Evaluation of Myocardial Ischemic Damage of Various Ages by Computerized Transmission Tomography

Time-dependent Effects of Contrast Material

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The potential role of computerized transmission tomography (CTT) in the detection and quantitation of acute myocardial ischemic damage was assessed in 42 excised canine hearts at 2 hours, 8 hours, and 48 hours after coronary occlusion. The CTT scan detected myocardial damage that was 2–48 hours old each time the presence of regional ischemia was confirmed by histochemical staining or epicardial electrocardiographic mapping. Intravenous administration of contrast material enhanced the x-ray attenuation of areas of ischemic damage of 8 and 48 hours duration compared with normal myocardium, but enhanced only normal myocardium in those of 2 hours duration. Volumetric estimation of the extent of damage from the CTT scans in dogs with ischemia of 48 hours duration showed a close linear relationship with the morphometric volume in the absence of contrast material. Quantitation of the area of ischemic damage from the CTT scan after contrast administration resulted in substantial underestimation of the volume of damaged tissue.

The capacity of computerized transmission tomography (CTT) to detect regions of myocardial ischemic damage has been shown in the nonbeating canine heart. Ischemically damaged myocardial tissue appears on the CTT scan as an area of decreased x-ray attenuation compared with the surrounding normal myocardium. The mechanism of this altered x-ray attenuation has been related to edema formation within the ischemically damaged tissue. Studies from our laboratory have revealed that the CTT scan was not only sensitive in detecting areas of myocardial damage 48 hours after coronary arterial ligation, but was also relatively accurate in quantitating the actual volume of this area.

After coronary arterial occlusion, ischemic changes evolve in the jeopardized myocardium, including loss of integrity of the myocardial cellular membranes, increased microvascular permeability, inflammatory cellular infiltrate, and finally, fibrotic replacement of myocardial cells. This dynamic process is characterized in the early phase by edema of the infarcted myocardium and in the late phase by fibrous replacement of myocardial tissue. Consideration of this time-related dynamic process suggests that the CTT image of a myocardial infarction and its interaction with radiographic contrast material may change with time.

The purpose of the current study was to: 1) determine the capacity of the CTT scan to detect myocardial ischemic changes at various time intervals after...
coronary occlusion; 2) define the earliest time interval after occlusion when ischemically damaged myocardium could be detected by computed tomography; 3) evaluate the effect of systemically administered contrast material on the CTT image of areas of myocardial ischemic damage of various ages; and 4) determine the accuracy of the CTT scan in quantitating the volume of regional myocardial damage in the presence and absence of systemically administered contrast material.

Method

Regional myocardial ischemic damage was produced in 42 adult mongrel dogs by ligation of a major branch of either the left anterior descending (four dogs) or circumflex (38 dogs) coronary arteries. Nine of the dogs were included in an earlier report. Seven sixteen dogs were sacrificed at 2 hours, eight dogs at 8 hours, and 18 dogs at 48 hours after coronary occlusion. All four dogs in which a branch of the left anterior descending artery was ligated were sacrificed at 48 hours, without having received contrast material. Some dogs sacrificed at each of the three time intervals received meglumine sodium diatrizoate (2 ml/kg) i.v. in a bolus 5 minutes before sacrifice. This contrast material contains 370 mg iodine/ml.

After the dogs were sacrificed with an overdose of pentobarbital sodium, the hearts were excised, washed, placed in a water bath, and scanned in an EMI cranial scanner (160 × 160 matrix). Scans were accomplished within 2 hours after sacrifice. Contiguous pairs of scans were commenced at the apex and proceeded to the base of the heart, using 8- and 13-mm collimators at 140 kilovolt peak (kvp) and 28 mA. Polaroid prints of the computed tomographic image at a window width of 50 units and 80 × 80 digital computer printouts of the EMI attenuation coefficient values were obtained for each heart. A window level of 30–34 was used in dogs that did not receive contrast material and a level of 36–42 in those that received contrast material.

The presence of myocardial ischemic damage was assessed by one or two methods. An area of myocardial ischemic injury was reflected by epicardial electrocardiographic mapping in dogs sacrificed at each of the time intervals. This was performed in a predetermined grid-like pattern over the exposed surface of the heart. Elevation of an ST segment by more than 2 mV at 30 minutes after ligation compared with the control epicardial map confirmed the presence of ischemic injury. This method had to be relied upon alone in the 2-hour-old infarctions, because the histologic appearance on light microscopy and the histochemical staining characteristics do not become abnormal until at least 6-8 hours after the onset of ischemia.

After completion of the computerized tomographic scan, the hearts excised at 8 and 48 hours were sliced transversely at 11-mm intervals. These slices corresponded to the thickness of the computerized tomographic sections, which with a nominally 13-mm collimator has been shown to be 11 mm. Histochemical staining was then performed by incubating the myocardial slices in a solution of nitroblue tetrazolium in phosphate buffer at pH 7.4 for 15 minutes. The precise area of the ischemic damage on the superior and inferior surface of each histologic slice was traced on a clear film overlay and the area measured by planimetry. From the measured area, the radius of an equivalent circle was calculated. Assuming that the shape of the infarcted tissue approximated that of a truncated cone, the volume of the infarcted tissue was calculated using the following formula of a truncated cone:

\[ V = \frac{\pi h}{3} \left( r_1^2 + r_1 r_2 + r_2^2 \right) \]

The damaged area delineated on each CTT section was determined by visual inspection and measured by planimetry. These area measurements were performed after optical magnification (3.3-fold) of the CTT sections. The volume of each infarct was computed as the sum of the product of the area of the infarct on each CTT section and the thickness of the sections (11 mm). The volume was corrected for minification on the scan image and subsequent optical magnification.

For the CTT scan, areas of ischemic damage were identified by visual inspection of the polaroid prints and confirmed by analysis of the computer printout of attenuation numbers. Attenuation numbers in the area of expected damage that were greater than 2 SD different from the average value in normal myocardium were considered abnormal. Areas of interest on the digital computer printouts corresponding to areas of normal and ischemically damaged myocardium were examined to determine the average attenuation coefficient of normal and infarcted myocardium. This was evaluated in the region that received no contrast material and in the group that received contrast material at each time interval.

The differences in attenuation values for normal and ischemically damaged myocardium were compared for statistical significance using the group t test. A p value <0.05 was considered significant. Regression analysis by the least squares method was performed for the relationship between the volumes calculated from histochemical staining and CTT.

Results

Detection of Regional Ischemic Damage by CTT at Various Time Intervals after Coronary Occlusion

An area of altered x-ray attenuation was clearly identified by visual inspection of the CTT scan in each of the 42 dogs that underwent coronary arterial ligation. The infarcted area was identified on histochemically stained myocardial slices in 26 dogs sacrificed at 8 and 48 hours after arterial ligation or predicted by epicardial mapping in 16 dogs sacrificed 2 hours after arterial ligation. While the time interval
between coronary occlusion and sacrifice did influence the distinctness of the CTT image of the infarcted area, all areas of myocardial ischemic damage were visible at each of the time intervals.

Regions of ischemic damage were detected as early as 2 hours after coronary occlusion as an area of visibly decreased x-ray attenuation compared with normal myocardium. Attenuating values in the area of ischemic damage were more than 2 s.d. below the average value in normal myocardium. The smallest infarction detected by computerized tomography was a 48-hour-old subendocardial infarction with a morphometric (histochemical stain) volume of 0.9 cm³.

**Appearance of the Area of Ischemically Damaged Myocardium in Relation to its Age (Without Contrast Material)**

The area of ischemic damage appeared as a focal region of diminished attenuation compared with the surrounding normal myocardium in the 16 dogs that did not receive contrast material. The sharpness of the margin between normal and damaged myocardium on the CTT scans improved with the increase in the time after coronary arterial ligation. In the dogs sacrificed 2 hours after arterial occlusion, the areas of ischemic damage were frequently poorly marginated and blended gradually with the adjacent normal tissue (fig. 1, right). In the dogs sacrificed 48 hours after coronary arterial occlusion, the damaged areas were better defined and sharply demarcated (fig. 1, left). The average attenuation numbers in dogs sacrificed at 2 hours was a 30.0 ± 0.9 (SEM) EMI units for normal myocardium and 23.8 ± 1.5 units for infarcted myocardium, a difference of 6.2 EMI units (table 1). In dogs with 48-hour-old infarcts, the average attenuation coefficient was 29.8 ± 1.1 units for normal myocardium and 22.5 ± 1.3 units for infarcted myocardium, respectively, a difference of 7.2 EMI units. The difference in the attenuation coefficient between normal and ischemically damaged myocardium was significant at both 2 hours and 48 hours.

**Table 1. Attenuation Values (EMI Units) of Myocardium in Dogs Sacrificed at Various Time Intervals After Coronary Occlusion**

<table>
<thead>
<tr>
<th>Time</th>
<th>Without contrast material</th>
<th>With contrast material</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal myo</td>
<td>Damaged myo</td>
</tr>
<tr>
<td>2 hr</td>
<td>30.0 ± 0.9</td>
<td>23.8 ± 1.5</td>
</tr>
<tr>
<td>8 hr</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>48 hr</td>
<td>29.8 ± 1.1</td>
<td>22.5 ± 1.3</td>
</tr>
</tbody>
</table>

Values are mean ± sem.  
Abbreviation: myo = myocardium.

FIGURE 1. These computerized transmission tomography (CTT) scans were obtained from two dogs that did not receive contrast material before sacrifice. The area of ischemic damage in each scan is displayed as localized decrease in x-ray attenuation (arrows) when compared with the surrounding normal myocardium. The cardiac CTT scan of a dog sacrificed 48 hours after coronary arterial occlusion (left) shows a sharper boundary between normal and damaged myocardium than that of a dog sacrificed 2 hours after occlusion (right). The scans are viewed from above; the left lateral ventricular wall is on the left.
after coronary arterial ligation \((p < 0.01)\), and similar at the two time intervals.

### Appearance of the Area of Ischemically Damaged Myocardium in Relation to its Age (With Contrast Material)

Contrast enhancement of the area of ischemic damage was not observed in any of the dogs after 2 hours of coronary arterial ligation. In dogs in which the arterial branches were ligated for 8 and 48 hours, there was a variable effect of the contrast material on the CTT image of ischemically damaged myocardium. This effect could be roughly grouped in three patterns: 1) a global contrast enhancement in which nearly the entire area of ischemic damage appeared as a region of increased attenuation; 2) partial contrast enhancement, where only a portion of the area of ischemic damage, often peripheral, appeared as an area of increased attenuation, while the remainder of the damaged area showed decreased attenuation; and 3) no contrast enhancement, where the entire ischemic area had diminished x-ray attenuation compared with the normal myocardium. An example of global contrast enhancement is given in figure 2; the attenuation coefficient in the ischemically damaged region was 49.2 EMI units, which was 12.1 EMI units greater than the normal surrounding myocardium (37.1 EMI units). A typical example of peripheral enhancement is given in figure 3, where the attenuation coefficient of 50.0 EMI units in the enhancing region is contrasted with a value of 25.6 EMI units in the nonenhancing portion of the ischemically damaged area and 39.9 EMI units in the surrounding normal myocardium.

The frequency of these three patterns changed with time (table 2). Two hours after coronary arterial ligation, all regions of ischemia appeared as areas of decreased attenuation and none showed contrast enhancement. However, 8 hours after coronary occlusion, contrast enhancement was noted in 75% of the ischemic regions; 50% showed global and 25% showed partial contrast enhancement. In the group sacrificed 48 hours after coronary arterial ligation, contrast enhancement was shown in 70% of the ischemic

| Table 2. Frequency Pattern of Contrast* Enhancement |
|-----------------|-------------|-------------|-------------|
|                | 2 hr \((n = 8)\) | 8 hr \((n = 8)\) | 48 hr \((n = 10)\) |
| Global enhancement | 0%          | 50%         | 40%         |
| Partial enhancement | 0%          | 25%         | 30%         |
| No enhancement | 100%        | 25%         | 30%         |

*Meglumine diatrizoate (Renografin-76), 2 ml/kg.
regions; 40% with global enhancement, and 30% with partial enhancement. In dogs sacrificed 2 hours after ligation, the attenuation coefficient of only the normal myocardium was enhanced (table 2). At 2 hours this contrast enhancement of normal myocardium tended to increase edge distinction between ischemically damaged and normal myocardium (fig. 4).

The areas of ischemic damage of 48 hours duration that showed contrast enhancement had an average mean attenuation coefficient value of 6.6 EMI units greater than the surrounding normal myocardium. In these instances the borders between normal and damaged myocardium were less well defined than on scans of dogs that did not receive contrast material.

Estimation of the Volume of Ischemically Damaged Tissue with and Without Prior Administration of Contrast Material

The volume of the area of ischemic damage 48 hours after ligation calculated from the CTT scan was compared with the volume calculated from histochemically stained myocardial slices (morphometric) in nine dogs that received contrast material intravenously and in nine dogs that did not receive contrast material. We considered the morphometric volume to be the true volume of damaged tissue. In the non-contrast-infused preparations there was a close linear relationship between the volume estimated from the CTT scan and the morphometric volume (fig. 5). The CTT scan tended to underestimate the volume of the damaged tissue, as shown by an average volume of 8.5 ml, estimated from the CTT scan compared with the morphometric volume of 10.5 ml; the CTT scan underestimated the volume by an average of 27%. In eight of the nine dogs that did not receive contrast material, the morphometric volume was greater than the volume calculated by CTT scan. In the remaining dog the volumes were equivalent.

Estimation of the volume of damaged myocardium from the CTT scan was considerably less accurate after the administration of contrast material. In this group of dogs there was a poor linear relationship between the volume calculated from the CTT scans and the morphometric volume (fig. 5). The volume delineated from the CTT scans substantially underestimated size. In eight of nine dogs, the volume estimated from the CTT scan was less than the morphometric volume, and in one dog the volumes were nearly equivalent by the two methods. The mean volume calculated from the CTT scans was 4.9 cm³, compared with a mean morphometric volume of 11.3 cm³, resulting in an average 57% underestimation of volume by the CTT scan in the presence of contrast material.

Discussion

The initial studies by Adams et al.⁴ and Ter-Pogossian et al.⁵ revealed that textural properties of ischemically damaged myocardium were sufficiently different from normal myocardium to permit its differentiation from normal myocardium on CTT scans. These initial observations stimulated subsequent evaluation of the CTT image of myocardial infarctions in the nonbeating canine heart in order to provide a foundation of information to be used in the eventual clinical evaluation of myocardial infarctions.
Figure 5. This graph plots the volume of myocardial damage as estimated from the computerized transmission tomography scan, with the volume defined by the histochemical stain. The regression line (solid line) for this relationship in dogs that did not receive contrast material is compared with that for dogs that received contrast material (broken line). This data is from dogs sacrificed after coronary arterial ligation for 48 hours.

When physiologically gated or very rapid CTT scanning becomes practical.7

The current study showed that under ideal scanning conditions (the nonbeating heart), electrocardiographically or histologically verified areas of myocardial ischemic injury were apparent by visual inspection of the CTT image. The position and extent of ischemically damaged tissue could be related qualitatively to the internal topography of the ventricular wall, the interventricular septum and the ventricular chambers. Involvement of papillary muscles, the interventricular septum and transmural extension were defined on the CTT scans. Infarcts were visualized over a wide range of sizes; the smallest area of ischemic damage detected by the CTT scan in the current study had a volume of 0.9 ml. Other reports5,6 have revealed a similar reliability of the CTT scan in detecting myocardial ischemic damage. In some instances, the CTT scan has failed to detect small, subendocardial areas of ischemic damage.2

The image of an area of myocardial ischemic damage on the CTT scan seems to reflect ischemia-induced changes in myocardial cellular fluid content.3,4 A previous study has revealed a linear relationship between the decreases in x-ray attenuation and the water content of the myocardium in dogs after coronary arterial occlusion.4 In this regard, ischemic injury to myocardial cells is known to produce alterations in membrane integrity, with consequent loss of the ability to actively extrude sodium ions and a tendency to accumulate intracellular water.10 It is well documented that significant electrolyte shifts do not occur in ischemic myocardium until 1–2 hours after cell injury, and that this process of edema formation is significantly accelerated by the reestablshment of blood flow to the ischemic area.10 Therefore, one would expect that the earliest time at which an area of myocardial ischemic damage could be detected by CTT scan would be within this 1–2 hour period. The current study reveals that there is sufficient alteration in the x-ray density of ischemically damaged myocardium by 2 hours after ligature to permit detection by the CTT scan. This finding is consonant with the findings of a recent report by Hessel et al.,15 which demonstrated that as early as 2 hours after coronary occlusion, myocardium with reduced perfusion was detected as an area of diminished x-ray attenuation on CTT scans. On the other hand, coronary occlusion for 1 hour does not produce a detectable decrease in x-ray density within the ischemically damaged area.5 However, coronary occlusion for 1 hour followed by 40 minutes of reperfusion uniformly produces focal regions of decreased attenuation on the CTT scans.4 CTT appears to be capable of detecting areas of myocardial ischemic damage at a time before that at which radionuclide scans become diagnostic.15,16

The current study indicates that the average difference in attenuation coefficient between normal and ischemically damaged myocardium did not differ appreciably between the 2–48 hour periods (table 1). However, edge distinction did vary with time — it became more clearly defined with increasing time after arterial ligation. At 2 hours, the boundary between ischemically damaged and normal tissue was often poorly defined. At 48 hours, a better definition of the peripheral limits of the damaged area was observed.

The CTT scan after intravenous administration of contrast material revealed an increase in the x-ray
attenuation of all or part of the ischemically damaged area in most of the dogs that had coronary occlusion for 8 and 48 hours. This observation is consistent with increased accumulation of iodinated contrast material within damaged vs normal myocardium.

After contrast administration in dogs with coronary arterial ligation of 2 hours duration, the increase in x-ray attenuation of normal myocardium produced better demarcation of the boundary between normal and infarcted myocardium. On the other hand, contrast enhancement of the ischemically damaged area at 48 hours tended to raise the attenuation value of portions of this area to near that of the surrounding normal myocardium, thereby rendering edge distinction more difficult.

The diminished accuracy of volume estimation in the presence of contrast material is probably due to sufficient enhancement of the edges of infarct so that it approximated the radiographic attenuation of normal myocardium. It is possible that scans obtained within 1–2 minutes of the administration of contrast material might have had a diagnostically influence. At this early time interval (myocardial perfusion phase), contrast enhancement of the normal myocardium alone might have more clearly delineated damaged from normal myocardium. A phase lag in the contrast enhancement of infarcted vs normal myocardium was indicated in a recent preliminary report.17

The exact pathophysiologic mechanism by which contrast enhancement of ischemically damaged myocardium occurs is unknown. It must be assumed that the increase in x-ray attenuation relates to an increase in the iodine content within the damaged myocardium. This assumption has recently been confirmed by fluorescent excitation analysis of myocardial tissue samples in preliminary reports from our laboratory.18, 19 The precise tissue locus where iodine accumulates has yet to be defined. Microvascular injury and thereby increased vascular permeability are known consequences of acute myocardial infarctions,8, 9 and might promote greater leakage of contrast material from the myocardial microvasculature. Other possible mechanisms responsible for contrast enhancement may be a slower time course for washout of contrast material from the extravascular interstitial space as a consequence of diminished perfusion of the ischemic myocardium. Contrast enhancement has previously been noted in two dogs after 1 hour of coronary occlusion followed by reflow for 24 hours.4 Under these conditions the contrast enhancement is probably at least partially a consequence of posts ischemic hyperemia. It is conceivable that this type of hyperemia might be supported through collateral flow in the no-reflow situation in the current study.

The uniform lack of contrast enhancement 2 hours after the onset of ischemic myocardial damage and the contrast enhancement at 8 and 48 hours show that the mechanism of contrast enhancement depends upon factors other than those promoting edema formation in ischemically damaged tissue. This fact may eventually aid in the elucidation of the pathophysiologic mechanism of contrast enhancement of ischemically damaged tissue. Further investigation is necessary to define the tissue locus and pathologic significance of differential accumulation of contrast material within ischemically damaged myocardium.

The reason for the variability of contrast enhancement within the area of ischemically damaged myocardium delineated by the histochemical stain is unclear. Since nitroblue tetrazolium is believed to stain viable myocardial cells, it must be considered that the entire area demarcated by the stain underwent ischemic damage. Contrast enhancement of only portions of this area may be a reflection of variability of collateral perfusion of the various regions of the damaged area. Variability of residual perfusion of experimental infarcts has previously been shown to be a controlling factor in the accumulation of technetium-99m pyrophosphate.20 Another consideration as the mechanism of the variable contrast enhancement is a nonhomogeneous degree of microvascular damage within the ischemically damaged area.8, 9 Finally, it is possible that the contrast material crosses the damaged myocardial membrane and that variable contrast enhancement throughout the damaged area reflects varying severity of myocardial cellular injury. Under normal circumstances, iodinated contrast materials are distributed only throughout the extracellular space.21

The sensitivity of the CTT scan in detecting areas of myocardial ischemic damage and the capability of this modality to provide a direct estimation of the volume of ischemically damaged tissue should have benefit in man when either physiologically gated or very fast scanners become practical. The latter information provided by the CTT scan is important, because the size of a myocardial infarction is the major determinant of the severity of hemodynamic impairment,22 the occurrence of serious arrhythmias23 and the ultimate prognosis. While indirect biochemical methods24, 25 have been primarily relied on for estimation of infarct volume, the CTT scan and another new diagnostic modality, positron emission transverse tomography,26 permit a direct estimation of infarct volume.

References

Evaluation of myocardial ischemic damage of various ages by computerized transmission tomography. Time-dependent effects of contrast material.
C B Higgins, P T Siemers, W Schmidt and J D Newell

_Circulation_. 1979;60:284-291
doi: 10.1161/01.CIR.60.2.284
_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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