Postinflammatory mitral and aortic valve prolapse: a clinical and pathological study

Takanobu Tomaru, M.D., Yasumi Uchida, M.D., Noboru Mohri, M.D., Wataru Mori, M.D., Akira Furuse, M.D., and Kenichi Asano, M.D.

ABSTRACT In this study we reevaluated whether the sole cause of mitral valve prolapse (MVP) and aortic valve prolapse (AVP) is myxomatous degeneration. Forty-two surgical cases of prolapsed valves with mitral and/or aortic regurgitation were reviewed (AVP in nine, MVP in 27, and combined AVP and MVP [CVP] in six). On microscopic examination, myxomatous degeneration was observed in 20 patients, including six with AVP, 13 with MVP, and one with CVP. In the other 22 patients, including three with AVP, 14 with MVP, and five with CVP, microscopic examination revealed fibrosis with vascularization and scattered infiltration of inflammatory round cells caused by postinflammatory changes with or without chronic inflammation. We coined the term “postinflammatory valve prolapse” (PIVP) to describe these valves. Both postinflammatory and myxomatous degeneration were observed in seven patients with floppy mitral valves attributable to PIVP. Rupture of chordae tendineae was present in six patients with myxomatous mitral valve and three with PIVP. Seven patients with PIVP had a history of rheumatic fever. The results suggest that valvular prolapse is produced not only by myxomatous degeneration but also by postinflammatory changes, including those caused by rheumatic fever.


MITRAL VALVE PROLAPSE (MVP) is a clinical syndrome that is usually diagnosed by echocardiography,1–7 angiocardiology,7–12 and phonocardiography.13,14 It has also been known as redundant cusp syndrome,15 floppy valve syndrome,16 or ballooning deformity.17 Recently, aortic valve prolapse (AVP) has also been diagnosed by echocardiography18–21 or by direct observation during surgery.22 Mitral or aortic regurgitation and congestive heart failure are the late sequelae of this syndrome.

Surgeons performing valve replacement for the regurgitant prolapsed valve have been impressed with the characteristic gross appearance of the floppy valve.15,16 Since the major histologic finding of the floppy valve is myxomatous degeneration, the etiology of the syndrome has been mostly related to the degenerative process and this entity has been recognized as a nonrheumatic change.16,17,23–29

Recently, however, we noted histologic changes characteristic of chronic inflammation in several excised prolapsed valves. To confirm this impression, we examined the excised specimens of the regurgitant prolapsed valves along with relevant clinical variables.

Methods

Forty-two consecutive surgical cases of regurgitant prolapsed valves and concomitant congestive heart failure at the University of Tokyo between 1978 and 1983 were reviewed. Twenty-five patients were men and 17 were women. Their ages ranged from 20 to 67 years (mean 43). Seven patients had a history suggestive of rheumatic fever. All patients had severe mitral (n = 27), aortic (n = 9), or combined mitral and aortic regurgitation (n = 6), and none had clinical valvular stenosis. The duration of symptoms ranged from 1 to 44 years (mean 12.8). The NYHA functional capacity was more than grade II in all patients. Atrial fibrillation was seen in 17 patients (63%) with mitral regurgitation, six (56%) with aortic regurgitation, and four (66%) with combined mitral and aortic regurgitation. This study did not include patients with atrial septal defect, ventricular septal defect, Marfan’s syndrome, or other disease that may accompany mitral or aortic valve prolapse. The diagnosis of valve prolapse was made by two-dimensional echocardiographic and surgical findings.

On two-dimensional echocardiography, mitral valve prolapse (MVP) was diagnosed when the mitral cusps protruded into the left atrium crossing the plane of the mitral annulus. During surgery, MVP was diagnosed by one surgeon when the intact valves protruded beyond the optimal position into the left atrium. Morphologic diagnosis of MVP included doming or intrachordal hooding of the mitral cusp into the left atrium. Aortic valve prolapse (AVP) was also diagnosed by the surgeon when
the aortic cusps protruded downward beyond the optimal position for closure of the valve. Two-dimensional echocardiography revealed various degrees of prolapse in all patients with MVP and in most with AVP. However, in three patients AVP diagnosed at surgery was not observed on echocardiography.

Based on the surgeon's description, MVP was graded as follows: grade I, prolapse of a small part of one cusp; grade II, prolapse of at least one-third of the posterior cusp or one-half of the anterior cusp; grade III, prolapse associated with major chordal rupture. AVP was graded as follows: grade I, prolapse of one cusp; grade II, prolapse of two cusps; grade III, prolapse of all three cusps. The mitral and/or aortic annular size and left ventricular size were evaluated by inspection. Gross abnormalities of the valve apparatus were also assessed.

A majority of the valves were removed in a uniform fashion. However, most of them were separated immediately into anterior and posterior cusps. The annular dimensions were measured in the resected aortic and mitral valves, the anulus of which was assessed by one pathologist. After excision, the specimens were fixed with 10% buffered formalin for more than 1 day before pathologic and microscopic examination. Twenty control valves were resected from the hearts of previously healthy subjects who died from accident, trauma, or apoplexia. The mean age of the control subjects at death was 39 years. The normal range of aortic or mitral annular dimension was determined by the examination of 204 hearts of consecutive autopsy cases without heart disease, hypertension, or cardiomegaly. The valve surface area of mitral valves was assessed as follows according to the method of King et al.25: all the anterior cusps were assumed to be triangular, and the base and height of them were measured in a uniform fashion. The thickness of the prolapsed portion of the mitral cusp was also measured. After gross morphologic examination, the sections of prolapsed area taken from the valves were stained with hematoxylin and eosin, elastica Van Gieson, and alcian blue stains.

The results are expressed as mean ± SD. The Student t test was used to compare the differences in age, valve area, valve thickness, and annular dimension between the groups. The incidence of chordal rupture, chordal elongation, and high-grade prolapse between the groups was compared by a chi-square test.

**Results**

**Gross morphology at surgery.** All patients with regurgitant prolapsed valves showed enlarged left ventricles, and 31 (94%) with MVP showed left atrial enlargement. The mitral or aortic anulus was dilated in various degrees in all patients.

**Location of prolapsing lesion.** Table 1 shows the location of the prolapsing cusp of the mitral valves. The anterior mitral cusp was involved in most of the cases of isolated MVP and combined MVP and AVP (CVP). Table 2 shows the sites of the prolapsing cusps of the aortic valves.

**Table 1**

Prolapsing leaflets of mitral valves

<table>
<thead>
<tr>
<th></th>
<th>MVP (n = 27)</th>
<th>CVP (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>PML</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>AML + PML</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

AML = anterior mitral leaflet; PML = posterior mitral leaflet.

**Histologic classification of valve prolapse and relevant gross morphologic features.** Twenty patients showed various degrees of myxomatous degeneration in the mitral valve (n = 13), aortic valve (n = 6), or both (n = 1). In the pars fibrosa of these specimens, collagen bundles were fragmented and disruption of the fibrosa was observed (figure 1). The majority of these valves had a widened pars spongiosa with moderate-to-marked acid mucopolysaccharide infiltration as demonstrated by alcian blue stain (figure 2). However, three patients with isolated MVP had degeneration of the pars fibrosa with minimal mucopolysaccharide infiltration. Three patients had minimal myxomatous degeneration in the chordae, which had been elongated or ruptured. Vascularization by thick-walled vessels with or without inflammatory round cell infiltration, which is the characteristic change of chronic inflammation or of a postinflammatory state, was not observed in these myxomatous valves. Therefore valves of this type were considered to show myxomatous valve prolapse (figure 3). The majority of the mitral cusps with myxomatous prolapse were large and were considered so-called floppy valves.16 The aortic cusps of these valves showed a similar appearance. Thinning and enlargement of the cusps were seen in three mitral and four aortic valves.

In the other 22 patients, the mitral valve (n = 14), aortic valve (n = 3), or both (n = 5) were diffusely vascularized with scarring, suggesting postinflammatory and/or chronic inflammatory changes. Destruction of valve architecture was prominent, and the pars spongiosa was decreased or absent because of scarring in a majority of these valves (figure 4). In six patients, infiltration of chronic inflammatory round cells, including lymphocytes and plasma cells, was also observed. We will refer to this condition as “postinflammatory valve prolapse” (PIVP).

In both groups, patients with CVP had concordant histologic changes in aortic and mitral valves. Figures 5 and 6 show the echocardiographic appearance of
PIVP in a mitral valve and the prolapse of the anterior cusp of the same valve at surgery. The cusps of the mitral valve with PIVP were relatively hard and thick, with minimal or moderate chordal fusion and thickening (figure 7). Seven cases of PIVP also showed chordal elongation. A soft mitral valve associated with myxomatous degeneration was seen in seven patients with PIVP. Both postinflammatory and myxomatous changes were observed in these valves (figure 8). The aortic cusps of PIVP were relatively hard (figure 9) and all cusps showed conspicuous prolapse toward the left ventricle at surgery.

Mitral valve area and valve thickness were assessed in the resected valves, examination of which was made by one pathologist. The area of the anterior mitral cusps was assessed in nine valves with myxomatous prolapse, eight with PIVP, and 20 control valves; that of the posterior mitral cusps was assessed in eight with myxomatous prolapse, seven with PIVP, and 20 control valves. The thickness of the prolapsed portion of the anterior cusps was also assessed in the same valves. The mitral annular dimensions were measured in eight valves with myxomatous prolapse, seven with PIVP, and 20 control valves, and the aortic annular dimensions were measured in four with myxomatous prolapse, five PIVP, and 20 control valves. Table 3
shows the mean anterior and posterior cusp areas and mean wall thickness of the prolapsed portion. The mean surface area of the anterior mitral cusps in valves with myxomatous prolapse was 720 mm$^2$ compared with 626 mm$^2$ in those with PIVP ($p < .01$) and 486 mm$^2$ in control valves ($p < .001$). The mean surface area of the posterior cusps in valves with myxomatous prolapse was 866 mm$^2$ compared with 798 mm$^2$ in those with PIVP and 568 mm$^2$ in control valves ($p < .001$). The mean thickness of valves with PIVP was 3.7 mm compared with 2.7 mm in valves with myxomatous prolapse ($p < .001$) and 0.98 mm in control valves ($p < .001$). The mean mitral annular dimension was 118 mm in valves with myxomatous prolapse compared with 109 mm in those with PIVP and 82 mm in control valves ($p < .001$). The mean aortic annular dimension was 82 mm in valves with myxomatous prolapse compared with 78 mm in those with PIVP and 67 mm in control valves. Normal ranges of aortic and mitral anulus dimensions are listed in table 3.
FIGURE 7. Surgically resected mitral valve with PIVP showing fibrous thickening and chordal fusion.

Grade of prolapsed portion. Table 4 shows the grades of MVP. Four cases of grade III MVP showed not only ruptured chordae tendeneae but also prominent doming of one or both cusps toward the left atrium. The incidence of more than grade II prolapse was higher in valves with myxomatous prolapse than in those with PIVP (p < .05). In grade I prolapse, chordal elongation and valvular deformities, including slight commissural fusion, were observed in three and marked annular dilatation in two. Table 5 shows the grades of AVP. All four prolapsed aortic valves of grade III were soft and large and belonged to the myxomatous prolapse group. The incidence of grade III AVP was higher in valves with myxomatous prolapse than in those with PIVP (p < .05). All three cases of grade I AVP had minimal cusp fusion with impairment of cusp coaptation.

Clinical and pathologic features of valve prolapse in relation to histologic classification. Table 6 summarizes the clinical and pathologic features of PIVP and myxomatous prolapse. All patients presented with congestive heart failure and grade III to IV regurgitant murmurs at the time of surgery. None of the 33 patients with myxomatous prolapse had the typical midsystolic click. The age at surgery and the age at the onset of symptoms were significantly different between two groups (p < .001). The age at surgery and at the onset of symptoms was lower in patients with PIVP than in those with myxomatous prolapse. One patient with myxomatous prolapse and two with PIVP had a history of infective endocarditis. Seven patients with PIVP and none with myxomatous prolapse had a history of rheumatic fever. The incidence of chordal rupture or elongation was lower in the PIVP group than in the myxomatous prolapse group. As mentioned before, the valve thickness was greater in the PIVP group than in the myxomatous prolapse group, and the valve surface area was larger in the myxomatous prolapse group than in the PIVP group.

Discussion

The term valve prolapse is used in echocardiography or angiography. However, prolapse has also been used as a descriptive term to express surgical or gross morphologic findings. On the other hand, the term “floppy valve” has been used by cardiac surgeons to describe the gross morphologic features of the myxomatous valve. Although the floppy valve has been regarded as the commonest cause of valve prolapse, the two are not identical. Some of our prolapsed valves had the characteristic appearance and histologic features of the floppy valve, but others did not.

A number of patients with valve prolapse showed postinflammatory changes in this study. Histologic examination of these valves showed destruction of valvular...
lar architecture, scarring, and diffuse vascularization by thick-walled vessels with or without scattered inflammatory round cell infiltration. These histologic changes are similar to those seen in rheumatic valvulitis. Therefore we used the term "postinflammatory valve prolapse" to describe these valves.

MVP may occur in diseases affecting the connective tissue such as Marfan's syndrome, Ehlers-Danlos syndrome, or Turner's syndrome. It may also be associated with hypertrophic cardiomyopathy, atrial septal defect, ischemic heart disease, and blunt chest trauma, which may cause mechanical or hemodynamic stress to the valvular apparatus. AVP may occur in patients with ventricular septal defect, annuloaortic ectasia with or without Marfan's syndrome, dissecting aortic aneurysm, or infective endocarditis. These diseases may cause degeneration of connective tissue in valves resulting in valve prolapse. Several investigators have suggested that AVP or MVP is also related to the aging process. However, in the majority of patients with MVP or AVP the etiology is unknown, in which case the condition is considered as primary or idiopathic. The pathogenesis is tentatively attributed to the weakening of the pars fibrosa as in the types of secondary valve prolapse mentioned above. Almost all studies dealing with valve prolapse or floppy valve have emphasized the presence of myxomatous degeneration resulting from the degeneration of collagen in the pars fibrosa, which occurs by an unknown mechanism. Several authors also described acid mucopolysaccharide infiltration or collagen degeneration shown by haphazard arrangement of fibrils with disruption or fragmentation. Recently, King et al. suggested collagen dissolution as the primary change. Most of these reports dealt with floppy valves that did not have any inflammatory changes.

Little attention has been paid to the relation of valve prolapse to postinflammatory changes or chronic valvulitis. Kern et al. demonstrated the presence of myxoid changes in valves showing the characteristic features of rheumatic valvulitis. Barlow also described the association of mitral valve prolapse with rheumatic fever. There was also one report on MVP associated with mitral stenosis. However, these studies gave no important clues to the etiology or pathogenesis of valve prolapse because of their vague definition of valve prolapse or the absence of clinical diagnosis by echocardiography. Echocardiographic diagnosis of MVP is generally made when the mitral leaflet protrudes into the left atrium crossing the valve ring; AVP is diagnosed when the aortic valve prolapses.

### TABLE 3

<table>
<thead>
<tr>
<th>Surface area of mitral valve (mm²)</th>
<th>Control</th>
<th>MyVP</th>
<th>PIVP</th>
<th>p value (MyVP vs PIVP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior cusp</td>
<td>486 ± 101</td>
<td>720 ± 111&lt;sup&gt;a&lt;/sup&gt;</td>
<td>626 ± 108&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Posterior cusp</td>
<td>568 ± 215</td>
<td>866 ± 224&lt;sup&gt;a&lt;/sup&gt;</td>
<td>798 ± 232&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
</tr>
<tr>
<td>Thickness of mitral valve (mm)</td>
<td>0.98 ± 0.51</td>
<td>2.7 ± 0.83&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.7 ± 0.66&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Annular dimension (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve (normal)</td>
<td>67 ± 9</td>
<td>82 ± 7</td>
<td>78 ± 6</td>
<td>NS</td>
</tr>
<tr>
<td>Mitral valve (normal)</td>
<td>82 ± 10</td>
<td>118 ± 12&lt;sup&gt;a&lt;/sup&gt;</td>
<td>109 ± 11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>NS</td>
</tr>
</tbody>
</table>

MyVP = myxomatous valve prolapse.
<sup>a</sup>p < .001 vs control.
into the left ventricle. Surgical findings of MVP are doming and expansion or dislocation of the mitral leaflet to the left atrium, and those of AVP are dislocation or prolapse of the aortic valve from the aortic ring to the left ventricle. Therefore the diagnosis of valve prolapse should be made regardless of floppy appearance or myxomatous degeneration. Chronic valvulitis may cause any form of valvular deformity, including chordal elongation, chordal infusion, and/or expansion of the cusps. \(^3\) As in many cases of PIVP in our study, it is not unreasonable to consider chronic valvulitis or postinflammatory changes as a cause of valve prolapse.

Surgical and gross morphologic findings of PIVP differed from those of myxomatous prolapse probably because of their different pathogenesis. Surgical and morphologic examinations disclosed that aortic or mitral valve prolapse with a large thin cusp was seen only in myxomatous prolapse and that localized prolapse was observed more commonly in PIVP. The aortic and mitral annular dimensions and mitral valve area of valves with myxomatous prolapse were greater than those with PIVP or control valves. Increases of valve area and anulus dimension are often seen in regurgitant valves. The greater increase of valve area and annular dimensions in myxomatous prolapse might result from weakening of valve apparatus caused by myxomatous degeneration. Most valves with PIVP had morphologic postinflammatory changes, including slightly fused chordae tendineae, minimal commissural fusion, and/or fibrous thickening of cusps. These findings in valves with PIVP simulate closely those of rheumatic valvulitis. \(^4\) Chronic infective endocarditis may also show histologic changes similar to those of PIVP. \(^4\) However, the valves of chronic or postacute infective endocarditis have been reported to show frequent perforation or destruction of the valve apparatus. \(^4\) The valves with PIVP in this study had neither perforation nor destruction. Therefore, in seven patients (32%) with PIVP who had a history of rheumatic fever, the morphologic and histologic changes of PIVP might have resulted from rheumatic fever with less severe valve destruction. On the other hand, it is preferable to designate the prolapsed valves of the remaining 15 patients with PIVP that are not clearly of infective etiology as “rheumatic type” but not as rheumatic. \(^4\) Burch et al. \(^4\) reported that “rheumatic fever negative” chronic valvular disease might be caused by virus-induced valvulitis, and Sun et al. \(^4\) have produced valvulitis with fibrous thickening and commissural adhesion in the monkey mitral valve with Coxsackie B virus. It may be supposed that some cases of PIVP resulted from virus-induced valvulitis. However, we have no clinical evidence of viral infection in PIVP and have not performed immunohistologic examination for detecting virus. Further investigations will be needed to study the complex etiologies of PIVP, including viral infection.

Although the absence of inflammatory changes has been considered as a hallmark of valve prolapse for clear-cut distinction from rheumatic valvulitis, we should not neglect the existence of PIVP with characteristic features of chronic valvulitis or postinflammatory changes. In PIVP, it seems unlikely that valve prolapse is caused simply by the weakening of the pars fibrosa of the aortic or mitral valve. Many other factors such as valvular deformity, annular dilatation, and elongated and/or ruptured chordae may contribute to valve prolapse. These other abnormalities of the valve apparatus were considered to be the cause of severe valvular regurgitation in the group with lower-grade PIVP. However, in the myxomatous valves with PIVP, weakening of the pars fibrosa could be a significant cause of valve prolapse.

The echocardiographic or angiocardiographic differentiation of PIVP from myxomatous prolapse may be difficult without pathologic examination. However, the age distribution in the two groups of patients may be a useful clue to the differential diagnosis of prolapse. The average age of patients with myxomatous prolapse was higher than that of patients with PIVP, and the onset of symptoms was at a younger age in patients with PIVP than in those with myxomatous prolapse. This is probably because myxomatous degeneration showed an increased incidence with increasing age\(^1\) and because rheumatic fever and in-

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Grade of MVP (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MyVP</td>
</tr>
<tr>
<td>Grade I</td>
<td>0</td>
</tr>
<tr>
<td>Grade II</td>
<td>8</td>
</tr>
<tr>
<td>Grade III</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
</tr>
</tbody>
</table>

Abbreviations as in table 3.

<table>
<thead>
<tr>
<th>TABLE 5</th>
<th>Grade of AVP (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MyVP</td>
</tr>
<tr>
<td>Grade I</td>
<td>0</td>
</tr>
<tr>
<td>Grade II</td>
<td>3</td>
</tr>
<tr>
<td>Grade III</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations as in table 3.
TABLE 6
Clinical and pathologic features of valve prolapse

<table>
<thead>
<tr>
<th>Feature</th>
<th>MyVP (n = 20)</th>
<th>PIVP (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40–67 (50.6±7.1)</td>
<td>20–59 (36.6±9.3)</td>
</tr>
<tr>
<td>Age at onset (yr)</td>
<td>26–66 (43.5±11.6)</td>
<td>2–33 (17.7±9.4)</td>
</tr>
<tr>
<td>History of rheumatic fever</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Gross morphology</td>
<td>Soft, large prolapsed valve (13/20)</td>
<td>Hard and thick valve</td>
</tr>
<tr>
<td>Elongated chordae</td>
<td>7/14 (50%)</td>
<td>7/19 (37%)</td>
</tr>
<tr>
<td>Chordal rupture</td>
<td>6/14 (42%)</td>
<td>3/19 (16%)</td>
</tr>
<tr>
<td>Histology</td>
<td>Myxomatous degeneration</td>
<td>Postinflammatory changes</td>
</tr>
</tbody>
</table>

Abbreviations as in table 3.

*p < .001 (MyVP vs PIVP).

Infections are common in children. Our cases of regurgitant AVP and/or MVP associated with congestive heart failure represented late and severe stages of valve prolapse. Therefore our study may have included more cases of valve prolapse caused by postinflammatory changes than the actual incidence of PIVP. There may also be some patients with PIVP and mild clinical manifestations, and these cannot be differentiated easily from patients with “valve prolapse due to myxomatous degeneration or other etiologies.”

We conclude that (1) valve prolapse was attributable not only to myxomatous degeneration but also to postinflammatory changes, (2) valvular deformities, chordal elongation, and/or rupture were regarded as the initiating factors of PIVP, and (3) the patients with PIVP were younger than those with myxomatous prolapse, probably because rheumatic fever and infections commonly occur in children and adolescents.

We acknowledge the assistance of Prof. William Currie and Dr. Daniel Murozek in the preparation of this manuscript.

References

28. Davies MJ, Moore BP, Brainbridge MV: The floppy mitral valve:
TOMARU et al.


Postinflammatory mitral and aortic valve prolapse: a clinical and pathological study.
T Tomaru, Y Uchida, N Mohri, W Mori, A Furuse and K Asano

Circulation. 1987;76:68-76
doi: 10.1161/01.CIR.76.1.68
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/76/1/68

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/