Linear Relationship Between the Distribution of Thallium-201 and Blood Flow in Ischemic and Nonischemic Myocardium During Exercise

ANTON P. NIELSEN, M.D., KENNETH G. MORRIS, M.D., ROBERT MURDOCK, B.S., FREDERICK P. BRUNO, M.S., AND FREDERICK R. COBB, M.D.

SUMMARY The purpose of this study was to compare the myocardial distribution of thallium-201 and regional myocardial blood flow during ischemia and the physiologic stress of exercise. Studies were carried out in six dogs with chronically implanted catheters in the atrium and aorta and a snare on the circumflex coronary artery distal to the first marginal branch. Regional myocardial blood flow was measured during quiet, resting conditions using 7-10 μ of radioisotope-labeled microspheres. Each dog was then exercised on a treadmill at speeds of 5-9 mph at a 5° incline. After 1 minute of exercise the circumflex coronary artery was occluded and thallium-201 and a second label of microspheres were injected. Exercise was continued for 5 minutes. The dogs were then sacrificed and the left ventricle was sectioned into approximately 80 1-2-g samples to compare thallium-201 activity and regional myocardial blood flow.

The maximum increase in blood flow ranged from 3.3-7.2 times resting control values. Each dog had myocardial samples in which blood flow was markedly reduced, to less than 0.10 ml/min/g. In each dog there was a close linear relationship between thallium-201 distribution and direct measurements of regional myocardial blood flow. Linear regression analyses demonstrated a correlation coefficient of 0.98 or greater in each dog. These data indicate that during the physiologic stress of exercise, the myocardial distribution of thallium activity is linearly related to regional myocardial blood flow in both the ischemic and nonischemic regions.

THALLIUM-201 is the most frequently used radioisotope tracer to evaluate regional myocardial perfusion. Although thallium-201 scintigrams of the heart during rest and exercise stress testing have been useful for diagnosing coronary artery disease, a number of patients with significant coronary artery disease by cardiac catheterization do not demonstrate deficits on thallium scintigrams.1,2 This apparent insensitivity to significant disease may be related to several variables, including limitation of available imaging equipment,4 inability to resolve small perfusion deficits,4 early redistribution of radioisotope,5 variable interpretation of significant anatomic disease, variable relationship between anatomic disease and clinical manifestation of ischemia,6 and inconsistent relationship between thallium-201 distribution and myocardial blood flow.6,8,9 Although experimental studies have demonstrated a close linear relationship between thallium-201 activity and direct measurements of regional myocardial blood flow after acute coronary artery occlusion,4,7 certain studies have indicated that the thallium-201 distribution may not be linearly related to myocardial perfusion when blood flow is increased above control values.6,8,9 The relationship between the myocardial distribution of thallium-201 and regional myocardial perfusion during ischemia and the physiologic stress of exercise has not been reported.

In this study we compared the myocardial distribution of thallium-201 and regional myocardial blood flow during exercise and ischemia. Direct measurements of regional myocardial blood flow were made using the radioisotope-labeled microsphere technique.10,11

Methods

Six mongrel dogs were trained to run on a motorized treadmill using positive reinforcement techniques. Each dog was anesthetized with thiamyl...
sodium 30–40 mg/kg i.v. and mechanically ventilated. A left thoracotomy was performed in the fourth left intercostal space. The circumflex coronary artery was dissected free just beyond the first marginal branch. A pneumatic cuff occluder was positioned around the vessel. Polyvinyl chloride catheters, 3 mm o.d., were filled with heparin and inserted into the left atrium via the left atrial appendage and in the aortic arch via the left internal thoracic artery. The occluder and catheters were tunneled to a subcutaneous pouch at the base of the neck.

At least 6 days were allowed to assure that the dogs had recovered from the surgery. The day before the study, the dogs were sedated with thiamylal sodium 10 mg/kg i.v., the pouch was infiltrated with lidocaine and the catheters and snare were exteriorized. Each dog was placed in a protective vest to prevent damage to the catheters and snare. A period of 14–24 hours was allowed for recovery from this procedure.

Each dog was given lidocaine 2 mg/kg i.v., and quinidine gluconate 6 mg/kg i.m. 15 minutes and 1 hour before the exercise study. Before exercise myocardial blood flow was measured using 89mNb-labeled 7–10-μ microspheres during quiet, resting conditions as previously described.10 11 The dogs were then placed on a motorized treadmill and run at speeds of 5–9 mph at a 5° incline. After 1 minute of running time, the circumflex coronary occluder was inflated. Thallium-201, 0.5 mCi, was injected into the left atrium 30 seconds after complete occlusion. Scandium-46-labeled microspheres were injected into the left atrium immediately after the thallium-201 injection, approximately 45 seconds after occlusion. Beginning with the injection of radioisotope, serial blood samples were withdrawn from the aortic catheter at a measured flow rate as previously described to facilitate calculation of regional blood flow,10 11 and to measure serial changes in arterial thallium activity. The dogs were run for a total of 5 minutes after coronary artery occlusion. Immediately after the exercise period, each dog was anesthetized with 40 mg/kg thiamylal sodium and the heart was fibrillated with potassium chloride solution. The heart was immediately removed and cooled to approximately 5–10°C.

The hearts were then prepared for sectioning by removing the right ventricle, atria, aorta and pericardial fat. The left ventricle was then sectioned into 4 transverse layers of approximately equal thickness as previously described.10 11 The apical ring was sectioned into anterior and posterior regions. The other rings were sectioned into anterior, anterior papillary, lateral, posterior papillary, posterior and septal regions. Each region was further sectioned into four transmural layers of approximately equal thickness. This procedure produced approximately 80 1–2-g tissue samples for comparison of blood flow and thallium-201 distribution.

Thallium-201 activity in each tissue and blood sample was counted in a gamma spectrometer, 50–100-keV window. The samples were held for 1 week to allow for high-energy contaminate isotopes of thallium-201 to decay. The tissue samples and reference blood samples were then counted for 89mNb and 46Sc radioactivity in a gamma spectrometer at optimum window settings selected to correspond to the peak energies of each nuclide. The counts per minute recorded in each window from the myocardial and reference blood samples were corrected for background activity and spillover activity contributed by the accompanying isotope by an appropriate computer program.10 11 Flow to each region of the myocardium was calculated in ml/min using the formula:

\[ Q_m = Q_r \times C_m/C_r \]

where \( Q_m \) = myocardial blood flow (ml/min), \( Q_r \) = reference blood flow (ml/min), \( C_m \) = counts activity in the myocardium, and \( C_r \) = count activity in reference blood samples. Myocardial blood flow (ml/min) was divided by the sample weight and expressed as ml/min/g.

The relationship between thallium-201 distribution and regional myocardial blood flow was analyzed by linear regression analyses.

**Results**

Table 1 lists mean blood flow during quiet resting conditions and the maximum blood flow during exercise in each dog. The maximum increase in blood flow in individual dogs ranged from 3.3–7.2 times values during resting conditions. In each dog there were myocardial samples in which blood flow was markedly reduced, to less than 0.10 ml/min/g. It was thus possible to compare the distribution of thallium-201 activity and myocardial blood flow over a wide range of ischemic and nonischemic blood flow measurements.

The relationship between the regional distribution of thallium-201 and myocardial blood flow during ischemia and treadmill exercise in each dog is illustrated in figure 1. In each dog there was a close linear relationship between thallium-201 distribution and direct measurements of regional myocardial blood flow; linear regression analyses demonstrated a correlation coefficient of 0.98 or greater in each dog. The intercept on the y-axis, thallium-201 activity, was significantly greater than zero, mean intercepts 0.10 × 10⁶, range 0.061–0.178 × 10⁶ counts/min/g (p < 0.05).

Table 2 is a representative illustration of thallium

<table>
<thead>
<tr>
<th>Dog</th>
<th>Myocardial blood flow (ml/min/g)</th>
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<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>1</td>
<td>0.85</td>
</tr>
<tr>
<td>2</td>
<td>0.80</td>
</tr>
<tr>
<td>3</td>
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<td>5</td>
<td>0.71</td>
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<td>6</td>
<td>0.90</td>
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activity in the arterial blood as a function of time after injection. Thallium activity in the arterial blood decreased as an exponential function. Five minutes after thallium injection and immediately before sacrifice, thallium activity in the arterial blood decreased approximately tenfold.

**Discussion**

Previous studies have demonstrated a close linear relationship between the myocardial distribution of thallium-201 and the distribution of myocardial blood flow after acute coronary artery occlusion. Other...
studies have concluded that when blood flow is increased above control values the distribution of thallium-201 and blood flow may not be linear.\textsuperscript{5, 6, 9} This apparent dissociation between the myocardial distribution of thallium-201 and blood flow during conditions of increased flow must be interpreted in terms of whether the augmentation in blood flow results from direct vasomotor effects on the coronary vasculature, increased metabolic demands of the myocardium, or a combination of the two factors. Adenosine and dipyridamole are potent coronary vasodilators that have direct vasomotor effects on the coronary vasculature. Adenosine infusion may increase myocardial blood flow four- to sixfold.\textsuperscript{10, 11} The increase in myocardial blood flow during adenosine infusion is associated with no change or a decrease in myocardial oxygen utilization and a marked decrease in coronary arteriovenous oxygen differences.\textsuperscript{12}

Transient myocardial ischemia may also effect maximum increase in myocardial blood flow.\textsuperscript{11} Although the reactive hyperemic response that follows transient ischemic stimulation is related to the metabolic state of the myocardium,\textsuperscript{13} the oxygen debt incurred during transient ischemia is overpaid three- to sixfold during the reactive hyperemic response and coronary arteriovenous oxygen difference decreases.\textsuperscript{14} Coffman and Gregg\textsuperscript{14} have suggested that transient ischemia is a greater stimulus to coronary blood flow than to myocardial oxygen utilization. Treadmill exercise, on the other hand, is a potent stimulus to myocardial metabolism; myocardial oxygen utilization and coronary arteriovenous oxygen difference increase during exercise.\textsuperscript{15} Myocardial blood flow may increase more than fourfold in dogs during heavy exercise on a treadmill.\textsuperscript{15, 16} Increasing the heart rate by artificial pacing is a relatively less potent stimulus to blood flow and myocardial oxygen demands; ventricular pacing at rates of 120-240 beats/min augmented coronary blood flow only approximately 50%.\textsuperscript{17, 18} Coronary arteriovenous oxygen difference increases during rapid ventricular pacing.\textsuperscript{16}

Struss et al.,\textsuperscript{6} using acute animal preparations, observed that thallium activity increased approximately 60% of that measured directly by microsphere techniques when blood flow was increased by transient myocardial ischemia. Weihe et al., using acute animal preparations,\textsuperscript{6} measured the myocardial extraction of thallium-201. They found that 87% of thallium-201 was extracted from the blood during the first pass through the heart and that the extraction fraction decreased when blood flow was increased above control values by transient ischemic stimulation or adenosine and minoxidil, but did not change when blood flow was increased by atrial pacing. The extraction fraction was not changed by insulin, propranolol, alkalesis, or acetyl strophanthan, but was reduced by hypoxia. These investigators reasoned that when blood flow increases in proportion to myocardial demands, the extraction fraction remained constant, but when blood flow exceeds myocardial demands, the extraction fraction decreases logarithmically. This hypothesis was not tested over a wide range of physiologic increases in blood flow and oxygen demands because atrial pacing increased coronary blood flow only approximately 88% above control values. Gould\textsuperscript{6} determined the ratio of myocardial/background counts of thallium-201 and technetium-99m-macroaggregated albumin microspheres in dogs in response to dipyridamole and treadmill exercise. He observed that during dipyridamole infusion the ratio of technetium-99m-macroaggregated albumin was 4.5, compared with a thallium-201 ratio of 2.4. In the studies by Gould, treadmill exercise resulted in smaller increases in the myocardial/background ratio of technetium-99m-macroaggregated albumin microspheres; the mean ratio during exercise was 2.3. In a representative study the myocardial/background ratio of thallium-201 was

\begin{figure}
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\caption{Serial measurement of arterial thallium-201 activity after left atrial injection.}
\end{figure}
1.5 at rest and 2.0 at exercise. These studies support the view that when myocardial blood flow is increased in excess of oxygen demands, the myocardial distribution of thallium-201 is not proportional to myocardial blood flow. Previous studies have not directly assessed the myocardial distribution of thallium-201 and regional blood flow over the wide range of physiologic flows that may occur during treadmill exercise.

In the present study the combination of ischemia and the physiologic stress of exercise provided a wide range of measurements for comparison of the myocardial distribution of thallium-201 and blood flow. Blood flow increased three- to sevenfold with the above control values; there were regions of severe ischemia with blood flow less than 0.10 ml/min/g in each dog. There was a close linear relationship between the myocardial distribution of thallium-201 and regional myocardial blood flow; regression analysis between thallium activity and regional myocardial blood flow demonstrated correlation coefficients of 0.98 or greater in each dog.

In the present study the animals were sacrificed 5 minutes after injection of thallium-201. Schwartz et al.19 observed that the myocardial extraction of thallium-201 may become negative approximately 10 minutes after i.v. injection, suggesting relatively early loss of thallium activity from the normal myocardium. Schwartz et al.18 and Pohost et al.5 have described early redistribution of thallium-201 activity to the ischemic region after restoration of blood flow. Therefore, when myocardial thallium-201 activity is assessed at longer intervals after i.v. injection, the myocardial thallium-201 activity may not accurately reflect regional myocardial blood flow at the time of injection in either the nons ischemic or ischemic regions.

The results of the present study indicate that during physiologic exercise sufficient to increase coronary blood flow three- to sevenfold, the initial myocardial distribution of thallium activity is linearly related to regional myocardial blood flow in both the ischemic and nonischemic regions.

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