Assessment of Drug Intervention on the Ischemic Myocardium: Serial Imaging and Measurement With Computerized Tomography

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Computerized tomography was evaluated as a technique for imaging and measuring the effect of an intervention on acutely ischemic myocardium. Because cell edema occurs with acute myocardial ischemia and decreases the X-ray attenuation coefficients (tissue density) of myocardium, computerized tomographic images were used to quantitate the effect of hyperosmotic mannitol on ischemia-induced edema. Canine hearts were arrested and scanned after (1) temporary occlusion of the proximal circumflex artery followed by reflow of blood, or (2) continued occlusion of the distal left anterior descending coronary artery. X-ray attenuation values (Hounsfield units) were linearly related to tissue wet/dry weight ratios ($r = 0.87, P < 0.001$). After 2 hours of occlusion of the left anterior descending coronary artery the hearts that received mannitol manifested a significant reduction ($P < 0.05$) in the volume of left ventricular wall involved with edema. Although the area of edema measured with computerized tomography tended to be smaller in the hearts treated with mannitol than in untreated hearts subjected to a 6 hour occlusion of the left anterior descending coronary artery, the size of the lesion was variable and did not differ significantly from that in untreated hearts. With either short periods of circumflex arterial occlusion followed by blood reflow, or with 2 or 6 hours of prolonged occlusion of the left anterior descending coronary artery, the difference in mean attenuation coefficients between the ischemic and nonischemic areas of myocardium in mannitol-treated and untreated hearts was significantly less.

These results indicate that computerized tomography in the arrested heart can detect and quantitate the lesion of early acute myocardial ischemia and can quantitate the effect of drug intervention.

Computerized tomography is a relatively new radiologic technique for imaging cross-sectional anatomy. This method has been successfully used for imaging of cardiac structures and pericardial effusions as well as noncardiac structures. The computerized tomographic picture is a map of tissue densities, represented mathematically as a matrix of X-ray attenuation coefficients, and it is possible with use of this map to detect differences of 0.5 percent between small adjacent points of the matrix of the scan. This high degree of contrast resolution permits differentiation of edematous and normal tissue.

Although the major emphasis today in the treatment of acute ischemic heart disease is on the detection and subsequent amelioration of acute ischemia associated with myocardial infarction, there is no entirely satisfactory biochemical or electrocardiographic means of quantitating the extent and severity of ischemia. Thus, it is difficult to evaluate the effect of various therapeutic interventions intended to decrease the severity of this precursor of eventual myocardial necrosis. Previous work has demonstrated that computerized tomography can detect edema that occurs with acute myocardial ischemia. The lesion of edema

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appears as a region of decreased X-ray attenuation coefficients compared with those of normal myocardium.12

Previous work from our laboratory16-17 documented that intracell edema occurs with acute myocardial ischemia in dogs. The extent of such edema during the early ischemic process correlates with the extent of eventual myocardial necrosis.19 Elevation of the extracell osmolality with an agent that remains mostly extracellular in a canine model of total interruption of blood flow followed by blood reflow is capable of reducing the extent of cell swelling and of bringing about a parallel reduction in the extent of eventual cell necrosis.16-18

Although hyperosmotic mannitol has not been shown to reduce the area of eventual necrosis in other canine models of ischemia, we chose this agent for our study because it has been documented to reduce cell swelling early in ischemia.16-18 We used it in this study as an intervention to examine the effectiveness of computerized tomography in detecting a possible change in edema during early myocardial ischemia.

Thus, in this study we attempted to test the sensitivity of computerized tomography in assessing changes in the amount and degree of ischemia in the heart. Specifically, we examined the ability of this procedure to quantify the extent and severity of edema associated with acute ischemia with and without elevation of the extracellular osmolality with hyperosmotic mannitol. Our studies were performed using a model of total interruption of blood flow to a region of the canine heart followed by blood reflow and a model of low flow myocardial ischemia.

Methods

Computerized tomography scans: These scans were performed with an EMI cranial scanning unit (EMI, Ltd., Hayes, Middlesex, England). The characteristics of this scanning unit have been described elsewhere.20-23 Each point in the matrix (160 by 160) of the scan represents a block of tissue 1.5 by 1.5 by 8 mm and is projected with a 10 level gray scale image with black corresponding to the lowest density of X-ray attenuation and white to the highest density. The numerical values corresponding to each of these blocks of tissue (attenuation coefficients or Hounsfield units) are scaled relative to water, with water arbitrarily having a value of 0, bone +500 and air −500.

Experimental protocol: In 18 dogs, after thoracotomy, a reversible snare was placed around the proximal circumflex branch of the left coronary artery within 2 cm of its origin. In 10 of these dogs, the proximal circumflex artery was subjected to occlusion with the snare for 45 minutes followed by 15 minutes of reflow of blood. In the remaining eight dogs, occlusion for 60 minutes was followed by 45 minutes of reflow. In this dog model, arterial occlusion associated with tightening of the snare produces complete and reproducible interruption of blood flow to the tip of the posterior papillary muscle.24,25

In each experimental protocol, half of the animal group received hyperosmotic mannitol (12.5 g/90 cc) intravenously for 30 minutes (15.3 cc/min for 15 minutes and 7.6 cc/min for 15 minutes) with a Harvard infusion withdrawal pump (model 600-000), and half received a control saline infusion for the same period of time. These infusions were begun 15 minutes before release of the arterial occlusion and continued through the first 15 minutes of reflow of blood to elevate the serum osmolality early during the reflow period.17 After the reflow period, each heart was arrested, perfused with formalin and scanned after contrast enhancement of the cardiac chambers with 30 percent meglumine diatrizoate (Reno-M-dip®, Squibb Laboratories).6,11,12

In 21 additional hearts, after thoracotomy, the left anterior descending coronary artery was ligated one third of the distance from its origin to the apex. In each heart the major collateral arteries to the distal portion of the ligated left anterior descending coronary artery were also ligated. In one group of four dogs the heart was scanned after removal from the thorax after 90 minutes of coronary occlusion. In a second group of nine dogs, five received hyperosmotic mannitol as described between 90 and 120 minutes of occlusion, and four received a control saline infusion. After 120 minutes of coronary occlusion the hearts in these nine dogs were then removed from the thorax and scanned. In a third group of eight dogs, four received hyperosmotic mannitol intravenously at 7.6 cc/min for 60 minutes between the third and fourth hours of occlusion, and four received a control saline infusion. After 6 hours of arterial occlusion the hearts of these eight dogs were then removed from the thorax and scanned. In all of these experiments the investigator performing the surgery did not know which hearts would receive mannitol.

Analysis of anatomic sections and tomographic scans: After computerized tomographic scanning, each heart was sliced manually into 8 mm transverse sections approximately corresponding to the plane of the tomographic scan. Each anatomic section of the heart was compared with the corresponding scan to verify structural identification (Fig. 1, top). Because the model of the circumflex arterial occlusion results in reproducible ischemia at the tip of the posterior papillary muscle, wet/dry weight ratios were determined for the tips of the ischemic posterior papillary muscles and for the control nonischemic anterior papillary muscles. In the hearts that underwent ligation of the left anterior descending coronary artery and major collateral vessels, the ischemic area of the sliced specimen was identified from the scan, and the corresponding transmural section of myocardium was obtained for wet/dry weight ratios. A control nonischemic area of myocardium was obtained from the opposite wall of the heart. Precise localization of the lesion in the cut specimen was more difficult in the hearts with ligation of the left anterior descending coronary artery. The muscle to be weighed was blotted on wax paper to remove excess blood, and the wet and dry weights were determined as previously described.11

The numerical printout (Fig. 1, bottom) of the scan matching each anatomic section from which the samples were taken was used for analysis of attenuation values. The endocardial and epicardial surfaces were outlined on these printouts. Regions corresponding to the papillary muscles and the underlying mid myocardium and epicardium were outlined as shown by the labeled hatched areas in Figure 1. The mean attenuation coefficient (in Hounsfield units) of the numbers within each area was determined. Matrix elements in the borders between ventricular cavity and endocardium, as well as those between Ringer's lactate and epicardium, were excluded because individual attenuation values are altered if the tissue they represent fails to occupy the full 1.5 by 1.5 by 8.0 mm³ volume of any matrix element. This is known as the partial volume phenomenon.26

Statistical analysis: Mean tomographic scan numbers and wet/dry weight ratios (expressed as percent water) for each sample were compared using linear regression analysis.27 For each protocol the differences between the mean tomographic
scan numbers of the ischemic and nonischemic areas of hearts and the extent of left ventricular wall involvement with and without mannitol intervention were compared using Student's t test. Where confidence limits are indicated, they always refer to the standard error of the mean. Probability (P) values were based on the single tailed t test.

Results

Attenuation coefficients of myocardium from all 39 hearts as a function of percent water content (Fig. 2): The data are from areas of ischemic and nonischemic myocardium, both with and without hyperosmotic mannitol administration. As can be seen, a linear correlation is present whether or not extracellular osmolality was elevated with mannitol. The best fit regression line without mannitol was not significantly different from that obtained with the administration of mannitol.

Extent of left ventricular wall involved: The ischemic lesion was defined as consisting of tomographic scan numbers of less than 25, a value greater than 2 standard deviations below the average tomographic scan value of normal myocardium (28.4 ± 1.6 standard deviation). The results of evaluating the extent of left ventricular wall involvement by edema associated with myocardial ischemia (the percent of attenuation coefficients with a value of less than 25) for the experiments with 45 minutes of circumflex arterial occlusion followed by 15 minutes of reflow of blood are shown in Figure 3. Figure 3 shows the data from five hearts that did not receive mannitol and from five additional hearts that received mannitol during the last 15 minutes of occlusion and the first 15 minutes of reflow of blood. Within each group of experiments, there is variability of the extent of wall involvement. Three hearts that did not receive mannitol had a lesion in more than 30 percent of the left ventricular wall, and only one heart, given mannitol had a lesion involving more than 30 percent of the left ventricular wall; this difference was not statistically significant (Table IA). Similarly, the extent of left ventricular wall involvement with attenuation coefficients of less than 25 was not significantly altered by the administration of hyperosmotic mannitol in the experiments with 60 minutes of circumflex arterial occlusion followed by 45 minutes of reflow (Table IB). In the model of left anterior descending coronary arterial occlusion, hyperosmotic mannitol resulted in a significant reduction (P < 0.05) in the extent of left ventricular wall involvement after 120 minutes of arterial occlusion (Table II A). Although the hearts given mannitol had a mean reduction in the extent of wall involvement in the experiments with 6 hours of arterial occlusion, the reduction was not significant (Table II B).
Effect of hyperosmotic mannitol on ischemia: The evaluation of the mean tomographic scan numbers of the ischemic and nonischemic areas of the hearts revealed that administration of hyperosmotic mannitol ameliorated the change in attenuation coefficient produced by ischemia in the experiment with 45 minutes of occlusion and 15 minutes of reflow (Table IA) and in both prolonged arterial occlusion protocols (Table II). However, in the severely ischemic model, which involved 60 minutes of proximal circumflex arterial occlusion followed by 45 minutes of reflow, the difference in attenuation coefficients between the ischemic and nonischemic papillary muscles was not narrowed by the administration of hyperosmotic mannitol (Table IB).

In the experiments with occlusion of the left anterior descending coronary artery, a lesion of decreased density was consistently seen in the anteroseptal region of the myocardium (Fig. 4). The administration of hyperosmotic mannitol narrowed the difference in attenuation coefficients between the ischemic anteroseptal region and the nonischemic posterior wall region (Fig. 5). This was accomplished with the administration of mannitol between 90 and 120 minutes after the onset of occlusion in those hearts that were scanned after 120 minutes of occlusion (Table IIA). Narrowing of the difference in attenuation coefficients was achieved with administration of mannitol between 3 and 4 hours after the onset of occlusion in those hearts that were subsequently scanned after 6 hours of occlusion (Table IIB).

Serum osmolality: Both the occlusion and reflow protocols were associated with a mean elevation of serum osmolality of 44 mOsm/liter (from 303 ± 2 to 347 ± 2 mOsm/liter in the 45 minute occlusion, 15 minute reflow experiments, and from 293 ± 6 to 337 ± 5 mOsm/liter in the 60 minute occlusion, 45 minute reflow experiments). In the experiments with left anterior descending coronary arterial ligation, the osmolality elevations were 30 and 27 mOsm/liter in the two protocols (from 316 ± 7 to 346 ± 4 in the 120 minute occlusion experiments and from 306 ± 5 to 333 ± 4) at the end of the 4th hour of the 6 hour occlusion experiments.

In the 6 hour occlusion experiments, the osmolality was still elevated at 323 ± 10 mOsm/liter at the 6th hour.

Discussion

Myocardial edema on computerized tomography as a reflection of ischemia: The data indicate that computerized tomography can assess the extent and severity of an acute ischemic process and has potential for evaluating the effect of a drug intervention. With computerized tomography providing a quantitative...
index of density changes, the effect of hyperosmotic mannitol on the edema associated with acute myocardial ischemia was imaged and measured. The differences in attenuation coefficients were small after administration of hyperosmotic mannitol. However, the technique does appear to possess the potential of quantitating the severity of edema in segments of ischemic myocardium.

Under conditions in which coronary blood flow is interrupted for a brief period and then reinstated or in the situation of low flow myocardial ischemia, elevation of the extracellular osmolality with the administration of mannitol is capable of reducing the severity of edema detected with computerized tomography. It is likely that the severity and extent of the edematous lesion, early during acute myocardial ischemia, have prognostic significance. Previous work has demonstrated that the extent of eventual cell necrosis in areas of ischemic myocardium correlates with the number of cells with histologic evidence of intracellular water accumulation early during the ischemic process. Computerized tomography quantitates only total water present in ischemic myocardium rather than providing a differential quantitation of intracellular versus extracellular distribution of water. However, the work of Whalen et al., who used the same occlusion and reflow model used in our study, suggests that most of the water gain in acutely ischemic myocardium is intracellular. Our previous studies, using the same experimental model, demonstrated that the reduction of intracellular water gain with hyperosmotic mannitol administered in the presence of acute ischemia is associated with a parallel reduction in the extent of eventual myocardial necrosis. Thus, when the data from all of these studies are combined, the use of computerized tomography to quantitate the acute reduction of myocardial edema associated with ischemia appears to provide a method of evaluating ischemic myocardium that is potentially of prognostic relevance.

Our data support the conclusion that computerized tomographic numbers reflect changes in tissue water because they are linear over a wide range of wet/dry weight ratios. This linear relation is not significantly altered by the administration of hyperosmotic mannitol. It is as yet unknown whether other effects may contribute to a reduction in the attenuation coefficients of the ischemic area in addition to the established effect of tissue edema.

<table>
<thead>
<tr>
<th>TABLE I</th>
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<tr>
<td>X-Ray Attenuation Coefficients of Hearts Undergoing Circumflex Artery Occlusion and Reflow</td>
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<table>
<thead>
<tr>
<th>Intervention</th>
<th>Extent LV Involved (%)</th>
<th>Control APM</th>
<th>Ischemic PPM</th>
<th>∆</th>
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</thead>
<tbody>
<tr>
<td><strong>A. 45 Minute Circumflex Arterial Occlusion, 15 Minute Reflow</strong></td>
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<td></td>
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</tr>
<tr>
<td>Saline solution</td>
<td>28.3 ± 3.3</td>
<td>28.0 ± 0.8</td>
<td>20.7 ± 1.0</td>
<td>7.3 ± 1.3</td>
</tr>
<tr>
<td>Mannitol</td>
<td>23.4 ± 7.9</td>
<td>29.9 ± 0.6</td>
<td>26.7 ± 1.3</td>
<td>3.2 ± 1.2</td>
</tr>
<tr>
<td><strong>B. 60 Minute Circumflex Arterial Occlusion, 45 Minute Reflow</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Saline solution</td>
<td>27.0 ± 4.1</td>
<td>28.2 ± 1.2</td>
<td>20.9 ± 0.2</td>
<td>7.3 ± 1.3</td>
</tr>
<tr>
<td>Mannitol</td>
<td>18.7 ± 5.8</td>
<td>29.6 ± 0.6</td>
<td>21.9 ± 7.0</td>
<td>7.8 ± 0.9</td>
</tr>
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APM = anterior papillary muscle; ∆ = difference between control and ischemic values with each intervention. LV = left ventricle; NS = not statistically significant at the probability (P) <0.05 level; PPM = posterior papillary muscle.

<table>
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<tr>
<th>TABLE II</th>
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<tr>
<td>X-Ray Attenuation of Hearts Undergoing Permanent Occlusion of the Left Anterior Descending Coronary Artery (LAD)</td>
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</table>

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Extent LV Involved (%)</th>
<th>Control PLV</th>
<th>Ischemic ALV</th>
<th>∆</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. 120 Minute LAD and Major Collateral Occlusion</strong></td>
<td></td>
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<tr>
<td>Saline solution</td>
<td>11.5 ± 0.7</td>
<td>29.4 ± 0.5</td>
<td>25.7 ± 0.7</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>Mannitol</td>
<td>7.7 ± 1.6</td>
<td>27.6 ± 0.5</td>
<td>24.9 ± 0.5</td>
<td>2.7 ± 0.1</td>
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<tr>
<td><strong>B. 6 Hour LAD and Major Collateral Occlusion</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Saline solution</td>
<td>15.2 ± 2.5</td>
<td>28.2 ± 0.5</td>
<td>23.8 ± 1.0</td>
<td>4.4 ± 0.7</td>
</tr>
<tr>
<td>Mannitol</td>
<td>11.7 ± 2.3</td>
<td>29.2 ± 0.5</td>
<td>27.9 ± 0.7</td>
<td>1.3 ± 0.8</td>
</tr>
</tbody>
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ALV = anterior left ventricle; LV = left ventricle; NS = not significant at the probability (P) <0.05 level; PLV = posterior left ventricle.
Effect of hyperosmotic mannitol on intracellular water and myocardial ischemia: The use of computerized tomography to quantitate the effect of hyperosmotic mannitol on edema in acutely ischemic myocardium will most likely underestimate rather than overestimate the extent of eventual salvage. In this study, the administration of hyperosmotic mannitol diminished significantly the severity of edema in the posterior papillary muscle after 45 minutes of occlusion of the proximal circumflex artery and 15 minutes of reflow of blood. However, it was not possible to detect with computerized tomography an effect of hyperosmotic mannitol on the edematous process after a more severe insult of 60 minutes of arterial occlusion followed by 45 minutes of reflow of blood. Our previous study, using the same protocols to produce myocardial ischemia, demonstrated that intracellular water accumulation, determined from histologic assessment of sarcolemmal elevation, was reduced with either of the two durations of arterial occlusion and that the extent of eventual necrosis was reduced in parallel. It is possible that a relatively modest reduction in intracellular fluid may be associated with a substantial enhancement of eventual myocardial salvage. Furthermore, reactive hyperemia may lessen the difference in attenuation coefficient between ischemic and nonischemic myocardium, because blood has the same attenuation coefficient as nonischemic heart muscle. Whatever the mechanism, it appears unlikely that quantitation of the reduction of edema in acutely ischemic myocardium with computerized tomography will result in an inflated estimate of the extent of eventual myocardial salvage.

Our finding that the administration of hyperosmotic mannitol can diminish the density difference (and the wet/dry weight ratio difference) between the ischemic and the control nonischemic areas of myocardium suggests that mannitol has an effect that is greater in ischemic than in nonischemic myocardium. The mechanism for the augmented effect remains to be determined. It is possible that this augmentation is related to the removal of more water from the ischemic area than from the nonischemic area or, alternatively, that it is related in part to a direct effect on the perfusion deficit with a secondary relief of tissue edema due to enhanced blood flow to the ischemic area. Clinical implications: The current study was carried out under optimal imaging conditions with arrested

![Figure 4](https://example.com/fig4.png)

**Figure 4.** Tomographic scan of a heart after 6 hours of permanent ligation of the left anterior descending coronary artery and its major collateral vessels. Note the lesion of decreased density in the anteroseptal region of the heart. LV = left ventricle; RV = right ventricle.

![Figure 5](https://example.com/fig5.png)

**Figure 5.** A, difference in density (Hounsfield units) between the ischemic anteroseptal region of myocardium and the normal posterior myocardium in hearts that underwent permanent ligation of the left anterior descending coronary artery (LAD) and its major collateral vessels as a function of time. Each point on the graph represents data collected from a group of four or five hearts. Note that the administration of mannitol for 30 minutes during occlusion decreased the difference in density between ischemic and normal myocardium (closed circles) compared with that of a control group of animals (open circles) (P < 0.003). B, difference in density (Hounsfield units) between ischemic anterior myocardium and control posterior myocardium in four different groups of four to five dogs each as a function of time. Note that the administration of hyperosmotic mannitol between the 3rd and 4th hours of permanent occlusion of the left anterior descending coronary artery and its major collateral vessels resulted at the 6th hour of occlusion in a significant (P < 0.02) decrease in the density difference. Data from hearts not receiving mannitol are depicted as open circles. Data from hearts receiving mannitol are depicted as closed circles.
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The degree of resolution in our study cannot currently be obtained with beating hearts, although progress is being made in defining cardiac structures in the intact human heart with the use of gating.20,21 Our study does demonstrate that with these limitations, a currently commercially available device for computerized tomography can detect the edematous lesion associated with acute myocardial ischemia and can quantitate the effect of an intervention administered to reduce intracellular edema.

Acknowledgment

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References

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