Effects of Milrinone on Left Ventricular Remodeling After Acute Myocardial Infarction

Praveer Jain, MBBS, MS; Edward J. Brown Jr., MD; Edward G. Langenback, PhD; Ernst Raeder, MD; Oneida Lillis, BS; Jeanne Halpern, BS; and John A. Mannisi, MD

Background. Left ventricular remodeling after an acute myocardial infarction may result in progressive left ventricular dilation that may be associated with increased mortality. We studied the effects of the phosphodiesterase inhibitor milrinone on left ventricular remodeling after acute myocardial infarction.

Methods and Results. Rats (n=90) were randomized to undergo either left coronary artery ligation or sham operation. Three weeks after surgery, rats received either no treatment or milrinone, which was continued until 2 days before the rats were killed. Ninety days after the initial surgery, hemodynamic measurements were made before and after volume loading. The rats were killed, the hearts were removed, and passive pressure-volume curves were obtained. The hearts were fixed at a constant pressure and analyzed morphometrically. Compared with untreated infarcted rats, milrinone-treated infarcted rats had a lower left ventricular end-diastolic pressure (1.7±0.4 versus 4.3±1.4 mm Hg, p<0.05), a lower left ventricular volume (1.2±0.20 versus 2.37±0.30 ml/kg, p<0.001) and a lower left ventricular wall stress index (1.3±0.2 versus 1.7±0.1, p<0.05). Left ventricular chamber stiffness was higher in milrinone-treated infarcted rats than in untreated infarcted rats. Milrinone had no cardiac effect on uninfarcted animals.

Conclusion. Chronic milrinone therapy after acute myocardial infarction improves cardiac hemodynamic indexes and attenuates progressive left ventricular dilation. (Circulation 1991;84:796-804)

There is growing evidence that survival after acute myocardial infarction is related to remodeling of noninfarcted myocardium.1-3 Loss of myocardium triggers acute and chronic responses that restore stroke volume. The acute distension of noninfarcted myocardium, activation of the Frank-Starling mechanism, and adrenergic stimulation combine to restore cardiac performance. However, when myocardial damage is extensive, these compensatory mechanisms are inadequate, resulting in chronic left ventricular dilation and increased wall stress. If the latter is not entirely reversed by myocyte hypertrophy, then progressive left ventricular enlargement, deterioration in cardiac performance, and increased mortality will ensue.3-6 Recent studies have examined the possibility that interventions that prevent progressive left ventricular enlargement improve survival.3

Milrinone, a phosphodiesterase inhibitor with positive inotropic and vasodilator properties, provides symptomatic relief to patients with left ventricular dysfunction.7 Improvement in survival after acute myocardial infarction in rats treated with milrinone8 has been observed and may be related to effects on left ventricular remodeling. The purpose of this investigation was to test the hypothesis that milrinone alters left ventricular remodeling and prevents progressive left ventricular dilation after acute myocardial infarction.

Methods

Experimental Myocardial Infarction

Female Sprague-Dawley rats (n=90) weighing 200–225 g underwent either left coronary artery ligation or sham operation. After anesthesia with 35 mg/kg methohexital i.p. and local anesthesia with 1% xylocaine, the trachea was exposed in the midline and the rats were intubated under direct vision and ventilated with room air. The chest was opened by anterolateral thoracotomy, and the pericardium was removed. The heart was retracted with an apical suture, and the left coronary artery was occluded with a 6-0 silk suture 1–2 mm below the left atrial
appendage. Successful occlusion was confirmed by pallor of the anterior wall of the left ventricle and ST segment elevation. If neither change was observed, the occlusion was repeated. The incisions were closed and 100,000 units benzathine penicillin was administered intramuscularly as a prophylaxis against infection. The rats were extubated and allowed to recover in individual cages. Sham animals underwent an identical procedure without coronary ligation. All rats received standard care including ad libitum food and water and a 12-hour day/night cycle.

Randomization and Treatment
Before surgery, the rats were randomized to one of four groups: group 1, left coronary ligation and no treatment (n=29); group 2, left coronary ligation and milrinone (n=31); group 3, sham surgery and no treatment (n=15); and group 4, sham surgery and milrinone (n=15). Three weeks after surgery, milrinone was added to the drinking water (15 mg/l) of the two treatment groups. Therapy was continued for 3 months after surgery until 48 hours before hemodynamic measurements, after which the rats were killed.

Hemodynamics
Forty-eight hours after milrinone was discontinued (24 half-lives), rats were anesthetized intraperitoneally with ketamine (60 mg/kg) and diazepam (7.5 mg/kg), intubated, and ventilated. A catheter was inserted into the left femoral vein for volume infusion. The chest was opened by a left parasternal incision and a 2.5-mm electromagnetic flow probe was placed around the ascending aorta. After a stabilization period of 10 minutes, a saline-filled 1-in. 21-gauge needle was inserted into the left ventricular cavity through noninfarcted myocardium and connected to a 5F micromanometer-tipped catheter through a short, plastic connector. Baseline hemodynamic measurements including heart rate, left ventricular pressure, left ventricular dp/dt, and cardiac output were recorded on an eight-channel Hewlett-Packard (Palo Alto, Calif.) recorder with the respirator temporarily disconnected.

The peak flow generating capacity of the heart was evaluated by infusion of 40 ml/kg/min of Ringer’s lactate at 37°C with continuous recording of all hemodynamic parameters until the peak cardiac output was attained.

At the conclusion of hemodynamic studies, the hearts were arrested by infusion of 30 mM KCl through the femoral vein, excised, and placed in ice-cold KCl to achieve uniform diastolic arrest.

Pressure–Volume Measurement
The passive pressure–volume relation of the left ventricle was determined within 10 minutes of cardiac arrest. After the hearts were removed, a double-lumen catheter was inserted into the left ventricular cavity through the aortic valve. The aorta was ligated around the catheter, and the atrioventricular groove was tied off to isolate the left ventricular cavity. The right ventricle was incised to prevent left ventricular compression. After gentle compression to remove all residual fluid from the left ventricle, normal saline was infused at 0.68 ml/min and left ventricular pressure was simultaneously recorded to produce pressure–volume curves over a range of 0–40 mm Hg.

Fixation and Preparation of the Heart
With the heart submerged in formalin, 10% phosphate-buffered formalin was infused continuously into the left ventricular cavity through the double-lumen catheter for 24 hours. The height of the exit port on the catheter resulted in a fixation pressure of 7.5 mm Hg and was constant for all hearts. After fixation, the hearts were weighed and then cut transversely from apex to base into four slices. Each slice was weighed, and the thickness was measured. Photographs of both sides of each slice were taken.

Analysis of Data
Hemodynamics. Resting heart rate, left ventricular pressure, dp/dt, and mean and phasic cardiac output were measured over six cardiac cycles and averaged. Left ventricular end-diastolic pressure was measured at the onset of the rapid rise of dp/dt. Cardiac index was calculated as cardiac output per kilogram of body weight. Peak hemodynamic measurements were made at the time of maximum cardiac output during the volume loading and averaged over six cycles.

Prefixation left ventricular volume measurement. Left ventricular volume was recorded from the pressure–volume curve at a pressure corresponding to the peak left ventricular end-diastolic pressure obtained during volume loading and corrected for body weight at the time the rats were killed.

Postfixation left ventricular volume measurement. After fixation, the base of the heart was excised at the level of the atroventricular groove. The cavity was blotted dry and then filled to capacity with normal saline using a 1-ml tuberculin syringe for direct estimation of left ventricular volume. Two determinations were averaged for each heart and corrected for body weight.

Left ventricular wall stress. An index of left ventricular end-diastolic wall stress was calculated by dividing postfixation left ventricular end diastolic volume by the heart weight.

Left ventricular chamber and myocardial stiffness. Ventricular volumes were determined from the passive pressure–volume curves at every 1 mm Hg from 0 to 40 mm Hg. A curve for each group was constructed from the mean volumes at each unit of pressure. Left ventricular chamber stiffness was expressed as dp/dv/p.

An estimate of myocardial stiffness was made by multiplying left ventricular chamber stiffness constant and volume-to-mass ratio of the left ventricle.9

Infarct size measurement. The initial infarct size was calculated as follows10:
A mean myocardial stiffness constant is reported for each of the four groups. Data are reported as mean±SEM and significance is assumed when \( p<0.05 \).

**Results**

Eighty rats survived to the killing date (26 sham, 54 infarcted). There were no deaths after drug treatment was initiated. Eighteen of 54 rats surviving coronary ligation did not develop transmural myocardial infarction (eight milrinone treated, 10 untreated, \( p=NS \)) and were excluded from further analysis. Infarct size was similar in untreated and milrinone-treated rats (28.6±3.2\% versus 30±3.2\%, \( p=NS \)). Treated rats received 1.50±0.03 mg milrinone/kg/day.

**Hemodynamic Measurements**

In infarcted rats, milrinone lowered left ventricular end-diastolic pressure at rest and at peak flow generating capacity to a level that did not differ from that found in uninfarcted animals (Figures 1 and 2). In uninfarcted rats, milrinone had no effect on left ventricular end-diastolic pressure. Other hemodynamic parameters, including heart rate, left ventricular systolic pressure, positive dP/dt, and cardiac index, were not altered by milrinone at rest (Table 1) or at peak flow generating capacity (Table 2) in either infarcted or uninfarcted rats.

**Left Ventricular Volume**

Left ventricular volumes were increased in both milrinone-treated and untreated infarcted rats but more so in untreated infarcted rats (milrinone treated, 1.25±0.20 ml/kg; untreated, 2.37±0.30 ml/kg; \( p<0.001 \); Figure 3).

---

**Statistical Analysis**

The data were analyzed by computing the Kruskal-Wallis statistic to avoid assumptions regarding the distribution of the data. Differences between groups were isolated by the Mann-Whitney rank sum test with Bonferroni adjustment for multiple comparisons. Passive pressure–volume curves were analyzed by two-way analysis of variance. A plot of log pressure versus mean volumes was constructed for each group to evaluate the slope that defines chamber stiffness for the pressure–volume relation of each group. Various intervals were tested for linearity by the method of least squares and evaluated by an \( F \) statistic. When the best linear segment was found, the slope and \( y \) intercept were calculated and stripped from the remaining curve by the method of residuals.\(^{11}\) The process was repeated until all data points could be predicted by a series of exponentials. Chamber stiffness constants of the four groups were compared by an analysis of covariance.
Arranging the left ventricular cavity volume data in each group from the lowest to the highest value in a quantile-quantile plot (Figure 4) demonstrated that milrinone had a favorable effect on volume in all heart sizes. Milrinone had no effect on left ventricular volume in uninfarcted hearts (milrinone-treated, 0.83±0.10 ml/kg; untreated, 1.12±0.15 ml/kg; p=NS; Figure 3). Postfixation volumes are shown in Table 3;

**FIGURE 2. Bar graph of left ventricular end-diastolic pressure (LVEDP) at peak pumping capacity in the four groups of rats. MI, myocardial infarction.**

**TABLE 1. Resting Hemodynamics in Four Groups of Rats**

<table>
<thead>
<tr>
<th></th>
<th>MI-H₂O</th>
<th>MI-Mil</th>
<th>Sham-H₂O</th>
<th>Sham-Mil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>309±14</td>
<td>318±8</td>
<td>293±20</td>
<td>281±18</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>99±7</td>
<td>103±5</td>
<td>110±9</td>
<td>99±6</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>4.2±1.4*</td>
<td>1.7±0.4</td>
<td>1.3±0.5</td>
<td>0.8±0.3</td>
</tr>
<tr>
<td>+dP/dt (mm Hg/sec)</td>
<td>2,727±303</td>
<td>3,214±194</td>
<td>3,140±304</td>
<td>2,745±183</td>
</tr>
<tr>
<td>Cardiac index (ml/min/kg)</td>
<td>122±22</td>
<td>114±17</td>
<td>100±12</td>
<td>104±15</td>
</tr>
</tbody>
</table>

MI-H₂O, infarcted untreated rats; MI-Mil, infarcted milrinone-treated rats; Sham-H₂O, uninfarcted untreated rats; Sham-Mil, uninfarcted milrinone-treated rats; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; +dP/dt, maximum rate of rise of LVSP.

*p<0.05 vs. shams and MI-Mil.

**TABLE 2. Peak Hemodynamics at Peak Pumping Capacity in Four Groups of Rats**

<table>
<thead>
<tr>
<th></th>
<th>MI-H₂O</th>
<th>MI-Mil</th>
<th>Sham-H₂O</th>
<th>Sham-Mil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>288±22</td>
<td>295±7</td>
<td>267±28</td>
<td>267±23</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>90±8</td>
<td>102±6</td>
<td>97±11</td>
<td>98±5</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>19.3±3.2*</td>
<td>9.6±0.8</td>
<td>10.3±0.9</td>
<td>8.7±0.8</td>
</tr>
<tr>
<td>+dP/dt (mm Hg/sec)</td>
<td>1,820±276</td>
<td>2,514±197</td>
<td>2,378±326</td>
<td>2,480±169</td>
</tr>
<tr>
<td>Cardiac index (ml/min/kg)</td>
<td>148±25</td>
<td>170±22</td>
<td>161±22</td>
<td>176±21</td>
</tr>
</tbody>
</table>

MI-H₂O, infarcted untreated rats; MI-Mil, infarcted milrinone-treated rats; Sham-H₂O, uninfarcted untreated rats; Sham-Mil, uninfarcted milrinone-treated rats; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; +dP/dt, maximum rate of rise of LVSP.

*p<0.001 vs. MI-Mil.
although they were lower than prefixation volumes, results from the two volume techniques were closely correlated ($r=0.83$, Figure 5).

**Left Ventricular Wall Stress**

Wall stress was increased in both milrinone-treated and untreated infarcted rats, but the increase was less in milrinone-treated infarcted rats (Table 3). Milrinone had no effect on wall stress in uninfarcted hearts. Left ventricular septal wall thickness was similar in the four rat groups.

**Pressure–Volume Curves**

The lower left ventricular volumes in the milrinone-treated rats were not entirely due to lower filling pressures and a move along a single pressure–volume curve. When the curves for the four groups were compared (Figure 6), there was a significant
leftward shift in the milrinone-treated infarcted group compared with the untreated infarcted group \((p<0.05)\). For any given infarct size or filling pressure, there was a significantly lower volume in the milrinone-treated infarcted rats. Treated and untreated sham group pressure–volume curves were similar. Both sham groups were shifted leftward compared with the milrinone-treated infarcted group \((p<0.01)\).

Left ventricular chamber stiffness constant was linear from 5 to 35 mm Hg in all four groups. In each group, only one linear segment was found. Both infarcted groups of rats had lower chamber stiffness constants than uninfarcted rats (Table 4). The chamber stiffness constant of infarcted milrinone-treated rats was higher than that of infarcted untreated rats. The chamber stiffness constants of untreated and milrinone-treated uninfarcted rats were similar. Estimated left ventricular myocardial stiffness was similar in all four groups of animals (Table 4).

### Discussion

The principal finding of this study was that chronic treatment with milrinone attenuates progressive left ventricular dilation after acute myocardial infarction. Milrinone improved hemodynamic parameters at rest and at peak cardiac output, decreased wall stress, increased left ventricular chamber stiffness, and resulted in left ventricular volumes that were less than half the volumes in untreated infarcted hearts with similar sized infarcts. Left ventricular myocardial stiffness was not altered by milrinone therapy.

### Determinants of Ventricular Remodeling

An acute myocardial infarction causes an immediate compensatory increase in left ventricular volume and activation of the Frank-Starling mechanism, which restores stroke volume. Over the ensuing weeks to months, remodeling of noninfarcted myocardium can result in progressive left ventricular dilation, which is pathological rather than compensatory and is associated with increased mortality.\(^1\)\(^-\)\(^6\) Although infarct characteristics including size, extent of transmurality, location, and extent of expansion can affect left ventricular remodeling, they were not a factor in this experiment because milrinone treatment was not started until healing of the infarct was complete. Changes in left ventricular size and func-

---

**Table 3. Wall Stress Index in Four Groups of Rats**

<table>
<thead>
<tr>
<th></th>
<th>MI–H₂O</th>
<th>MI–Mil</th>
<th>Sham–H₂O</th>
<th>Sham–Mil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall thickness (mm)</td>
<td>1.8±0.2</td>
<td>2.2±0.2</td>
<td>2.1±0.1</td>
<td>2.2±0.2</td>
</tr>
<tr>
<td>Left ventricular volume</td>
<td>1.66±0.2*</td>
<td>1.16±0.2</td>
<td>0.73±0.1</td>
<td>0.60±0.1</td>
</tr>
<tr>
<td>(postfixation) (ml/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart weight (g)</td>
<td>1.00±0.05†</td>
<td>0.92±0.03‡</td>
<td>0.83±0.03</td>
<td>0.80±0.03</td>
</tr>
<tr>
<td>Wall stress index</td>
<td>1.7±0.1§</td>
<td>1.3±0.2‖</td>
<td>0.9±0.1</td>
<td>0.7±0.1</td>
</tr>
</tbody>
</table>

The wall stress index is the quotient of left ventricular volume and heart weight. MI–H₂O, infarcted untreated rats; MI–Mil, infarcted milrinone-treated rats; Sham–H₂O, uninfarcted untreated rats; Sham–Mil, uninfarcted milrinone-treated rats.

\*\(p<0.001\) vs. shams and MI–Mil; †\(p<0.01\) vs. Sham–H₂O; ‡\(p<0.05\) vs. Sham–Mil; §\(p<0.005\) vs. Sham–H₂O and <0.05 vs. MI–Mil; ‖\(p<0.025\) vs. Sham–Mil.

**FIGURE 5.** Scatterplot showing relation of volumes measured by prefixation and postfixation techniques in the four groups of rats. MI, myocardial infarction.
tion were therefore due to effects on noninfarcted myocardium.

Increases in afterload produced by aortic banding, hypertension, and exercise have been associated with progressive left ventricular dilation. Milrinone may prevent left ventricular dilation by reducing afterload by relaxing smooth muscle cells. Blockade of the renin-angiotensin system with captopril will prevent left ventricular dilation, but this effect does not appear to be essential because milrinone has no effect on this enzyme system. Captopril decreases blood volume and may increase levels of bradykinin, which reduces preload. However, milrinone has no known acute effect on preload; decreased left ventricular end-diastolic volume and filling pressure in the milrinone-treated infarcted group may be a consequence of altered cardiac remodeling rather than a direct drug hemodynamic effect. Milrinone inhibits cardiac phosphodiesterase, and the resulting positive inotropic action may contribute to effects on left ventricular remodeling. Other milrinone properties that may affect remodeling are possible inhibition of the sympathetic nervous system and improvement in diastolic performance. Increased wall stress may be a stimulus to progressive left ventricular dilation and reduced wall stress in milrinone-treated rats may have contributed to attenuation of ventricular dilation.

Analysis of the pressure–volume curves reveals that after myocardial infarction, left ventricular chamber stiffness was decreased. Treatment with milrinone increased left ventricular chamber stiffness in infarcted hearts but not in sham hearts. Estimated left ventricular myocardial stiffness remained unchanged after myocardial infarction. Treatment with milrinone did not alter myocardial stiffness in infarcted or sham groups of hearts. Left ventricular chamber stiffness is a function of myocardial stiffness and left ventricular mass-to-volume ratio, and since myocardial stiffness and left ventricular mass were not different in the two infarcted groups, a difference in chamber stiffness between these two groups is primarily a function of decreased left ventricular volume with milrinone treatment.

The Model Used and Potential Limitations

The model of infarction used has demonstrated relevance to clinical myocardial infarction. Pfeffer et al reproduced the attenuation of left ventricular volume with captopril in rats in a clinical study of postinfarction patients. Compared with human infarcts, rat infarcts heal more rapidly with complete healing in 3 weeks. It is likely that remodeling of the left ventricle also occurs more rapidly in rats, and the 3-month observation period in this investigation may be equivalent to a much longer time period in humans. In this model, there are no repeated ischemic events, and remodeling is initiated solely by ligation of the left coronary artery. A potential

| Table 4. Left Ventricular Chamber and Myocardial Stiffness in Four Groups of Rats |
|-----------------------------------|----------------|----------------|----------------|
| Chamber stiffness                | MI–H₂O         | MI–Mil         | Sham–H₂O       | Sham–Mil       |
|                                  | 1.691*         | 2.095†         | 2.588          | 2.495          |
| Myocardial stiffness             | 3.20±0.44      | 3.07±0.48      | 2.60±0.42      | 2.07±0.59      |

MI–H₂O, infarcted untreated rats; MI–Mil, infarcted milrinone-treated rats; Sham–H₂O, uninfarcted untreated rats; Sham–Mil, uninfarcted milrinone-treated rats.

*<p<0.001 vs. MI–Mil and Sham–H₂O; †<p<0.001 vs. Sham–Mil.
limitation to be considered when comparing the effects of interventions on remodeling in rats and humans is incomplete knowledge of the hemodynamic effects of drugs in rats. One report demonstrated no phosphodiesterase inhibition by milrinone in the rat myocardium.\textsuperscript{25} Observations on left ventricular remodeling after an acute myocardial infarction may not apply to left ventricular dysfunction resulting from causes other than coronary artery disease. Whether left ventricular dilation continues indefinitely is also not known.

The infarct size measurement technique used corrects for resorption of tissue in the infarct zone, hypertrophy of the noninfarcted myocardium, and any lengthening of the infarct segment that may occur over the 3-month observation period.\textsuperscript{10} Left ventricular end-diastolic pressures in infarcted rats were lower than pressures observed by others.\textsuperscript{16} This is not due to smaller infarct size but may be accounted for by open-chest hemodynamics and anesthesia with ketamine and diazepam, which have minimal hemodynamic effects.\textsuperscript{26} Two methods of volume measurement were used in this study: 1) the prefixation method, which has the advantage of volume measurement at a predictable left ventricular end-diastolic pressure (i.e., left ventricular end-diastolic pressure at peak pumping capacity); and 2) the postfixation method, a simpler technique that correlated well with the prefixation method. This is because both peak left ventricular end-diastolic pressure and the fixation pressure for the postfixation technique (7.5 mm Hg) occurred on the steep portion of the pressure–volume curve in all four groups of rats.

**Clinical Implications**

Progressive ventricular dilation may temporarily restore diminished stroke volume, but it can become mechanically disadvantageous, resulting in worsening congestive heart failure.\textsuperscript{27} Increased left ventricular volume is a predictor of decreased survival, and interventions that attenuate volume increases should decrease symptoms of congestive heart failure and improve survival. Captopril, which reduces progressive left ventricular dilation after myocardial infarction experimentally and clinically, improves survival with moderate-sized infarcts.\textsuperscript{3} Improved survival with milrinone after myocardial infarction in rats\textsuperscript{8} may be related to attenuation of progressive left ventricular dilation observed in this study. Clinical studies with milrinone have raised concerns about deterioration of left ventricular function\textsuperscript{28,29} and increased incidence of ventricular arrhythmias.\textsuperscript{30} An ongoing trial is investigating the effect of milrinone on survival in patients with severe left ventricular dysfunction.\textsuperscript{31} The beneficial effects of milrinone on left ventricular function seen in the current study may not be seen with intervention at a very late stage of disease when the left ventricle has no inotropic reserve and is already severely dilated.

**Acknowledgments**

We acknowledge the invaluable secretarial assistance of Ms. Carol Pascale. Milrinone was supplied by Sterling Drug Inc.

**References**


KEY WORDS: left ventricular chamber stiffness • wall stress • left ventricular dilation • left ventricular remodeling • phosphodiesterase inhibitor
Effects of milrinone on left ventricular remodeling after acute myocardial infarction.
P Jain, E J Brown, Jr, E G Langenback, E Raeder, O Lillis, J Halpern and J A Mannisi

Circulation. 1991;84:796-804
doi: 10.1161/01.CIR.84.2.796
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 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/84/2/796

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/