Undersized Mitral Annuloplasty Alters Left Ventricular Shape During Acute Ischemic Mitral Regurgitation

Frederick A. Tibayan, MD; Filiberto Rodriguez, MD; Frank Langer, MD; David Liang, MD, PhD; George T. Daughters, MS; Neil B. Ingels, Jr, PhD; D. Craig Miller, MD

Background—Underlying left ventricular (LV) dysfunction contributes to poor survival after operation to correct ischemic mitral regurgitation (IMR). Many surgeons do not appreciate that a key component of the Bolling undersized mitral ring annuloplasty concept is to decrease LV wall stress by altering LV shape, but precise 3-dimensional (3-D) geometric data do not exist substantiating this effect. We tested the hypothesis that annular reduction decreases regional circumferential LV radius of curvature (ROC) in a model of acute IMR.

Methods—Eight adult sheep underwent insertion of an adjustable Paneth-type annuloplasty suture and radiopaque markers on the LV and mitral annulus. The animals were studied with biplane videofluoroscopy during baseline conditions, then before and after tightening the annuloplasty suture during proximal left circumflex occlusion. End-systolic circumferential regional LV ROC and mitral annular area were computed.

Results—Acute IMR was eliminated (MR grade 2.1 ± 0.4 to 0.4 ± 0.4, mean ± SD, P < 0.05) by tightening the Paneth annuloplasty suture. Paneth suture tightening during circumflex occlusion also decreased end-systolic regional circumferential radii of curvature at the basal (anterior, 3.40 ± 0.16 to 3.34 ± 0.14 cm; posterior, 3.31 ± 0.23 to 3.24 ± 0.26 cm; P < 0.05) and equatorial levels (anterior, 2.99 ± 0.21 to 2.89 ± 0.29 cm; posterior, 2.86 ± 0.38 to 2.81 ± 0.41 cm; P < 0.05).

Conclusions—Acute proximal circumflex occlusion caused IMR and increased end-systolic LV radii of curvature in this experimental preparation. Annular reduction sufficient to abolish IMR also decreased end-systolic anterior and posterior LV ROC, which would be expected to reduce LV wall stress and oxygen consumption in these regions, both potentially beneficial effects. The long-term effects of undersized annuloplasty on LV remodeling and function, however, will require further study in chronic animal preparations or patients with chronic IMR. (Circulation. 2004;110[suppl II]:II-98–II-102.)

Key Words: annuloplasty mitral regurgitation ischemia

For patients with ischemic cardiomyopathy and functional mitral regurgitation (FMR), undersized mitral annuloplasty has been proposed as an "annular solution to a ventricular problem," aimed at improving both leaflet malcoaptation and left ventricular (LV) shape.1 Bolling et al reported mid-term success with this procedure and have suggested that undersizing the annulus acutely remodels the base of the heart, giving the ventricle a more eccentric shape, thereby unloading the cardiomyocytes.2 LV shape, as quantified here by radius of curvature, relates to wall stress by the law of Laplace. Precise data on changes in LV shape after undersized mitral annuloplasty, however, are lacking. We therefore measured end-systolic regional circumferential radii of curvature (ROC) at the basal, equatorial, and apical LV levels in an ovine model of acute ischemia to test the hypothesis that undersized mitral annuloplasty eliminates acute ischemic mitral regurgitation (MR) and reduces regional circumferential LV radii of curvature.

Methods

Surgical Preparation

The operative techniques for marker implantation have been described previously in detail and will be only summarized here.3 Before marker implantation, a double loop of 2-0 polypropylene suture was placed around the left circumflex coronary artery proximal to the first obtuse marginal branch for induction of reversible posterolateral LV myocardial ischemia and acute IMR. A perforated occluder was placed around the inferior vena cava. On cardiopulmonary bypass, radiopaque markers were implanted on the left
ventricle at 3 levels (basal, equatorial, and apical) around 4 meridians (anterior, lateral, posterior, and septal) and around the mitral annulus, as shown in Figure 1. A modified Paneth–Burr suture annuloplasty was performed as follows. A double-armed, pledgeted 2-0 polypropylene suture was anchored at the right fibrous trigone, sutured around the posterior annulus, and externalized through the mid-lateral annulus to an epicardial tourniquet as shown in Figure 2. A similar suture was placed from the left fibrous trigone, sutured around the anterior annulus, and externalized through the mid-lateral annulus on a separate tourniquet. After weaning from cardiopulmonary bypass, a micromanometer pressure transducer (PA4.5-X6; Konigsberg Instruments, Inc) was placed in the LV chamber through the apex. The animal was then transferred to the experimental catheterization laboratory and studied intubated and with open chest, with anesthesia maintained by inhalational isoflurane (1.5% to 2.0%).

Data Acquisition
Data acquisition and reconstruction of 3-dimensional (3-D) marker coordinates were performed as described previously. For each animal, 3 consecutive steady-state beats during control conditions and during circumflex ischemia both before and after tightening of the suture annuloplasty to maximally reduce IMR were designated as baseline, ischemia, and annular suture pull (ASP), respectively. It is important to note that in this model of acute ischemia (as opposed to infarction), circumflex occlusion was continued until the onset of significant (at least mild–moderate) MR before data acquisition. For the ASP runs, the animals experienced additional circumflex occlusion, which might be expected to further insult the myocardium. This experimental design allowed paired (“before and after”) comparison of results in the same animals, reducing the number of animals needed. End-systole was defined at the videofluoroscopic frame associated with the peak rate of decline of LV pressure (−dP/dt), and end-diastole was defined as 2 frames before maximum rate of LV pressure increase (+dP/dt). Instantaneous LV volume was computed from the epicardial LV markers by a space-filling multiple tetrahedral volume method. LV end-systolic volumes and pressures determined during preload reduction via vena caval occlusion were used to calculate end-systolic elastance (Ees), a relatively load-insensitive measure of LV contractility. IMR, assessed by color Doppler transesophageal echocardiography, was graded by an experienced cardiologist (D.L.) according to the extent and width of the regurgitant jet as none (0), trace (0.5+), mild (1+), moderate (2+), moderate-to-severe (3+), or severe (4+).

Data Analysis
Mitral annular area was calculated by determining the centroid of the 8 annular markers, then summing the areas of the 8 triangles formed by 2 contiguous annular markers and the annular centroid. Mitral annular septal–lateral and commissure–commissure diameters were calculated as the distance in 3-D space between the markers at the mid-septal and mid-lateral annulus (22 to 18) and anterior and posterior commissural markers (16 to 20), respectively. LV sphericity was calculated as previously described by dividing the LV longitudinal diameter (the distance in 3-D space between markers 22 and 1; Figure 1) by a short-axis diameter (the distance between markers 13 and 7). Epicardial circumferential radius of curvature of the basal lateral wall was calculated from the 3-D coordinates of the basal lateral wall marker and the 2 adjacent wall markers at end-systole (4, 13, and 10; Figure 1). These 3 points define a circle in space, and the radius of this circle (by definition the radius of curvature) at end-systole was determined. End-systolic regional radii of curvature for the basal, equatorial, and apical anterior, lateral, posterior, and septal walls were also calculated in this fashion.

All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health (DHEW NIH Publication 85-23, revised 1985). This study was approved by the Stanford Medical Center Laboratory Research Animal Review committee and conducted according to Stanford University policy.

Statistical Analysis
All data are reported as mean±1 SD, unless otherwise stated. Hemodynamic and mitral valve geometrical data were compared at baseline, after induction of ischemia, and after tightening of the...
suture annuloplasty (baseline, ischemia, and ASP) using repeated measures ANOVA with Dunnett test for multiple comparisons.

Results
Table 1 summarizes group mean (n = 8) hemodynamic and mitral annular geometric data at baseline, ischemia, and during ischemia with cinching of the suture annuloplasty (ASP). During ischemia, ESV, annular area, annular septal–lateral and commissure–commissure diameters, LV sphericity, and MR increased significantly, whereas, as expected, dP/dt and Ees decreased. Tightening the annuloplasty suture during ischemia (ASP) decreased annular area, annular septal–lateral, and commissure–commissure diameters, returned MR to baseline levels, and slightly increased Ees, but did not affect LV dP/dt, ESV, or stroke volume. LV sphericity increased with ischemia and decreased after tightening of the suture annuloplasty.

Table 2 summarizes end-systolic regional circumferential radii of curvature during baseline, ischemia, and ASP conditions. Acute circumflex occlusion increased circumferential radii of curvature in all regions at the basal and equatorial levels (∼3% to 10% greater than control; Table 2). Circumferential regional ROC with ASP were still generally 3% to 8% more than control levels, but when compared with the ischemic condition, undersizing the mitral annulus resulted in a less spherical ventricle, smaller end-systolic anterior and posterior regional radii of curvature at both the basal and equatorial levels, and smaller end-systolic anterior regional radius of curvature at the apical LV level (Figure 3). Septal and lateral end-systolic radii of curvature did not significantly change when cinching the ASP suture.

Discussion
The results of this experiment support the contention that undersized mitral annuloplasty eliminates acute ischemic MR and reduces regional circumferential end-systolic LV radii of curvature, specifically in the anterior and posterior regions at both the basal and equatorial levels and the anterior region at the apical level.

Importance of LV Shape in Coronary Heart Failure
The shape of the LV wall plays an important role in the pathophysiology of ischemic cardiomyopathy and FMR. In the setting of ischemia, infarction, or volume overload secondary to mitral regurgitation, the ventricle dilates in a compensatory effort to maintain forward stroke volume, but this also increases LV radius of curvature, which is an important determinant of LV wall stress. Elevated wall

---

**TABLE 1. Hemodynamics and Left Ventricular Volumes and Function**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Ischemia</th>
<th>ASP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR (0–4+)</td>
<td>0.3 ± 0.3</td>
<td>2.1 ± 0.4*</td>
<td>0.6 ± 0.5†</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>106 ± 21</td>
<td>96 ± 31</td>
<td>99 ± 21</td>
</tr>
<tr>
<td>dP/dt, mm Hg/s</td>
<td>2666 ± 351</td>
<td>1813 ± 425*</td>
<td>1648 ± 301</td>
</tr>
<tr>
<td>Ees, mm Hg/mL</td>
<td>3.0 ± 1.1</td>
<td>1.7 ± 1.3*</td>
<td>2.2 ± 1.1†</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>101 ± 33</td>
<td>127 ± 39*</td>
<td>126 ± 44</td>
</tr>
<tr>
<td>SV, mL</td>
<td>31 ± 4</td>
<td>31 ± 3</td>
<td>26 ± 6</td>
</tr>
<tr>
<td>MAA, cm²</td>
<td>5.1 ± 1.2</td>
<td>6.5 ± 1.2*</td>
<td>4.8 ± 1.6†</td>
</tr>
<tr>
<td>MA S-L, cm</td>
<td>2.3 ± 0.3</td>
<td>2.7 ± 0.4*</td>
<td>2.1 ± 0.3†</td>
</tr>
<tr>
<td>MA C-C, cm</td>
<td>3.1 ± 0.4</td>
<td>3.4 ± 0.4*</td>
<td>2.9 ± 0.5†</td>
</tr>
<tr>
<td>LV sphericity</td>
<td>0.62 ± 0.07</td>
<td>0.65 ± 0.07*</td>
<td>0.63 ± 0.07†</td>
</tr>
</tbody>
</table>

*P<0.05 baseline vs. ischemia.
†P<0.05 ischemia vs. ASP, repeated measures ANOVA with Dunnett test.

ASP indicates annular suture pull during ischemia; MR, mitral regurgitation; dP/dt, maximum rate of LV pressure vs. time; Ees, end-systolic elastance; ESV, end-diastolic volume; SV, stroke volume; MAA, end-systolic mitral annular area; MA S-L, end-systolic mitral annular septal–lateral diameter; MA C-C, end-systolic mitral annular commissure–commissure diameter; LV sphericity, end-systolic LV short-axis/long-axis ratio.

**TABLE 2. End-Systolic Left Ventricular Regional Circumferential Radii of Curvature**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ischemia</th>
<th>Δ From Control (%)</th>
<th>ASP</th>
<th>Δ From Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal anterior ROC, cm</td>
<td>3.22 ± 0.31</td>
<td>3.40 ± 0.16*</td>
<td>+6</td>
<td>3.34 ± 0.14†</td>
<td>+4</td>
</tr>
<tr>
<td>Basal lateral ROC, cm</td>
<td>3.48 ± 0.30</td>
<td>3.59 ± 0.37*</td>
<td>+3</td>
<td>3.65 ± 0.26</td>
<td>+4</td>
</tr>
<tr>
<td>Basal posterior ROC, cm</td>
<td>3.14 ± 0.43</td>
<td>3.31 ± 0.23*</td>
<td>+5</td>
<td>3.24 ± 0.26†</td>
<td>+3</td>
</tr>
<tr>
<td>Basal septal ROC, cm</td>
<td>3.39 ± 0.27</td>
<td>3.49 ± 0.27*</td>
<td>+3</td>
<td>3.52 ± 0.23</td>
<td>+4</td>
</tr>
<tr>
<td>Equatorial anterior ROC, cm</td>
<td>2.77 ± 0.21</td>
<td>2.99 ± 0.21*</td>
<td>+8</td>
<td>2.89 ± 0.29†</td>
<td>+4</td>
</tr>
<tr>
<td>Equatorial lateral ROC, cm</td>
<td>3.12 ± 0.45</td>
<td>3.41 ± 0.41*</td>
<td>+9</td>
<td>3.31 ± 0.38</td>
<td>+6</td>
</tr>
<tr>
<td>Equatorial posterior ROC, cm</td>
<td>2.61 ± 0.42</td>
<td>2.86 ± 0.38*</td>
<td>+10</td>
<td>2.81 ± 0.41†</td>
<td>+8</td>
</tr>
<tr>
<td>Equatorial septal ROC, cm</td>
<td>2.99 ± 0.27</td>
<td>3.21 ± 0.21*</td>
<td>+7</td>
<td>3.15 ± 0.16</td>
<td>+5</td>
</tr>
<tr>
<td>Apical anterior ROC, cm</td>
<td>2.60 ± 0.43</td>
<td>2.61 ± 0.38</td>
<td>+0</td>
<td>2.54 ± 0.40†</td>
<td>−2</td>
</tr>
<tr>
<td>Apical lateral ROC, cm</td>
<td>1.95 ± 0.36</td>
<td>2.14 ± 0.34</td>
<td>+10</td>
<td>2.19 ± 0.41</td>
<td>+12</td>
</tr>
<tr>
<td>Apical posterior ROC, cm</td>
<td>2.42 ± 0.33</td>
<td>2.48 ± 0.23</td>
<td>+3</td>
<td>2.48 ± 0.19</td>
<td>+3</td>
</tr>
<tr>
<td>Apical septal ROC, cm</td>
<td>2.46 ± 0.62</td>
<td>2.51 ± 0.49</td>
<td>+2</td>
<td>2.46 ± 0.44</td>
<td>+0</td>
</tr>
</tbody>
</table>

*P<0.05 baseline vs. ischemia.
†P<0.05 ischemia vs. ASP, repeated measures ANOVA with Dunnett test.
ASP indicates annular suture pull during ischemia; ROC, radius of curvature.
stress, in turn, is likely to contribute to ongoing LV systolic dysfunction and pathological remodeling in cardiomyopathy. The increased hemodynamic load resulting from elevated wall stress is one of the initial stimuli in the development of heart failure, leading to changes at genetic, molecular, and neurohormonal levels. The ventricle responds to the increased LV volume associated with myocardial infarction and MR by sarcomeric replication in series and myocyte lengthening. In this study, acute circumflex artery occlusion resulted in depressed LV contractile performance, MR, ventricular dilation, and increased end-systolic regional radii of curvature. Although acute loss of contractility in the ischemic myocardium is the primary cause of decreased systolic performance, greater afterload caused by the increased radii of curvature exacerbates the functional decline.

LV dilation, as occurred during acute ischemia, may over time have additional deleterious effects on the ventricle by reducing systolic torsion, the twisting motion of the LV that modulates transmural gradients of fiber strain and oxygen demand. Animal and computer models suggest that a larger ventricle equalizes the lengths of the endocardial and epicardial lever arms, reducing the net torsional moment and decreasing systolic LV torsion. Human and ovine studies of dilated cardiomyopathy indicate that this equalization of endocardial and epicardial lever arms also increases the amount of cross-fiber shortening in the epicardial layers, which decreases the epicardial angle of principal strain, which pari passu might further decrease systolic torsion and increase the relative workload of the endocardial cardiomyocytes. Thus, changes in LV size and shape, and specifically regional curvature, can be involved in a cycle of progressive ventricular decline.

The Concept of “Reverse” LV Remodeling

The attenuation or reversal of geometric LV remodeling is an important aim in the modern treatment of cardiomyopathy, with or without FMR. Pharmacological methods of reducing wall stress, such as angiotensin-converting enzyme inhibitor therapy, have shown favorable effects in reducing LV remodeling, improving systolic performance, and decreasing mortality in patients with coronary heart failure (CHF). Left ventricular assist devices mechanically unload the myocardium and reverse structural LV remodeling, as well as abnormalities of contractile function, energetics, and gene expression. The observed benefits of reduction of wall stress in patients with CHF have spurred a new emphasis on surgical procedures that alter geometric determinants of LV wall stress, particularly the radius of the LV cavity minor axis. Transventricular tension members, external reshaping bars, and surgical ventricular restoration all aim to enhance LV wall curvature (ie, a smaller ROC) and thereby unload the failing myocardium. Bolling et al proposed undersized MR annuloplasty as a surgical alternative in patients with cardiomyopathy complicated by FMR, suggesting that the small ring would decrease LV wall stress by remodeling the base of the heart and restoring a more elliptical shape to the LV cavity. In the present study, undersized annuloplasty not only slightly decreased global LV sphericity but also decreased the end-systolic regional LV radii of curvature, an important determinant of wall stress. Additionally, this effect was not just limited to the base of the ventricle, as originally postulated. Regional radii of curvature were also smaller at the equatorial and even the apical levels, well away from the annuloplasty. Although such a decrease in ROC could result from a reduction in LV volume, end-systolic LV volume did not change between the ischemia and ASP conditions, indicating that the annuloplasty caused a true change in LV shape, and not just a change in global LV size. Previous clinical studies of LV remodeling surgery invoking the law of Laplace (which, strictly speaking, only applies to thin-walled cylinders and spheres, and in this setting is used only identify the determinants of wall stress [pressure, wall-thickness, and radius of curvature]) have measured LV volume, not curvature per se. Procedures that reduce LV volume may lower wall stress through a reduction in curvature, but reduced curvature may result in lower wall stress without a change in volume. The continued LV dilation observed after tightening the suture annuloplasty is not unexpected given the persistent acute ischemia, and a study of annular reduction in chronic ischemic MR (presently underway) would be necessary to determine the effects on curvature, volume, and LV function in a more relevant setting.

Consistent with the notion that decreased ROC reduces regional LV wall stress, tightening the suture annuloplasty was associated with a modest increase in $E_{\infty}$. Such an improvement in contractile performance has been observed after other surgical LV reshaping procedures. In addition, combined mitral and tricuspid annuloplasty was recently shown to decrease global LV sphericity and improve LV function. Even after tightening the suture annuloplasty, LV systolic dysfunction persisted, but this was not unexpected given the persistent LV ischemic conditions in this experimental preparation. Furthermore, the potential benefits of decreased wall stress extend beyond an improvement in ejection indices of LV pump function. Lower wall stress secondary to LV reshaping is likely to lower oxygen consumption, improve LV systolic torsion, and, perhaps most importantly, provide less of a stimulus for ongoing pathologic remodeling.

Tightening of the suture annuloplasty caused only a slight reduction in anterior and posterior regional end-systolic LV radii of curvature and was unable to return any regional ROC to control levels. Bolling et al opined that undersized ring annuloplasty achieves sufficient acute geometrical remodeling to begin a slower process of “auto-remodeling” over time. Power et al hypothesized that even a small reduction in LV workload might allow reverse remodeling to occur and showed that even passive ventricular restraint was sufficient to attenuate LV dilation and progressive functional decline in an experimental heart failure model. Significant changes in ROC were seen in anterior and posterior (not septal and lateral) regions, probably because the ASP suture resulted in greater reduction of mitral annular septal–lateral diameter (corresponding to LV remodeling in the septal–lateral direction) as opposed to mitral annular commissure–commissure diameter (corresponding to remodeling in the anterior–posterior direction).
Conclusions
In this ovine model of acute ischemic MR, undersized mitral suture annuloplasty caused LV shape changes, reducing global sphericity as well as anterior and posterior end-systolic circumferential radii of curvature not only at the base of the heart but also at the equatorial and apical ventricular levels. Although it is difficult to quantify the physiological significance of such remodeling in this acute model, these alterations in end-systolic regional LV curvature should theoretically tend to reduce LV wall stress, decrease oxygen consumption, improve systolic performance, and reduce the stimulus for further pathological remodeling. These data support Bolling’s concept that undersized ring annuloplasty is effective in patients with CHF and FMR as “an annular solution to a ventricular problem.” The long-term effects of this approach on LV shape and remodeling, however, require further study; most importantly, postoperative long-term serial echocardiographic or magnetic resonance imaging studies in patients who have undergone a “Bolling procedure” are essential to validate the initial postulates of Bolling and confirm the findings of this experiment.

Limitations
This study used an anesthetized, open-chest sheep model of acute circumflex occlusion; therefore, these results cannot be directly extrapolated to the clinical arena. Proximal circumflex coronary occlusion reliably produces acute IMR, LV dilation, and systolic dysfunction, allowing testing of the hypothesis that annular reduction changes the shape of a dilated heart with impaired systolic function. Tightening of the suture annuloplasty did not return hemodynamics or regional circumferential ROC to baseline levels. Part of this may be because during the ASP runs, the animals were experiencing ongoing myocardial ischemia. Follow-up studies are needed to determine the effect of such annular procedures in models of chronic IMR. Another major consideration is the difference between the small annuloplasty ring operation advocated by Bolling and the suture-type annuloplasty used in this experiment. A suture annuloplasty ring operation advocated by Bolling and the suture-type annuloplasty used in this experiment. A suture annuloplasty caused LV shape changes, reducing global sphericity as well as anterior and posterior end-systolic circumferential radii of curvature not only at the base of the heart but also at the equatorial and apical ventricular levels. Although it is difficult to quantify the physiological significance of such remodeling in this acute model, these alterations in end-systolic regional LV curvature should theoretically tend to reduce LV wall stress, decrease oxygen consumption, improve systolic performance, and reduce the stimulus for further pathological remodeling. These data support Bolling’s concept that undersized ring annuloplasty is effective in patients with CHF and FMR as “an annular solution to a ventricular problem.” The long-term effects of this approach on LV shape and remodeling, however, require further study; most importantly, postoperative long-term serial echocardiographic or magnetic resonance imaging studies in patients who have undergone a “Bolling procedure” are essential to validate the initial postulates of Bolling and confirm the findings of this experiment.

Acknowledgments
The authors gratefully acknowledge the superb technical assistance provided by Carol W. Mead, Maggie Brophy, Katha Gazda, and Mark Grisdaile.

References
Undersized Mitral Annuloplasty Alters Left Ventricular Shape During Acute Ischemic Mitral Regurgitation
Frederick A. Tibayan, Filiberto Rodriguez, Frank Langer, David Liang, George T. Daughters, Neil B. Ingels, Jr and D. Craig Miller

doi: 10.1161/01.CIR.0000138395.45145.45
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 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/110/11_suppl_1/II-98

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/