Causes of failure and pathologic findings in surgically removed Ionescu-Shiley standard bovine pericardial heart valve bioprostheses: emphasis on progressive structural deterioration

Frederick J. Schoen, M.D., Ph.D., Javier Fernandez, M.D., Lorenzo Gonzalez-Lavin, M.D., and Aurel Cernaianu, M.D.

ABSTRACT Twenty-three Ionescu-Shiley standard bovine pericardial bioprostheses (15 aortic, seven mitral, and one tricuspid) removed at surgery from 21 adults, 28 to 75 years old (mean 55 at reoperation), were examined after functioning for as long as 84 months (mean 26). Reoperation was necessitated by active or healed endocarditis (10 valves), paravalvular leak (three), structural deterioration (eight), and other causes (two). Valves with degenerative dysfunction functioned 32 to 84 months (mean 68). Six had intrinsic cuspal calcification, one with stenosis, and there was regurgitation through secondary cuspal defects in five. Six valves had cuspal defects clearly associated with commissural sutures (“alignment stitches”) unique to this valve design. One valve had a large basal cuspal tear. Other prominent pathologic features included gross cuspal thickening and mild stretching and microscopic deep fluid insudation, separation of collagen bundles, and mononuclear inflammation. Thus, structural disruption due to calcific tissue degeneration and design-related cuspal tears or commissural perforations are the predominant modes of degenerative failure of Ionescu-Shiley standard bovine pericardial valves.


Bioprostheses fabricated from glutaraldehyde-pretreated porcine aortic valves or bovine pericardium are commonly used to replace diseased human cardiac valves. Primary tissue degeneration due to intrinsic cuspal calcification is the most frequent cause of failure of porcine aortic valve bioprostheses.1–5

Commercially prepared glutaraldehyde-preserved bioprosthetic heart valves fabricated from bovine pericardium, introduced into general clinical practice in 1976, are now widely used. Actuarially determined freedom from primary tissue failure of the popular Ionescu-Shiley standard pericardial valve has been variably reported to be 60% at 6 years,6 80% to 95% at 6 years,7–9 and 90% at 11 years.10, 11 Although clinical observations suggest that degenerative failures are related to cuspal tearing, calcification, or both,6–9, 12–14 there has not been detailed description of removed valves. Two previous studies that examined the detailed morphologic features of removed pericardial valves were limited with respect to duration of valve function and specimen number.15, 16 In particular the extent to which specific degenerative mechanisms will limit the long-term durability and the pathologic correlates of extended function of pericardial bioprostheses are largely yet unknown. The purpose of this study was to investigate the causes of failure and morphologic spectrum of Ionescu-Shiley bovine pericardial valves removed at reoperation at a single institution, with emphasis on long-term structural changes.

Materials and methods

The Ionescu-Shiley bioprosthesis (Shiley Laboratories, Irvine, CA) is fabricated from glutaraldehyde-fixed bovine pericardium mounted on a double-velour Dacron cloth-covered titanium frame.8, 9 Twenty-three Ionescu-Shiley standard bovine pericardial bioprostheses removed at surgery at the Deborah Heart and Lung Institute from 21 adults, 28 to 75 years old (mean 55) at reoperation, after function up to 84 months (mean 26) were studied. These included seven mitral, one tricuspid, and 15 aortic valves. One patient underwent aortic and mitral replacement with pericardial bioprostheses; the valves were removed simultaneously and both are included. One patient had sequential aortic pericardial bioprostheses. Two patients with double
valve replacement had aortic pericardial valves and mitral por-
cine bioprostheses. Assignment of a cause of valve failure
included consideration of detailed clinical data, including pre-
operative catheterization reports and operative summaries.

As in previous studies of bioprosthetic valve pathology from
this laboratory, each valve was fixed in formalin, described
grossly, photographed from inflow and outflow aspects, and
radiographed (35 kV × 1.0 min, Faxitron, Model 43805, Hew-
lett-Packard, McMinnville, OR). The degree of mineralization
was graded by inspection of the radiograph as 0 = not present;
1+ = mild; 2+ = moderate; 3+ = more severe; 4+ = most
severe. For microscopic examination, multiple specimens were
taken of the valve cusps at their centers and at their commissures,
embedded in either paraffin or glycolmethacrylate medium (JB-
4, Polysciences, Warrington, Pennsylvania), or both, sectioned
at 6 μm (paraffin) or 2 μm (plastic), and stained with hema-
toxylin and eosin and von Kossa’s method (for calcium phos-
phate). Selected sections were stained with Masson’s trichrome
stain (for collagen), Gram’s stain (for bacteria), methenamine
silver or periodic acid–Schiff (PAS) stains (for fungi), or Fraser-
Lendrum and phosphotungstic acid hematoxylin (PTAH) stains
(for fibrin).

Results

The causes of valve failure, summarized in table 1, included endocarditis (10 valves), bland paravalvular leak (three), and primary structural dysfunction (eight).

One additional valve required removal 2 months post-
operatively due to a suture looped around a stent post
at implantation. Another was removed for early supra-
aortic valvular obstruction due to prosthetic dispro-
portion or malposition.

The diagnosis of endocarditis was used conserva-
tively in this study, being assigned when there was a
history of previous prosthetic valvular infection and a
subsequent paravalvular leak or valve dysfunction
required removal, whether or not clinical or pathologic
evidence of infection was well established. As such,
infection involved the valve cusps, caused ring abscess,
or both, necessitating removal of 10 valves that had
been functioning for 1 to 28 months (mean 8). Three
patients with a history of endocarditis had paravalvular
leak; one had scarring of the aortic root interfering with
valve function. Typical valves with active endocar-
iditis, illustrated in figure 1, had large vegetations
involving the cusps but no cuspal tears or perforations.
Organisms and considerable numbers of deep mono-
nuclear and polymorphonuclear inflammatory cells
were demonstrated far below the cuspal surface with
local lysis of the pericardial collagen structure. In the
six patients in whom active infection was present, the
valves had been in place for 1 to 8 months; the organ-
isms demonstrated histologically or by culture were
Streptococcus aureus (one), enterococcus (one), unde-
defined gram-positive and gram-negative organisms (one
each), and Candida albicans (two). Widespread extrin-
sic mineralization was noted in the vegetations of a case

of active infection. One patient with inactive but pre-
viously documented endocarditis had an aortic peri-
cardial valve and a mitral porcine bioprosthesis, the latter with a paravalvular leak.

Bland paravalvular leak (with no history of infection)
caused failure of three other valves that had been in
place for 0.5 to 4 months (mean 3 months). These
valves were grossly and microscopically unremark-
able.

Eight valves with degenerative dysfunction (primary
tissue failure) functioned for 32 to 84 months (mean 68).
Gross and histologic findings of degradation, illus-
trated in figures 2 to 5, were calcification, cuspal tears
and focal cuspal perforations, cuspal stretching, deep fluid
insulation, and diffuse collagen bundle separation
and architectural disruption.

Intrinsic cuspal calcification was noted in seven peri-
cardial valves from six patients (figure 2). The patient
from whom one of these valves was taken had a history of
endocarditis; the cause of failure was considered to be
inactive endocarditis. One valve functioning for 84
months had pure calcific stenosis (degree of calcification
2+). This patient also had a mitral porcine valve
with regurgitation due to calcification (1+) with cuspal
ears. Intrinsic mineralization with a cuspal tear neces-
sitated valve removal as early as 32 months. In the
one patient with aortic and mitral pericardial bioprostheses
implanted and removed simultaneously, both were
calci ï ed (both 1+), each had commissural perforations,
and the aortic valve had a cuspal tear as well. Five
valves in all had degenerative cuspal defects and focal
mineralization (of degree 1+, 1+, 1+, 2+, 2+).

Calcific nodules were preferentially observed at the
cuspal commissures, but were also noted at the cuspal
attachment margins, free edges, and bodies. They were

| TABLE 1
<p>| Causes of failure of Ionescu-Shiley standard bovine pericardial valves |</p>
<table>
<thead>
<tr>
<th>Causes of failure</th>
<th>Mitral (tricuspid)</th>
<th>Aortic Total</th>
<th>Duration (mo)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>2 (1)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Healed</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Paravalvular leak</td>
<td>2</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5–4 (4)</td>
</tr>
<tr>
<td>Degenerative dysfunction</td>
<td>8</td>
<td></td>
<td>32–84 (68)</td>
</tr>
<tr>
<td>Calcified (+/– cuspal defect)</td>
<td>1</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Noncalcified (+/– cuspal defect)</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Looped suture</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Prosthetic disproportion</td>
<td>0</td>
<td>1</td>
<td>0.2</td>
</tr>
<tr>
<td>All causes</td>
<td>7 (1)</td>
<td>15</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.2–84 (26)</td>
</tr>
</tbody>
</table>

*Values in parentheses are mean values.
SCHOEN et al.

frequently large (half or more of the cuspal thickness), and ulcerated through the cuspal surface. Mineral deposits were generally deep-seated in the tissue fibrosa and dissected through the tissue in the plane of the cusp. Near to calcific deposits, there was focal architectural disruption with splaying of collagen bundles and associated deep mononuclear inflammatory infiltrate in some cases. However, inflammation was separate from the calcific nodules in other cases. Extrinsic calcification within thrombotic deposits was occasionally superimposed on intrinsic calcific deposits.

Seven valves had cuspal tears or perforations, or both. Two valves had linear tears at the basal attachment sites of the cusps (figure 3). In six valves, there

FIGURE 1. Infective endocarditis of pericardial bioprostheses. a and b, Gross photographs of bacterial (enterococcus) and fungal (Candida) endocarditis, respectively. c, Deep cuspal inflammation (arrow) and extrinsic calcification (double arrow) in vegetation of valve shown in a. d, Characteristic yeast and filamentous forms of Candida albicans deep in cusp. e, Hematoxylin and eosin stain; d, periodic acid Schiff (PAS) stain; c and d, original magnification \( \times 150 \).
were cuspal defects at the location of and associated with the commissural sutures ("alignment stitches") that held the cusps in apposition. This is a structural feature unique to the Ionescu-Shiley standard design (figure 4). A spectrum of such defects was noted, from a small hole at the site of the suture to a larger, ovoid defect oriented perpendicularly to the free edge. In a valve analyzed incidental to this study, a larger tear extended to the free edge near the stent post. Microscopically, these defects were associated with focal tissue thickening, architectural disruption, inflammation, and focal calcification. Empty rhomboidal spaces resembling cholesterol crystals were noted at this site in several cases, indicative of lipid uptake or cellular breakdown. One valve had focal tissue thickening and yellow discoloration with incipient perforation at all six alignment suture sites on the valve.

Additional nonspecific microscopic features of potential clinical importance were noted (figure 5). Almost all valves had superficially adherent mononuclear inflammatory cells with or without thrombus, with focal deep mononuclear inflammation and rare multinucleated giant cells. Small thrombotic deposits were frequently noted at cuspal basal attachment sites, most prominently at the inflow surface. Most valves that had been functioning several years or more had mild cuspal thickening and/or stretching noted grossly, and deep fluid insudation and separation of collagen bundles noted microscopically. Fluid insudation, prominent in five valves, was associated with cuspal stiffening in three (all of which were degenerative failures) and cuspal redundancy in another. Both pericardial valves removed from a single patient after 84 months had prominent insudated fluid in the thickened cusps. Areas of fluid insudation in tissue sections stained strongly for fibrin. Also, the inflow surface of many valves was grossly roughened by separation and or fragmentation of collagen bundles from the underlying tissue bulk.

Discussion

Causes of failure of pericardial bioprosthetic valves. The Ionescu-Shiley standard bovine pericardial bioprosthetic valve has excellent hemodynamic function and a low incidence of thromboembolism.6–13, 18–21 However, extended follow-up of patients with pericardial valves is yielding a significant incidence of valve failures from leaflet disruption, calcification, and other degenerative changes, many of which occur less than 5 years postoperatively.6–9, 12–14 The present study demonstrates that sterile structural degeneration causes dysfunction by both calcific and noncalcific mechanisms and that prominent subclinical pathologic changes contribute to tissue deterioration. Although some mechanisms of deterioration appear related to specific design features of this valve type, the spectrum of failure modes for valves fabricated from bovine pericardium and porcine aortic valves appears largely similar, despite the structural differences between these two biological materials.22

The long-term failure rate and morphologic correlations of porcine bioprosthetic valves are well established.1–5, 17 The overall probability of porcine bioprosthetic valve failure from all causes in adults (defined as death or reoperation due to periprosthetic leak, thromboembolic complications, infective endocarditis, or degenerative dysfunction), predicted at various institutions by actuarial statistics, is 20% to 30% at 7 to 10 years.1–5 Clinically significant degeneration of porcine valves is highly time dependent, with a markedly accelerating incidence of failures as follow-up exceeds 4 to 5 years. Late valve deterioration in the absence of antecedent endocarditis (primary tissue failure), occurring by cuspal tearing or calcification or both, is the predominant late valve-related complication associated with porcine bioprostheses.1–5, 17 Valve failure (especially by calcification) is markedly accelerated in children and adolescents with either left- or right-sided intracardiac or conduit-mounted bioprostheses. Fewer than 60% of valves in this population remain intact 3 to 5 years postoperatively.23, 24

Calcification. The present study suggests that, as with porcine bioprostheses, the development of calcific (calcium phosphate) deposits within the cuspal tissue will contribute strongly to limitation of the late durability of pericardial valves. As with porcine aortic valves, young patients and patients with bovine pericardial valves who have abnormal calcium metabolism probably have an accelerated rate of calcification.25, 26

Degenerative calcific deposits generally predominate at the cuspal commissures and basal attachments of porcine valves, the sites of highest dynamic mechanical stress during function.27 This location was similarly preferred, but not exclusively so, in the pericardial valves studied. Although calcific deposits in porcine valves are most extensive in the spongiosa,1, 17 calcific deposits in pericardium in this study were located deep in the valve cusps, with no specific anatomic localization. Ultrastructurally, calcific deposits are related to cuspal connective tissue cells and collagen in both clinical28 and experimental porcine valve specimens29 and in experimental pericardium.30, 31 However, the ultrastructural features of calcification in clinically pericardial bioprostheses have not yet been described.
FIGURE 2. For legend see opposite page.
Studies using pericardial tissue implanted subcutaneously in young rats demonstrate that the morphologic features, kinetics, and degree of mineral accumulation in this material are strikingly similar to those previously determined for porcine aortic valve in the same preparation\textsuperscript{29, 31} and in pericardial bioprostheses implanted as mitral and tricuspid valve replacements in sheep,\textsuperscript{32} despite the architectural differences between the two materials.\textsuperscript{22} It is not surprising then that the morphology of mineralization demonstrated in the present study, predominantly intrinsic to the valve cusps, was essentially the same as that previously described for clinical porcine valves.\textsuperscript{1, 17} Calcification of bovine pericardium has also been noted in other experimental\textsuperscript{33} and clinical studies.\textsuperscript{34, 35}

**Noncalcific cuspal defects and other pathology.** Cuspal defects are frequently associated with calcification in bioprostheses made from both porcine valve and pericardium, but some cuspal defects are not related to mineralization. Noncalcific cuspal tears in porcine valves reflect direct mechanical destruction of collagen architecture with stress-induced collagen deterioration, revealed by scanning electron microscopy as fraying and disruption of collagen fibers.\textsuperscript{36} The present study suggests that the contribution to failure of noncalcific degenerative processes may be more important in clinical pericardial than porcine bioprostheses.

Large, noncalcific tears of pericardial valves have been reported, particularly in mitral replacements. Two variants have been described.\textsuperscript{7, 10, 11} One type is associated with the basal attachment site of the cusp to the supporting stent. Some investigators hypothesize that this is a consequence of the continuous abrasion of tissue against the bare Dacron cloth.\textsuperscript{5, 12} The other tear morphology is initiated at or near the cuspal free edge near the stent posts. Our findings support the notion, previously suggested,\textsuperscript{8} that such tears result from excessive strain at the free edge or from the presence of a suture and its associated holes in the tissue in the Ionescu-Shiley standard pericardial bioprosthesis. This suture, termed the “alignment stitch,” is used to maintain proper alignment of the valve leaflets and their apposition at each commissure.\textsuperscript{*} In the more recently designed low-profile model, this stitch is placed closer to the cuspal base, via attachment holes in the stent post (Shiley Inc., brochure describing Ionescu-Shiley low-profile pericardial valve). The present study clearly

---

\* Bumb S: Personal communication (Shiley Incorporated, Irvine CA).

**FIGURE 2.** Degenerative cuspal calcification contributing to or causing failure of pericardial bioprostheses. \(a\) and \(b\), Gross photographs of valves functioning for 32 and 79 months, respectively, removed for mixed stenosis and regurgitation. Calcific nodules and secondary commissural tears are evident. \(c\), Gross photograph of valve with calcific stenosis after functioning for 84 months. \(d, e,\) and \(f\), Radiographs of valves shown in \(a, b,\) and \(c\), respectively. \(g,\) Photomicrograph of extensive cuspal mineralization intrinsic to cusp. \(h,\) Photograph of mixed intrinsic/extrinsic mineralization. \(g\) and \(h,\) Stained with von Kossa’s reagent (calcium phosphate black), original magnification \(\times 60.\)
demonstrates that the alignment stitch is associated with progressive and clinically important pathology. When these pathologic changes contribute to loss of commissural tissue apposition, cuspal excursion is increased and the likelihood of cuspal tears is probably enhanced. Regurgitation through a peripheral cuspal perforation could be interpreted at cardiac catheterization as a paravalvular leak.8

The gross pathology of noncalcific failure is generally reproduced in vitro by pulse acceleration devices.12 That the pathology associated with the alignment stitch has not been revealed in vitro suggests that a biologic interaction is contributory. Although inflammation, structural disruption, and focal lipid accumulation were observed frequently in the present study, whether these changes contribute to cuspal perforation or tearing is unknown. Regurgitation through a peripheral cuspal perforation could be interpreted at cardiac catheterization as a paravalvular leak.8

Stretching of cuspal pericardial tissue associated with considerable collagen bundle loosening, observed in experimental implants39 and noted occasionally in this study, could ultimately cause regurgitation, especially in designs with larger cusps. The cause of pericardial stretching is unknown. However, a recent study demonstrated heterogeneity in the mechanical properties of bovine pericardium among anatomic sites within the sac, with extensibility of one particular site particularly high.37 Implanted pericardium frequently elicits an aggressive host inflammatory response with local tissue disruption, as noted in both clinical38 and experimental implants,32,39 but the potential clinical

FIGURE 4. Commissural alignment suture and associated cuspal pathology. a, Gross photograph of valve removed shortly after implantation, demonstrating intact commissural sutures (arrows), a design feature unique to the Ionescu-Shiley standard valve. b, Close-up gross photograph demonstrating frank cuspal perforation at this site (arrow). c, Close-up photograph of an Ionescu-Shiley standard pericardial bioprosthesis, not from this study, removed for pure regurgitation from a patient 66 months after implantation. Note commissural tear near hole at alignment suture (arrow). It is likely that the abnormal mechanical stresses in this area caused the tear after loss of cuspal apposition. (Valve courtesy of R. T. Brownlee, M.D., Victoria, B.C., Canada.) d, Photomicrograph of alignment suture region from valve in the present study demonstrating deep inflammation and structural distortion at alignment suture. Hematoxylin and eosin stain, original magnification ×150.
FIGURE 5. Photomicrographs of other pathologic conditions noted in the cusps of Ionescu-Shiley pericardial bioprostheses after short- and long-term function. 

- **a**, Macrophages lining surface of valve.  
- **b**, Extension of these inflammatory cells below surface, distorting and separating collagen bundles.  
- **c**, Loose, splayed collagen bundles on inflow pericardial surface (arrow), correlating with gross appearance of roughened inflow surface of valves after long-term function. This process undermines the intrinsic valve structure.  
- **d**, Characteristic thrombotic deposit (asterisk) at the junction of cusps with basal attachments noted frequently on both inflow and outflow surfaces.  
- **e**, Deep cuspal pooling of plasma-derived fluid (asterisk), with separation of large collagen bundles.  

In **f**, Fraser-Lendrum stain for fibrin (black deposit) suggests derivation of this material from plasma.  

- **a** through **e**, Hematoxylin and eosin stain.  
- **a** and **b**, original magnification ×375;  
- **c**, ×80;  
- **d** through **f**, ×150.
importance of cuspal inflammation is unknown. In previous reports and in the present study, loss of cuspal architectural definition and deep fluid insulation were prominent, the latter likely contributing to failure in several of the present cases, and lipid deposition (cholesterol crystal formation) was focally prominent. Both fibrin and lipid deposition have been previously noted with porcine valves. Tissue overgrowth, reported to cause failure in two pericardial valves implanted in children, was not prominent in this study.

Endocarditis was encountered in almost half of the specimens studied. However, the relative frequency of specific failure modes in studies of pathologic specimens does not necessarily represent their true clinical incidence. Analyses of causes of failure of valve prostheses in which mean follow-up intervals are comparatively short may tend to overemphasize problems that generally occur at earlier postoperative intervals. Endocarditis is generally an earlier complication (mean 8 months in this study) than degenerative failure (mean 68 months). This unavoidable selection bias in pathologic specimens has been demonstrated in our previous studies of failed porcine valves. In an initial morphologic analysis of 23 consecutive porcine valve failures, endocarditis caused eight (35%). When our experience had expanded to 58 porcine bioprostheses, endocarditis had caused 19% of failures. After 112 porcine valves had been analyzed, endocarditis was noted in only 10% of specimens. Throughout this experience, the valves had been implanted and removed by the same group of cardiac surgeons, which has reported a relatively low and essentially time-invariant clinical incidence of endocarditis. The clinically reported actuarial incidence of endocarditis with pericardial bioprostheses is not excessive, either in general or at the institution in which the present valves were implanted. Moreover, a modest clinical rate of endocarditis was reported in a large experience of over 2600 patients with pericardial valves (maximum 5 year follow-up, mean 2 years).

Nevertheless, there were almost as many failures due to endocarditis as there were those due to leaflet disruption or calcification, and over one-third of reoperations were necessitated by endocarditis. Thus, as clinical follow-up is extended and experience with removed pericardial valves accumulates, the relative frequency with which endocarditis appears to cause failure will likely decrease, and the relative proportion of valves failing by degenerative dysfunction will likely increase sharply.

The inadvertent looping of a suture around a stent post that has been previously described may be more difficult to avoid with a pericardial than a porcine valve as a result of the shorter and less bulky stent. Moreover, the consequences of this technical difficulty with a pericardial bioprosthesis may be greater than with a porcine valve since the suture will entrap a greater fraction of the cuspal area near the commissure.

In conclusion, like porcine aortic valve bioprostheses, bovine pericardial bioprostheses are associated with a spectrum of failure modes in which degenerative mechanisms play a dominant role, as determined by examination of late explants. Intrinsic cuspal calcification was present in most valves removed for structural dysfunction. Cuspal perforations associated with commissural suture of the Ionescu-Shiley design were also frequent. This study suggests that both calcific and noncalcific modes of degradation will limit the long-term success of bovine pericardial bioprostheses.

We are grateful to the Department of Pathology, Deborah Heart and Lung Center, for cooperation in providing the specimens studied, so Sara Murray and Helen Shing for technical assistance, and to Roberta A. Baxter for typing the manuscript.

References


34. Ross EM, McIntosh CL, Roberts WC: “Massive” calcification of a right ventricular outflow tract pericardial patch in tetralogy of Fallot. Am J Cardiol 54: 691, 1984


44. Silver MA, Oranburg PR, Roberts WC: Severe mitral regurgitation immediately after mitral valve replacement with a parietal pericardial bovine bioprostheses. Am J Cardiol 52: 218, 1983
Causes of failure and pathologic findings in surgically removed Ionescu-Shiley standard bovine pericardial heart valve bioprostheses: emphasis on progressive structural deterioration.

F J Schoen, J Fernandez, L Gonzalez-Lavin and A Cernaianu

_Circulation_. 1987;76:618-627
doi: 10.1161/01.CIR.76.3.618

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/76/3/618

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

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

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