Effect of amrinone on right ventricular function: predominance of afterload reduction

Marvin A. Konstam, M.D., Steven R. Cohen, M.D., Deeb N. Salem, M.D., Dhirendra Das, M.D., Mark J. Aronovitz, and Barbara A. Brockway

ABSTRACT Although the bipyridine agent amrinone is reported to have a positive inotropic effect on the left ventricle, the effect of this drug on right ventricular contractility in the clinical setting is unknown. We studied the effect of short-term intravenous administration of amrinone on right ventricular systolic function in nine patients with severe congestive heart failure and, using radionuclide ventriculography, examined the right ventricular end-systolic pressure-volume relationship to determine whether reduced right ventricular afterload or increased contractility predominantly accounted for the observed improvement in right ventricular systolic function. In each patient the right ventricular end-systolic pressure-volume relationship was derived with use of varying doses of nitroprusside. After nitroprusside was stopped, intravenous amrinone (3 mg/kg) caused decreases from baseline in pulmonary arterial end-systolic pressure in eight of nine patients (23 ± 11% [overall mean ± SE], p < .05), and in pulmonary vascular resistance in all patients (38 ± 6%, p < .001). Right ventricular end-systolic volume decreased (23 ± 8%, p < .01) and right ventricular ejection fraction increased (31 ± 10%, p = .01). The amrinone-induced decrease in right ventricular end-systolic volume was compared with that predicted for right ventricular afterload reduction alone based on the effect of amrinone on pulmonary arterial end-systolic pressure and the pressure-volume relationship observed during infusion of nitroprusside. With amrinone, a trend was observed toward a shift in the right ventricular end-systolic pressure-volume relationship in seven of nine patients; however, for the group as a whole, the observed effect of amrinone was not significantly different from that predicted from the degree of right ventricular afterload reduction. In conclusion, in patients with severe congestive heart failure, amrinone decreases right ventricular afterload, reduces right ventricular end-systolic volume, and increases right ventricular ejection fraction. The effect of amrinone on right ventricular systolic function results predominantly from right ventricular afterload reduction.


The BIPYRIDINE COMPOUND amrinone has been shown to have both inotropic and vasodilator actions in isolated tissue preparations1-3 and to improve hemodynamics in patients with congestive heart failure.4-13 Examination of both isovolumetric phase contractile indexes4 and ventricular end-systolic pressure-volume relationships13 have indicated that at least some of the hemodynamic responses observed in man during the infusion of amrinone may be attributed to augmented left ventricular inotropic state.

From the Departments of Medicine and Radiology, Tufts University and New England Medical Center, Boston.
Supported in part by grants from the American Heart Association, Dallas, and the American Lung Association, New York.
Address for correspondence: Marvin A. Konstam, M.D., Division of Cardiology, Tufts–New England Medical Center, Box 108, 171 Harrison Ave., Boston, MA 02111.
Received Nov. 26, 1985; revision accepted May 15, 1986.

Vol. 74, No. 2, August 1986

The effect of amrinone on the right ventricle has not been extensively studied and its effect on right ventricular contractility has not been demonstrated. In patients with congestive heart failure, amrinone reduces pulmonary arterial pressure,4,5 presumably due to combined effects on left ventricular contractility and systemic and pulmonary vascular tone. The resulting diminution in right ventricular afterload would be expected to improve right ventricular systolic performance. The extent to which augmented contractility of the thin-walled right ventricle contributes to improved right ventricular ejection during the infusion of amrinone is unknown.

Using radionuclide ventriculography in patients with congestive heart failure, we have previously demonstrated a linear relationship between pulmonary arterial end-systolic pressure and right ventricular end-systolic volume during administration of vasodilators
that is analogous to the left ventricular end-systolic pressure-volume relationship. In the present study, we compared the effects of intravenous amrinone and nitroprusside, examining right ventricular end-systolic pressure-volume relationships to test the hypothesis that the amrinone-induced decrease in right ventricular end-systolic volume exceeds that predicted for right ventricular afterload reduction, indicating a significant inotropic effect.

Methods

The study population consisted of nine patients, six men and three women, ranging in age from 26 to 72 (mean 59) years. All were in New York Heart Association functional class III or IV. Four patients had congestive cardiomyopathy, and five patients had coronary artery disease with healed myocardial infarcts. All gave written informed consent.

Study protocol. All patients underwent simultaneous hemodynamic-radionuclide studies while they were in the postabsorptive state. Diuretics and vasodilators were discontinued at least 12 hr before the study, and no patients received premedication with sedatives. Right heart catheterization was performed via the antecubital or femoral vein with a balloon-tipped thermodilution catheter, and systemic arterial pressure was monitored with a brachial or radial arterial cannula. Simultaneously with hemodynamic measurements, sequential equilibrium-gated radionuclide ventriculograms were obtained as previously described. Red blood cells were labeled in vivo by intravenous injection of stannous pyrophosphate followed in 20 min by 15 to 20 mCi of 99mTc pertechnetate. A portable gamma camera was positioned in the modified left anterior oblique view with use of a 25 degree, caudally tilted, slant-hole collimator, and the degree of obliquity was chosen to maximize interventricular and right atrioventricular separation. Scans were acquired for 5 min in a 64 × 64 matrix mode on a magnetic disk with use of a nuclear medicine computer with a 15% window centered at the 99mTc peak. Data acquisition was gated to the patient's cardiac cycle, with each cardiac cycle divided into 24 frames.

Pressure measurements and heart rates were recorded during the first 2 min and last 2 min of each radionuclide acquisition and each pair of measurements was averaged. Pulmonary arterial dicrotic notch pressure was taken as an estimate of end-systolic pressure. In canine studies, we have found close agreement (r = .99, SEE = 1.0 mm Hg) between pulmonary arterial dicrotic notch pressure measured with a balloon-tipped fluid-filled catheter and that measured with a micromanometer during a series of interventions performed to vary dicrotic notch pressure from 6 to 48 mm Hg. We have also observed that right ventricular pressure at end-systole, defined as the crossover point between simultaneous micromanometer right ventricular and pulmonary arterial pressures, tends to slightly exceed, but closely parallel, pulmonary arterial dicrotic notch pressure (r = .99, SEE = 1.5 mm Hg).

Thermodilution cardiac output (average of three recordings with less than 10% variation) was also measured simultaneously with each scan acquisition. After baseline hemodynamic and radionuclide recordings, nitroprusside was infused intravenously at an initial rate of 0.3 μg/kg/min, with the dose raised in increments of 0.3 μg/kg/min until either mean arterial pressure had fallen to 80% of baseline or a dose of 5 μg/kg/min was reached. Radionuclide and hemodynamic measurements were made in each patient during the infusion of nitroprusside at one or more infusion rates to achieve several data points for deriving pressure-volume relationships in each patient. Before each scan, the drug infusion rate was held constant, and systemic arterial pressure, pulmonary arterial pressure, and cardiac output were observed to remain constant for at least 5 min. After the infusion of nitroprusside was stopped, systemic arterial pressure, pulmonary arterial pressure, and cardiac output were permitted to return to baseline, at which time repeat baseline hemodynamic and radionuclide recordings were made. Amrinone was then infused intravenously at an initial bolus of 1 mg/kg, followed by 0.5 mg/kg every 10 min to a total of 3 mg/kg. After stabilization of pressures and cardiac output for at least 10 min, final hemodynamic and radionuclide recordings were obtained. During each scan acquisition, variation in pulmonary arterial end-systolic pressure was less than 10%, and variation in heart rate was less than 5%.

Radionuclide analysis. Radionuclide studies were analyzed by previously described methods. The right ventricular end-diastolic region was initially drawn on the end-diastolic frame. A summation of stroke volume and paradox images, which aided in delineating the right atrioventricular plane, was used to redraw the right ventricular region if necessary. In drawing the right ventricular end-diastolic region, the right atrioventricular separation was delineated based on examination of the end-systolic image and of an endless-loop movie format display. Background was subtracted with the use of counts per pixel in a paraventricular background region at the end-systolic frame, and right ventricular ejection fraction was calculated as:

\[
\text{Ejection fraction} = \frac{\text{End-diastolic counts} - \text{end-systolic counts}}{\text{End-diastolic counts}}
\]

To avoid potential errors in absolute right ventricular volume calculation resulting from errors in the estimation of count attenuation, we expressed right ventricular volumes as a percent of baseline or as fractional change from baseline. Right ventricular end-diastolic and end-systolic counts per second were derived by dividing right ventricular counts by total acquisition time per frame. Activity in 5 ml heparinized blood samples, drawn at the midpoint of each scan acquisition, was counted with the same gamma camera and collimator as those used for cardiac imaging, and counts were corrected for decay occurring between the times of cardiac and blood sample scan acquisitions. Changes in end-diastolic and end-systolic volumes compared with baseline were calculated as fractional changes in the ratios of ventricular counts per second to decay-corrected blood counts per second at end-diastole and end-systole, respectively.

We have validated our method for quantifying right ventricular function in patients with right ventricular pressure overload, volume overload, and/or depressed systolic function. Intrareplicate variability of our radionuclide measurements has been tested by analysis of duplicate scans with duplicate blood sample acquisitions in a series of 10 patients. Coefficients of variation for right ventricular end-diastolic volume, end-systolic volume, and ejection fraction were 5.1%, 4.9%, and 3.3% (percent of measured ejection fraction), respectively.

Statistical methods. We compared baseline hemodynamic and radionuclide measurements with those obtained after drug administration using paired t tests. We evaluated the relationship between nitroprusside-induced changes in pressure and volume in each individual using linear regression analysis. The significance of the linear right ventricular systolic pressure-volume relationships for the entire population was tested by stepwise linear regression. Comparison of fractional changes in hemodynamics and ventricular volumes achieved in each patient with nitroprusside vs amrinone was performed by paired t test.
TABLE 1
Mean ± SD effects of nitroprusside and amrinone on hemodynamics and right ventricular function

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Nitroprusside</th>
<th>Repeat baseline</th>
<th>Amrinone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>94 ± 12</td>
<td>93 ± 12</td>
<td>95 ± 10</td>
<td>99 ± 10</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>91 ± 21</td>
<td>71 ± 10</td>
<td>99 ± 18</td>
<td>88 ± 18</td>
</tr>
<tr>
<td>Mean PCW pressure (mm Hg)</td>
<td>28 ± 7</td>
<td>17 ± 8</td>
<td>31 ± 5</td>
<td>19 ± 10</td>
</tr>
<tr>
<td>Mean RA pressure (mm Hg)</td>
<td>12 ± 6</td>
<td>7 ± 3</td>
<td>16 ± 8</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>PAES pressure (mm Hg)</td>
<td>44 ± 7</td>
<td>28 ± 10</td>
<td>46 ± 9</td>
<td>34 ± 14</td>
</tr>
<tr>
<td>PAPS pressure (mm Hg)</td>
<td>66 ± 14</td>
<td>44 ± 15</td>
<td>69 ± 15</td>
<td>53 ± 22</td>
</tr>
<tr>
<td>Cardiac index ([l/min/m²])</td>
<td>2.2 ± 0.8</td>
<td>2.9 ± 0.8</td>
<td>1.9 ± 0.8</td>
<td>2.7 ± 0.8</td>
</tr>
<tr>
<td>PVR (dyne-sec-cm⁻¹)</td>
<td>378 ± 216</td>
<td>207 ± 108</td>
<td>440 ± 265</td>
<td>280 ± 226</td>
</tr>
<tr>
<td>RVEF</td>
<td>0.32 ± 0.15</td>
<td>0.42 ± 0.20</td>
<td>0.31 ± 0.17</td>
<td>0.42 ± 0.25</td>
</tr>
<tr>
<td>RVEDV (% change)</td>
<td>—</td>
<td>-18 ± 17</td>
<td>—</td>
<td>-13 ± 18</td>
</tr>
<tr>
<td>RVESV (% change)</td>
<td>—</td>
<td>-29 ± 23</td>
<td>—</td>
<td>-23 ± 24</td>
</tr>
</tbody>
</table>

PAES = pulmonary arterial end-systolic; PAPS = pulmonary arterial peak systolic; PCW = pulmonary capillary wedge; PVR = pulmonary vascular resistance; RA = right atrial; RVEDV = right ventricular end-diastolic volume; RVEF = right ventricular ejection fraction; RVESV = right ventricular end-systolic volume.

*p < .05 vs baseline; **p < .01 vs baseline.

Results

The effects of nitroprusside and amrinone on hemodynamic and radionuclide measurements are listed in table 1. Neither drug significantly altered resting heart rate. Both nitroprusside (p < .005) and amrinone (p < .005) significantly reduced mean arterial pressure. Both drugs significantly decreased mean pulmonary capillary wedge pressure (p < .01) and mean right atrial pressure (p < .001). Pulmonary arterial end-systolic pressure decreased in all patients during administration of nitroprusside (p < .001) and in eight of nine patients after amrinone (p < .05), with no significant difference between the effects of the two drugs (figure 1). Pulmonary arterial peak systolic pressure was likewise reduced by both nitroprusside (p < .001) and amrinone (p < .05). Both drugs significantly increased cardiac output (p < .001) and decreased pulmonary vascular resistance (p < .001; figure 1). Both nitroprusside and amrinone significantly reduced right ventricular end-diastolic (p < .01 and p < .05, respectively) and end-systolic (p < .01) volumes (figure 2). Baseline right ventricular ejection fraction varied widely from 0.14 to 0.58 (mean 0.32 ± 0.15 [SD]) and increased to a similar degree after nitroprusside (p < .01) and amrinone (p = .01; figure 2).

To test the hypothesis that the effect of amrinone on right ventricular end-systolic volume exceeded that predicted from the reduction in right ventricular afterload, we first examined the relationship between nitroprusside-induced changes in end-systolic pressure and volume in each patient (figure 3). The decrease in end-systolic volume expected with amrinone based only on right ventricular afterload reduction was then estimated from individual nitroprusside-derived right ventricular end-systolic pressure-volume slopes and from the amrinone-induced fractional reduction in pulmonary arterial end-systolic pressure. The observed effect exceeded that predicted to result from afterload reduction in seven of nine patients, although there was no significant difference between mean predicted and observed effects (figure 4). For the entire patient group combined, the average fractional change in pulmonary arterial end-systolic or peak systolic pressure was plotted against the average fractional change in right ventricular end-systolic volume induced by both nitroprusside and amrinone (figure 5). The amrinone data points were not significantly displaced from the regression lines derived from nitroprusside data, indicating that the overall effect of amrinone on end-systolic volume could be explained predominantly on the basis of right ventricular afterload reduction.

Discussion

The bipyridine amrinone has been shown to have cardiac inotropic effects in isolated tissue preparations.1-4 In addition, amrinone has been shown by Benotti et al.4 to increase left ventricular isovolumetric phase indexes of contractility in patients with congestive heart failure. More recently, the left ventricular inotropic effects of the bipyridines has been demonstrated by direct intracoronary drug infusion25 and by examination of the relationship between systolic loading and contractile performance.13,26 In the present study, we compared the effects of nitroprusside and
HEMODYNAMIC EFFECTS

<table>
<thead>
<tr>
<th>NITROPRUSSIDE</th>
<th>AMRINONE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>A</td>
</tr>
<tr>
<td>PA END-SYSTOLIC PRESSURE (mmHg)</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CARDIAC INDEX (l/min m²)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PVR (dynes. cm⁻²)</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td></td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 1. Effect of nitroprusside (N) and amrinone (A) on pulmonary arterial (PA) end-systolic pressure, cardiac index, and pulmonary vascular resistance (PVR). Both drugs significantly reduced PA end-systolic pressure and PVR and increased cardiac index, with no significant differences between the magnitude of effects of the two drugs.

amrinone on the right ventricular end-systolic pressure-volume relationship and found that in the majority of patients with congestive heart failure the amrinone-induced decrease in right ventricular end-systolic volume exceeded that predicted to result from administration of a pure vasodilator, suggesting some right ventricular inotropic effect. However, this effect appeared to be modest and was not statistically significant, indicating that the response of right ventricular systolic function to amrinone can be explained predominantly on the basis of right ventricular afterload reduction.

Studies in isolated canine left ventricles and in man have demonstrated that the relationship between left ventricular end-systolic pressure and volume during acute afterload alteration is linear and responsive to changes in inotropic state. The characteristics of this relationship do not appear significantly altered when ventricular peak systolic or arterial diastolic notch pressure is substituted for ventricular end-systolic pressure. We have previously found that short-term amrinone significantly alters the left ventricular end-systolic pressure-volume relationship in patients with severe congestive heart failure, indicating an inotropic contribution to the effect of this drug on left ventricular systolic performance.

In the present study we found that amrinone augmented right ventricular systolic performance over the short term in patients with congestive heart failure, as indicated by a reduction in right ventricular end-systolic volume and an increase in ejection fraction. Several direct effects of amrinone could contribute to these observed responses, including (1) augmented right ventricular contractility, and (2) reduced right ventricular afterload due to (a) augmented left ventricular contractility, and (b) decreased systemic and/or pulmonary arteriolar resistance. In addition to their inotropic effects, the bipyridines have been shown in isolated tissue preparations to directly relax systemic and pulmonary vascular smooth muscle, and clinical evidence exists to suggest that these actions contribute substantially to the derived hemodynamic benefit.

We therefore examined the short-term effects of amrinone on the relationship between right ventricular
end-systolic pressure and volume and compared them with the effects of nitroprusside to identify the predominant mechanism for amrinone’s improvement of right ventricular systolic function. In the isolated canine right ventricle, Maughan et al. have demonstrated that the right ventricular end-systolic pressure-volume relationship is analogous to that observed for the left ventricle, with the slope similarly responsive to acute changes in contractility. Using pulmonary artery dicrotic notch pressure and radionuclide-derived estimates of changes in right ventricular end-systolic volume, we have previously observed that the characteristics of the right ventricular end-systolic pressure-volume relationship during administration of vasodilators in patients with congestive heart failure are similar to those of the left ventricular relationship; there is linearity within a physiologic range of afterload alteration and correlation between the pressure-volume slope and other parameters of systolic performance. Furthermore, Brent et al. using techniques similar to ours, have found that an acute pharmacologically induced increase in right ventricular contractility results in a discernible shift of the systolic pressure-volume relationship from that derived during administration of vasodilators. In our patients, we first constructed individual right ventricular end-systolic pressure-volume relationships using various doses of nitroprusside and then determined whether the effect of amrinone on right ventricular end-systolic volume differed significantly from that observed with nitroprusside for the degree of reduction in pulmonary arterial end-systolic pressure. We observed an amrinone-induced decrease in right ventricular afterload in all but one patient, and this effect was the predominant factor responsible for the improvement in right ventricular systolic function.

Compared with our previous findings for the left ventricle, the lesser evidence for a right ventricular inotropic effect is likely to be related to differences in myocardial mass of the two ventricles and to the fact that systolic function is more strongly dependent on changes in afterload for the right ventricle than for the left ventricle. Several prior studies have demonstrated the strong link between pulmonary arterial pressure...
and the systolic performance of the thin-walled right ventricle.\textsuperscript{14, 15, 35-39} In patients with comparable depression of left and right ventricular function, we have found the slope of the end-systolic pressure-volume relationship to be consistently shallower for the right ventricle than the left ventricle, indicating that a given reduction in systolic pressure results in greater augmentation of systolic performance for the right ventricle than for the left ventricle.\textsuperscript{15} Changes in radionuclide-derived ejection phase indexes have been found to correlate closely with changes in pulmonary arterial pressure.\textsuperscript{14, 40} These differences between the two ventricles in terms of the relative responsiveness to inotropic stimulation and the relative dependence of systolic function on afterload alteration are not surprising, given the marked differences in myocardial mass and wall thickness between the left and right ventricles.

Limitations. Because of structural complexity, estimation of absolute ventricular volume is unlikely to be as accurate for the right ventricle as for the left ventricle. For the purpose of our present analysis, we therefore estimated only the changes from resting values for right ventricular end-systolic volume that were induced by nitroprusside and amrinone. We have previously validated our method of assessing right ventricular function in patients with a wide variety of disorders affecting the right ventricle.\textsuperscript{19} As confirmed in the present population, we have found that the right ventricular end-systolic pressure-volume relationship during the infusion of nitroprusside has characteristics analogous to that observed in the left ventricle, although with shallower pressure-volume slopes.\textsuperscript{14, 15} Measurement of absolute right ventricular volumes was not necessary for the purpose of our analysis, in which the effects of amrinone and nitroprusside were compared and each patient served as his own control.

The potential effect of tricuspid regurgitation in some patients on the accuracy of our measurements should be considered. Thermodilution cardiac output measurements have been widely used in similar populations to determine the general effect of pharmacologic interventions,\textsuperscript{5, 7, 9, 11, 12, 37} although in individual patients the presence of tricuspid regurgitation may reduce the accuracy of this technique. Our conclusions regarding the relative inotropic vs afterload-reducing effects of amrinone on the right ventricle are based on pressure and radionuclide volumetric measurements, rather than on thermodilution cardiac output. In similar populations, any tricuspid regurgitation that may have been present did not appear to adversely affect the accuracy of radionuclide right ventricular measurements\textsuperscript{19} or to alter the expected characteristics of the right ventricular end-systolic pressure-volume relationship.\textsuperscript{14, 15} Furthermore, experimental evidence indicates no effect of acute changes in right ventricular diastolic load on the end-systolic pressure-volume relationship.\textsuperscript{34}

Right ventricular afterload would be more closely approximated by ventricular systolic stress than by end-systolic volume. However, the complex shape of
the right ventricle and difficulty in estimating chamber dimension and wall thickness by presently available techniques render the ability to measure right ventricular wall stress questionable in the clinical setting. We therefore approximated acute drug-induced changes in right ventricular afterload from changes in pulmonary arterial dicrotic notch pressure using methodology analogous to that which has been widely used for the left ventricle2022, 29-31 and which we14, 15 and others23 have previously described for the right ventricle.

Because of the long plasma half-life of amrinone (3 to 15 hr),41 it was not practically feasible to randomize the order of drug administration, and the possibility of a carryover of hemodynamic effects from nitroprusside must be considered. However, the duration of effect after cessation of nitroprusside is short, and the persistence of rebound hemodynamic effects into the period of amrinone infusion was minimized because hemodynamics were allowed to return to a steady-state baseline level before amrinone was initiated. There was no observed difference between initial and repeat (postnitroprusside) baseline hemodynamics.

Our findings should not be construed to indicate that amrinone never exerts inotropic effects on the right ventricle. After administration of amrinone, some right ventricular inotropic effect was suggested in the majority of our patients by a decrease in end-systolic volume beyond that expected for the degree of afterload reduction, although this effect was not statistically significant. The magnitude of any change in right ventricular contractility was small in its contribution to the observed improvement in systolic performance, which resulted predominantly from the amrinone-induced reduction in right ventricular afterload. However, we studied only patients with severe left ventricular failure due to either coronary artery disease or cardiomyopathy. It is possible that patients with greater degrees of right ventricular hypertrophy related to cor pulmonale, primary pulmonary hypertension, or valvular or congenital heart disease would manifest more evidence of an amrinone-induced right ventricular inotropic effect.

References

Vol. 74, No. 2, August 1986


Effect of amrinone on right ventricular function: predominance of afterload reduction.
M A Konstam, S R Cohen, D N Salem, D Das, M J Aronovitz and B A Brockway

doi: 10.1161/01.CIR.74.2.359

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 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/74/2/359

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/