Detection and Quantitation of Myocardial Infarction
In Vivo Using Transmission Computed Tomography

PAUL W. DOHERTY, M.B., MARTIN J. LIPTON, M.D., WALTER H. BERNINGER, PH.D.,
CLAES G. SKIOLDEBRAND, M.D., ERIC CARLSSON, M.D.,
AND ROWLAND W. REDINGTON, PH.D.

SUMMARY In vivo studies were performed on 28 dogs to evaluate the usefulness of transmission computed
tomography (CT) in the detection and quantitation of experimentally induced myocardial infarction. In
travenously administered contrast material was required to define the internal structure of the heart and to
differentiate normal from infarcted tissue. Transmural infarcts with homogeneous central regions were
visualized as areas of diminished contrast enhancement compared with the normal myocardium. All
transmural infarcts of at least 24 hours' duration showed a surrounding border zone of patchy necrosis that
was variable in size and had high CT numbers due to slow washout of the contrast material from this region.
Infarct area determined from the images for individual slices correlated well \( r = 0.976 \) with that calculated
using pathology. The technique is very sensitive and can detect infarction within a papillary muscle. Non-
transmural or patchy infarcts show up as areas of diffuse contrast enhancement without a central core of
diminished enhancement. The distribution of the contrast material is similar to that of technetium-99m
pyrophosphate in the border zone of the infarct in infusion studies, but in bolus studies it behaves more like
thallium-201.

IN VIVO computed transmission tomography (CT) adds to noninvasive cardiac imaging the capacity for
high spatial resolution imaging. CT studies of myocardial infarction in vitro\(^1\) suggested the value of this
technique in the detection and quantitation of myocardial infarcts. It was believed that with the scan times
available, cardiac motion would prevent practical application.\(^2\) In this feasibility study, performed using
experimentally induced myocardial infarctions in dogs, the capability of a whole-body scanner, which
has a scan time of 4.8 seconds, to provide useful images was assessed. The studies were aimed at answer-
ing the following questions:

1. How early after coronary arterial ligation can infarcts be identified in vivo?
2. Must the scans be performed with contrast enhancement, and if so, is it better to deliver the con-
   trast agent by infusion or by bolus?
3. How well does infarct size determined by CT scanning correlate with histopathologic measure-
   ments?
4. How do the findings on CT scans relate to those obtained with the standard imaging agents, thallium-
   201 and technetium pyrophosphate?
5. What are the advantages of ECG gating?

Materials and Methods

Instrumentation

These studies were performed using a whole-body scanner (General Electric CT/T 7800) with software
and hardware modifications designed to permit rapid sequence scanning and retrospective ECG gating. The
data for the gated reconstructions were obtained retrospectively by selecting appropriate views from a
series of scans taken with a simultaneous continuous recording of the ECG as previously described.\(^3\) The
gating window was typically about 100 msec, and by using a time overlapping sequence, up to 24 gated im-
ages per cardiac cycle could be displayed in a non-
flicker cine mode similar to those obtained with gated
isotope studies. Special display software permitted
reformatting of the display data from a series of con-
tiguous axial slices into any plane (coronal, sagittal or
oblique). Image data were scaled in accord with the
old Hounsfield (± 500) scale, in which 5 units corre-
spond to approximately 1% of the attenuation co-
efficient of water.

Imaging and Contrast Enhancement

Before imaging, the fasting dogs were anesthetized
with sodium pentobarbital (30 mg/kg), paralyzed with
succinylcholine (2 mg/kg), intubated, and ventilated
with a Harvard dual-phase respirator using humid-
ifed room air. The dogs were held supine in a Plexi-
glas cradle and placed head first in the scanner. The
level of the cardiac apex was found by palpation
and marked on the chest. This reference mark was used
with the instrument's alignment lights to position the
dog in the scanner. A series of scans was obtained
without contrast medium from the apex to the base of
the heart at 1-cm intervals to confirm the position of
the heart and to act as control scans. Respiration
was suspended at full inspiration throughout the duration
of each scan. Scans were then repeated with contrast enhancement. The contrast medium, meglumine diatrizoate (Renografin 76), was administered through a 19-gauge intercath placed in a peripheral vein. In the method used for infarct area determination in this study, the dye was infused, using a Harvard infusion pump, at a rate of 7 ml/min for 10 minutes; then the infusion rate was reduced to 2 ml/min. The measurements were made near the start of the slow-infusion phase. This method produced a nearly constant contrast differential between the ventricular chambers and the myocardium during the slow-infusion stage, and this differential was readily apparent in the reconstructed images.

ECG-gated studies were also performed during the slow-infusion phase. During the gating study, the heart rate was kept below 100 beats/min using a combination of propranolol and morphine sulphate administered by intermittent bolus doses. Ventricular arrhythmias were suppressed by infusion of lidocaine. The CT infarct area was defined as an area in the reconstructed image, taken during infusion, that had a substantially lower CT number than either the normal myocardium or the ventricular cavity. Calculation of this CT infarct area from the images first involved visual identification. Then the mean CT numbers and the standard deviation were computed for a rectangular region of interest within the CT infarct area (fig. 1). The boundary was defined by the density contour inside which all the pixels had a CT number within 1 standard deviation of the calculated mean value. The area was computed by the number of pixels enclosed by the boundary, multiplied by the pixel area (1.7 mm²). Once the initial region of interest was defined, the rest of the procedure was accomplished automatically without operator intervention. The CT infarct area was then compared with the infarct area determined pathologically in the corresponding slices.

The washout of contrast medium was studied using repeated scans either after a bolus injection or after termination of an infusion. Regions of interest were defined within the left ventricular cavity, the normal myocardium, the infarct center and the zone surrounding the infarct. The mean CT number in these regions was then plotted vs time. For the bolus studies, 2-3-second doses (10-20 ml) of contrast medium were hand injected and the transit of the bolus through the circulation was followed using a rapid sequence of scans at the same level. The injection commenced at the beginning of the first scan of a sequence, which typically consisted of six 4.8-second duration scans with 1.2-second interscan delay. Each level studied required a separate injection.

**Animal Preparation and Correlative Studies**

Twenty-eight adult mongrel dogs that weighed 17-28 kg were used in this study. Five acted as normal controls and the rest had myocardial infarcts produced by coronary ligation via a left thoracotomy. Anterior infarcts were produced in 16 dogs by ligating the proximal left anterior descending coronary artery just distal to the first septal perforator, and posterior infarcts were produced in seven dogs by ligating the

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Transverse tomographic slices through the left ventricle at the level of the posterior papillary muscle 3 cm above the apex taken during an infusion of contrast medium. (left) An anterior transmural infarct is seen as the dark area with very little contrast enhancement. (right) The infarct contour had been outlined and the area calculated using information derived from the computed tomographic numbers within the rectangular regions of interest.
circumflex coronary artery distal to the origin of the first marginal branch. Eight dogs were imaged within 12 hours of infarction. Four of these were scanned at hourly intervals after ligation for 6 hours. The others were first scanned between 24 and 72 hours. Nine were first marginal branch. Eight dogs were imaged within periods of 4 months. In the dogs in whom CT and pathologic infarct sizes were compared (n = 8), all the infarcts were 24-48 hours old. After the dogs were sacrificed with an overdose of pentobarbital, the hearts were removed and the left ventricle was dissected free from the rest of the heart. It was then sliced in rings 1 cm thick from apex to base. The rings of myocardial tissue were stained with nitroblue tetrazolium, the regions that did not take up the stain were traced on transparent paper and the area was calculated by planimetry. In two cases after the scans had been completed, the dogs were frozen in position in order to preserve the anatomic relationships that existed in vivo and were then cut into 1-cm-thick transverse slices with a band saw.

The distribution of contrast material at tissue level was determined from the postmortem distribution of 131I-labeled contrast medium injected 10 minutes before sacrifice. This was correlated (n = 4) with a microsphere determination of blood flow and with measurement of thallium-201 (1.5 mCi 10 minutes before sacrifice) and technetium-99m pyrophosphate uptake (10 mCi 45 minutes before sacrifice).

The ring where the infarct was most prominent on nitroblue tetrazolium staining was further sliced into sections passing from normal tissue to infarct border into the infarct center, with as many as 20 specimens obtained from each slice and further cut so that the endocardial layers were separated from the epicardial layers. Samples were placed in 10% buffered formalin solution and counted in a Hewlett-Packard gamma spectrometer. Window settings were selected to correspond to the peak energies for each radionuclide, and appropriate correction for scattered radiation and decay were performed. Results were expressed as counts/min per 0.1 g of tissue. After counting, selected samples from the border zone and infarct center were processed in a conventional manner for histology7 and sections were stained with hematoxylin-eosin. The presence of infarction was documented by light microscopic examination of the sections.

Results

When the heart is imaged in vivo without gating or contrast enhancement in animals with a normal hematocrit, one cannot reliably distinguish either internal architecture or areas of myocardial infarction from the rest of the heart. Sharp definition of the pericardial lung interface is present without apparent motion blurring in the nongated images. However, if ventilation is not controlled, streak artifacts often occur, which originate from intrascn movement of the high-contrast ribs. A clear distinction between the cardiac chambers and the myocardium is obtained when scanning is performed with contrast enhancement (fig. 2). The lowest slices show only the left ventricular myocardium and cavity. When the right ventricle comes into view, the septum, which lies between the right and left ventricles, is sharply outlined. Good definition of both the posterior and anterior papillary muscles is obtained. Proceeding cranially, a gap appears posteriorly in the left ventricular myocardial ring corresponding to the level of the mitral valve, and at this level one can frequently obtain a four-chamber view on a single slice (fig. 2). In the upper slices, the

Figure 2. (left) Ungated, 1-cm-thick slices in a normal dog selected from an apex-to-base survey (S9-15) with contrast infusion. Posteriorly, a defect in the myocardial ring occurs at the level of the mitral valve. (right) A slice showing a four-chamber view. The contour of the ventricles has been enhanced in the display. RV = right ventricle; LV = left ventricle; RA = right atrium; LA = left atrium; ANT PAP MUSC = anterior papillary muscle; POST PAP M = posterior papillary muscle.
right ventricular cavity has a more anterior position and the right and left ventricular outflow tracts can be followed up to the junction with the pulmonary artery and aorta, respectively. In normal dogs, the myocardium shows almost homogeneous opacification.

When dogs with homogeneous transmural myocardial infarcts were imaged during and after contrast infusion, three classes of tissue were apparent (figs. 3 and 4). These three classes of tissue could be distinguished by the kinetics of contrast uptake and washout (fig. 5). The normal myocardium opacified at a rate approximately 50% lower than the ventricular cavity. The infarct center showed only slight enhancement compared with the normal myocardium. Surrounding the infarct was a border zone that opacified, during infusion runs, at a rate similar to the normal myocardium. However, the washout time constant was approximately six times larger than that of normal myocardium. Figure 6 shows the good correlation that was found on comparison of the area of the unenhanced myocardium determined from the CT image data taken during infusion with that obtained postmortem \( r = 0.976, y = 0.861 x + 0.33 \). The CT infarct area consistently tended to underestimate infarct size in slices with small amounts of infarcted tissue (fig. 6). The smallest area of infarction in the slices measured 0.35 cm\(^2\) from a dog whose total infarct weight was 1.3 g. The extreme sensitivity of the technique for detecting small regions of infarct can best be demonstrated from the example (fig. 4) in which we could visualize infarction within the posterior papillary muscle.

The configuration of the border zone was that of an overlying dome, which was most prominent at the junction between the infarct and the normal tissue at its lateral boundary and which extended anteriorly in the superficial epicardial layers. This phenomenon was not usually present in the endocardial layers, but did occur in two dogs with left anterior descending coronary artery infarcts, where the proximal portion of the infarcts had taken up a midmyocardial position. A comparison of images from the beginning of an infusion study and those during the washout phase showed that the border zone sometimes appeared, in the later images, to have extended into the region initially devoid of contrast. When scanning was performed in the first 12 hours after ligation, the border zone was only apparent in three of eight dogs, the earliest being at 6 hours. All 16 dogs studied 24–72 hours after ligation had a border zone. The size of the border zone appeared to be greatest by 48 hours and was still evident in the two dogs studied 3 months later.

Using the bolus technique (fig. 7), the area subsequently identified as infarcted was imaged as a perfusion defect in three of four dogs studied within 1 hour of ligation. The defect region encompassed both the infarct center and the border zone. In the bolus measurements, neither the infarct center nor the border zone showed significant contrast enhancement compared with the normal myocardium. In dogs with

---

**Figure 3.** Serial apex-to-base slices from left to right in a dog with an anterior transmural infarct: (A) without contrast, (B) during contrast infusion (the infarct is visualized as the dark areas) and (C) during washout phase, showing persistence of contrast in the border zone.
either patchy or predominantly subendocardial infarcts (n = 5), no central core of unenhanced myocardium was visualized during infusion (fig. 8). However, the region including the infarcted tissue could still be detected by bolus injection as a perfusion defect.

The ECG-gated scans were performed on animals with infarction (n = 7) and in normal controls (n = 5). Wall motion abnormalities (fig. 9) were detected in all the infarct animals at the site of the infarct, and were not seen in the normals. The gated scans, compared

**Figure 4.** (A) Large transmural posterior infarct, which involves the posterior papillary muscle (middle image). The contour of the infarct has been enhanced in the display. (B) Transverse slice through myocardium in plane of scan showing the infarct involvement of the posterior papillary muscle (arrows).

**Figure 5.** Change in computed tomographic number, with time computed from various regions of interest in a series of scans performed during the infusion and washout of contrast. Open arrows indicate when syringes were changed; solid arrow shows time infusion was stopped.
Three of these were identified by the bolus method and the two not seen by either technique were small subendocardial infarcts. One of these was identified when a repeat study was performed 48 hours after ligation. The false-positive result was caused by increased contrast present on the surface of the heart.

**TABLE 1. Sensitivity and Specificity for Detecting Infarction**

<table>
<thead>
<tr>
<th>Pathology</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>+</td>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>-</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{TP}{TP + FN} = 0.916 \)
Specificity = \( \frac{TN}{TN + FP} = 0.833 \)
Positive predictive value = \( \frac{TP}{TP + FP} = 0.956 \)
Negative predictive value = \( \frac{TN}{TN + FN} = 0.714 \)
Accuracy = \( \frac{TP + TN}{TP + FP + TN + FN} = 0.9 \)

Abbreviations: CT = computed tomography; TP = true positive; TN = true negative; FP = false positive; FN = false negative.
associated with an area of lung atelectasis. Two technically inadequate studies were not included in the analysis. One had artifacts produced by air in the pericardium and another had excessive adhesions and lung collapse producing gross cardiac distortion. In the eight dogs in which repeat studies were performed within 1 hour, the findings were reproducible. The four dogs in which the tissue distribution studies were performed had transmural infarcts. Histologically, the infarct centers consisted of a homogeneous population of cells that showed poor staining and relaxed myofibrils with hypereosinophilic cytoplasm, whereas the border zone showed foci of normal cells interlaced with a pleomorphic group of cells. These cells showed a variable degree of myofibril disruption, frequent contraction bands, and some had basophilic cytoplasm. There was a greater degree of neutrophil infiltration in the border than in the center. The highest concentration of $^{18}$I-labeled contrast medium and technetium-99m pyrophosphate occurred in the tissues that histologically contained predominantly border zone tissue, at both the lateral boundaries of the infarct and in the epicardial layers (fig. 11). Compared with normal tissue, the maximum ratios were

**Figure 8.** Patchy anterior infarct. (A) During infusion, the infarct areas show increased contrast, with no central core of diminished enhancement. (B) Persistence of contrast seen in washout part of the study.

**Figure 9.** End-diastolic (SI), end-systolic (S12) and two intermediate gated images (S8,18). A gating window of 100 msec from a cardiac cycle of 500 msec was used. The contour of the chambers has been enhanced in the display. Note lack of motion in posterolateral wall to right of papillary muscle, which was infarcted.
Discussion

The results of this investigation, although based on a small number of observations, show that diagnostically useful CT images of the heart can be obtained in vivo with an instrument that has a scan time of 4.8 seconds. To obtain images that provide useful anatomic and physiologic information, contrast enhancement was essential. Infarct regions can be detected as areas of reduced contrast (cold-spot imaging) as soon as the coronary artery is ligated. However, we could not demonstrate contrast enhancement (hot-spot imaging) reliably until 24 hours after ligation, findings similar to those with thallium and pyrophosphate. We could not confirm the findings of Powell et al., who showed a progressive decrease in CT number in the infarct region within 3 hours after ligation, which they suggested was due to edema formation. In fact, on a blind basis, we could not consistently locate the infarct in the early hours in a noncontrast scan. With 24-48-hour-old infarcts, some scans did show decreased absorption in the infarct region (fig. 3A), but not at a quantitatively useful level. The difference between our in vivo study and the in vitro studies could be due to differences in technique or animal preparation, or might result from the artifact level associated with scanning the heart in an intact, living animal.

The 10-ml bolus injection provides a transient peak of contrast enhancement in the myocardium greater than that seen with the infusion. It shows the infarct as an unenhanced perfusion defect compared with the contrast enhanced normal tissue. This provided a higher differential in CT number between the normal myocardium and the infarcted tissue than the infusion method. Sometimes, it was the only method to demonstrate the acute infarction site when the dogs were studied within 24 hours of ligation. The defect is not, however, specific for actual infarction; similar findings are obtained when a coronary artery is transiently occluded and represents, at tissue level, an area of myocardium that is not being perfused at the time of the scan. The images obtained with the bolus technique have more artifacts and are not of as high quality as those obtained during infusion, because of the rapid changes in density that occur in the heart while the scan is being performed, which produce motion artifacts in the reconstructed image.

The infusion technique provides a steady state for collecting ECG-gated data and also allows slices from multiple levels to be obtained. It can be used to detect homogeneous infarcts as unenhanced areas surrounded by a region of contrast enhancement, with scans obtained during the steady-state or washout phase. The differences in CT number were approximately 30 and were proportional to the total amount of contrast injected. This difference was most prominent on images obtained during the washout phase, about 10 minutes after the infusion was terminated. The maximum difference was more than 180 units when contrast was injected directly into the coronary arteries. It is the best method for detecting the area of increased contrast enhancement in the border zone. We usually used about a 70-ml dose of contrast medium. We have shown that by increasing the infusion rate to 15 ml/min, good-quality scans can be obtained within 2 minutes, reducing the total dose to less...
than 50 ml. However, one has to balance the advantages of using a lower total dose with the risk of producing undesirable hemodynamic changes, particularly with acute infarction. The enhanced region around the infarct, which we have shown is due to slow washout of contrast, which is predominantly an intravascular tracer,\(^9\) appears similar to that observed in some brain scans.\(^{10-11}\) Using excitation analysis to detect the presence of iodine, Higgins et al.\(^{12}\) showed that the maximum ratio between normal and infarcted myocardium was 8:1 and occurred 180 minutes after injection, in agreement with our in vivo data.

Delayed contrast enhancement shown with the infusion technique is a good marker for the presence of myocardial damage because it is not seen when the coronary artery is transiently occluded for as long as 10 minutes.\(^{13}\) Its absence in the early hours of infarction, the way it surrounds transmural infarcts and its prominence throughout regions with predominantly subendocardial or patchy infarction are features that have been observed with pyrophosphate imaging.\(^{14}\) Differences do exist, however. For example, the zones of contrast enhancement and high pyrophosphate uptake are only partially overlapping. The zone of contrast enhancement includes more peripheral tissue, while the zone of pyrophosphate uptake extends more toward the center of the infarct (fig. 11). The zone of contrast enhancement and high pyrophosphate uptake include normal, ischemic and foci of infarcted myocardium. Thus, our CT infarct area measurements described above represent only the homogeneously infarcted region. Previous pyrophosphate studies and the in vitro CT studies included the border zone as part of the infarct volume. However, this choice counts the admixed normal and ischemic tissue in the border zone as infarcted. Thus, neither choice provides a definitive measurement of the total area of infarcted muscle. Infarct size evaluation in patchy or predominantly subendocardial infarcts was not attempted in this study because the presence of areas of normal myocardium intermingled with infarcted tissue in these contrast-enhanced regions precludes a simple analysis.

The results of our in vivo study can be compared with those of Gray et al.,\(^4\) who studied isolated arrested hearts using a head scanner. Both studies show that infarcts as small as 1 g can be identified and that there is a consistent tendency to underestimate infarct size. Their correlation with homogeneous transmural infarcts (\(r = 0.80\)) was lower than ours (\(r = 0.96\)). They correlated infarct volume with infarct weight and we used infarct area on both the CT scan and on postmortem. Determination of volume from CT area measurements has been reported\(^{15}\) in an application involving the measurement of ventricular cast volume. A similar procedure is used to calculate infarct volume, i.e., the CT infarct area is multiplied by the slice thickness and contributions from all slices are added to give the total volume. Their correlation with anterior infarcts was better (\(r = 0.94\)) than their homogeneous transmural infarct result.

The distribution relationships between pyrophosphate and thallium-201 with flow measured with microspheres agree with those of other workers.\(^16\) The \(^{131}\)I measurement of contrast distribution is similar to that of pyrophosphate in the periphery or border zone of transmural infarcts. In the homogeneously infarcted center the \(^{131}\)I shows behavior similar to thallium. Experimentally, these flow and distribution measurements correspond to an infusion washout. The thallium-like behavior is useful in bolus studies where it provides "cold-spot" imaging with potential for early infarct detection. The pyrophosphate was injected 30 minutes before the contrast and this may well explain its better penetration into the infarct center.
The 4.8-second ungated myocardial scan produces an image with data collected over five to 10 heart cycles, depending on the heart rate, and thus represents some average over the heart cycle. Motion-blurring artifacts large enough to obviously degrade these contrast-enhanced images were present in only a minority of cases. In the region of the infarct itself, good images of the infarcts can be obtained on the ungated scans, because there is very little intrinsic motion. The principal value of ECG gating in these studies was the demonstration of abnormal wall motion associated with the infarcts. The present system's gating window of 7–10% of the cardiac cycle is short enough to perform these qualitative wall motion studies. However, calculation of slice ejection fraction from-area time curves yields values that are less than the true value because of an overestimation of end-systolic and an underestimation of end-diastolic dimensions.4 The reformatted images in the coronal and sagittal planes, although not adding any new information not available in the individual slices, did provide images in the right anterior oblique and left anterior oblique views, which can be useful when comparing the results with studies performed with other methods such as contrast or isotope angiography.

The advantages of CT for infarct sizing are those generally associated with CT: spatial resolution approaching 1 mm and the ability to demonstrate local contrast absorption coefficient differences equivalent to 0.5% of the absorption coefficient of water. These measurements are much better than those available with either gamma scintillation cameras18 or emission tomographic scanners.19-20 However, the vascular contrast medium used with CT is detected only as a change in absorption and, moreover, does not have the specificity provided by tracer-labeled compounds involved in metabolism. Compared with biplane cineangiography, it allows an unambiguous differentiation of epicardial vs endocardial changes. Its principal disadvantage is that it is not truly noninvasive. It requires injecting a significant amount of contrast medium, which has the risk of allergic reaction and may present problems associated with myocardial depression and arrhythmias. Dosimetry must also be considered. For the infusion method, a typical human dose would be 1.5 rads. The bolus method and retrospective gating both require a number of scans at the same cross section that increases the dose proportionally. The radiation dose for the infusion method, which was used for the size comparison, is similar to or lower than that of other infarct sizing methods.

Acknowledgment

The authors express their appreciation for the technical assistance of J. Gray, R.T., and for the development of software modifications by W.M. Leue, B.A.

References

Detection and quantitation of myocardial infarction in vivo using transmission computed tomography.

P W Doherty, M J Lipton, W H Berninger, C G Skioldebrand, E Carlsson and R W Redington

doi: 10.1161/01.CIR.63.3.597

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 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/63/3/597

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/