The Effect of Ischemia on Thallium-201 Clearance from the Myocardium

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SUMMARY To determine the effect of ischemia on myocardial clearance of thallium-201 (\(^{201}\)TI), we studied 12 dogs with ischemia produced after the injection of TI. \(^{201}\)TI was given I.V. 10 minutes before left anterior descending (LAD) coronary artery ligation. \(^{85}\)Sr-microspheres (MS) were administered 5 minutes later, and control biopsies were obtained from the myocardium. The LAD was tied and repeat biopsies obtained from the ischemic zone (IZ) and normal zone (NZ) 15 minutes and 2 hours later. \(^{45}\)Sc-MS were given just before the final biopsy.

\(^{201}\)TI activity in the IZ was not significantly different from that in the NZ either before LAD occlusion or 15 minutes and 2 hours later. \(^{201}\)TI clearance at the end of 2 hours was not significantly different (27 ± 5% vs 28 ± 5%, IZ vs NZ respectively) between the two zones. The half-time of \(^{201}\)TI clearance from both the IZ and NZ was calculated at 4.5 hours (consistent with previously reported normal values). This occurred despite a decrease in regional myocardial blood flow to 24 ± 6% of control (P < 0.01) in the IZ and an increase to 147 ± 14% of control (P < 0.01) in the NZ during the study. We conclude that myocardial ischemia does not alter the normal rate of \(^{201}\)TI clearance from the myocardium.

ALTHOUGH THALLIUM-201 (\(^{201}\)TI) is quite useful for myocardial imaging, its kinetics in the myocardium are still not completely understood. It is well-known that initial \(^{201}\)TI uptake under conditions of both normal and decreased coronary blood flow correlates well with myocardial perfusion as measured by microspheres.\(^1\) However, there is little information available concerning what factors, if any, alter the rate at which \(^{201}\)TI leaves the myocardium. In particular, the effect of ischemia on \(^{201}\)TI clearance from the myocardium has not been previously investigated. Since the appearance of the \(^{201}\)TI image depends on myocardial content, the net difference between uptake and loss of the radionuclide, it would be interesting to know if myocardial ischemia altered the normal rate of \(^{201}\)TI clearance from the myocardium. This information would be especially useful in interpreting serial \(^{201}\)TI scans made during and/or following an episode of myocardial ischemia. To determine the effect of ischemia on myocardial loss of \(^{201}\)TI, we performed studies in dogs in which myocardial ischemia was produced after the injection of thallium.

Materials and Methods

Twelve adult mongrel dogs (mean weight 23 kg, range 19–23 kg) were anesthetized with chloralose (140 mg/kg I.V.) and urethane (1400 mg/kg I.V.), intubated and placed on an Emerson respirator with 10 cm of PEEP and 100% O\(_2\). The heart was exposed via left thoracotomy and then suspended in a pericardial cradle. A 20 cm vinyl catheter was then inserted in the left atrium and held in place by a pursestring suture. Next, a #7 NIH catheter was placed in the brachial artery and positioned at the aortic arch to obtain specimens of blood for pH and blood gas determination. In addition, another 20 cm vinyl catheter was advanced from the opposite brachial artery to the aortic arch and attached to a Holter pump in order to obtain reference samples for microsphere determination of regional myocardial blood flow (RMBF). Two other catheters were inserted — one, a large bore cannula in the femoral vein for administration of fluids (whole blood from “bleeder” dogs and/or Ringer’s lactate) to maintain mean arterial pressure above 80 mm Hg during the experiment, and a second polyethylene line in a brachial vein for the administration of drugs. Finally, the left anterior descending (LAD) coronary artery was dissected free just above the origin of the second diagonal branch and a 3-0 silk suture positioned, but not tied, at that point. The animals’ ECG (lead II), systemic arterial pressure and left atrial pressure (Statham P23Db transducers) were monitored continuously throughout the experiment and recorded on paper with a Hewlett-Packard recorder (Model #7788A). Specimens of arterial blood were obtained at frequent intervals to assess pH, Po\(_2\) and Pco\(_2\), and appropriate adjustments made to maintain pH and Pco\(_2\) in the physiologic range (i.e., pH 7.35 to 7.45 and Pco\(_2\) 35 to 45). Arterial Po\(_2\) was maintained above 90 mm Hg throughout the experiment (mean ± SEM = 395 ± 52).

Figure 1 shows the experimental protocol. After obtaining baseline steady-state hemodynamic and metabolic measurements, 1.5 mCi of \(^{201}\)TI was administered I.V. Five minutes later, a bolus of \(^{85}\)Sr labelled microspheres was administered via the left atrial catheter. The spheres were thoroughly suspended in 2 ml of normal saline and 0.01% Tween-80 by agitating them for 5 minutes in a Vortex mixer just before administration. Approximately two million
spheres (9 \pm 1 \mu m in diameter), with a total activity of 10\mu Ci, were administered. Two to 3 minutes later a drill biopsy of the myocardium was obtained in an area distal to the LAD artery ligation (designated ischemic zone (IZ)) and in an area in the distribution of the circumflex coronary artery (normal zone (NZ)). The biopsies were obtained using a trephine needle (2 mm in diameter) attached to a high speed drill as previously described.\textsuperscript{2} Lidocaine 40 mg was given I.V. just before this and subsequent biopsies. Biopsy holes which did not stop bleeding were closed using superficial epicardial mattress sutures. Control biopsies from IZ and NZ were obtained in eight dogs and from only the IZ in the remaining four dogs. After these biopsies had been obtained, the LAD suture was tied. Fifteen minutes later a set of biopsies were obtained from the IZ, which in all cases manifested cyanosis and systolic bulging, and from the NZ. One hundred minutes later a second set of microspheres (\textsuperscript{46}Sc) was given by the method used for the \textsuperscript{85}Sr microspheres. The total number, mean size and total radioactivity of the \textsuperscript{46}Sc spheres were the same as for the \textsuperscript{85}Sr spheres. Five minutes later, repeat final biopsies from the ischemic and normal zones were obtained. Immediately after the final biopsy, the animal was sacrificed, the heart was removed and block sections were obtained from the IZ and NZ.

Regional Thallium Activity — Biopsy Material

The biopsy samples were placed in precisely weighed plastic tubes. The tubes containing the sample were then weighed in order to determine the weight of the sample. The material was placed in a well counter and counted for minutes using a 15–300 kev window-width setting. The activity in each biopsy was then expressed as counts/5 min/mg. In these specimens, which were counted within 24 hours, Sr and Sc activities were found to comprise less than 1% of the counts in the TI window. The counts in the IZ were considered to be 100% for each animal and all other counts in both ischemic and non-ischemic zones normalized as a percentage of these counts. Since microsphere activities were extremely low, microspheres could not be quantified from biopsy samples.

Regional Myocardial Blood Flow — Postmortem Material

After the heart was removed, it was thoroughly washed in tap water and then sectioned. The epicardial fat and blood vessels were carefully removed along with the right ventricle and septum. The regions immediately surrounding the IZ and NZ biopsy sites were then excised from the remainder of the left ventricle and carefully weighed. These samples were then preserved in 10% formalin solution until the TI activity had decayed enough to permit accurate counting of the Sr and Sc microspheres. The samples were then divided into inner, middle and outer thirds from endo- to epicardium, respectively. Each third was then “diced” and placed in an accurately pre-weighed vial for counting. The vials were weighed again with samples contained and then counted in a well counter for 5 minutes. The Sr window was set at 442–586 kev, and the Sc window at 820–1300 kev. A computer program was used to correct for activity spilling from one window into another. RMBF was calculated by the computer from the sample activity and activity in reference blood samples obtained simultaneously with the administration of each radioisotope.\textsuperscript{3} The mean transmural flow for each section was determined by adding the total flow in each inner, middle and outer sub-section and dividing by the total weight of the entire section. Results were expressed as ml/min/g of myocardium.

Statistical Methods

All results are expressed as mean \pm 1 SEM. The significance of difference between the means was assessed using the Student t test. The significance of correlations between various parameters was determined by using linear regression analysis.

Results

Hemodynamic Response

The heart rate (HR), mean arterial pressure (MAP) and mean left atrial pressure (LAP) were continuously
monitored and specifically noted at each biopsy for each animal. MAP at control and 15- and 120-minute* biopsies was 109 ± 3.4, 102 ± 3, and 100 ± 5.2 mm Hg, respectively. These values were not significantly different from one another. LAP was 4.8 ± 0.5, 5.4 ± 0.6 and 7.2 ± 1.2 mm Hg at control, 15- and 120-minute time periods, respectively. The change between control and 120 minutes was significant (P = 0.05), whereas the other differences were not. HR decreased significantly between control and the 15-minute biopsies (170 ± 8.3 to 160 ± 7.2 beats/min, P < 0.02), but did not change significantly thereafter (156 ± 10.4 at 120 minutes).

**Biopsy Data**

Figure 2A depicts Tl counts (expressed as counts/5 min/mg) in the NZ plotted against counts in the future IZ. A very close correlation between the two exists (r = 0.95). The Tl activity in both ischemic and normal zones at 15 and 120 minutes post-LAD occlusion is shown in figure 3. Although 201TI activity tended to decrease by 15 minutes after occlusion in both ischemic and normal zones, these changes were not significant. In addition, although the 201TI activity at 15 minutes was slightly lower in the IZ compared with the NZ, this difference was not statistically significant. Two hours after occlusion both the ischemic and normal zones revealed not only a significant (P < 0.001), but also an almost identical, decline in 201TI activity to 72 ± 5% and 73 ± 4% of control, respectively. In addition, a highly significant linear correlation between 201TI activity in the two zones (r = 0.97) (fig. 2B) persisted despite marked changes in RMBF (vide infra).

**Regional Myocardial Blood Flow**

Before LAD occlusion, RMBF (ml/min/g) was similar in the designated ischemic and normal zones — 1.06 ± 0.14 and 1.05 ± 0.14, respectively (r = 0.99) (fig. 4). However, 2 hours after LAD ligation, flow in the IZ had decreased to mean of value of 0.25 ± 0.05 ml/min/g (P < 0.0001), whereas in the NZ there was a significant increase in flow to 1.47 ± 0.16 ml/min/g (P < 0.001).

**Discussion**

Thallium uptake by myocardial cells depends on both delivery and the extraction ability of the cell.\(^1\)\(^,\)\(^4\)\(^,\)\(^5\) However, once Tl has been distributed in the myocardium, its subsequent metabolism is not well understood. We know from previous work in our laboratory that 201TI is lost from normal canine myocardium with a half life of 7 hours, while it actively redistributes into regions of transient ischemia within 30–60 minutes after Tl administration.\(^4\)\(^,\)\(^5\) The effect of ischemia on 201TI loss is not known. Clearance of Tl may or may not depend on myocardial perfusion. If Tl were analogous to potassium in this regard, loss of Tl from ischemic zones would be flow-
FIGURE 3. Plot of thallium-201 (\(^{201}\text{TI}\)) activity (% control) in the ischemic and normal zones before and at 15 minutes and 2 hours after ligation of the left anterior descending coronary artery. There is no significant change in \(^{201}\text{TI}\) activity in either zone at 15 minutes post-occlusion. At 2 hours post-occlusion, \(^{201}\text{TI}\) activity has decreased significantly (P < 0.001) in both zones, compared with control and 15 minutes post-occlusion periods. However, there still is no significant difference between \(^{201}\text{TI}\) activity in the two zones.

FIGURE 4. Plot of regional myocardial blood flow in the designated ischemic zone vs the normal zone before ligation of the left anterior descending coronary artery. A highly significant linear correlation between the two zones is demonstrated (\(r = 0.99\)). Note that \(n = 11\), since one dog died before the end of the experiment, and as a result the heart was not counted for microsphere activity.

Since there was no significant difference between ischemic and normal zone TI activity at 15 minutes and 2 hours post-occlusion, the data obtained in the present study suggest that TI clearance from the myocardium is independent of blood flow over a wide range (25 → 147% of control). Two observations in our study support this conclusion. First, the highly significant linear correlation (fig. 2B) between \(^{201}\text{TI}\) activity in ischemic and normal areas at 2 hours after occlusion suggests that loss of TI is similar from both zones. Second, TI content in the ischemic and normal zones was 72% ± 5 and 73% ± 4 of the control value, respectively, at the end of 2 hours. This occurred in the face of a reduction in RMBF to 24 ± 6% of control in the ischemic zones, a level at which enhanced efflux of potassium has been shown to occur. This clearance rate (27 ± 5% in 2 hours) is in the range of previously determined normal half-times of 4.4 to 7 hours for TI in the myocardium. Thus, while there was a marked difference in regional blood flow between the ischemic and normal zones, there was no difference in the rate at which \(^{201}\text{TI}\) was cleared from each of them. Furthermore, the normal myocardial clearance half-time for K+ is 78 minutes, while that of \(^{201}\text{TI}\) is substantially longer. Thus, even under normal circumstances both K+ and TI are cleared at different rates from the myocardium, suggesting that the intracellular metabolism of the two is different. These differences most likely account for the failure of TI to "leak" from the myocardium during ischemia, in contrast to potassium.

Clinical Implications

The data suggest that with serial imaging, zones of normal myocardium, which subsequently become
ischemic or infarcted after Tl has already been administered, might not change in appearance in later images. Ischemic and normal zones would appear similar on later images, since both zones lose Tl at the same rate. Second, since it has been observed that a defect on scan may appear to increase in size on serial images following a single dose of Tl during ischemia and/or infarction, factors other than a true loss in Tl must be responsible. For example, alterations in left ventricular regional geometry and wall motion might explain apparent enlargement of a defect in the absence of a real decrease in Tl activity. With ischemia and/or infarction, dyskinesis would lead to systolic thinning, rather than thickening, of the involved region of myocardium. As a result, a defect in the myocardial image may appear to be present without an actual change in thallium concentration in the IZ.

In conclusion, the present study demonstrates that a zone of myocardium which is initially normal during thallium administration and then is rendered ischemic, will show Tl washout at a rate similar to that in normal zones. These data suggest that clearance of thallium from the myocardial cells is relatively slow and that its resultant clearance rate is independent of flow. In clinical terms this implies that a lack of increase in defect size on serial images after \(^{201}\)Tl administration does not exclude extension of the ischemic and/or infarct process. Conversely, an apparent increase in defect size on serial images following increasing ischemia at these levels of perfusion and/or infarction is most probably due to other factors than a true loss of Tl activity from such zones.

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