Temporal Changes in Sequential Quantitative Thallium-201 Imaging Following Myocardial Infarction in Dogs: Comparison of Four- and Twenty-Four-Hour Infarct Images

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Thallium-201 (201TI) myocardial perfusion imaging allows definition of zones of myocardial infarction and ischemia. The temporal changes in sequential quantitative 201TI infarct imaging was studied 4 and 24 hours in dogs subjected to closed-chest anterior wall myocardial infarction. A temporal decrease in 201TI imaged infarct areas was noted in 10 of 13 animals. In no animal did the infarct area increase. The imaged infarct area decreased by an average of 30% from 12.9 ± 6.2 cm² at 4 hours to 9.1 ± 5.1 cm² at 24 hours (p < 0.001), and involved 34 ± 16% of the total 201TI left ventricular distribution at 4 hours and 22 ± 14% at 24 hours (p < 0.001). The magnitude of temporal change in imaged infarct area was not predicted by initial image defect or final histopathologic infarct size. Thus, the results of 201TI infarct imaging in the early period of infarction are clearly dependent upon the time at which the procedure is performed.

INTRODUCTION

Thallium-201 (201TI) myocardial perfusion imaging has been shown to be of value for detection of regions of left ventricular ischemia and infarction [1-5]. The pathophysiologic basis for the utility of 201TI imaging resides in the excellent correlation between myocardial tissue levels of the radionuclide and (a) radioactive microsphere estimates of myocardial blood flow, (b) tissue creatine kinase estimates of regional myocardial viability, and (c) histopathologic evidence of myocardial necrosis [6,7]. Furthermore, in animals subjected to closed-chest anterior myocardial infarction, a good correlation has been noted between the size of 201TI myocardial perfusion defects determined by quantitative imaging at 24 hours and histopathologic infarct size [8]. A similar linear correlation has been reported in man when the size of antemortem 201TI perfusion defects were compared to postmortem assessment of infarct size [9].

These studies indicate the potential of quantitative 201TI imaging for the serial
assessment of infarct size. However, several observations made during clinical $^{201}$T1 infarct imaging suggest that the temporal sequence of imaging is of major importance, necessitating significant standardization prior to employing the technique in a quantitative manner for infarct sizing [4]. First, the sensitivity of $^{201}$T1 imaging for infarct detection is maximal in the first hours after infarction. Substantial differences exist in the ability to detect infarcts within the first 6 hours after myocardial infarction as compared to 24–48 hours following infarction. Second, qualitative visual assessment of the $^{201}$T1 imaged infarct areas obtained by sequential imaging in patients within 6 hours of infarction and then again 24 hours later frequently indicate an apparent decrease in imaged infarct area, or even its disappearance.

Clearly, it is necessary to define the intrinsic temporal variability of quantitative $^{201}$T1 imaging during the first 24 hours following infarction. Such data are critical if this technique is to have a role in monitoring regional ischemia and viability during the early period when intervention to salvage ischemic myocardium would be most appropriate. The current study was undertaken to determine the variability in sequential quantitative $^{201}$T1 images of experimental canine infarction obtained at 4 hours and again at 24 hours following infarction.

**Methods**

Thirteen adult mongrel dogs of either sex (weighing between 22 and 29 kg) were subjected to anterior myocardial infarction. Animals were placed under light anesthesia with intravenous sodium pentobarbital (30 mg/kg). The trachea was intubated and respiration maintained with a Harvard respirator. An intravenous infusion line was established in a peripheral vein for administration of fluid, medication, and radionuclide. All animals were pretreated with lidocaine infusion (2 mg/min) prior to and for one hour after infarction. Electrocardiographic monitoring was carried out during this period and bursts of ventricular ectopic activity were treated with additional 50-100 mg boluses of intravenous lidocaine.

Closed-chest myocardial infarction was produced by a previously described catheter plug embolization technique [10]. Briefly, a number 7 Sones catheter was introduced into the aortic root via the right carotid artery. Following fluoroscopic positioning of the catheter in the proximal portion of the left anterior descending coronary artery, a guide wire impaled plug present at the catheter tip was dislodged. The solid plug, which was 2-4 mm in length and made of radiopaque catheter material, usually lodged in the distal one-half to one-third of the coronary artery. Following infarction the catheter was removed and the neck incision closed. One hour after infarction animals were weaned gradually from the respirator.

In each animal $^{201}$T1 imaging was performed on two occasions: four and again twenty-four hours following infarction. These time periods were selected to provide a temporal sequence allowing comparison of images corresponding to the earliest time at which a clinical image would likely be obtained (4 hours), and a second time when clinical imaging could be performed routinely without excessive logistic difficulty (24 hours). At the time of imaging the animals were lightly anesthetized and lay quietly on their right sides beneath the scintillation camera. During the interval between studies the animals were returned to the kennel where they received routine care.

A 37 photomultiplier tube scintillation camera (Searle LFOV) equipped with a parallel hole high resolution collimator and interfaced with a small computer (PDP8, Digital Corporation) was used for all studies. Animals were imaged in the 40° left anterior oblique position using a 20 percent energy window centered around the 80 keV photopeak of $^{201}$T1. Analog images of 400,000 counts were obtained on both
Polaroid and X-ray film. Data also were acquired simultaneously on computer and stored on magnetic tape for subsequent off-line quantitative image analysis.

A separately injected $^{201}$T1 (as thallous chloride, New England Nuclear Corporation, Billerica, MA) dose was used for each of the two studies. The 4-hour image was performed following injection of 1.0 mCi of the radionuclide; while a 2.0 mCi dose of $^{201}$T1 was employed for the 24-hour images. The large $^{201}$T1 dose used in the second imaging procedure was chosen in an attempt to compensate for residual activity emanating from the initial dose of the 73-hour half-life radionuclide. Images were obtained beginning 10 minutes after $^{201}$T1 injection. Imaging time averaged 7 minutes per view for the 4-hour study and 4 minutes per view for the 24-hour study.

$^{201}$T1 images were quantified from digital data initially stored on magnetic tape in a $64 \times 64$ memory array. A rectangular region of interest which included the left ventricle was selected. The maximal number of counts in any one digital location within the area of interest was determined. This location always resided within the left ventricle. Background activity was taken to represent all locations with 0–35 percent of this maximum activity. Normal myocardial regions were arbitrarily defined as locations with 66–100 percent of maximum activity. In normal dogs, left ventricular $^{201}$T1 uptake always falls within this activity range. Abnormal infarct zones were defined as regions with 36–65 percent maximal activity. It is recognized that this is an arbitrary manner of quantifying $^{201}$T1 infarct size. However, in the absence of an universally accepted current modality of quantifying true regional activity, this technique represents a standardized reproducible manner of estimating the size of imaged infarct areas with this radionuclide. This technique has been previously applied to a study of infarct size in dogs, in which a good linear correlation was demonstrated between data obtained by radionuclide and pathologic sizing methods [8]. Abnormal zones of decreased $^{201}$T1 uptake were expressed both as a percentage of the total $^{201}$T1 left ventricular area and as an absolute area (since the image of the 39 cm diameter detector is stored in a 64 addressed diameter, each address will represent 0.378 cm$^2$).

Following the 24-hour imaging procedure, the animals were sacrificed. The hearts were excised immediately and cut transversely in 1–2 cm intervals. The slices were trimmed of epicardial fat and coronary arteries, weighed, and incubated in a buffered tetrazolium solution (2,3,5-triphenyl tetrazolium chloride) for 40 minutes at 37° centigrade in a constant water bath. The incubation was performed without the addition of exogenous substrates. With this macroscopic staining technique, normal myocardium appears bright red, while infarct zones appear unstained or only faintly stained. After incubation, the slices were weighed individually. The infarcted tissue then was dissected away from the remaining myocardium and weighed. An estimate of total infarct size and weight could be obtained from the summed data of all slices [11].

Different investigators each performed the embolic infarct procedure, radionuclide imaging and analysis, and histopathologic infarct sizing. All individual analyses were made independent of knowledge of corroborating data obtained by other techniques. Statistical comparisons of data obtained at 4 and 24 hours following infarction were made by paired $T$ test, with $p < 0.05$ considered significant. Linear correlations were derived in a standard manner.

**Results**

When sequential $^{201}$T1 images at 4 and 24 hours following infarction were compared, a temporal decrease in infarct area was noted in 10 of 13 animals (Figs. 1}
and 2). In 2 animals the infarct defect noted at 4 hours was barely discernible at 24 hours. Infarct area in the remaining 3 animals was unchanged; in no animal did the $^{201}$TI infarct area increase. The imaged infarct area averaged ($\pm$ SEM) $12.9 \pm 6.2$ cm$^2$ at 4 hours, and $9.1 \pm 5.1$ cm$^2$ at 24 hours (Fig. 3). This average decrease in infarct area of 30 percent was highly significant ($p < 0.001$). The image infarct defect involved $34 \pm 16\%$ of the total $^{201}$TI left ventricular distribution at 4 hours, and $22 \pm 14\%$ at 24 hours ($p < 0.001$).

Histopathologic infarct size in the 13 animals averaged $18 \pm 5$ gm and involved $16 \pm 3\%$ of the left ventricle. Attempts were made to determine if 24-hour histopathologic infarct size was a predictor of the magnitude of change in image $^{201}$TI infarct area over the initial 24 hours of infarction. That is, within the range of infarcts studied, can a greater percentage decrease in imaged infarct area be expected in large or small infarcts? However, no meaningful correlation was noted ($r = -0.16$) between the decrement in imaged infarct areas and final pathologic infarct size (Fig. 3). Likewise, no meaningful correlation ($r = 0.38$) was evident when comparison was made between the size of the initial 4-hour $^{201}$TI infarct area and its subsequent diminution in size 20 hours later (Fig. 3).

DISCUSSION

The results of the present study indicate that a significant decrease in the size of experimentally induced infarct images with $^{201}$TI can be expected when animals are studied between 4 and 24 hours following infarction. This decrease occurs in the absence of any intervention designed to limit infarct size. Furthermore, neither the extent of the initially imaged perfusion defect associated with infarction, nor final
FIG. 2. Change in $^{201}$TI imaged infarct defect between 4 and 24 hours. To the left the $^{201}$TI defect, expressed as a percent of the total left ventricular image, is compared at 4 and 24 hours. To the right the $^{201}$TI image defect, expressed as an absolute area in cm$^2$, is compared at 4 and 24 hours. Each animal is represented by closed circles, while the mean values are shown as open circles with lines through them. Changes from 4 to 24 hours are highly significant ($p < 0.001$).

FIG. 3. The relationships between the change in $^{201}$TI imaged infarct area and initial 4-hour defect size (left) and pathologic infarct size at 24 hours (right). Note the absence of any meaningful correlation ($r = 0.38$ for 4-hour defect size, $r = -0.16$ for pathologic infarct size).
pathologic infarct size at 24 hours can be used as predictors of the degree of change in 201T1 infarct images over this 20 hour period. Thus the results of 201T1 imaging in the early period of experimental infarction are clearly dependent upon the time when the procedure is performed. A sequential decrement in the size of the imaged infarct zone can be routinely expected during the initial 24 hours, even in the absence of interventions.

Several mechanisms may account for this decrease in 201T1 imaged infarct areas. Abnormalities in 201T1 images reflect both infarction and ischemia. Within normal and abnormally low flow ranges, the radionuclide is distributed within the left ventricular myocardium in direct proportion to regional myocardial blood flow. This has been established in animal models of acute coronary occlusion as well as 24-hour-old infarction. Several laboratories have demonstrated significant changes in regional myocardial blood flow over the first 24 hours of canine infarction. Using the radioactive microsphere technique in conscious animals, Rivas et al. noted that blood flow in the infarct zone increased significantly between 45 seconds and 2 hours following infarction and again between six and 24 hours; while it remained unchanged between 2 and 6 hours [12]. At six and 24 hours mean blood flow in infarct zones averaged 0.39 ± 0.05 and 0.53 ± 0.07 ml/min/g, respectively. Furthermore, subsequent increments in blood flow following coronary occlusion were greater in epicardial than endocardial layers. No change was noted in blood flow to noninfarcted myocardium using similar techniques. Bishop et al. observed no change in abnormal flow patterns in ischemic and infarct zones over the first 6 hours following coronary occlusion, while at 24 hours flow was moderately increased in all areas except the central subendocardial core of the infarct [13]. Further increments in regional flow were noted at 96 hours. Thus, an increase in collateral flow to infarct zones during the imaging sequence of 4 and 24 hours following infarction could result in an augmented flow-related deposition of 201T1 in regions that manifested a greater degree of hypoperfusion at four hours. The early image abnormality presumably would represent both ischemia and infarction, while the later image, only infarction.

There may be additional metabolic factors at the infarct border which also might affect the temporal pattern of 201T1 imaging. Herse et al. reported the presence of peri-infarct zones 8 to 15 mm in width in which patterns of changing metabolic and electrophysiologic events were noted shortly after coronary occlusion in the dog [14]. Changes in regional adenosine triphosphate, lactate, and creatine phosphate all could have a bearing upon 201T1 accumulation in the early infarct period.

Alterations in ventricular geometry also may explain the changes noted in 201T1 imaging patterns. Dyskinesis, or paradoxical systolic expansion, is noted routinely within minutes of coronary ligation [15]. This regional contraction pattern is an evanescent one, with subsequent development of absence of contraction or akinesis. The imaged 201T1 distribution within the left ventricular myocardium is dependent, to an extent, upon the degree of distortion of left ventricular geometry and cavitary dimensions. During the dyskinetic period the regional 201T1 defect might appear larger than in the later appearing akinetic phase when aneurysmal bulging is no longer present. Hence, temporal variation in regional contractile performance might result in temporal variation in imaged infarct patterns. Finally, temporal changes in the extent of regional edema or regional cationic radionuclide extraction efficiency also might play relevant mechanistic roles in the imaging patterns noted [16].

The results of this study in an experimental infarct model are relevant to the clinical and investigative use of 201T1 imaging. Clearly, differences in collateral flow patterns exist between normal dogs with acute coronary occlusion, and patients with
chronic ischemic heart disease and superimposed acute myocardial infarction. Nevertheless, our results are strikingly similar to those of Wackers et al. obtained with qualitative \^1\textsuperscript{Tl} imaging over the first 24 hours of myocardial infarction in man [4]. Currently, this radionuclide imaging technique is employed frequently for clinical infarct definition. Optimal results are forthcoming when patients are imaged as early as possible after admission. Intrinsuc temporal variation in imaging patterns must be considered if this approach is to be applied investigationally to the study of interventions designed to modify ischemic necrosis. Our data would indicate that for this imaging technique to be used most appropriately, great care must be taken to standardize the time following infarction during which studies are obtained. In addition, if early images indicate the extent of both ischemia and infarction and late images only the extent of infarction, evaluation of sequential image patterns may provide prognostic insight into the amount of myocardium remaining at risk for subsequent infarction.

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