Myocardial Infarct Quantification in the Dog by Single Photon Emission Computed Tomography

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SUMMARY  Radionuclide techniques for sizing acute myocardial infarction have been hampered by the intrinsic limitations of the scintillation camera. Emission computed tomography can overcome these limitations. Single photon emission computed tomograms of the distribution of technetium-99m pyrophosphate in acute anterior and posterior infarcts were obtained in 16 dogs after death. Tomograms were also obtained in 10 dogs during life without gating. The size of the infarcts was determined by staining gross sections of the heart with nitro blue tetrazolium, dissecting out the infarcted tissue and weighing it. Infarct sizes were determined from the tomographic images and compared with the measured infarct sizes. Good images showing the location and three-dimensional extent of the infarcts were obtained in all dogs. The measured and calculated infarct sizes correlated well ($r = 0.85$). Comparison of the calculated sizes in the living (non-gated) and dead ("physiologically" gated) animals showed reasonable agreement ($r = 0.87$). Single photon emission computed tomography is a feasible and useful technique for localizing and sizing acute myocardial infarctions.

ACCURATE QUANTIFICATION of acute anterior myocardial infarction by radionuclide techniques has been demonstrated by a number of investigators.\(^1\)\(^-\)\(^6\) Extension of these techniques to infarcts in other portions of the myocardium has been hampered by a fundamental problem in conventional radionuclide imaging. Conventional imaging techniques represent a compression of three-dimensional structure onto a two-dimensional image plane. Areas of the myocardium such as the left ventricular anterior free wall which can be seen "head on" can be accurately measured from such simple projective images. Other areas of the myocardium, such as the inferior or posterior portions of the myocardium which are seen "edge on," cannot be so accurately assessed. A method is needed to depict the three-dimensional distribution of radionuclides within the myocardium. The techniques of emission computerized tomography (ECT) offer such a method.\(^4\)

Most work done in the area of ECT imaging of the heart has used positron-emitting radionuclides. In contradistinction to positron emitters, virtually all of the radionuclides in medical use today are single photon emitters, i.e., unlike positron emitters they do not give off a pair of opposed gamma rays during radioactive decay. Most of the readily available nuclear medicine imaging equipment is thus designed for imaging single photon emitting radionuclides. A technique which combines this available single photon radiopharmaceutical and imaging technology with the benefits of computerized tomography could be an advantage. This approach, which we shall call single photon ECT, has been investigated in our laboratory for several years. This paper presents the results of a feasibility study on the application of single photon ECT to the problems of myocardial imaging and myocardial infarct quantification.

Materials and Methods

All studies were conducted using a single photon emission computed tomograph, the Humongotron, which has been previously described.\(^7\) Studies were performed using either of two parallel hole collimators in a mode which gave a system response function of between 15-18 mm full width at half maximum.

All studies were performed using a canine model for acute myocardial infarction. Mongrel dogs of either sex weighing between 11-18 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg). The dogs were intubated and ventilated with room air using a Harvard respirator. Using aseptic surgical technique, a left thoracotomy was performed in the fourth or fifth intercostal space and the pericardium was opened. Anterior infarcts were produced by isolating the left anterior descending coronary artery (LAD) below the tip of the left atrial appendage. The LAD was occluded partially for 30 minutes by tying a silk ligature around both the vessel and a 20 gauge hypodermic needle and then removing the needle. The artery was then totally occluded with a second silk ligature. Posterior infarcts were produced by the method described by Lucchesi et al.\(^8\) The left circumflex artery (LCX) was isolated proximal to its first branch. This vessel was first partially occluded as described for the LAD and was then totally occluded with a Silastic tubing ligature. After 60 minutes of total occlusion, the Silastic ligature was released and partial flow was permitted to resume. The thoracotomy was closed, and in most cases a 48-hour
period was allowed for recovery. In one dog the recovery period was 24 hours, and in one dog 72 hours. A total of 16 dogs survived the recovery period and form the basis for these studies.

After the recovery period, the dogs were anesthetized again with sodium pentobarbital (20 mg/kg) and injected with 15 mCi of technetium-99m pyrophosphate. Imaging was begun 60–90 minutes later. As our present tomographic system incorporates no provisions for gating, all dogs were imaged tomographically immediately after sacrifice to "physiologically" model the effects of gating. In addition, 10 dogs were also imaged tomographically immediately before sacrifice to provide an ungated series of images for comparison. Between 20–30 minutes were required for each set of images. Anterior, left anterior oblique, and left lateral conventional scintigrams were taken for orientation and comparison immediately after completing the tomographic imaging.

Twenty to 90 minutes after sacrifice, when all imaging was complete, the heart was removed and sectioned in 10 mm thick slices cut perpendicular to the base-apex axis. In most cases, an image of the slices was obtained by placing them directly on the face of the gamma camera collimator to provide a comparison with the tomographic reconstructions.

Gross morphological measurements of infarct size were obtained by incubating the slices for 15–20 minutes at 37°C in a solution of nitro blue tetrazolium (NBT) and phosphate buffer. A deep blue color develops where intracellular dehydrogenases exist in undamaged tissue. The infarcted and/or damaged ischemic regions which are depleted of dehydrogenases appear as unstained pale zones that can be easily differentiated from the normal, undamaged myocardium. Lucchesi et al. have reported that tissue samples taken from areas of infarct as demarcated by NBT show pathological evidence of necrosis.8

The stained slices were traced onto clear acetate sheets to provide a record of infarct location and extent. The damaged tissue was then removed by careful dissection and weighed. The right ventricular wall was removed and the left ventricle, including the septum plus the damaged tissue, was weighed to yield the total left ventricular weight.

Computer reconstructed tomograms of each dog were obtained using a filtered backprojection algorithm without attenuation correction. Contiguous slices approximately 8 mm thick were reconstructed to include the entire volume of myocardium. For most dogs this required five to eight sections. The total volume of myocardial infarct was determined for each dog from the reconstructed tomograms by first subtracting an average background and then setting a rectangular region of interest around the infarct. Within this region a least squares, second order polynomial was fitted to the data and the magnitude of the gradient of this function was approximated by selecting the maximum of four directional derivatives (0°, 45°, 90°, 135°) at each point. The infarct boundary was plotted by tracking the maximum gradient. This was done for each section demonstrating the infarct. The boundary so determined is always oversize because of the poor spatial resolution of the system relative to the infarct dimensions. To compensate for this a threshold set equal to the highest average count density in the series of sections was then applied to the outlined infarct in all sections. Points within the infarct boundary above the threshold were considered to represent the true infarct. The total number of picture elements representing infarct in all sections of the reconstruction were then multiplied by an appropriate size factor (0.128 cc per picture element) to determine the total volume of infarcted tissue. This volume was then multiplied by average myocardial density (1.05 g per cc) to yield a weight value which could be compared with the measured myocardial infarct weight.

Results

Figure 1 shows tomographic reconstructions of a posterior infarct compared to conventional scintigraphic images, and is representative of the quality of images produced by this technique. In almost all studies there was excellent correlation between the location and extent of the infarct as visualized on the tomographic studies compared to the gross morphology of the infarct. This was true with very small infaracts (including two infarcts under 3 g) and infarcts which were subendocardial rather than transmural. The single exception was a dog in which an acute anterior myocardial infarction was difficult to separate from the overlying ribs and sternum.

Table 1 lists the 16 animals studied showing the type of infarct, the measured size of the infarct from the NBT-stained sections and the corresponding calculated infarct size. We were able to obtain an estimate of the infarct size from the tomographic reconstructions in all cases.

There was a good correlation between the size of the infarcts determined from the gross sections and the size of the infarcts determined from the tomographic reconstructions. The r value for all studies was 0.85. There is a systematic tendency to overestimate the size of the smaller infarcts as shown by the slope of the regression line, which is 0.8. This is discussed further below, and these relationships are illustrated in figure 2. Figure 2 also shows the relationship between the measured and calculated infarct sizes for those dogs with anterior myocardial infarctions and those with posterior infarctions. The r values for these two subgroups were 0.83 and 0.88, respectively.

For the 10 animals which were imaged during life

Figure 1. Posterior infarction. A and B are conventional anterior and left lateral views. C through F are tomographic sections viewed from above with anterior surface of chest up. Section C is near the base of the heart; subsequent sections are progressively more caudal.
without gating, there was little appreciable degradation in overall image quality compared to the reconstructions obtained in the same animals after death. The infarct sizes calculated in the living animals showed a good correlation ($r = 0.87$) with the sizes calculated after death and with the measured sizes ($r = 0.86$). There was, however, a tendency to underestimate the size of larger infarcts in the ungated studies (table 2).

### Table 1. Infarct Sizing in the Non-Beating Heart

<table>
<thead>
<tr>
<th>Dog</th>
<th>Site of occlusion</th>
<th>Total measured left ventricle size (g)</th>
<th>Infarct measured size by NBT (g)</th>
<th>Infarct calculated size (g)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LAD</td>
<td>74.2</td>
<td>20.1</td>
<td>14.3</td>
<td>Large subendocardial infarct</td>
</tr>
<tr>
<td>2</td>
<td>LCX</td>
<td>76.7</td>
<td>11.8</td>
<td>7.7</td>
<td>Very small subendocardial infarct</td>
</tr>
<tr>
<td>3</td>
<td>LAD</td>
<td>77.9</td>
<td>19.7</td>
<td>17.4</td>
<td>Very small subendocardial infarct</td>
</tr>
<tr>
<td>4</td>
<td>LCX</td>
<td>48.2</td>
<td>2.9</td>
<td>4.7</td>
<td>Massive infarct. Illustrated in figure 1</td>
</tr>
<tr>
<td>5</td>
<td>LCX</td>
<td>59.8</td>
<td>15.9</td>
<td>13.7</td>
<td>Massive infarct. Images show decreased tracer in center of lesion</td>
</tr>
<tr>
<td>6*†</td>
<td>LCX</td>
<td>57.6</td>
<td>27.7</td>
<td>22.1</td>
<td>Images show decreased tracer in center of lesion</td>
</tr>
<tr>
<td>7*</td>
<td>LAD</td>
<td>56.2</td>
<td>14.7</td>
<td>20.9</td>
<td>Images show decreased tracer in center of lesion</td>
</tr>
<tr>
<td>8*</td>
<td>LCX</td>
<td>56.9</td>
<td>2.9</td>
<td>9.4</td>
<td>Images show decreased tracer in center of lesion</td>
</tr>
<tr>
<td>9</td>
<td>LAD</td>
<td>77.1</td>
<td>30.0</td>
<td>35.9</td>
<td>Discuss infarction sizes</td>
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<tr>
<td>10*†</td>
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<td>14.9</td>
<td>13.2</td>
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</tr>
<tr>
<td>11*</td>
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<td>70.0</td>
<td>17.5</td>
<td>15.3</td>
<td>Discuss infarction sizes</td>
</tr>
<tr>
<td>12*</td>
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<td>69.8</td>
<td>7.6</td>
<td>12.8</td>
<td>Discuss infarction sizes</td>
</tr>
<tr>
<td>13*</td>
<td>LCX</td>
<td>49.3</td>
<td>9.7</td>
<td>14.3</td>
<td>Discuss infarction sizes</td>
</tr>
<tr>
<td>14*</td>
<td>LAD</td>
<td>65.0</td>
<td>11.7</td>
<td>16.3</td>
<td>Discuss infarction sizes</td>
</tr>
<tr>
<td>15*</td>
<td>LCX</td>
<td>49.4</td>
<td>10.8</td>
<td>11.8</td>
<td>Discuss infarction sizes</td>
</tr>
<tr>
<td>16*</td>
<td>LAD</td>
<td>66.2</td>
<td>24.9</td>
<td>26.6</td>
<td>Discuss infarction sizes</td>
</tr>
</tbody>
</table>

*Also imaged live – see table 2.  
†Imaged 24 hours post-infarction.  
Imaged 72 hours post-infarction.  
Abbreviations: LAD = left anterior descending; LCX = left circumflex.

### Discussion

These results indicate that the technique of ECT can be successfully applied to the imaging of the myocardium using conventional single photon emitting radionuclides. By using a scintillation camera as the basic detector in an emission computed tomograph, most of the problems inherent in conventional scintillation camera imaging of the myocardium are eliminated, while the advantages of camera imaging are retained. Since the images are effectively three-dimensional, the problem of superimposition of non-myocardial foreground and background activity upon the myocardial uptake of tracer is eliminated so that the final images have excellent contrast.

This ability to depict accurately the myocardial distribution of radionuclides in three dimensions is also the major advantage of the technique for the quantification of infarct size. Although accurate sizing of myocardial infarctions using conventional scintigraphy has been demonstrated for anterior myocardial infarctions which can usually be seen "head on" so that the entire area of the infarct can be measured, there has been little success in applying these techniques to the quantification of posterior and inferior myocardial infarctions which are only seen on edge in conventional scintigraphic images. The present study demonstrates that infarcts in the latter areas can be equally well sized using ECT.

Several aspects of the present study require critical examination. Chief among these are the problems of attenuation correction and image resolution.

All of the reconstructions in the present study were done without correction for the attenuation of radiation which occurs within the body of the subject. Such attenuation produces significant distortions in tomographic images of the distribution of radio-
activity. In general, the distortions produced are in the relative activities depicted in various areas of the tomogram rather than in the spatial relationships of the activity distribution. Consequently, attenuation corrections must be applied during the reconstruction process if the resulting images are to be used to quantify the amount of activity present. As our purpose was to quantify the volume occupied by the radioactivity rather than the absolute amount of activity present in that volume, we were able to disregard the need for attenuation correction.

The results of our study demonstrate empirically that accurate volumetric quantification of myocardial infarcts is possible even though the actual amount of radioactivity present in the infarct may not be accurately measured by the technique. In part, these good results may be a consequence of the high target to non-target contrast present in pyrophosphate images of acute infarcts. It seems quite likely that for ECT with low contrast agents such as thallium-201, or in situations with greater attenuation, such as the human chest, attenuation correction will be necessary even for accurate depiction of spatial relationships. It will certainly be necessary for quantitative measurements of the true amount of activity present in the myocardium. Should the need for attenuation correction arise, there are several techniques known for accomplishing this with single photon ECT systems.9,10

The relationship of the resolution of the imaging system to the results obtained with that system is also important. The resolution of our ECT system is approximately 15–18 mm, expressed as a system response function, meaning that the transaxial tomographic image of a thin (1 mm) line source is an approximately Gaussian function having a full width at half maximum of 15–18 mm. This response function can be viewed somewhat simplistically as a proportionality constant which relates the object to the image. A specific response function does not imply that this is the smallest object that can be imaged, nor that quantitative information about objects smaller than this cannot be extracted from images of those objects. If this proportionality is known, some quantitative information can still be obtained by appropriate image processing techniques, even for very small objects.

We have used a combination of maximum gradient edge finding followed by thresholding to extract true infarct size from our images. The tendency of this technique to overestimate the size of smaller infarcts reflects the fact that it is difficult to totally remove the effects of system resolution, particularly for objects smaller than the system response function. The better the system resolution, the easier it becomes to accurately measure spatial relationships. We feel that single photon ECT systems with resolutions on the order of 6–10 mm are feasible with current technology.

A problem which we cannot explain is the tendency of our technique to underestimate the size of larger infarcts in ungated studies on beating hearts. This may be related to heart movement, which is uncompensated by our edge finding technique; but why this should disportionately affect larger infarcts is unclear.

The models which were chosen for anterior and posterior wall infarcts also deserve special comment. A reflow model was chosen for the posterior wall infarcts, primarily because it improves the survival of animals subject to acute circumflex occlusion. Since the uptake of pyrophosphate in acutely infarcted tissue in part depends on residual blood flow,11 it is possible that this technique could lead to enhanced uptake and hence detection of infarcts in this area. However, the problems in sizing posterior and inferior wall infarcts have not been due to difficulty in detecting the infarct, but to problems in the geometry of this area as it is seen in conventional scintigrams. The primary advantage to the ECT presentation is in eliminating this geometrical problem. Also, we found little difference in accuracy in sizing anterior infarcts which did not employ reflow as compared to posterior infarcts. Hence, we do not feel that our choice of models contributed significantly to the results we obtained.

Ongoing developments in ECT raise the possibility of widespread availability of this technique in the future and significantly enhanced clinical usefulness. At least one commercial manufacturer is field testing a single photon emission transaxial tomograph which incorporates two opposed wide-field-of-view gamma cameras. Use of such a system with proper collimation should permit images of the myocardium with 1 cm or better resolution and imaging times of under 10 minutes. Such instrumentation capability, together with further advances in radiopharmaceuticals, offers good potential for the application of these techniques to clinical problems.

Conclusions

Single photon ECT of the myocardium is a feasible method for accurately quantifying the size of acute myocardial infarctions. The technique produces images of good quality which, in effect, depict the distribution of radionuclides within the myocardium in three dimensions. The resulting images are volumetrically accurate and can be used to quantify the size of a myocardial infarction. The technique appears promising for clinical trials in humans. Re-
cent advances in available instrumentation and radio-pharmaceuticals promise even further improvement in the future.

References
Myocardial infarct quantification in the dog by single photon emission computed tomography.
J W Keyes, P F Leonard, S L Brody, D J Svetkoff, W L Rogers and B R Lucchesi

Circulation. 1978;58:227-232
doi: 10.1161/01.CIR.58.2.227

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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