Evaluation of the Severity of Mitral Stenosis and Regurgitation

By Albert J. Libanoff, M.D., and Simon Rodbard, M.D., Ph.D.

The decision for surgical intervention in the treatment of stenosis and regurgitation of the mitral valve demands an objective, quantitative evaluation of the relative severity of the two processes.

In 1951 Gorlin and Gorlin\(^1\) adapted the Torricelli orifice formula\(^2\) to estimate the area of the orifice of the mitral valve:

\[
\text{Valve orifice area in cm.}^2 = \frac{\text{flow (mL/sec.)}}{31 \sqrt{P_{\text{mean atrial}} - P_{LV \text{diastolic}}}}
\]

in which P is pressure and LV is left ventricle.\(^*\)

Since technics for the measurement of the left ventricular diastolic pressure were not available in 1951, this pressure was arbitrarily considered to be 5 mm. Hg. It is now known that the mean left ventricular pressure in mitral stenosis may range from 3 to 12 mm. Hg.

Even after direct measurements of left atrial and left ventricular pressures became available, other uncontrolled factors reduced the value of the formula. Thus, the lack of definition of the instant in diastole when the atrioventricular pressure gradient was to be measured introduced a complication into the meaning of the calculation. For example, some workers used the early diastolic pressures,\(^3\) others utilized the mean diastolic pressures,\(^4\) and still others considered the end-diastolic pressure difference to be the important value.\(^5\) Depending on this decision, the orifice cross section area in a given patient may be reported to have a remarkably wide range.

It is not always appreciated that the Torricelli formula is used properly only for a constant pressure difference and a resulting steady rate of flow. Pressures in the cardiac chambers and flow across the communicating orifice, however, always exhibit marked changes from moment to moment. Errors in the calculation of the orifice area increase with the severity of the regurgitation that commonly accompanies valvular stenosis. The failure to consider the metabolic requirements for cardiac output in terms of body surface area further diminished the utility of the formula. The foregoing, and other complications soon demonstrated the limitations of the orifice formula as a means for the evaluation of the severity of the disease at the valve.\(^6\)

In 1957, Morrow et al.\(^7\) attempted to define the degree of mitral stenosis and insufficiency in terms of the numerical value of the index:

\[\frac{\text{Rate of atrial y descent, mm. Hg/0.1 sec.}}{\text{mean left atrial pressure, mm. Hg}} \times 10\]

A value of 1 to 3 was considered to indicate significant stenosis, and values of 5 or more indicated that regurgitation was predominant. A value of 4 indicated that the valve was normal or that the severity of the stenosis was balanced by the severity of the regurgitation. The usefulness of this index was soon found to be limited, in part because it was not affected directly by the pressure differences.
SEVERITY OF MITRAL STENOSIS

gradient across the valve, or by the cardiac output.

Even though these indices are calculated with ease, the appreciation of their inadequacies led to their general abandonment, and the ultimate decision for the mode of treatment reverted to clinical evaluation.

In the present study, disease of the mitral valve has been reexamined on the basis of hydrodynamic considerations. New indices of mitral stenosis and insufficiency are proposed that provide a more satisfactory quantification of these two discrete processes.

Clinical Methods

Following intramuscular administration of 50 mg. of meperidine (Demerol) and 25 mg. of promethazine (Phenergan), cardiac catheterization was performed in 40 patients. A no. 8 catheter of 71.5 cm. length, introduced by percutaneous puncture into the right femoral vein or by cutdown into the right saphenous vein, was advanced into the right atrium and ventricle. Puncture of the atrial septum with a 73-cm. 17-gauge Ross needle8, 9 permitted advancement of the catheter into the left atrium and ventricle. Retrograde cardiac catheterization provided simultaneous recordings of left atrial and ventricular pressures in 10 patients. Systemic arterial pressure was obtained by means of a 19T-gauge needle introduced percutaneously into the radial or brachial artery.

To prevent clotting, sterile saline containing heparin was flushed intermittently into the needles and catheters. The arterial needle and the intracardiac guide catheter were connected to strain-gauge manometers. Pressures were recorded on a multichannel photographic recorder.10 The pressure-recording system gave a flat response up to 10 cycles/second in the 0 to 200 mm. Hg range.11 Cardiac output was measured by the Fick method,12 and by dye dilution13, 14 by means of the forward triangle method.15 Surface area was estimated from measurements of weight and height.16

Materials

Anatomic Classification

Table 1 separates the patients into five categories. Surgical or autopsy data were utilized

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Diagnosis</th>
<th>Stenosis and regurgitation areas</th>
<th>Cardiac index (L./min./M.²)</th>
<th>Half-time of AV pressure fall (sec.)</th>
<th>Stenosis index</th>
<th>Regurgitation index</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal</td>
<td>4 to 6 cm.²</td>
<td>2.7</td>
<td>0.010</td>
<td>0.4</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No regurgitation</td>
<td>(assumed)</td>
<td>to</td>
<td>to</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Predominant mitral stenosis</td>
<td>0.2 to 0.8 cm.²</td>
<td>1.8</td>
<td>0.140</td>
<td>5.7</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less than a grade-1</td>
<td>to</td>
<td>to</td>
<td>to</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>regurgitant jet</td>
<td>2.7</td>
<td>0.240</td>
<td>10.0</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.3</td>
</tr>
<tr>
<td>5</td>
<td>Mitral stenosis with mild regurgitation</td>
<td>0.5 to 1.0 cm.²</td>
<td>2.0</td>
<td>0.110</td>
<td>3.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade-1 to -2</td>
<td>to</td>
<td>to</td>
<td>to</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>regurgitant jet</td>
<td>3.0</td>
<td>0.240</td>
<td>9.0</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.5</td>
</tr>
<tr>
<td>10</td>
<td>Predominant mitral regurgitation</td>
<td>Greater than normal with a grade-3</td>
<td>1.8</td>
<td>0.014</td>
<td>0.6</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or more regurgitant jet</td>
<td>to</td>
<td>to</td>
<td>to</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.0</td>
<td>0.040</td>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.0</td>
</tr>
<tr>
<td>10</td>
<td>Combined stenosis and regurgitation</td>
<td>1.0 to 1.8 cm.²</td>
<td>2.0</td>
<td>0.060</td>
<td>5.5</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade-3</td>
<td>to</td>
<td>to</td>
<td>to</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or more regurgitant jet</td>
<td>2.7</td>
<td>0.200</td>
<td>9.6</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17.5</td>
</tr>
</tbody>
</table>

Circulation, Volume XXXIII, February 1966
to classify 35 of the patients as having predominant stenosis with or without mild insufficiency, predominant regurgitation, or combined stenosis and regurgitation.

The remaining five subjects were considered on the basis of clinical and catheterization data as having physiologically normal mitral valves. Three of these patients had "functional" cardiac murmurs. Two were catheterized 6 months after repair of ventricular septal defect. In these subjects the mitral orifice area was assumed to be normal (4.0 to 6.0 cm²).

**Physiologic Classification**

Data obtained during catheterization were used to calculate indices of stenosis and regurgitation.

**Stenosis Index**

At the onset of ventricular diastole (fig. 1) the ventricular pressure fell sharply, the mitral valve opened, and ventricular filling began as the left atrial pressure inscribed the end of the v ascent. Zero time was considered to be the onset of the rise of the left ventricular diastolic pressure. The gradient across the mitral valve was measured at intervals of 0.02 second. The logarithm of the atrioventricular pressure difference was plotted against time. The time required for the atrioventricular pressure difference to fall to half its initial value was recorded as the half-time. The mitral stenosis index was calculated by multiplying the half-time of the pressure difference across the mitral valve by 100, and dividing by the cardiac index.

**Regurgitation Index**

As the mitral valves closed and bulged into the atrial chamber at the onset of ventricular systole, the atrial c wave was generated. After a momentary oscillation, the continuing pulmonary venous return raised the atrial pressure (v ascent).

Ventricular systole was completed as the mitral valve opened, at the peak of the atrial v ascent. The atrial pressure rise during ventricular systole at 0.02-second intervals after the inscription of the c wave was plotted against time.

The mitral regurgitation index was calculated

---

**Figure 1**

*Simultaneous left atrial and ventricular diastolic pressures in a patient with predominant mitral stenosis. The electrocardiogram is given above. The vertical axis is in mm. Hg. The horizontal axis is time. The distance between the long vertical lines is 1 second; the original recording speed was 100 mm./second. The diastolic pressure difference starting at the onset of ventricular filling, is measured at 0.02-second intervals as shown by the short vertical lines. The long vertical arrows give the half-times of the two diastolic periods shown. The shaded areas show the pressure gradient changing with time. Symbols: P.L.V.E.D., left ventricular end-diastolic pressure; $\Delta P_d$, atrioventricular diastolic pressures gradient (shaded).*
SEVERITY OF MITRAL STENOSIS

as 10 times the slope of the left atrial ascent during ventricular systole in mm. Hg/0.02 second, divided by the cardiac index.

Results

The data are presented in terms of the indices characteristic of stenosis, regurgitation and combined lesions, and the relationship of the stenosis index to the regurgitation index.

Stenosis Index

Figure 2 is a graph of the changing mitral transvalvular difference during ventricular diastole in five normal patients and in the 10 subjects with predominant mitral stenosis. Estimations at closed mitral commissurotomy in the group showing anatomic evidence of mitral stenosis with less than a grade-1 regurgitant jet, had valve areas of 0.2 to 0.8 cm.². The cardiac indices, which in the normal subjects ranged from 2.7 to 4.0 L./min./M.², were reduced below normal in the group with predominant stenosis from 1.8 to 2.7 L./min./M.² (table 1).

At the onset of the diastolic rise of ventricular pressure, the mitral transvalvular pressure gradient varied from 2 to 17 mm. Hg in the normal, and from 15 to 36 mm. Hg in stenosis. In normal patients the transvalvular pressure gradient fell rapidly as the blood literally dropped out of the atrium into the ventricle, with half-times of 0.025 second or less. Subjects with mitral stenosis showed half-times of 0.14 to 0.24 second, 6 to 10 times as long as in the normal patients (fig. 2).

Simultaneous left atrial and ventricular pressures in a patient with predominant mitral stenosis are illustrated in figure 1. The orifice was estimated by the surgeon, after digital examination, to be 0.4 cm.², with no evidence of regurgitation. The half-time of the diastolic transvalvular pressure gradient was 0.16 second. The mitral stenosis index was 8.

The effectiveness of the half-time technic in mitral valve stenosis was clearly evident in atrial fibrillation (fig. 1). When the end-diastolic gradient was used to determine the orifice area, the result varied from beat to beat. Thus, a significant end-diastolic gradient was observed when the diastolic interval was short (first beat, fig. 1). With prolonged diastolic periods, the end-diastolic gradient was eliminated even in the presence of severe stenosis (second beat, fig. 1). The half-times remained unchanged regardless of the cycle length.

At closed mitral commissurotomy five subjects were reported by the surgeon as having valve orifice area ranging between 0.5 and 1.0 cm.² with regurgitant jets graded as 1 or 2. The cardiac index was usually reduced, ranging from 2.0 to 3.0 L./min./M.² The half-times were prolonged. The mitral stenosis index was elevated essentially as in patients with predominant mitral stenosis (table 1).

Regurgitation Index

A "greater than normal valve area" associated with predominant mitral valve regurgitation was found at surgery in six patients, and at autopsy in four others. The cardiac index in eight of these patients was subnormal, ranging from 1.8 to 2.5 L./min./M.². Two patients had indices of 3.0 L./min./M.², in the

**Figure 2**

Half-time. The diastolic mitral transvalvular pressure gradient in five normal subjects (solid lines) and in 10 patients with mitral stenosis (broken lines). The vertical axis gives the atriocentrical pressure difference in mm. Hg on a logarithmic scale. The horizontal axis is time beginning with the ventricular diastolic pressure rise. The half-times are given by the black dots.
Atrial v ascent. The atrial systolic pressure rise (v ascent) in five normal subjects (solid line) and in 10 patients with mitral regurgitation (broken line). The vertical axis is the atrial v ascent (pressure rise) in mm Hg. The horizontal axis is the ventricular systolic time. The delay from the onset of the v ascent is due primarily to the occurrence of the c wave.

low normal range. The half-time of the atrioventricular pressure difference ranged from 0.014 to 0.040 second, essentially as in normal subjects. The mitral stenosis index varied from 0.6 to 2.0, being higher than in the controls but less than in the patients with predominant stenosis (table 1).

The time patterns of the rise in atrial pressure during ventricular systole in 10 patients with predominant mitral regurgitation are compared with the rises in five normal subjects (fig. 3). Mitral regurgitation was associated with steep rises of atrial pressure of 2 or more mm Hg/0.02 second. Starting from higher than normal values in regurgitation, the atrial pressure rise began early, ranging from 0 to 0.12 second, while in the normal

this interval varied from 0.12 to 0.25 second.

The simultaneously recorded left atrial and left ventricular pressures in a patient with predominant mitral regurgitation are illustrated in figure 4. The absence of the c wave, resulting from failure of complete closure of the diseased valve and the resulting early regurgitant flow, was associated with an early onset of the atrial ascent during ventricular systole. The slope of the left atrial ascent was 3 mm Hg/0.02 second. By contrast, after the registration of the c wave during ventricular systole, the slope of the left atrial ascent in mitral stenosis was 1 mm Hg/0.02 second (fig. 1). The high atrial pressure fell rapidly as the mitral valve opened, with a half-time of 0.04 second (fig. 4). This value was slightly longer than in normal subjects, but significantly less than in patients with mitral stenosis.

The mitral regurgitation indices in the five normal subjects varied from 2.5 to 3.7. In stenosis the regurgitation indices ranged from 3.3 to 7.5 even when mild regurgitation was present, while subjects with predominant regurgitation had values of 8.0 to 15.0.

The Indices in Combined Valvular Disease

At the time of surgical correction, the mitral orifice area in 10 patients with mixed mitral valve disease was estimated by the surgeon to be 1.0 to 1.8 cm², with regurgitant jets of grade 3 or more. The cardiac indices ranged from 2.0 to 2.7 L/min./M², all lower than normal values. The half-time of the pressure fall was 0.06 to 0.20 second. The mitral stenosis indices ranged from 5.5 to 9.6 Thus, the half-time was prolonged, and the stenosis index was elevated in a manner similar to that of patients with predominant mitral stenosis. The rate of the left atrial ascent during ventricular systole was 2.0 to 3.0 mm Hg/0.02 second. The mitral regurgitation indices varied from 8.3 to 17.5, values of the order of those observed in predominant mitral regurgitation (table 1).

Relationships of the Regurgitation and Stenosis Indices

A graph of the stenosis index against the regurgitation index clearly separated the se-
Simultaneous left atrial and ventricular pressures in a patient with predominant mitral regurgitation resulting from dehiscence of the sutures of a prosthetic mitral valve. The vertical axis is in mm. Hg. The horizontal axis is time; the distance between two long vertical lines is 1 sec. The atrial ascent begins almost immediately with ventricular systole. The rise in pressure per 0.02 sec. is marked by the short horizontal lines.

Discussion

The interrelationships among the factors affecting the left atrial pressure and the clinical evaluation of patients with mitral valve disease are discussed in terms of the normal valve, the severity of stenosis, the severity of regurgitation, the significance of stenosis in

ries of patients studied into four definite categories (fig. 5). The stenosis and regurgitation indices were elevated in accord with the relative severity of each process at the mitral valve, as indicated on an anatomic basis.

In mixed valvular disease the relative predominance of the two processes in a given patient was indicated by a ratio of the regurgitation index to the stenosis index. This ratio was approximately 1 in patients in whom the stenosis was dominant, and approximately 5 in subjects in whom regurgitation was predominant. Intermediate values indicated the relative degrees of stenosis and regurgitation.

The key to the state of compensation in patients with mitral valve disease is the pressure at the venous end of the pulmonary capillaries. The normal mitral valve area\(^2\) of 5 ± 1 cm. is sufficient to permit the flow of many times the normal resting cardiac output without a significant rise in pulmonary venous pressure. Any combination of mitral stenosis and regurgitation elevates the left atrial pressure. In both cases the elevation of pulmonary venous pressure increases the production of pleural fluid and the degree of engorgement of the alveolar capillaries with ultimate transudation into the airway and the development of signs of pulmonary edema.\(^1\)\(^8\) The patterns of rise in pressure differ with each process.

The clinical significance of the valvular disease is reflected by the limits placed by the progressive elevation of the left atrial pressure
A plot of the mitral stenosis index against the mitral regurgitation index, utilizing anatomic data. Comparison of anatomic disease at the mitral valve with indices based on hemodynamic findings. The patients are characterized on the basis of surgical or autopsy evidence as normal (solid squares), pure mitral stenosis (open circles), predominant stenosis with mild regurgitation (+), mixed valvular disease (solid circles), and pure regurgitation (X).

**Figure 5**

and by the volume of forward flow. The height of the left atrial pressure is determined by the ratio of the rate of pulmonary venous return to the mitral orifice area. Thus, the pulmonary venous pressure can be reduced either by reducing the rate of the pulmonary venous return (cardiac output) or by providing a more adequate orifice.

The obligatory resting cardiac output is generally held to be related to the number of square meters of surface area, as calculated from tables for heights and weights of healthy persons. Both the flow through the mitral orifice and the orifice area must be evaluated in terms of the metabolic requirements of the individual under study. Obviously a normal orifice area sufficient to permit the flow of the cardiac output for a small person of 45 Kg. may be inadequate for a person of 90 Kg. or more. The evaluation of the severity of the valvular disease must therefore take the size of the patient into account. By dividing the cardiac output by the surface area, the resulting cardiac index provides a more meaningful basis for the evaluation of the valvular disease in a given patient.

**The Severity of the Stenosis**

The impedance to the flow of blood offered by a predominantly stenotic mitral valve elevates the atrial pressure to values that are then sufficient to drive the venous return through the narrowed orifice. A reduction in orifice area to 1.5 cm² may be tolerated without serious elevation of the atrial pressure, provided the venous return is not increased. When the orifice area is less than 1.0 cm² the obstruction to flow elevates the left atrial pressure to high values even at resting cardiac outputs.¹ ¹⁰ ²⁰

With the onset of ventricular diastole, the low pressure in the ventricle results in opening of the mitral valve and the atrial pressure begins to fall (atrial y descent), while ventricular pressure rises. When the mitral orifice is large, the flow is rapid and the atroventricular pressure difference quickly disappears. In the normal subjects and in those with predominant mitral regurgitation the atrial and ventricular pressures equalized within about 0.10 second, and the half-times were very short. When the mitral orifice was stenotic, the equality of pressure was achieved more slowly, the half-time was prolonged, and this was usually associated with a reduced cardiac index.²²

The mitral stenosis index, i.e., the halftime divided by the cardiac index, provides a quantitative basis for the evaluation of the hemodynamic significance of the mitral obstruction in each patient and appears to be a clinically meaningful index of the severity of the anatomic stenosis (table 1).

**The Severity of the Regurgitation**

In subjects with normal valves or with predominant mitral stenosis, a significant rise in left atrial pressure was delayed by approxi-
mately 0.12 second after the onset of ventricular contraction during the inscription of the c wave. The slope of the pressure rise in the normal subjects and in the patients with mitral stenosis was 1 mm. Hg/0.02 second. The c wave was absent in mitral regurgitation and the atrial upstroke began within 0.12 second of the opening of the mitral valve. The rise in atrial pressure progressed at a rate of 2 mm. Hg or more/0.02 second. Since the time of onset of the atrial pressure rise was not always easily defined (figs. 1 and 4), we have utilized the slope of the atrial pressure rise during ventricular systole as a measure of the degree of regurgitation. This slope increased with the degree of regurgitation, and the retrograde loss of blood from the ventricle reduced the cardiac index.20 In each patient the height of the values of the mitral regurgitation index was associated with the clinical and hemodynamic severity of the valvular regurgitation.

The indices thus appeared to have value in differentiating predominant stenosis from predominant insufficiency even though some component of the other process was usually present.

The Severity of Combined Valvular Disease

A special problem in the evaluation of disease of the mitral valve was that the degree of the regurgitation during systole affected the stenotic process of diastole.24 This relationship resulted in normal values in the Morrow index when the severity of the stenosis and regurgitation were approximately equal.7 Both indices proposed in the present study were elevated in patients with mixed mitral disease. The relative elevation of the two indices appeared to indicate the lesion of relative predominance.

Chronic Compensation

Many patients with mitral disease survive for many years and appear to improve clinically even though the disease process becomes inexorably progressive. This “compensation” results from the severe disability that markedly limits activity and progressively increases the time at bed rest. As the disease leads to atrophy of the skeletal muscles and diminished activity, the metabolic burden on the circulation falls to two thirds or even half that required by the same healthier well-developed, well-nourished resting subject. The reduced volume of flow necessary to maintain the bodily economy can then pass through the diseased orifice, especially under the urging of an elevated left atrial pressure. Superficially the cardiac status of the withered patient appears to have improved over the earlier, more robust state. This “compensation,” however, is actually a measure of progressive invalidism. Unless the cardiac index of the well-developed, well-nourished individual is considered, the clinical evaluation of the severity of the disease may be deceptive in terms of the mitral valve orifice area.

Summary

Indices have been developed that provide an improved means for evaluation of the degrees of severity of mitral stenosis and regurgitation. The severity of anatomic mitral valve disease found at surgery or autopsy was considered to be the determinant of the state of the valve. An index of the time for the diastolic atrioventricular pressure gradient to fall to half its value multiplied by 100 and divided by the cardiac index was shown to be comparable to the severity of anatomic stenosis. This index ranged from 5.7 to 10 in mitral stenosis, 0.4 to 0.8 in normal subjects, and 0.6 to 2.0 in patients with predominant mitral regurgitation.

Mitral regurgitation was estimated by an index of the rate of the atrial pressure rise during ventricular systole in mm. Hg/0.02 second multiplied by 10, and divided by the cardiac index. In predominant mitral regurgitation, this index ranged from 8.0 to 15; in mitral stenosis these values were 3.7 to 6.3, and normal subjects had an index varying from 2.5 to 3.7.

Both indices were significantly elevated in patients in whom stenosis and regurgitation were present at surgery. Mitral stenosis complicated by a mild degree of regurgitation gave significantly elevated stenotic indices,
while the regurgitation indices were normal or slightly elevated. These indices facilitate the evaluation of either mitral stenosis or regurgitation even when both processes are present together.

The significance of these indices in the evaluation of the degree of invalidism in patients with valvular disease is also discussed.

References


Evaluation of the Severity of Mitral Stenosis and Regurgitation
ALBERT J. LIBANOFF and SIMON RODBARD

Circulation. 1966;33:218-226
doi: 10.1161/01.CIR.33.2.218

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/33/2/218

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/