Gamma Camera Quantitation of Thallium-201 Redistribution at Rest in A Dog Model

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SUMMARY Defects seen at rest on thallium-201 (201TI) scintigraphy can disappear over time. We obtained sequential 5-minute scans over 127 ± 9.4 minutes in seven open-chest dogs with fixed, stable regional flow reductions (normal zone flow 0.76 ± 0.09 ml g⁻¹ min⁻¹, ischemic zone flow 0.49 ± 0.04 ml g⁻¹ min⁻¹ [mean ± SEM], p < 0.05) as determined by microsphere injection. Sequential 5-minute scans were obtained after i.v. injection of 1.5 mCl of 201TI. Data were stored in a 64 × 64 pixel computer matrix. Qualitatively, defects that showed redistribution were seen in all dogs. Quantitatively, greater count loss from peak activity distinguished the normal zone, but overlap was great. Alternate quantitative methods using background subtraction altered the characteristics of the time-activity curves, but did not enhance the separation of ischemic from normal zones. Patterns of 201TI redistribution from gamma camera imaging are profoundly influenced by the method of quantitation. No single method of quantitative analysis separated ischemic from normal zones in all dogs. The clinical significance of patterns at rest requires redefinition.

IN PATIENTS with severe angiographic coronary artery disease, defects at rest on thallium-201 (201TI) scintigraphy can disappear over time.¹⁻³ Quantitative analysis of the scans in these patients suggested that 201TI uptake in hypoperfused, but presumably viable, regions played the dominant role in 201TI redistribution.⁴⁻⁶ If correct, the concept of delayed uptake of 201TI into myocardial regions with subnormal coronary flow is important for two reasons. First, it would aid in identifying ischemic zones in patients with qualitatively normal scans³⁻⁶ and help separate infarct from ischemia. Second, it could lead to a quantitative method of blood flow determination from time-activity curves, because preliminary data indicate that the rate of uptake is related to the degree of flow reduction.⁵⁻⁶

However, Leppo et al.⁹ presented data showing that washout rather than washin dominates the process of redistribution when flow is segmentally enhanced. If the animal model of Schelbert et al.⁸ applies, delayed uptake will occur only when resting flow has been reduced by 80% of normal. Patients reported to show areas of myocardium with delayed 201TI uptake were asymptomatic and showed no ECG evidence of acute ischemia at the time of 201TI injection.⁵ Catheterization at another time revealed no wall motion abnormalities in many of these patients.

Thus, the mechanism and significance of scintigraphic patterns of redistribution are controversial. Our study was designed to explore methods of quantitating gamma camera scans and to use these methods to characterize patterns of 201TI redistribu-
tion in a dog model of sustained regional myocardial flow reduction at rest.

Materials and Methods

Mongrel dogs (average weight 22.5 kg) were premedicated with i.m. morphine sulfate (2 mg/kg), anesthetized with sodium pentobarbital (20 mg/kg) and mechanically ventilated through an endotracheal tube. Additional barbiturates were given whenever necessary. After a left thoracotomy, the proximal left circumflex coronary artery was dissected free (in the first two dogs) to allow placement of a circumferential flow probe, an occluder to produce intermittent zero flow and a distal constrictor. The purpose of this constrictor was to produce a sustained reduction of resting blood flow. In the next five dogs studied, the left anterior descending coronary artery was cannulated distal to its second major branch with an extracorporeal flow probe system connected to the right carotid artery. Flow reduction was adjusted by a screw clamp applied over the Silastic tubing just distal to its exit from the carotid artery. Such a system also allows pressure monitoring of the perfused coronary artery. Intravascular catheters were then placed into the left atrium through its appendage for microsphere injection; into the right atrium for injection of indocyanine green dye (ICG); into the right femoral artery for recording ICG dilution curves (Giford IR 103) and collecting arterial reference blood during the injection of microspheres; and into the descending thoracic aortic through the left femoral artery for pressure monitoring and collecting duplicate arterial reference blood during microsphere injection. A catheter in the femoral vein allowed infusion of fluid and injection of 201TI.

After baseline coronary flow was recorded with the flowmeter, the left circumflex (first two dogs) or the extracorporeal line to the anterior descending coronary artery (next five dogs) was constricted so that resting flow was reduced and held steady. With the thoracotomy left open, the left lung pushed away from the heart and the heart suspended in a pericardial cradle. A gamma camera (Picker Nuclear) with an all-purpose collimator was positioned approximately 6 inches from the lateral surface of the heart and fixed there for the duration of the experiment.

Two to three ICG dilution cardiac outputs were then determined. Two million to 4 million microspheres, 15 μm in diameter and labeled with 46Sc diluted in 10 ml of 6% dextran and 2 drops of Tween, were ultrasonicated to ensure proper mixing. These were slowly injected (15 seconds) into the left atrium while dual reference arterial blood samples were collected (at 10 ml/min for 2 minutes) from the femoral artery and the descending thoracic aorta. Within 5 minutes of the microsphere injection, 1.5 mCi of 201TI were flushed rapidly (1–2 seconds) into the femoral vein and continuous recording of gamma camera images was begun on a PDP 1134 computer (Digital Equipment Corporation). The computer was programmed to store the gamma camera data in a 64 × 64 pixel matrix in 30-second frames starting 1 minute after 201TI injection and continuing for the next 30–60 minutes. Subsequently, 5-minute collections at 15-minute intervals were stored for up to approximately 2 hours after 201TI injection (127 ± 9.4 minutes, mean ± sem). At least 400,000 counts were contained in each 5-minute collection. Approximately 1 hour after the injection of 201TI, repeat hemodynamic measurements and cardiac outputs were recorded. Regional myocardial blood flow was again assessed, this time by the injection of 2–4 million 113Sn microspheres 15μ in diameter.

Immediately after the final scan, the heart was fibrillated with excess potassium chloride. The heart was removed and the area supplied by the stenosed or cannulated coronary artery was demarcated by injection of Evans blue dye into the poststenotic segment. After removal of the atrial and the right ventricular free wall, the left ventricular free wall and septum were cut into seven to nine rings in a plane parallel to that of the mitral valve. The rings were then frozen and sectioned the next day. The sectioning was done so that wedge-shaped transmural pieces weighing 0.5–1.0 g were obtained. The gamma activity of the tissue pieces and the reference arterial blood was then counted on a gamma spectrometer (Nuclear Chicago, 1185), simultaneously counting 201TI, 113Sn and 46Sc.

Data Reduction

The ICG dilution curves were manually integrated and exponentiated to translate them to cardiac output. Gamma well counter data were analyzed by computer to allow reduction of isotopic activities to their net by correcting for background, energy overlap and isotopic decay incurred during the counting procedure. Knowing the average arterial blood activity during the microsphere injection (the difference between the dual sampling was 0–7% of their mean), we calculated coronary flow to each region (ml·g⁻¹·min⁻¹). The myocardial areas enclosed by the blue dye (constriction zone CZ) were summed with an interactive computer program, as were the unstained areas (normal zone NZ) to allow determination of the weight of the two regions, their microsphere flow early and late after 201TI injection, and their 201TI activity at the time of death. The regions bordering these two zones and the basal regions were excluded.

Stored gamma camera data were summed to produce sequential 5-minute images of myocardial 201TI activity. After interpolation, the images were photographed from the video display monitor on Polaroid film for qualitative analysis of the defects, which were graded by two of the investigators (4 signifies most severe defect and 0 no defect). For quantitative analysis, all computer generated ventricular images were subdivided into 10 6-pixel regions so that all areas of myocardium were encompassed. Ventricular activity was also analyzed using 1-pixel slices through visually appreciated defects and opposing normal walls. Nontarget background activity contributes to count rates within myocardial regions. Periventric-
ular and lung backgrounds were empirically selected for quantitative analysis, as the proximity and magnitude of the former and the dynamic nature of the latter profoundly influenced the visual scintigraphic appearance of the hearts. Therefore, 6-pixel background regions were placed adjacent to their corresponding ventricular regions and 1 pixel removed from the outer ventricular edge. A 6-pixel background region was also placed further removed from the ventricular edge over the lung (fig. 1). Finally, background was also determined using the bilinear interpolation method of Goris et al., assuming a variable but monotone background contribution to target counts.

The 5-minute images spanning minutes 10–14 after $^{201}$TI injection (initial scan) were inspected and the ventricular regions in the center of the scintigraphic defect (SDW) and opposing normal wall (SNW) were selected for further analysis. Although these regions correspond to the CZ and NZ distributions described above, the SDW and SNW cannot be construed to describe exactly the regions that are, or are not, demarcated by Evans blue dye. Rather, they represent low and normal flow areas as would be assessed by clinical scintigraphy. Quantitative analysis of each of the sequential scans was then performed using five methods of data reduction: method Ia: mean $^{201}$TI activity from the 6-pixel region in the SDW, SNW, adjacent backgrounds and lung; method Ib: SDW and SNW regions minus their respective periventricular backgrounds; method Ic: SDW and SNW regions minus lung background, method II: SDW and SNW regions minus interpolated background; and method III: interpolated background was subtracted from peak ventricular activity determined from 1-pixel slices through the defect and normal wall (table 1). Time-activity curves so generated were analyzed for time to peak (maximal) counts. The change in counts from initial to peak, peak to final and initial to final scans were also tabulated. Count data are expressed as counts/pixel/5 minutes. All grouped data are expressed as mean ± SEM. The significance of differences within a heart was determined using a paired $t$ test.

### Results

For the seven dogs studied, the hematocrit was 41 ± 1.8% and the arterial $P_a$ was 81 ± 9.4 mm Hg. The heart rate averaged 129 ± 13.2 beats/min. The mean left atrial pressure averaged 6 ± 3.3 mm Hg. Cardiac output was 2.3 ± 0.2 l/min and significantly declined to 2.0 ± 0.11 l/min after 1 hour ($P < 0.05$). The mean aortic pressure was 102 ± 8.7 mm Hg and the mean coronary artery pressure was 72 ± 7.2 mm Hg for the five dogs with constriction of the extracorporeal line ($P < 0.05$). Left ventricular weight was 116.3 ± 11.0 g and the normally perfused region averaged 59.4 ± 5.4% of this, while the constriction regions averaged 20.0 ± 3.3%. The intermediate areas, especially at the base, were not used to separate the two regions.

Table 2 is a summary of the data from microsphere and $^{201}$TI gamma well counter analysis. Regional flow by the microsphere technique at the time of $^{201}$TI injection was higher to the NZ (0.76 ± 0.09 ml·g⁻¹·min⁻¹) than to the CZ (0.49 ± 0.04 ml·g⁻¹·min⁻¹, $P < 0.05$), as was in vitro $^{201}$TI activity (CZ/NZ = 0.80 ± 0.06) at the time of death. Blood flow to the NZ and CZ assessed by repeat microsphere injection did not change significantly over the course of the experiment (CZ = 0.60 ± 0.07 ml·g⁻¹·min⁻¹, NZ = 0.83 ± 0.11 ml·g⁻¹·min⁻¹).

Table 3 lists the qualitative grading of the scintigraphic defects as a function of time. Scintigrams spanning the first 10 minutes after $^{201}$TI injection could not be interpreted due to high background activity. Hence, the 10-minute scan (minutes 10–14) was used as the initial scan. All qualitative defects became less apparent with time (fig. 2A). Dog 1, which had the highest grade of persistent resting defect at 120 minutes, had the lowest postmortem $^{201}$TI CZ/NZ ratio (table 2). Dog 4, which had the lowest CZ/NZ weight and an intermediate CZ/NZ flow of 77%, had the most rapidly disappearing qualitative defect.

The $^{201}$TI scintigrams and time-activity curves from representative experiments are presented in figure 2. Counts without background correction (method Ia) from the SNW showed varying patterns, with activity

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**Figure 1.** Thallium-201 scans photographed from the computer video display monitor. Representations of 6-pixel ventricular regions (black rectangles), background regions (white rectangles) and 1-pixel slice (dashed line) used for quantitative analysis are shown. The white rectangle at 2 o'clock, further removed from ventricular edge, is lung background.

**Table 1.** Methods of Quantitative Scan Analysis

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Mean counts from 6-pixel ventricular, periventricular and lung regions.</td>
</tr>
<tr>
<td>Ib</td>
<td>Counts from ventricular regions minus corresponding periventricular background as determined in Ia.</td>
</tr>
<tr>
<td>Ic</td>
<td>Counts from ventricular regions minus lung background as determined in Ia.</td>
</tr>
<tr>
<td>II</td>
<td>Mean counts from ventricular regions (as in Ia) minus interpolated background.</td>
</tr>
<tr>
<td>III</td>
<td>Peak counts from 1-pixel profiles through the normal and defect zones minus interpolated background.</td>
</tr>
</tbody>
</table>
Table 2. Gamma Well Counter Analysis

<table>
<thead>
<tr>
<th>Dog</th>
<th>CZ/NZ wt (%)</th>
<th>Time of $^{201}$Tl injection</th>
<th>Time of sacrifice CZ/NZ $^{201}$Tl activity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CZ flow (ml/g/min)</td>
<td>NZ flow (ml/g/min)</td>
</tr>
<tr>
<td>1</td>
<td>62</td>
<td>0.52</td>
<td>1.16</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>0.39</td>
<td>1.01</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>0.50</td>
<td>0.68</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>0.46</td>
<td>0.60</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>0.42</td>
<td>0.53</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>0.46</td>
<td>0.56</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>0.70</td>
<td>0.79</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>34 ± 7.6</td>
<td>0.49 ± 0.04</td>
<td>0.76 ± 0.09</td>
</tr>
</tbody>
</table>

$p < 0.05$

Table 3. Qualitative Scan Analysis

<table>
<thead>
<tr>
<th>Dog</th>
<th>SDW grade after $^{201}$Tl injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4 3 3 3 3 2</td>
</tr>
<tr>
<td>2</td>
<td>3 3 3 2 1</td>
</tr>
<tr>
<td>3</td>
<td>3 3 3 2 1</td>
</tr>
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<td>4</td>
<td>2 2 1 0 0</td>
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<td>5</td>
<td>2 2 1 1 1</td>
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<tr>
<td>6</td>
<td>3 3 2 2 1</td>
</tr>
<tr>
<td>7</td>
<td>2 1 1 1 1</td>
</tr>
</tbody>
</table>

Abbreviation: SDW = ventricular region in center of scintigraphic defect.
Discussion

The patterns of $^{201}$TI deposition and redistribution at rest have been extensively studied using in vitro myocardial counting techniques. Initial myocardial $^{201}$TI concentration correlates strongly with regional blood flow, but redistribution soon follows toward a pattern closely paralleling myocardial mass. Thus, if image acquisition is delayed, defects may be lost to redistribution. However, the segmental patterns of this redistribution may be used to clinical advantage using quantitative analysis. Recent animal experiments have demonstrated delayed washin of $^{201}$TI into myocardial zones held transiently ischemic for 4-10 minutes after $^{201}$TI injection. In these studies, the ischemic zone was repurfused when serum $^{201}$TI concentration was markedly reduced from peak values but still above lower equilibrium levels. For example, Beller et al. found that in transiently ischemic zones, the bulk of washin occurred within 30 minutes of $^{201}$TI injection, and the steepest washin slope was seen immediately after reflow (10 minutes after injection), followed by more gradual washout. The behavior of the NZ was characterized by an early peak (occurring less than 10 minutes after $^{201}$TI injection) with gradual washout over time. This model of transient ischemia is analogous to the short-lived spasm seen in patients with normal coronary arteries and variant angina pectoris.

Preliminary studies in animals with severe fixed coronary stenoses have also shown that redistribution can occur at rest. However, in these models, the washin of $^{201}$TI into the ischemic zone has not been as dramatic or consistent as that with transient occlusions. Okada et al., using implanted miniature left ventricular scintillation probes in animals with chronic stable regional flow reductions, demonstrated a gradual increase in $^{201}$TI activity in ischemic zones (8.2 ± 3.6% of initial concentration per hour) when moderate flow reduction was present. With severe flow reduction (less than 30% of normal), $^{201}$TI activity rose early and fell gradually with time (−5.6 ± 2.2% per hour over the first 2 hours). This pattern closely
resembled that of the normal wall. Contrasting these findings with those of Beller et al., the very rapid washin of $^{201}$TI into transiently ischemic zones may in part be related to the augmented flow of reactive hyperemia (although perhaps with a diminished extraction fraction) when serum $^{201}$TI concentration is still falling rapidly. More gradual washin may be expected when the flow reduction is sustained.

Gamma camera analysis of patterns of $^{201}$TI redistribution is complicated by tissue attenuation,
dynamic noncardiac background, heterogenous myocardium within the solid angle of the camera field and patient and cardiac movement. Our study was therefore designed to investigate redistribution after a rest injection of $^{201}$TI in a model of sustained, moderate flow reduction using available gamma camera and computer techniques. Qualitatively, all defects were variably reperfused over the 2 hours of observation. Minimal changes by qualitative analysis (one grade) were not associated with in vitro evidence of redistribution.

By most quantitative methods, counts in the SDW were significantly lower than those of the SNW early after the injection of $^{201}$TI at rest and this relationship applied over the course of the study. Therefore, for this group of experiments, quantitative analysis correctly identified lower flow zones. However, the lack of correlation between SDW/SNW and in vitro measures of flow at the time of $^{201}$TI injection, points to the coarse nature of the scintigraphic quantitation.

For $^{201}$TI to be used in conjunction with microspheres as a measure of regional myocardial blood flow, myocardial sampling of $^{201}$TI activity must be done when the amount of $^{201}$TI not extracted during the first pass is balanced by the amount entering with recirculation. In humans, this time varies, but occurs early after $^{201}$TI injection. It is possible that the relatively late sampling time after $^{201}$TI injection (minutes 10–14) in our study impaired the value of scintigrams as a measure of blood flow. However, the low target-to-background ratio early after injection precluded earlier sampling. Late after $^{201}$TI injection (127 ± 9.4 minutes), SDW/SNW ratios correlated with in vitro analysis (fig. 5). Therefore, although the gamma camera regions are not precisely comparable to in vitro CZ or NZ, a fairly close relationship was seen between the two approaches when lung background was significantly lower. These results suggest that background contributions still influenced gamma camera quantitation of CZ and NZ relationships despite background correction and an experimental protocol designed to minimize background contribution (open-chested animals with lung retracted).

For this group of experiments, after $^{201}$TI injection at rest, patterns of redistribution from methods using no background subtraction, lung background subtraction or interpolated background subtraction provided the best discrimination between defect and normal zones. However, patterns showed great overlap between dogs, and conclusions on the mechanisms of redistribution differ depending upon which method of analysis is chosen. Without background subtraction, the SNW was characterized by a greater count fall from peak. When interpolated background subtraction was used, SDW counts peaked more slowly than did SNW counts and the count difference between the two zones decreased significantly over time. With lung background subtraction,
the count difference also decreased over time, but in this instance through a pronounced increase in SDW activity. In humans at rest, Hamilton et al.\textsuperscript{23} showed that counts in both normal myocardium and background regions can decrease rapidly after $^{201}$TI injection, but the ratio of myocardial counts to background counts increases progressively for the first 20 minutes. Background correction would therefore force myocardial time-activity curves upward early after $^{201}$TI injection at rest and, as shown in this experiment, more profoundly influence the defect zone in which initial counts are lower.

Recently, partial or complete resolution of resting defects during asymptomatic interludes in patients with coronary artery disease and anginal syndromes was demonstrated.\textsuperscript{3} Although this finding was not entirely sensitive or specific for angiographically significant coronary artery disease (75% stenosis) or ventricular asynergy, it forced a reevaluation of the meaning of resting defects on $^{201}$TI scans. In a study using quantitative analysis of resting $^{201}$TI scans (with interpolated background subtraction), resting $^{201}$TI defects were seen in the majority.\textsuperscript{2} Seventy-six percent of these defects demonstrated redistribution (defined as a 15% change in $^{201}$TI activity over 2–4 hours) and 24% persisted. The mechanism of redistribution in some of these patients involved delayed washin of $^{201}$TI into initially hypoperfused segments. After coronary artery bypass grafting, of 48 segments that had shown preoperative redistribution, 37 reverted toward normal patterns, 10 showed no change and one became a persistent defect. Of 18 segments with persistent defects preoperatively, 12 reverted to normal, one showed a pattern of redistribution and five remained persistent postoperatively. No data are available to correlate these findings with postoperative regional wall motion and graft patency. Since persistent preoperative defects did not preclude enhanced postoperative perfusion as assessed by $^{201}$TI scintigraphy, the significance of the redistribution pattern requires further definition.

Our study has shown that after $^{201}$TI injection at rest, zones supplied by normal coronary arteries can slowly accrue $^{201}$TI with time in a pattern similar to...
that of "ischemic" zones. Clinically, when background subtraction is used in resting scintigraphy, ventricular regions (e.g., posterolateral wall) adjoining rapidly falling background activity (lung) may demonstrate apparent enhanced washin regardless of actual myocardial 201TI kinetics. Further, the size of the ischemic area and the magnitude of flow reduction may influence the gamma camera quantitation of redistribution. Although significant differences were observed between normal and lower flow regions in our study, the dog-to-dog variability in patterns of redistribution and the profound influence of background correction must be recognized. These considerations must temper conclusions on myocardial 201TI kinetics and diagnostic statements drawn from quantitation of serial resting gamma camera images. Thus, despite strong experimental evidence for differential 201TI uptake at rest related to the degree of flow reduction, quantitation of 201TI redistribution by gamma camera and computer did not effectively separate normal from low flow zones in individual dogs. Ultimately, resting 201TI scintigrams with delayed images must be analyzed in large numbers of subjects with normal and abnormal coronary anatomy to empirically define the clinical value of patterns of redistribution on quantitative scintigraphy.

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