need for long-term anticoagulation.

More recently, structural changes in glutaraldehyde-fixed porcine heterografts have been found in heterograft tissue obtained at surgical replacement of the valve or at postmortem examination. These alterations have included focal thrombosis and degeneration of the cusps, fibrin deposits on inflow and outflow surfaces of the cusps, inflammatory cellular infiltrates, giant cell formation, focal disruption of the fibrocollagenous structure of the cusps, focal calcification, and, in some cases, associated in-
Gross and histopathologic findings in patient 4, who had a porcine heterograft in the aortic valve position for 2-2/3 years before progressive cardiac failure and pulmonary edema developed. (A) On the inflow (left ventricular) surface, the cusps have a roughened, granular appearance due to the presence of extensive calcific deposits. (B) On the outflow (aortic) surface, the cusps exhibit raised nodular masses (arrows) that represent partially calcified thrombi. (C) Histologic section shows one nodular thrombus (T) that is partially calcified (Ca). The thrombus is attached to a portion of the cusp that is also extensively calcified (arrows) (hematoxylin and eosin stain, magnification × 148). (D) Calcium (Ca) also is deposited in areas of the cusps without attached thrombi (hematoxylin and eosin stain, magnification × 370).

Infection with various microorganisms. Although calcification of fresh aortic homograft valves can be a significant problem,14,15 calcification of Hancock prosthetic valves has also been reported.3,8,12 Carpentier et al. described calcification and perforation of a glutaraldehyde-fixed heterograft 1 year after operation; this heterograft was implanted in a tubed conduit for the treatment of pulmonary valve atresia.9 The severity of the gross and microscopic alterations in the prostheses has been directly related to the length of implantation.8,13 Previous investigators have suggested degeneration of collagen and endothelium as a possible basis for the alterations in the glutaraldehyde-fixed Hancock prostheses,10,11 and have emphasized that the porcine bioprostheses are not biologically inert in the human circulation.8,9

The frequency of clinically significant complications associated with degenerative changes of the porcine bioprostheses is an important issue. Earlier studies have suggested that severe valvular dysfunction caused by degenerative changes is rare, although one patient described by Fishbein et al.9 had diffuse prosthetic...
thrombosis causing stenosis. Others have suggested a 1–2% incidence of calcific and fibrotic alterations of Hancock valves resulting in clinical dysfunction. The incidence of clinical complications appears to be higher in children and in patients with chronic renal disease or clotting abnormalities. There is an additional report of marked thrombus formation with acute obstruction of a Hancock porcine valve and sudden death in a young man with aortic regurgitation as his initial valve lesion.  

In the six patients reported here, significant calcification or thrombosis of the porcine prostheses developed. In one patient, sudden death occurred when a glutaraldehyde-fixed Hancock porcine aortic valve heterograft was obstructed by massive thrombus deposition (table 1). Two patients died as a result of thrombosis of mitral porcine heterografts associated with systemic embolization; in one of these patients, the thrombi were infected with Candida sp. Another patient with an aortic porcine heterograft died with progressive left ventricular failure associated with extensive calcification of cusp tissue and adjacent organizing thrombi. In the remaining two patients, Hancock mitral valve prostheses developed organizing thromboses with calcification, resulting in large gradients and significant obstruction across the
of endothelium and collagen may be involved.\textsuperscript{10, 11} Nevertheless, cardiologists and cardiovascular surgeons must now be aware of the phenomenon of porcine heterograft dysfunction in order to identify patients in whom clinical deterioration is related to obstruction of porcine prostheses and to allow careful scrutiny of the frequency of this phenomenon in large numbers of patients undergoing cardiac valve replacement with these prostheses. Whether similar degenerative changes and marked thrombus deposition will occur on the Carpentier porcine prosthesis is uncertain, but the similarity of the fixation process and other general similarities between these prostheses suggest that such may occur. Whether anticoagulation would protect against thrombus formation on porcine prostheses is unknown.

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Figure 5. Porcine mitral valve heterograft from patient 6, whose condition deteriorated clinically 3 years after insertion of the prosthesis. A 20-mm Hg mean gradient across the valve was found at cardiac catheterization and the mitral valve area was 0.5 cm\textsuperscript{2}. (A) On the inflow (left atrial) surface, the cusps exhibit a roughened appearance due to the presence of numerous calcific deposits that increased the stiffness of the cusps. (B) On the outflow (left ventricular) surface, nodular calcified thrombi are seen. Histologic findings were similar to those in figures 3 and 4.
Diagnostic Criteria for Acute Myocardial Infarction in Patients Undergoing Coronary Artery Bypass Surgery

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SUMMARY Current techniques for diagnosing perioperative myocardial infarction were studied in 58 patients who underwent coronary bypass surgery. All patients had preoperative and postoperative ECGs and technetium-99m stannous pyrophosphate myocardial scintigrams; serum CK-MB was measured immediately after surgery and daily for 3 days. Postoperative bypass graft visualization and left ventriculography were performed before hospital discharge in every patient. Nine patients (16%) had new Q waves postoperatively. Five of these nine patients had positive pyrophosphate scintigrams, positive CK-MB and new wall motion abnormalities, and the remaining four had negative CK-MB, negative pyrophosphate scintigrams and no new wall motion abnormalities. Seven patients (12%) had newly positive postoperative pyrophosphate scintigrams, positive CK-MB and new wall motion abnormalities on postoperative ventriculography, but only four had new Q waves postoperatively. Eight patients (14%) had new wall motion abnormalities; seven had positive pyrophosphate scintigrams and all had positive CK-MB, but only five had new Q waves. Sixteen patients (28%) had positive CK-MB, including all patients with either positive pyrophosphate scintigrams or new wall motion abnormalities. Eight patients had positive CK-MB without other evidence of perioperative infarction.

A newly positive postoperative pyrophosphate scintigram is more sensitive and specific than the development of new postoperative Q waves for the diagnosis of hemodynamically significant perioperative myocardial infarction. CK-MB is highly sensitive, but too nonspecific to be useful for the diagnosis of perioperative infarction.

THE GOALS of coronary artery bypass surgery, in addition to relief of angina and prolonging life, include prevention of myocardial infarction and preservation of functional left ventricular muscle. To assess the efficacy of surgery in reaching these goals, the incidence of perioperative myocardial infarction must be considered. Accurate detection of myocardial infarction in patients undergoing coronary artery bypass surgery, however, may be difficult. The postoperative development of new Q waves on the ECG, elevation of serum cardiac enzymes or the finding of myocardial uptake of technetium-99m stannous pyrophosphate on a postoperative myocardial scintigram have all been proposed as diagnostic criteria for perioperative infarction. However, false-positive and false-negative results have been noted with all of these techniques.

In the absence of pathologic examination of the heart, the most specific indicator of perioperative infarction is the development of a new area of abnormal ventricular contraction. Studies of the incidence of new wall motion abnormalities after bypass surgery have shown that most patients with new postoperative Q waves on electrocardiography have corresponding areas of new postoperative left ventricular dyssnergy on ventriculography. However, for a variety of reasons, some patients with new Q waves do not show new wall motion abnormalities. The relationships among postoperative development of Q waves, pyrophosphate myocardial scintigraphy and new wall motion abnormalities have not been examined.

The current study was undertaken to examine the...
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