Myocardial Uptake of Technetium-99m Stannous Pyrophosphate Following Direct Current Transthoracic Countershock

VINCENT C. DiCOLA, B.A., GERALD S. FREEDMAN, M.D., S. EVANS DOWNING, M.D., AND BARRY L. ZARET, M.D.

SUMMARY The effect of direct current (DC) countershock upon myocardial technetium-99m stannous pyrophosphate (PYP) uptake was studied in 22 dogs. All eight dogs imaged had positive abnormal PYP scintigrams that were usually indistinguishable from experimental infarction. In three animals, additional areas of radionuclide uptake were seen in overlying noncardiac tissue. Left and right ventricular myocardial PYP uptake averaged (± SEM) 23 ± 5 times control and 24 ± 6 times control, respectively. These activity ratios occurred without reduction in regional myocardial blood flow (RMBF), and were associated with histologic evidence of necrosis. The necrosis was usually epicardial, corresponding to the transmural site of greatest PYP uptake.

The magnitude of PYP accumulation and the weight of damaged tissue increased with increasing applied energy. Thus, PYP uptake following DC countershock could result in false-positive interpretation of acute ischemic myocardial infarction. Since RMBF is normal in regions of PYP uptake, the major determinant of radionuclide accumulation is the extent of cellular damage.

This study was undertaken to further define, in the experimental animal, the effects of direct current countershock upon myocardial PYP accumulation. Myocardial PYP uptake was assessed by both myocardial imaging and direct tissue radioactivity levels. The distribution and magnitude of myocardial PYP uptake were related to the amount of delivered electrical energy, to measurement of regional blood flow, and to histologic and histochemical assessment of tissue necrosis.

Methods

Countershock studies were performed in 22 healthy mongrel dogs of either sex weighing between 11 and 28 kg (average 18 ± 1 kg) (table 1). Animals were lightly anesthetized with intravenous sodium pentobarbital. Endotracheal intubation was performed and respiration maintained with a Harvard respirator. Lead II of the surface electrocardiogram was used for routine ECG monitoring. All animals were in sinus rhythm prior to countershock. An intravenous infusion of 5% dextrose in water was begun in all animals. Chest hair was removed with electric clippers. Electrode paste (Redux Paste, Hewlett Packard) was generously applied to 4 cm diameter chest padle electrodes which were then applied to the chest wall.

One paddle electrode was placed over the point of maximal cardiac impulse, while the second was placed opposite it on the right lateral chest wall at the same thoracic level. One to three nonsynchronized direct current countershocks of varying energy were then applied. A B-D Electrodyne Model ELD-5B DC pulse external defibrillator was used for all studies. At an external setting of 400 W-sec (joules), this unit will deliver 320 W-sec across a 50 ohm resistance. When multiple countershocks were employed, the duration between each shock was approximately one minute.

ECG monitoring was carried out throughout the procedure. All animals received an intravenous bolus injection of 100 mg of lidocaine one to two minutes prior to the initial countershock. Following countershock, marked sinus bradycardia or sinus arrest were treated with intravenous atropine, while ventricular tachycardia (three dogs) was treated with intravenous xylocaine or repeat D.C. countershock. In no instance did any animal sustain a period of

From the Cardiology Section, Department of Internal Medicine, Nuclear Medicine Section, Department of Diagnostic Radiology, and Department of Pathology, Yale University School of Medicine, New Haven, Connecticut. Supported in part by NHLI Contract NOI HV 52898, American Heart Association Grant 75-723, and a grant from the Greenwich Health Association and the Southwestern Connecticut Chapter of the American Heart Association.

Address for reprints: Barry L. Zaret, M.D., Yale University School of Medicine, Section of Cardiology, 87 LMP, 333 Cedar Street, New Haven, Connecticut 06510.

Received March 8, 1976; revision accepted July 15, 1976.
TABLE 1. Countershock Protocols in 22 Dogs

<table>
<thead>
<tr>
<th># Shocks/Energy (joules)</th>
<th># animals</th>
<th>Tissue uptake</th>
<th>Imaging</th>
<th>Regional blood flow</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/400</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2/400</td>
<td>13</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>1/400</td>
<td>3</td>
<td>3</td>
<td>--</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1/200</td>
<td>2</td>
<td>2</td>
<td>--</td>
<td>--</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>20</td>
<td>8</td>
<td>8</td>
<td>14</td>
</tr>
</tbody>
</table>

Anoxia or ischemia lasting longer than one minute. Electrocardiographic monitoring was continued for 60-90 min following the last countershock. The endotracheal tube was generally removed within 30 min of the last countershock.

Twenty-four hours following countershock, all animals received 10 mCi PYP (Mallinckrodt) intravenously while in the conscious state. Following the radionuclide injection, several protocols were carried out (table 1). Within the group of 20 dogs that had tissue uptake studies, additional measurement of regional myocardial blood flow was obtained in eight, and myocardial imaging was performed in six. Flow and imaging studies were performed in the same animals in five of these studies. Histopathologic study was obtained in 14 animals including all in whom additional blood flow or imaging protocols had also been performed. The remaining two of 22 animals underwent only sequential imaging studies.

In eight animals imaged (each having received either two or three 400 W-sec countershocks) myocardial imaging was performed 60-90 min following radionuclide injection. The animals were sedated again with pentobarbital prior to imaging. In six animals, the imaging procedure was performed with a 5-inch rectilinear scanner with a 32-hole high resolution collimator (Picker Magnascanner 500). In two animals, the imaging procedure was performed with a Searle large field of view scintillation camera using a high resolution parallel hole collimator (fig. 1). Five-hundred thousand count images were obtained in the anterior, 45° left anterior oblique and left lateral positions. In six of the animals normal control images were also obtained 48 hours prior to countershock. In two animals, sequential images were obtained one, three, four, and seven days following delivery of direct current discharge.

In the 20 dogs studied with tissue data, anesthesia was instituted; the beating heart was removed via a left lateral thoracotomy at least one hour following PYP injection. Generally, major portions of the left and right ventricle were divided into samples weighing approximately 1.0–1.5 g. In six dogs, for technical reasons, only the left ventricle was sampled. The topography of each sample was recorded. Samples were trimmed of epicardial fat and blood vessels and were then divided into endocardial and epicardial parts of approximately equal thickness. Following weighing, samples were counted in a well-type scintillation counter at a window of 120–160 KeV. A total of 224 left ventricular and 104 right ventricular samples were counted for the 20 animals so studied. Sample activities were calculated as counts per minute per gram of tissue. Tissue samples with abnormal PYP uptake were expressed as an activity ratio between the sample and the mean of five–six normal samples from the same ventricular wall. Overlying skeletal muscle tissue was not examined.

In eight of the above animals, relative regional myocardial blood flow as determined by the radioactive microsphere technique was also assessed. In these animals, following left lateral thoracotomy, the left atrial appendage was cannulated and 4–6 million, 15 ± 5 μ diameter chromium-51 labelled carbonized microspheres (3M Corporation) were administered. The microspheres had previously been agitated in an ultrasonic bath for at least 15

![Figure 1. Sequential PYP images in the left lateral position obtained one, three, four, and seven days following delivery of two 400 W-sec countershocks. Note the abnormal myocardial uptake over the four days following countershock, with subsequent resolution and a normal PYP myocardial scintigram seven days following countershock. Uptake below the heart probably reflects skeletal muscle accumulation.](http://circ.ahajournals.org/doi/abs/10.1161/01.CIR.81.7.981)
min, and the syringe in which they were contained was vigorously shaken prior to injection. The microspheres were suspended in a volume of 1–2 cc of 10% dextran at a specific activity of 10.8 mCi per gram. This relatively large number of spheres was employed to assure adequate counting statistics. Injection of a similar number of microspheres has been previously shown not to significantly alter coronary blood flow or peak reactive hyperemic coronary blood flow.18 Two minutes following microsphere injection, the heart was removed and samples obtained as outlined in the preceding paragraph. Utilizing differential spectrometry, chromium-51 activity was counted at a window of 300–340 KeV and technetium-99m at a 120–160 KeV window. Utilizing a correction ratio obtained from known standards, appropriate corrections for 51Cr activity in the 99mTc window was obtained. Microsphere activity was also calculated as counts per minute per gram and expressed as an activity ratio between a given sample and the mean value of five–six normal samples from the same ventricle. The microsphere technique, when applied to small segments, will demonstrate a considerable heterogeneity of flow (an average standard deviation from the mean of 17.3%). This is due to both technical considerations and inherent heterogeneity of flow to the left ventricular myocardium.19

In the 14 dogs studied histologically, myocardial samples obtained for histopathologic and histochemical analysis were compared to radioactivity levels in the same tissue. A total of 27 full thickness myocardial samples were fixed in 10% formalin and embedded in paraffin. All sections were stained with hematoxylin and eosin, Masson trichrome, and hematoxylin basic fuchsin picric acid (HBFP) stains.14 Sections were examined and graded independently by one of the authors (S.E.D.) for evidence of coagulation necrosis, hemorrhage, polymorphonuclear leukocyte infiltration, or additional specific histochemical abnormality consistent with necrosis. Interpretation was also categorized according to the transmural distribution of abnormality, with specific notation as to whether a pathologic lesion was epicardial, endocardial, midzonal, or transmural.

Data were statistically compared employing the non-parametric Wilcoxon rank sum test.16

Results

In all animals imaged at least 24 hours following countershock, PYP myocardial scintigraphy revealed abnormal myocardial uptake patterns which were for the most part indistinguishable from those noted in experimental myocardial infarction (fig. 1). These abnormalities were not present in control images and reverted to normal by seven days following countershock. In three animals, a portion of the visualized abnormality could be attributed to abnormal pyrophosphate uptake in overlying skeletal muscle and cutaneous structures, since the outermost border of region of increased radionuclide uptake protruded past the sternum in the lateral or oblique views. In addition, in a subsequent series of 14 animals, comparable defects were readily noted when the excised heart was imaged outside the body.*

The impressions gained from external imaging were amply confirmed by studies obtained following sacrifice of

the animal. Examination of the removed hearts frequently demonstrated regions of discolored myocardium involving the lateral left ventricle and right ventricle grossly corresponding to sites of entrance and exit of the electric current. In two animals (15, 25) the right ventricle was the only site of local change. The most marked abnormal PYP uptake was demonstrable in these regions (fig. 2). Of the total 224 left ventricular samples, 140 demonstrated a definite abnormal PYP activity ratio of at least 3:1. In these abnormal samples, PYP activity ratios were usually significantly higher than 3:1; and 85% of the samples had ratios of greater than 6:1, and 72% greater than 10:1. In the abnormal right ventricular samples (68/104 segments), 78% likewise demonstrated activity ratios of greater than 10:1. Maximal and mean abnormal regional left ventricular PYP uptake averaged (± SEM) 41 ± 8 and 23 ± 5 times that of control samples respectively (table 2). Similarly, maximal and mean abnormal regional right ventricular pyrophosphate uptake averaged 34 ± 9 and 24 ± 6 that of control samples respectively (table 2). Pyrophosphate uptake was predominantly epicardial throughout (fig. 3). In the left ventricle, mean regional epicardial/endocardial ratios averaged 5.4 ± 0.9 with maximal transmural ratios for each experiment averaging 13.0 ± 2.6. In the thinner walled right ventricle, mean ratios averaged 2.6 ± 0.3, while maximal epi/endo ratios for each experiment averaged 3.8 ± 0.6 (table 2).

In addition, a dose response curve could be constructed when myocardial PYP uptake at different amounts of total delivered energy was assessed (fig. 4). Greatest myocardial PYP uptake was noted in animals receiving the maximal number of countershocks at the highest energy. The

---

* Schneider RM, Zaret BL, unpublished data.
TABLE 2. Tissue Uptake Data in 20 Dogs Studied Following Countershock

<table>
<thead>
<tr>
<th>Dog</th>
<th># shocks/energy level</th>
<th>Mean PYP uptake</th>
<th>Max PYP uptake</th>
<th>Mean PYP epi/endo</th>
<th>Maximum PYP epi/endo</th>
<th>Mean uptake</th>
<th>Max PYP uptake</th>
<th>Mean PYP epi/endo</th>
<th>Maximum PYP epi/endo</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3/400</td>
<td>47</td>
<td>101</td>
<td>6.7</td>
<td>26.3</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3/400</td>
<td>82</td>
<td>103</td>
<td>6.2</td>
<td>14.5</td>
<td>82</td>
<td>103</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>16</td>
<td>3/400</td>
<td>18</td>
<td>25</td>
<td>1.5</td>
<td>3.0</td>
<td>19</td>
<td>25</td>
<td>0.7</td>
<td>1.3</td>
</tr>
<tr>
<td>20</td>
<td>3/400</td>
<td>21</td>
<td>37</td>
<td>5.8</td>
<td>11.6</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2/400</td>
<td>12</td>
<td>31</td>
<td>3.7</td>
<td>7.6</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2/400</td>
<td>11</td>
<td>25</td>
<td>1.8</td>
<td>3.2</td>
<td>7</td>
<td>13</td>
<td>2.4</td>
<td>3.1</td>
</tr>
<tr>
<td>10</td>
<td>2/400</td>
<td>44</td>
<td>64</td>
<td>1.4</td>
<td>3.1</td>
<td>55</td>
<td>98</td>
<td>2.2</td>
<td>3.4</td>
</tr>
<tr>
<td>11</td>
<td>2/400</td>
<td>45</td>
<td>71</td>
<td>6.2</td>
<td>14.5</td>
<td>51</td>
<td>55</td>
<td>3.5</td>
<td>3.7</td>
</tr>
<tr>
<td>13</td>
<td>2/400</td>
<td>8</td>
<td>12</td>
<td>11.0</td>
<td>15.3</td>
<td>22</td>
<td>132</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>15</td>
<td>2/400</td>
<td>1</td>
<td>1</td>
<td>1.3</td>
<td>1.5</td>
<td>25</td>
<td>36</td>
<td>3.3</td>
<td>6.7</td>
</tr>
<tr>
<td>18</td>
<td>2/400</td>
<td>7</td>
<td>15</td>
<td>0.5</td>
<td>1.4</td>
<td>12</td>
<td>22</td>
<td>3.1</td>
<td>5.0</td>
</tr>
<tr>
<td>19</td>
<td>2/400</td>
<td>12</td>
<td>19</td>
<td>8.1</td>
<td>12.9</td>
<td>7</td>
<td>15</td>
<td>3.7</td>
<td>5.2</td>
</tr>
<tr>
<td>21</td>
<td>2/400</td>
<td>45</td>
<td>79</td>
<td>13.1</td>
<td>39.6</td>
<td>27</td>
<td>38</td>
<td>2.1</td>
<td>2.9</td>
</tr>
<tr>
<td>28</td>
<td>2/400</td>
<td>15</td>
<td>29</td>
<td>13.3</td>
<td>32.0</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>2/400</td>
<td>46</td>
<td>110</td>
<td>7.4</td>
<td>32.6</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>1/400</td>
<td>7</td>
<td>11</td>
<td>11.0</td>
<td>17.2</td>
<td>ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>1/400</td>
<td>9</td>
<td>30</td>
<td>3.8</td>
<td>7.3</td>
<td>20</td>
<td>21</td>
<td>5.3</td>
<td>9.5</td>
</tr>
<tr>
<td>25</td>
<td>1/400</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
<td>1.0</td>
<td>4</td>
<td>8</td>
<td>3.5</td>
<td>5.4</td>
</tr>
<tr>
<td>26</td>
<td>2/200</td>
<td>1</td>
<td>11</td>
<td>0.9</td>
<td>1.0</td>
<td>1</td>
<td>1</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>27</td>
<td>1/200</td>
<td>2</td>
<td>2</td>
<td>1.4</td>
<td>2.3</td>
<td>2</td>
<td>3</td>
<td>1.6</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Mean: 23 41 5.4 13.0 24 34 2.6 3.8
SEM: 5 8 0.9 2.6 6 9 0.3 0.6

Abbreviations: ND = not done; Max = maximal.

FIGURE 3. Transmural distribution of left ventricular PYP uptake at various levels of delivered energy expressed as number of shocks/energy level. "n" refers to the number of animals studied in each group. PYP uptake is expressed as a sample/normal activity ratio. Epicardial (EPI) uptake is indicated by the unfilled columns, endocardial (Endo) uptake by the cross-hatched columns. The standard deviation for each determination is given. Note the predominance of epicardial uptake at all levels except for one shock at 200 joules where PYP uptake was minimal. There was no significant difference between the EPI:ENDO ratios at each of the three higher delivered energy levels.

FIGURE 4. Maximal (broken line) and mean (solid line) epicardial PYP uptake related to amount of delivered energy. The difference in uptake between shocks at 400 joules, and one shock at 200 joules is statistically significant (P < 0.05).
magnitude of PYP uptake significantly decreased as both number of discharges and energy decreased and was most notable when comparison was made between data obtained with two 400 W-sec countershocks and one 200 W-sec shock. Similar directional changes were noted in left and right ventricular tissue. Animals receiving one countershock at 200 W-sec demonstrated only minimal pyrophosphate uptake. Microsphere estimates of regional myocardial blood flow in ventricular segments with abnormal PYP uptake were normal, indicating that at the time of study the observed radionuclide uptake was not secondary to an ischemic process (fig. 5).

All samples associated with increased PYP uptake examined histologically and histochemically demonstrated evidence of significant myocardial necrosis manifest by
coagulation necrosis, polymorphonuclear leukocyte infiltration, and hemorrhage (fig. 6). There was general agreement between the qualitative histopathologic assessment of the magnitude of necrosis and the magnitude of abnormal pyrophosphate uptake. The histologic site of necrosis was usually epicardial or midzonal and rarely extended to the subendocardial fibers. This paralleled the site of maximal PYP uptake noted by tissue counting in the same specimens.

An estimate of the extent of damaged myocardial tissue was obtained by summing the weights of all myocardial segments (epicardial or endocardial) defined as abnormal by PYP uptake of at least three times greater than control. The extent of myocardial damage as assessed by this abnormal PYP uptake parameter decreased as the amount of total applied energy similarly decreased (fig. 7).

Discussion

Although the use of direct current countershock for the treatment of major cardiac rhythm disturbances remains a standard clinical procedure, its potential for damaging myocardium in man has not been fully evaluated. Clinical data concerning potential cardiac necrosis following countershock have been derived primarily from analysis of serum enzyme patterns, a technique a recent study found to reflect primarily skeletal rather than cardiac muscle. The cardiac isoenzyme MB was detected in only 2/30 patients who had undergone countershock treatment.

Myocardial necrosis can be regularly noted following repeated countershock in the dog. Dahl et al. have identified several factors associated with development of significant necrosis following this procedure. These include not only the amount of delivered energy but duration between discharges and paddle electrode size. The possibility of myocardial necrosis developing following countershock, a standard clinical tool, and the potential for this procedure to produce abnormal PYP myocardial uptake patterns similar to those found after acute myocardial infarction comprised the impetus for this study.

We have demonstrated significant myocardial uptake of PYP following as little as one 400 W-sec transthoracic countershock in the dog. The uptake of PYP was invariably associated with histochemical and histopathologic evidence of myocardial necrosis, the transmural distribution of which paralleled the transmural pattern of radionuclide deposition. Furthermore, the magnitude of abnormal pyrophosphate uptake increased as the amount of delivered energy increased, and the extent of myocardial damage, as measured by abnormal PYP uptake, likewise increased with an increasing delivered energy input.

The pattern of myocardial radionuclide uptake following direct current countershock can be contrasted to that seen following experimental myocardial infarction. In regions of myocardial infarction, PYP uptake is dependent upon both the presence of cellular damage and the delivery of the radionuclide to the region of compromised blood supply. As a result of the interrelation between these two factors, maximal PYP uptake occurs in regions within the infarct where regional myocardial blood flow is 30-40% of normal. In countershock-induced myocardial injury, 24 hours following perturbation regional myocardial blood flow to the damaged region is normal. Hence, it is not surprising that mean PYP uptake ratios in this study, where delivery of the radionuclide to the damaged region is not a factor, were significantly higher than those seen in infarction.

In the countershock situation, PYP uptake is predominantly epicardial; the pathological site corresponds to the site of major tissue damage. In extremely low flow regions of infarction PYP uptake is similarly concentrated in the epicardium; but in this instance, the site of maximum necrosis is the endocardial portion of the ventricular wall. This somewhat paradoxical situation can be explained by the influences of flow reduction on PYP uptake. In low flow infarct regions, endocardial flow is compromised to greater extent than is flow to the epicardial region. Consequently, a greater amount of PYP is delivered to the epicardial zone. In border zones of the infarct where regional myocardial blood flow is greater than 60% of normal, delivery of PYP to the infarct zone is more adequate and the predominantly endocardial radionuclide uptake parallels the distribution of cell damage more closely.

Both the finding of tissue damage after countershock and the possibility that countershock therapy could diminish the diagnostic accuracy of myocardial PYP uptake in cases of suspected infarction should concern the clinician. So far data are based primarily on animal studies. We recognize that it is difficult to extrapolate these data from the experimental animal laboratory to the clinical situation because of differences in chest anatomy and the amount of applied energy necessary to induce myocardial damage. Recent preliminary reports by Pugh et al. have, in fact, indicated that abnormal PYP images are not following D.C. countershock in man. These authors suggested that, in addition to myocardial PYP uptake, a significant factor in the genesis of these abnormal scintigrams was PYP uptake.
in injured skeletal muscle at the site of paddle application.

In addition, myocardial PYP uptake following countershock provides a potentially valuable investigational means of assessing the adequacy of radionuclide technique in determining the extent of myocardial damage or necrosis. Several studies have used PYP imaging to size anterior and anterolateral myocardial infarction in the dog. Unlike myocardial infarction, the post-countershock experimental model allows such assessment at a time when there are no major alterations in blood flow. Thus, the magnitude and topography of regional myocardial PYP activity in this instance should provide direct quantitative reflections of the magnitude and extent of tissue damage. The use of quantitative myocardial imaging or measurement of tissue radioactivity levels in this situation might allow assessment of the effects of such metabolic interferences as glucose-insulin-potassium in altering the extent of myocardial tissue damage in a single animal or in groups of animals.

Acknowledgment

The technical assistance of John Grella and Carol Orr, and the secretarial assistance of Judy Cuomo are gratefully acknowledged.

References

Myocardial uptake of technetium-99m stannous pyrophosphate following direct current transthoracic countershock.

V C DiCola, G S Freedman, S E Downing and B L Zaret

*Circulation*. 1976;54:980-986
doi: 10.1161/01.CIR.54.6.980

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 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/54/6/980

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/