Estimation of Infarct Size by Myocardial Emission Computed Tomography with Thallium-201 and Its Relation to Creatine Kinase-MB Release After Myocardial Infarction in Man

SHUNICHI TAMAKI, M.D., HISAYOSHI NAKAJIMA, M.D., TOMOYUKI MURAAMI, M.D., YOSHIKI YUI, M.D., HIROFumi KAMBARA, M.D., KAZUNORI KADOTA, M.D., AKIRA YOSHIDA, M.D., CHUICHI KAWAI, M.D., NAGARA TAMAKI, M.D., TAKAO MUKAI, M.D., YASUSHI ISHII, M.D., AND KANJI TORIZUKA, M.D.

SUMMARY We evaluated emission computed tomography (ECT) for thallium-201 (201T1) myocardial imaging in estimating infarct size (IS). In 18 patients in whom IS was estimated enzymatically at the time of the acute episode, planar 201T1 perfusion scintigraphy and ECT with a rotating gamma camera were performed 4 weeks after the first myocardial infarction. From the size of 201T1 perfusion defects, the infarct area in planar images and the infarct volume in reconstructed ECT images were measured by computed planimetry. When scintigraphic IS was compared with the accumulated creatine kinase-MB isoenzyme release (CK-MBr), infarct volume determined from ECT correlated closely with CK-MBr (r = 0.89), whereas infarct area measured from planar images correlated less satisfactorily with the enzymatic IS (for an average infarct area from three views, r = 0.69; for the largest infarct area, r = 0.73). Although conventional scintigraphic evaluation is useful for detecting and localizing infarction, quantification of ischemic injury with this two-dimensional technique has a significant inherent limitation. The ECT approach can provide a more accurate three-dimensional quantitative estimate of infarction, and can corroborate the enzymatic estimate of IS.

THE IMPORTANCE of quantifying infarct size (IS) stems from findings that in both acute and old myocardial infarction, morbidity and mortality are related to the extent of myocardial damage.1-3 In addition, various therapeutic interventions have been proposed that may limit IS4 and possibly improve the patient's chances for survival. Several methods have been developed to measure IS in man,4-11 Radionuclide methods are particularly attractive because they can be used in patients in the intensive care setting and are potentially capable of measuring IS noninvasively.

Experimental studies have shown that myocardial uptake of thallium-201 (201T1) correlates inversely with myocardial creatine kinase (CK) depletion12,13 and relative decrease of myocardial blood flow.14 Clinical studies have proved the efficacy of 201T1 imaging in detecting myocardial ischemia or scar.15-17 Good qualitative relationships between location of 201T1 myocardial perfusion defects and electrocardiography,17 ventriculography,18 cardiac enzymes,19 coronary angiography,17,18 or postmortem studies9 have been reported; but several clinical studies9,19,20 have suggested that the accuracy of planar imaging for sizing myocardial infarction is only fair. With conventional imaging techniques, a three-dimensional structure is compressed onto a two-dimensional image plane, so the extent of the damaged myocardium cannot be determined accurately.
In our institution, single-photon emission computed tomography (ECT) with a rotating gamma camera applied to $^{201}$TI myocardial imaging markedly improved the diagnostic accuracy of myocardial infarction over that of planar imaging. The purpose of this study was to validate and compare the accuracy of $^{201}$TI myocardial tomography in sizing myocardial infarct with that of planar imaging with reference to biochemically measured IS in man.

**Materials and Methods**

**Patients**

The study population included all 18 patients admitted to our coronary care unit from September 1980 through December 1981 who satisfied the following criteria: (1) first acute transmural myocardial infarction diagnosed by typical rise and fall of CK-MB isoenzyme and serial electrocardiographic changes and (2) uncomplicated course after the completion of the enzyme sampling until the time of scintigraphic imaging. Thallium-201 myocardial scintigraphy was performed during the postinfarct convalescence after the patients’ condition had stabilized.

**Enzymatic Estimate of Infarct Size**

Blood samples were withdrawn from an indwelling catheter placed in the pulmonary artery at 4-hour intervals for the first 48 hours and 12-hour intervals for the next 24 hours. Specimens were collected and immediately centrifuged to separate the serum, which was stored at $-70^\circ$C. CK-MB isoenzyme activity was separated from sera by DEAE-Sephadose column chromatography using minicolumns. Enzyme activity of the column eluate was determined according to Rosalki. The coefficient of variation of replicate assays for CK-MB was 5.0%. A Hewlett-Packard computer was used to generate each serum CK-MB time-activity curve, to fit an exponential to the downslope of the curve by the least-squares method, and to derive an individual disappearance constant (Kd) of CK-MB from serum for each patient. The accumulated release of CK-MB (CK-MBr) was calculated using a modification of the original formula of Shell et al. CK-MBr represents the total amount of CK-MB that would appear in the serum in the absence of enzyme disappearance. CK-MBr was used to estimate IS enzymatically in this study (fig. 1).

**Planar Myocardial Scintigraphy**

Myocardial scintigrams were obtained 4 weeks after the onset of myocardial infarction. Each patient received 2 mCi of $^{201}$TI intravenously at rest and was imaged approximately 10 minutes later with a large-field-of-view gamma camera (Gamma-View, Hitachi) equipped with a low-energy, high-resolution, parallel-hole collimator. Anterior, 45° left anterior oblique (LAO) and left lateral scintigrams were recorded on Polaroid film; 300,000 counts were acquired in each view. The scintigrams were also stored as $64 \times 64$ digitized images in the memory disk of a computer (PDP 11, DEC). These images were subjected to weighted nine-point smoothing and were processed by an interpolative background subtraction method described by Goris et al. In processed images, the size of the $^{201}$TI perfusion defect measured by computerized planimetry in the manner of Wackers et al. was expressed as infarct area (cm$^2$) and as a percentage of the total area of the left ventricle in each view. The average size of the defect in three views and the size of the largest defect were used as planar scintigraphic IS. Each scintigram was evaluated independently by two of the authors without prior knowledge of the patient at the time of the study. When discrepancies occurred, repeated measurements were performed at random and persistent discrepancies were averaged.

**Tomographic Myocardial Scintigraphy**

**The Detection System**

Immediately after planar imaging, single-photon ECT of the myocardium with $^{201}$TI was performed. The ECT used in this study consisted of a large-field-of-view gamma camera and a high-resolution, parallel-hole collimator on a tunnel-figured gantry (Maxi 400-T, GE), which rotated 360° around the body of the patient, collecting data from 64 views. Data collection required 22 minutes for myocardial imaging. The data were reconstructed into 12-mm-thick multiple slices in transaxial planes by a filtered back-projection method with Chersler’s filter using a convolution reconstruction algorithm. It took the computer (PDP 11, DEC)
20 seconds to reconstruct each transaxial slice, which was stored as a 64 × 64 matrix on the disk. Attenuation correction was performed by Sorenson’s method.28 Frontal and sagittal tomograms were reorganized from a series of transaxial tomograms. Each reconstructed slice contained 150,000–200,000 counts. The spatial resolution is 17 mm in a full width at half maximum and is nearly independent of the position in the section. Data collection was started from the LAO projection, so the frontal and sagittal tomograms nearly corresponded to the cross section and longitudinal section in relation to the cardiac axis, respectively (figs. 2 and 3).

Evaluation of the Extent of Perfusion Defects

We analyzed the tomograms in the most appropriate section that showed the defect transversely, selecting transaxial sections in anterior myocardial infarction and frontal sections in inferior myocardial infarction. Contiguous slices approximately 12 mm thick were reconstructed to include the entire volume of the myocardium. For most patients, this required four to six slices. These tomographic images were processed by substracting 45% of the maximal radioactivity. In each tomogram, the outer and inner outlines of the myocardial contour were drawn with a light pen. When a defect extended to the periphery of the image, the outline was completed by connecting the adjacent portions of the drawn silhouette circumference. Both the area of the entire myocardium (the region between the two outlines) and the defect area (nonvisualized region) were calculated from each reconstructed tomogram by computer-aided planimetry (fig. 4).

A defect region was defined as one with ⁹⁹mTl uptake less than 45% of the maximal uptake in any image element. This percentage was chosen on the basis of the results of a phantom study. Using a cardiac phantom with various-sized transmural defects,21 the volume of the defect was estimated from ECT images at various cutoff levels to determine the cutoff level that had the best fit with the actual volume. A 45% cutoff method yielded the ECT-estimated volume that was closest to the actual volume of the defect (fig. 5). Therefore, we used the 45% cutoff level in the present study.

The number of image elements occupied by the left ventricular myocardium or perfusion defects in all slices of the reconstructed sections was multiplied by the size factor (0.432 ml per image element) to determine the volume of the total left ventricular myocardium.
um or infarcted myocardium. From these calculations, the volume of infarcted myocardium (ml) and the percentage of left ventricular myocardium infarcted were obtained. Thallium-201 myocardial tomograms were assessed independently by two of the authors, neither of whom had prior knowledge of the results of the enzymatic analysis.

Reproducibility was studied by having the same observer recalculate the same data in 18 patients 1 month later. The interobserver variation was assessed by having a second observer perform these 18 studies without knowledge of the results of the first observer.

Data Analysis

The size of the perfusion defect in planar and tomographic 201Tl myocardial scintigrams of each patient were compared with CK-MBr by linear regression. Correlation coefficients were obtained for each comparison.

Results

Eighteen patients (12 men, six women), ages 40–79 years, were studied. Eight patients had anterior and 10 had inferior myocardial infarctions. All patients had an uncomplicated infarction and had no recurrence of ischemia or myocardial infarction during the study.

Myocardial Emission Tomography with Thallium-201

Figure 2 shows tomographic reconstructions of 201Tl myocardial images and their anatomic orientation in a normal subject. In the transaxial and sagittal sections, the left ventricle appeared horseshoe-shaped. The open end of the horseshoe corresponded anatomically to the mitral and aortic valves. The frontal sections were doughnut-shaped. The absent activity at the center of the doughnut corresponded anatomically to the left ventricular cavity. The distribution throughout the left ventricular walls was nearly homogenous. Right ventricular and atrial activity could not be detected after the background subtraction.

In all patients with myocardial infarction, 201Tl uptake was markedly reduced in areas corresponding to the infarct location. Figure 3 shows frontal tomographic reconstructions and conventional planar images in a patient with inferior infarction. The borders between the normal myocardial activity and reduced activity were abrupt and clearly defined by the tomographic image. The planar image of this patient showed the defect in the tangential view, but the measurement of the extent of the defect was influenced by superimposition of adjacent normal myocardium over regions of reduced perfusion; this superimposition was caused by the two-dimensional display.

Reproducibility of Tomographic Estimate

The intraobserver variation was 2.4 ± 1.5 ml (range 0.4–5.5 ml) for calculations of infarct volume and 2 ± 1.3% (range 0.4–5.0%) for measurements of percent of left ventricle infarcted. The interobserver variation was 2.8 ± 2.5 ml (range 0.5–9.2 ml) for infarct volume and 2.9 ± 2.4% (range 0.5–9.0%) for percent of left ventricle infarcted.

Correlations Between Scintigraphic and Enzymatic Estimates

Table 1 lists the scintigraphic and enzymatic data. The volume of infarcted myocardium determined from ECT correlated closely with CK-MBr (r = 0.89) (fig. 6). Infarct area measured from planar images correlated less satisfactorily with CK-MBr (for an average infarct area from three views, r = 0.69; for the largest infarct area, r = 0.73) (fig. 7).

The IS estimated by ECT or planar images was expressed as infarct volume or infarct area. However, IS has been expressed as a percentage of the left ventricle.9, 24 Table 2 shows the correlation coefficients between the scintigraphic and enzymatic estimates of IS in the 18 patients when scintigraphic IS was expressed in these various ways. Although the use of infarct area improved the correlation of the planar scintigraphic estimate with the enzymatic estimate of IS, the volume

![Figure 4. Estimation of the size of the thallium-201 defect from reconstructed tomographic images. Each tomogram was processed by subtracting 45% of the maximal radioactivity (left). The regions of interest were outlined (middle; N = normal region, D = defect region). In the schematic illustration (right), the dotted area represents the normal region; the solid area, the defect region. Both the area defining a defect (D) and the total area of potential thallium uptake (N plus D) were measured by computerized planimetry.](image)

![Figure 5. Phantom study. Effects of different cutoff levels on relation of the actual volume to the defect volume estimated by emission computed tomography. Solid lines represent the regression relation for each cutoff level. The dashed line is a line of identity.](image)
of infarcted myocardium correlated best with the enzymatic IS.

**Discussion**

Determining IS from CK and CK-MB isoenzyme activity is regarded as by far the best clinically and is the accepted reference method, but its validity is controversial. Because there is no standard for quantifying IS in living patients, other independent methods of describing IS are needed to corroborate the CK and CK-MB methods.

Thallium-201 myocardial perfusion scintigraphy could be a valid means of measuring IS, but its validity is controversial. However, attempts to estimate the size of the perfusion defect by a standard gamma camera technique have been hampered by the constraints of two-dimensional imaging. Tomographic imaging techniques overcome the geometric limitations of the planar scintigraphic methods. Keyes et al. demonstrated that IS can be measured in vivo by ECT with technetium-99m pyrophosphate in experimental myocardial infarction. They also showed the feasibility of calculating viable and infarcted myocardial mass from thallium-201 in an isolated heart model. Vogel et al. reported a higher sensitivity using thallium-201 exercise test with seven-pinhole tomographic imaging compared with planar imaging. However, limited-angle tomography such as the seven-pinhole method has been reported to have severe quantitative limitations that create several distortions because of its physical properties.

We have applied ECT with a rotating gamma camera (360° data collection) to thallium myocardial imaging. This technique increased the accuracy of detecting myocardial infarction compared with planar and seven-pinhole tomographic techniques, and also showed improved quantitative capability. We were interested in testing the infarct-sizing capability in man of our ECT (360° tomography), which used a thallium tracer.

In the present study, visualization of the myocardium by ECT with a rotating gamma camera and thallium tracer, 201Tl

---

**TABLE 1. Clinical, Enzymatic and Scintigraphic Data**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Location of MI</th>
<th>Enzymatic IS CK-MBr (IU/l)</th>
<th>Infarct area on planar images (cm²)</th>
<th>Infarct volume on ECT (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>78</td>
<td>M</td>
<td>Inferior</td>
<td>152</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>F</td>
<td>Anterior</td>
<td>798</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>M</td>
<td>Inferior</td>
<td>372</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>M</td>
<td>Inferior</td>
<td>73</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>M</td>
<td>Anterior</td>
<td>138</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>M</td>
<td>Inferior</td>
<td>94</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>M</td>
<td>Anterior</td>
<td>353</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>M</td>
<td>Inferior</td>
<td>112</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>79</td>
<td>M</td>
<td>Inferior</td>
<td>167</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>F</td>
<td>Inferior</td>
<td>143</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>11</td>
<td>75</td>
<td>F</td>
<td>Anterior</td>
<td>64</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>70</td>
<td>F</td>
<td>Anterior</td>
<td>214</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>13</td>
<td>64</td>
<td>F</td>
<td>Anterior</td>
<td>311</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>40</td>
<td>M</td>
<td>Anterior</td>
<td>268</td>
<td>22</td>
<td>18</td>
</tr>
<tr>
<td>15</td>
<td>60</td>
<td>M</td>
<td>Inferior</td>
<td>121</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>16</td>
<td>50</td>
<td>M</td>
<td>Anterior</td>
<td>224</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>17</td>
<td>77</td>
<td>M</td>
<td>Inferior</td>
<td>52</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>74</td>
<td>F</td>
<td>Inferior</td>
<td>110</td>
<td>13</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviations: MI = myocardial infarction; IS = infarct size; CK-MBr = the accumulated creatine kinase-MB isoenzyme release; 201Tl = thallium-201; ECT = emission computed tomography of the myocardium.

---

**Figure 6.** Correlation between infarct volume estimated by emission computed tomography with thallium-201 and enzymatic infarct size. CK-MBr = the accumulated creatine kinase-MB isoenzyme release. MI = myocardial infarction.
considerably improved the resolution and quantification of myocardial perfusion defects compared with planar imaging. Since the images are effectively three-dimensional, the problem of superimposition of activity of adjacent structures on the myocardial distribution of the tracer, which is inherent in planar imaging, is eliminated. Thus, the tomographic images permit precise localization of myocardial perfusion defects and clearly delineate infarct borders with excellent contrast of infarcted to normal myocardium. Our ECT can reconstruct the transaxial, frontal and sagittal sections of the myocardium because of wide data collection. Therefore, we could choose the myocardial tomograms in the most appropriate section that showed the defect tangentially and thus, we could detect and size inferior myocardial infarcts that could not be accurately assessed in planar images because of inadequate projection of the damaged area.

Clinically, it would be useful to express scintigraphic IS as a percentage of left ventricle infarcted. However, because the enzymatic estimate in this study was not an index of the proportion of the left ventricle infarcted, but an absolute value (the total measurable CK-MBr), correlations between scintigraphic and enzymatic estimates of IS were understandably improved when scintigraphic IS was expressed as infarct volume or infarct area rather than as percent left ventricle infarcted (table 2). The volume of infarcted myocardium determined from ECT correlated closely with CK-MBr (fig. 6). On the other hand, because of the geometric limitations and poor delineation of perfusion defects (fig. 7), planar scintigraphic IS correlated less satisfactorily with enzymatic IS.

Wackers et al. observed that \(^{201}\)TI perfusion defects tend to diminish in size over time after acute myocardial infarction. Silverman et al. reported that large \(^{201}\)TI defects may be associated with small infarcts at postmortem examination, which supports the notion that areas of reduced \(^{201}\)TI uptake represent both ischemia and necrosis in the first few hours of infarction. Our patients were studied at rest 4 weeks after the onset of infarction. By this technique we hoped to measure the fixed myocardial scar. In our study, enzymatic and tomographic estimates correlated closely. This finding indicates that \(^{201}\)TI perfusion defects on resting scintigraphy during the postinfarct convalescence period, as in the present study, appear to reflect the extent of myocardial injury estimated from the enzyme release during the evolving acute infarction, and represent myocardial necrosis rather than ischemia.

Although the present study demonstrated a close correlation between the \(^{201}\)TI perfusion defect on tomography and enzymatic IS, there may be occasional discrepancies between the two techniques. As Strauss et al. mentioned, a comparably close correlation would not necessarily be anticipated between estimates from these two methods in patients with inferior infarction, because the tomographic estimates were confined to the left ventricle, but the enzymatic estimate is influenced by the enzyme release from the frequently concomitantly injured right ventricular myocardium. In this study, no patient with inferior infarction had clinical, hemodynamic or scintigraphic signs of right ventricular involvement.

Recently, positron-emission tomography of the myocardium with carbon-11 palmitate and its use in sizing myocardial infarction have been reported. Carbon-11 palmitate shows a pattern of uptake similar to that of \(^{201}\)TI. Accurate quantification of IS with this technique would be possible because of complete attenuation correction. With single-photon ECT, exact attenuation correction is not yet possible. However, Murphy et al. pointed out that the inability of the

---

**Table 2. Comparison of Various Ways for Expressing Thallium-201 Scintigraphic Infarct Size**

<table>
<thead>
<tr>
<th>Definition of scintigraphic IS</th>
<th>Correlation of scintigraphic IS and CK-MBr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct volume</td>
<td>( r = 0.89 )</td>
</tr>
<tr>
<td>Percent of LV infarcted</td>
<td>( r = 0.85 )</td>
</tr>
<tr>
<td>Planar images</td>
<td></td>
</tr>
<tr>
<td>Average in three views</td>
<td></td>
</tr>
<tr>
<td>Infarct area</td>
<td>( r = 0.69 )</td>
</tr>
<tr>
<td>Percent of LV infarcted</td>
<td>( r = 0.66 )</td>
</tr>
<tr>
<td>The view with the largest defect</td>
<td></td>
</tr>
<tr>
<td>Infarct area</td>
<td>( r = 0.73 )</td>
</tr>
<tr>
<td>Percent of LV infarcted</td>
<td>( r = 0.67 )</td>
</tr>
</tbody>
</table>

Abbreviations: \(^{201}\)TI = thallium-201; IS = infarct size; CK-MBr = the accumulated creatine kinase-MB isoenzyme release; ECT = emission computed tomography of the myocardium; LV = left ventricle.
single-photon ECT system to correct fully for attenuation did not appear to be a significant drawback, especially in the case of such a small organ as the heart. A major advantage of the single-photon approach is the applicability of widely available low-energy pharmaceuticals. We believe that ECT with \(^{201}\)TI can provide geometrically reliable three-dimensional sections of the myocardium.

As for single-photon ECT, Ritchie et al.\(^4\) reported that the spine interferes with visualization of the left posterolateral segment and that this segment therefore can be deleted. We also attempted a 180° rotation mode without collecting data from the posterior half of the myocardium, which did not cause any apparent image distortions.\(^2\) An incomplete rotation method can reduce the imaging time and makes ECT more practical. Moreover, this method may be applicable for ECG-gated myocardial tomography to minimize distortions of the image.

The definition of boundaries of infarcted myocardium used in this study may have limitations. The assumption of completely circular boundaries for the myocardium was used in the experiment of Keyes et al.\(^3\) We manually traced and measured the region by planimetry. Although our results show that the reproducibility is acceptable, computer applications for an objective method for quantifying the extent of \(^{201}\)TI perfusion abnormalities may provide even greater accuracy in sizing myocardial infarcts.

In conclusion, ECT for \(^{201}\)TI myocardial imaging with a rotating gamma camera can provide more accurate three-dimensional quantification and detection of both infarcted and residual viable myocardium in comparison with planar imaging, and can corroborate enzymatic estimates of IS.

Acknowledgment

We gratefully thank Yukisono Suzuki, M.D., for his cooperation throughout these studies, and Joseph Nicholson for his assistance in preparation of this manuscript.

References

28. Sorenson JA: Quantitative measurement of radioactivity in vivo by whole body counting. In Instrumentation in Nuclear Medicine, vol
201TI EMISSION CT IN INFARCT SIZING/Tamaki et al.

2. edited by Hine GJ, Sorenson JA. New York, Academic Press, 1974; p 311


Estimation of infarct size by myocardial emission computed tomography with thallium-201 and its relation to creatine kinase-MB release after myocardial infarction in man.
S Tamaki, H Nakajima, T Murakami, Y Yui, H Kambara, K Kadota, A Yoshida, C Kawai, N Tamaki, T Mukai, Y Ishii and K Torizuka

Circulation. 1982;66:994-1001
doi: 10.1161/01.CIR.66.5.994

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 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/66/5/994

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/