Thallium-201 Kinetics in Nonischemic Canine Myocardium


SUMMARY Myocardial thallium-201 (201TI) kinetics have not been precisely defined because reliable techniques to determine continuous activity in vivo have not been available. In this study, an implantable miniature cadmium telluride radiation detection device was inserted through the left ventricular apex, positioned against the endocardium, and used for continuous on-line monitoring of myocardial 201TI activity for 260–810 minutes in 18 dogs. Blood was serially sampled and counted. Microsphere-determined myocardial blood flow was measured before administration of 201TI and was not significantly different from that measured at the end of the experiment in 11 of 18 dogs. Thallium was administered intravenously. Myocardial and blood activity curves were analyzed using a nonlinear least-squares estimation of the decay constant \( \lambda \) (min\(^{-1} \)). Myocardial activity reached 80% of peak within 1 minute, peaked in a mean time of 23.7 ± 17.9 minutes (±SD), then decreased monoexponentially with a mean \( \lambda_1 = 0.00176 ± 0.00054 \) min\(^{-1} \) (half-time \( T_{1/2} = 437.2 ± 126.3 \) minutes) \((r = 0.95–0.99)\). Blood activity decreased triexponentially with a mean \( \lambda_1 = 0.36782 ± 0.20414 \) min\(^{-1} \) (\( T_{1/2} = 2.4 ± 1.1 \) minutes), mean \( \lambda_2 = 0.06134 ± 0.02973 \) min\(^{-1} \) (\( T_{1/2} = 14.1 ± 7.1 \) minutes) and mean \( \lambda_3 = 0.00177 ± 0.00075 \) min\(^{-1} \) (\( T_{1/2} = 445.5 ± 201.6 \) minutes) \((r = 0.99–1.00)\). The mean final blood \( \lambda_3 \) was almost identical to the mean myocardial \( \lambda \).

To determine the relationship between myocardial and blood clearance rates of 201TI after i.v. and intracoronary administration, 201TI was administered by the intracoronary route in four dogs. Myocardial 201TI activity peaked in a mean time of 2.0 ± 0.8 minutes, then decreased monoexponentially with a mean \( \lambda = 0.00833 ± 0.00115 \) min\(^{-1} \) (\( T_{1/2} = 84.2 ± 12.5 \) minutes) \((r = 0.94–0.98)\). Thallium clearance from the myocardium after intracoronary 201TI was significantly greater than after i.v. 201TI \((p < 0.0001)\).

The data suggest that 201TI washout after peak activity is reached in nonischemic myocardium is monoexponential. The rate of 201TI clearance from the myocardium is related to the rate of 201TI clearance from the blood after i.v. administration of the tracer.

THALLIUM-201 (201TI) imaging has been used to determine regional myocardial perfusion patterns at rest, during exercise, during pharmacologic vasodilatation and during acute myocardial infarction.\(^1\)–\(^7\) Defects after 201TI injection on initial images may be due to ischemia or infarction. Disappearance of defects on images obtained 2–4 hours later implies reversible ischemia.\(^8\)–\(^10\) Clinical studies have attempted to identify ischemic myocardium by determining regional 201TI time-activity curves in patients using quantitative approaches to serial gamma camera images.\(^11\)–\(^12\) Such approaches require an understanding of normal myocardial 201TI kinetics. Canine studies using multiple needle biopsies or multiple dog sacrifices have shown overall 201TI clearance from nonischemic myocardial zones after 4 hours.\(^13\)–\(^14\) However, myocardial 201TI kinetics have not been well defined because techniques to continuously determine myocardial activity in vivo have not been available.

For the present study, we developed a miniature radiation detection device for continuous on-line monitoring of myocardial 201TI activity. The purposes of the present study were to study 201TI myocardial activity in nonischemic myocardium as a function of time after i.v. administration and to determine the relationship between myocardial and blood clearance rates of 201TI after i.v. and intracoronary administration of the tracer.

Materials and Methods

Twenty-two adult mongrel dogs (mean weight 20 kg, range 15–23 kg) were anesthetized with chloralose (140 mg/kg) and urethane (1400 mg/kg), intubated, and placed on an Emerson respirator with 5 cm of positive end-expiratory pressure and 100% oxygen. The heart was exposed through a left thoracotomy and suspended in a pericardial cradle. A 20-cm vinyl catheter was inserted into the left atrium to monitor left atrial pressure and to inject microspheres in the 11 dogs in which myocardial blood flow was determined. In 18 dogs, a vinyl catheter was inserted into the right atrium for central venous injection of 201TI. A #7 NIH catheter was placed in the brachial artery and positioned in the aortic arch to measure arterial pH, Pco\(_2\), and Po\(_2\), to obtain reference samples for microsphere determination of regional myocardial blood flow and to monitor aortic pressure. The femoral artery and vein were cannulated and connected to a reservoir overflow column to maintain a mean arterial pressure of 90–100 mm Hg. Pacing elec-
trodes were attached to the right atrium to maintain a heart rate greater than 145 beats/min.

Four additional dogs underwent intracoronary administration of 201T1. In these dogs, a roller pump (Cardiovascular Instruments) was used to remove systemic blood from the subclavian artery. This blood was then distributed using a Y-connector to two metal cannulas that had been inserted through the brachial artery and the ascending aorta into the orifices of the right coronary artery and left main coronary artery. Flow through this system was adjusted with the roller pump to maintain a mean pressure within the Y-tubing of 90–100 mm Hg.

In all dogs, electrocardiographic lead II and pressures (Statham P23Db transducers) were monitored continuously throughout the experiment and recorded on paper with a Hewlett-Packard recorder (model #7788A). Arterial blood was obtained frequently to assess pH, Po2 and PCO2. These variables were maintained in the physiologic range (pH 7.35–7.45 and PCO2 30–40 mm Hg). Arterial Po2 was maintained above 100 mm Hg throughout the experiment.

A miniature cadmium telluride radiation detector probe attached to a modified surgical arterial clamp was inserted through the left ventricular apex, positioned against the anterior wall endocardium and used to monitor 201T1 activity continuously (fig. 1). The probe was connected by means of a preamplifier to a multichannel analyzer that allowed monitoring and display of 201T1 activity (Canberra Series 30). Probe data were recorded on paper tape as counts per minute. The data (counts vs time) were also displayed on the multichannel analyzer cathode ray display and photographed on Polaroid film. Sonomicrometer transducer crystals (3-mm-diameter) attached to both arms of the arterial clamp and connected to a sonomicrometer (Norland Instruments model NI-202-4R) permitted simultaneous measurements of wall thickness (fig. 1).

The probe has been described and validated in our laboratory.18 Briefly, the probe consists of a 2-mm³ cadmium telluride crystal surrounded by lead foil on the back and sides. The crystal and shielding are housed in a 4-mm (o.d.) steel cylinder. The lead foil provides collimation such that 75% of measured activity is within a core of solid angle of 60°. In vitro validation was performed by comparing probe-determined activity with well-counter-determined activity of 201T1 samples (r = 0.996). In vivo validation compared probe-determined activity with serial needle biopsy measurements in 10 dogs (r = 0.90). Background activity from noncardiac structures was virtually eliminated by positioning the probe against the left ventricular anterior wall endocardium and by aligning the probe in the direction of the opened thoracotomy. The absence of background activity from noncardiac structures was confirmed by comparing the presacrifice probe measurement with a postsacrifice measurement after the heart had been removed from the thorax.

Figure 2 shows the experimental protocol for the 18 dogs that received i.v. 201T1. Baseline steady-state hemodynamic measurements were recorded. In the 11 dogs in which myocardial blood flow was determined, approximately 4.5 million 46Sc-labeled 8–10-μ microspheres (total activity 30 μCi) (New England Nuclear) were administered into the left atrium. The microspheres were thoroughly suspended in 10 ml of normal saline and 0.01% Tween-80 by agitation in a vortex mixer for 5 minutes. In all 18 dogs, background activity was measured with the probe. Thallium-201 (0.8 mCi) (New England Nuclear) was

![Figure 1. Miniature radiation detector (curved arrow) attached to modified arterial clamp. The sonomicrometer crystals used for monitoring changes in wall thickness are also shown (straight arrows).](image)
then injected into the right atrium. Probe counts were collected continuously at 60-second intervals. After \(^{201}\text{TI}\) injection, 1-ml arterial blood samples for \(^{201}\text{TI}\) activity were collected at 2, 4, 6, 8, 10, 20, 30, 60, 90 and 120 minutes, and then every 60 minutes thereafter. The experiment continued for 260–810 minutes after administration of \(^{201}\text{TI}\) (mean 428 minutes), depending on the hemodynamic stability of the canine preparation. Just before sacrifice, \(^{113}\text{Sn}\)-labeled microspheres (New England Nuclear) were injected into the left atrium in the 11 dogs in which myocardial blood flow was determined. The total number and total radioactivity of the \(^{113}\text{Sn}\) microspheres were similar to those of the \(^{48}\text{Sc}\) microspheres.

The experimental protocol for the four dogs in which \(^{201}\text{TI}\) was injected into the heart was similar to that described above. In these dogs, however, 0.1 mCi of \(^{201}\text{TI}\) was injected just proximal to the Y-tubing. Total coronary sinus blood flow for 1 minute after injection of \(^{201}\text{TI}\) was collected and discarded.

After the experiment in the 11 dogs in which myocardial blood flow was determined, the heart was removed and the area of myocardium under the probe was subdivided into inner, middle and outer segments. The fresh myocardial samples weighed 0.8–1.2 g. The myocardial and blood reference samples were counted in a counter (Auto-Gamma Scintillation Spectrometer, Hewlett-Packard) after \(^{201}\text{TI}\) activity had decayed 1–2 half-lives. Samples were counted for 5 minutes to collect at least 10,000 counts for each isotope. The \(^{48}\text{Sc}\) was counted at 800–1200 keV and the \(^{113}\text{Sn}\) at 350–435 keV. A computer program was used to correct for activity spilling from one window into another and for physical decay of \(^{201}\text{TI}\) during the counting period. In addition, regional myocardial blood flow was calculated by the computer from the sample activity, and the activity in the blood reference samples was obtained simultaneously with the administration of each labeled microsphere bolus. Arterial blood samples were counted in the well counter within 12 hours after the experiment. The samples were counted for 5 minutes with a \(^{201}\text{TI}\) window of 60–110 keV.

**Analysis of Data**

All results are mean ± sd. The significance of a difference between two means was assessed using the \(t\) test. Myocardial and blood time-activity curves were then analyzed using a computer-assisted, nonlinear least-squares estimation of the decay constants (\(\lambda\) min\(^{-1}\)) and the total half time (\(T_{1/2}\) min). In the case of a triexponential fit, \(\lambda_1\) was the initial decay constant, \(\lambda_2\) the intermediate decay constant and \(\lambda_3\) the final decay constant.

The specific activity of a sample of blood was calculated from the counts/min/g of that sample and the counts/min/g of a \(^{201}\text{TI}\) standard containing a known amount of activity.

**Results**

**Intravenous Administration of Thallium-201**

Table 1 lists the data for the 18 dogs given i.v. \(^{201}\text{TI}\). The experiments lasted 260–810 minutes after injection of \(^{201}\text{TI}\) (mean 428 ± 148 minutes). The heart rate, mean left atrial pressure and mean arterial blood pressure were 148 ± 7 beats/min, 5.1 ± 1.1 mm Hg and 94.4 ± 4.4 mm Hg, respectively, before administration of \(^{201}\text{TI}\), and 148 ± 7 beats/min, 4.9 ± 1.0 mm Hg and 90.9 ± 3.5 mm Hg, respectively, after the experiment (NS compared with values before \(^{201}\text{TI}\)). The mean microsphere-determined myocardial blood flow was 1.32 ± 0.50 ml/g/min before administration of \(^{201}\text{TI}\) and 1.27 ± 0.73 ml/g/min after the experiment in the 11 dogs in which blood flow was measured (NS). Left ventricular wall thickness in the area of the probe did not change significantly during the experiment in the seven dogs in which it was measured.

In all 18 dogs, myocardial \(^{201}\text{TI}\) activity reached at least 80% of peak activity within 1 minute. The mean time to peak activity was 23.7 ± 17.9 minutes (range 2–50 minutes). Thereafter, activity decreased monoexponentially, with a mean decay constant \(\lambda = 0.00176 ± 0.00054\) min\(^{-1}\) (\(T_{1/2} = 437.2 ± 126.3\) minutes) (figs. 3 and 4). For the monoeponential nonlinear least-squares fit, \(r = 0.95–0.99\). The initial arterial peak \(^{201}\text{TI}\) level during the first transit of the tracer was not measured. At 2 minutes and thereafter, arterial blood \(^{201}\text{TI}\) activity decreased triexponentially, with a mean decay constant \(\lambda_1 = 0.36782 ± 0.20141\) min\(^{-1}\) (\(T_{1/2} = 2.4 ± 1.1\) minutes), \(\lambda_2 = 0.06134 ± 0.02973\) min\(^{-1}\) (\(T_{1/2} = 14.1 ± 7.1\) minutes) and \(\lambda_3 = 0.00177 ± 0.00075\) min\(^{-1}\) (\(T_{1/2} = 445.5 ± 201.6\) minutes) (fig. 4). The second and third phases of blood \(^{201}\text{TI}\) clearance were established by mean times of 8.9 ± 0.5 and 44.6 ± 4.7 minutes, respectively. For the triexponential nonlinear least-squares fit, \(r = 0.99–1.00\). The decay constants \(\lambda\) for the myocardium did not differ significantly from the final decay constants \(\lambda_3\) for the blood. Specific blood \(^{201}\text{TI}\) activities were 0.0570 μCi/g at 2 minutes (10.0% of injected dose in blood) and 0.0046 μCi/g at 120 minutes (0.8% of injected dose in blood) after i.v. administration.

**Intracoronary Administration of Thallium-201**

Table 2 lists the data for the four dogs given intracoronary \(^{201}\text{TI}\). The mean duration of the experiment after injection of \(^{201}\text{TI}\) was 181 ± 76 minutes (range 113–290 minutes). The heart rate, mean left atrial pressure and mean coronary perfusion pressure were 150 ± 2 beats/min, 5.0 ± 0.1 mm Hg and 93.8 ± 2.5 mm Hg, respectively, before administration of \(^{201}\text{TI}\), and 150 ± 2 beats/min, 5.1 ± 0.1 mm Hg and 92.5 ± 1.5 mm Hg, respectively, after the experiment (NS compared with values before \(^{201}\text{TI}\)). Myocardial \(^{201}\text{TI}\) activity peaked rapidly in a mean time of 2.0 ± 0.8 minutes (range 1–3 minutes). Thereafter, activity decreased monoexponentially, with a mean decay constant \(\lambda = 0.00833 ± 0.00115\) min\(^{-1}\) (\(T_{1/2} = 84.2 ± 12.5\) minutes) (fig. 5). For the monoeponential nonlinear least-squares fit, \(r = 0.94–0.98\). Arterial blood \(^{201}\text{TI}\) activity decreased triexponentially, with a mean decay constant \(\lambda_1 = 0.17345 ± 0.04333\) min\(^{-1}\) (\(T_{1/2} = 4.1 ± 1.0\) minutes), \(\lambda_2 = 0.02350 ± 0.03731\) min\(^{-1}\) (\(T_{1/2} = 199.9 ± 288.7\) minutes), and \(\lambda_3 = 0.00047 ± 0.00035\) min\(^{-1}\) (\(T_{1/2} = 2791.8 ± 2836.2\) minutes). The second and third phases of blood \(^{201}\text{TI}\) clearances were established by mean times of 9.7 ± 0.8 and 36.3 ± 4.7 minutes,
Table 1. Data for Dogs Given Intravenous Thallium

<table>
<thead>
<tr>
<th>Dog</th>
<th>Duration of experiment (min)</th>
<th>Time to peak myocardial activity (min)</th>
<th>$\lambda$ Myo (min$^{-1}$) $[T_{1/2}(min)]$</th>
<th>$\lambda_1$ Bld (min$^{-1}$) $[T_{1/2}(min)]$</th>
<th>$\lambda_2$ Bld (min$^{-1}$) $[T_{1/2}(min)]$</th>
<th>$\lambda_3$ Bld (min$^{-1}$) $[T_{1/2}(min)]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>550</td>
<td>10</td>
<td>0.0026 ($r = 0.99$) $[266.5]$</td>
<td>0.3539 ($[1.9]$)</td>
<td>0.0501 ($[13.8]$)</td>
<td>0.0029 ($r = 1.00$)</td>
</tr>
<tr>
<td>2</td>
<td>810</td>
<td>3</td>
<td>0.0016 ($r = 0.95$) $[433.2]$</td>
<td>0.6011 ($[1.2]$)</td>
<td>0.1054 ($[6.5]$)</td>
<td>0.0018 ($r = 1.00$)</td>
</tr>
<tr>
<td>3</td>
<td>640</td>
<td>2</td>
<td>0.0015 ($r = 0.98$) $[462.1]$</td>
<td>0.2495 ($[2.8]$)</td>
<td>0.0450 ($[15.4]$)</td>
<td>0.0015 ($r = 1.00$)</td>
</tr>
<tr>
<td>4</td>
<td>360</td>
<td>50</td>
<td>0.0012 ($r = 0.99$) $[577.6]$</td>
<td>0.1950 ($[3.5]$)</td>
<td>0.0361 ($[19.2]$)</td>
<td>0.0018 ($r = 1.00$)</td>
</tr>
<tr>
<td>5</td>
<td>620</td>
<td>20</td>
<td>0.0017 ($r = 0.96$) $[407.7]$</td>
<td>0.3069 ($[2.3]$)</td>
<td>0.0361 ($[19.2]$)</td>
<td>0.0008 ($r = 0.99$)</td>
</tr>
<tr>
<td>6</td>
<td>480</td>
<td>40</td>
<td>0.0024 ($r = 0.99$) $[288.8]$</td>
<td>0.2489 ($[2.8]$)</td>
<td>0.0814 ($[8.5]$)</td>
<td>0.0026 ($r = 1.00$)</td>
</tr>
<tr>
<td>7</td>
<td>540</td>
<td>40</td>
<td>0.0012 ($r = 0.99$) $[577.6]$</td>
<td>0.1950 ($[3.5]$)</td>
<td>0.0214 ($[32.4]$)</td>
<td>0.0008 ($r = 1.00$)</td>
</tr>
<tr>
<td>8</td>
<td>340</td>
<td>10</td>
<td>0.0017 ($r = 0.98$) $[407.7]$</td>
<td>0.1954 ($[3.5]$)</td>
<td>0.0438 ($[15.8]$)</td>
<td>0.0018 ($r = 1.00$)</td>
</tr>
<tr>
<td>9</td>
<td>370</td>
<td>12</td>
<td>0.0017 ($r = 0.99$) $[407.7]$</td>
<td>0.2501 ($[2.8]$)</td>
<td>0.0755 ($[9.2]$)</td>
<td>0.0031 ($r = 1.00$)</td>
</tr>
<tr>
<td>10</td>
<td>315</td>
<td>5</td>
<td>0.0010 ($r = 0.98$) $[693.1]$</td>
<td>0.5581 ($[1.2]$)</td>
<td>0.1320 ($[5.2]$)</td>
<td>0.0009 ($r = 0.99$)</td>
</tr>
<tr>
<td>11</td>
<td>400</td>
<td>10</td>
<td>0.0028 ($r = 0.99$) $[247.5]$</td>
<td>0.4248 ($[1.6]$)</td>
<td>0.0443 ($[15.6]$)</td>
<td>0.0023 ($r = 0.99$)</td>
</tr>
<tr>
<td>12</td>
<td>385</td>
<td>10</td>
<td>0.0014 ($r = 0.99$) $[495.1]$</td>
<td>0.1550 ($[4.5]$)</td>
<td>0.0603 ($[11.5]$)</td>
<td>0.0014 ($r = 0.99$)</td>
</tr>
<tr>
<td>13</td>
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<td>25</td>
<td>0.0013 ($r = 0.99$) $[533.1]$</td>
<td>0.3999 ($[1.7]$)</td>
<td>0.0789 ($[8.8]$)</td>
<td>0.0012 ($r = 0.99$)</td>
</tr>
<tr>
<td>14</td>
<td>360</td>
<td>40</td>
<td>0.0021 ($r = 0.96$) $[330.1]$</td>
<td>0.3476 ($[1.9]$)</td>
<td>0.0977 ($[7.1]$)</td>
<td>0.0026 ($r = 1.00$)</td>
</tr>
<tr>
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<td>10</td>
<td>0.0025 ($r = 0.99$) $[400.0]$</td>
<td>0.8464 ($[0.8]$)</td>
<td>0.0261 ($[26.5]$)</td>
<td>0.0019 ($r = 1.00$)</td>
</tr>
<tr>
<td>16</td>
<td>370</td>
<td>50</td>
<td>0.0019 ($r = 0.99$) $[364.8]$</td>
<td>0.3900 ($[1.7]$)</td>
<td>0.0754 ($[9.2]$)</td>
<td>0.0019 ($r = 1.00$)</td>
</tr>
<tr>
<td>17</td>
<td>330</td>
<td>40</td>
<td>0.0020 ($r = 0.99$) $[364.5]$</td>
<td>0.7432 ($[0.9]$)</td>
<td>0.0564 ($[12.3]$)</td>
<td>0.0021 ($r = 0.99$)</td>
</tr>
<tr>
<td>18</td>
<td>313</td>
<td>50</td>
<td>0.0011 ($r = 0.97$) $[630.1]$</td>
<td>0.1599 ($[4.3]$)</td>
<td>0.0383 ($[18.1]$)</td>
<td>0.0015 ($r = 0.99$)</td>
</tr>
<tr>
<td>Mean ± sd</td>
<td>428 ± 148</td>
<td>23.7 ± 17.9</td>
<td>0.00176 ± 0.00054 $[437.2 ± 126.3]$</td>
<td>0.36782 ± 0.20141 $[2.4 ± 1.1]$</td>
<td>0.06134 ± 0.02973 $[14.1 ± 7.1]$</td>
<td>0.00177 ± 0.00075 $[445.5 ± 201.6]$</td>
</tr>
</tbody>
</table>

Abbreviations: $\lambda$ Myo = decay constant for myocardium; $\lambda_1$ Bld = first decay constant for blood; $\lambda_2$ Bld = second decay constant for blood; $\lambda_3$ Bld = third decay constant for blood; $T_{1/2}$ = total half-time.

respectively (NS compared with i.v. injection). For the triexponential nonlinear least-squares fit, $r = 0.99-1.00$. The decay constant $\lambda$ for the myocardium differed significantly from the final decay constant $\lambda_3$ for the blood ($p < 0.01$). Specific blood $^{201}$TI activities were $p = 0.0028 \mu Ci/g$ at 2 minutes (3.9% of injected dose in blood) and $0.0003 \mu Ci/g$ at 120 minutes (0.4% of injected dose in blood) after intracoronary administration.

The four dogs that received intracoronary $^{201}$TI had a shorter time to peak $^{201}$TI myocardial activity ($p < 0.01$), a greater decay constant $\lambda$ for $^{201}$TI myocardial activity ($p < 0.00001$) and a smaller final decay constant $\lambda_3$ for $^{201}$TI blood activity ($p < 0.001$) than the 18 dogs that received i.v. $^{201}$TI (fig. 6). There were no significant differences between the i.v. $\lambda_1$ and intracoronary $\lambda_1$, and between the i.v. $\lambda_2$ and intracoronary $\lambda_2$. The ratios of specific blood $^{201}$TI activities with intracoronary vs i.v. injection were 0.05 at 2 minutes and 0.06 at 120 minutes after tracer injection.

Discussion

The present study provides insight into the kinetics of $^{201}$TI uptake and clearance in nonischemic myocardium after i.v. administration. The use of a miniature implantable cadmium telluride radiation detector probe allowed for continuous monitoring of $^{201}$TI myocardial activity, which is not possible using serial needle biopsies. The probe also allowed monitoring of myocardial $^{201}$TI activity in a single small area of interest, whereas serial biopsies involve several areas of myocardium.
The present study shows that myocardial $^{201}$Tl activity reaches at least 80% of peak activity within 1 minute, peaks at a mean time of 23.7 minutes, then decreases monoexponentially, with a mean decay constant of $\lambda = 0.00176$ min$^{-1}$ ($T_{1/2} = 7.3$ hours). This total half-time (physical plus biologic clearance) for myocardial $^{201}$Tl activity is similar to half-times from other studies, in which either multiple biopsies or external counting were used, i.e., 4.4 to more than 8 hours.$^{17-19}$ Blood $^{201}$Tl activity decreased at least triexponentially after i.v. injection, with a very rapid decrease in activity during the first 5 minutes. Bradley-Moore and associates also observed an early rapid decrease in blood activity.$^{19}$

In the present study, four dogs received intracoronary $^{201}$Tl to determine the relationship between blood and myocardial clearance rates of $^{201}$Tl after this form of administration. This intrinsic myocardial clearance after intracoronary administration depends on factors intrinsic to the mycardium, because it avoids the myocardial uptake of $^{201}$Tl from a large blood reservoir after the first pass through the heart. After intracoronary administration, myocardial $^{201}$Tl activity peaks in a mean time of 2.0 minutes, then decreases monoexponentially, with a mean decay constant of $\lambda = 0.00833$ ($T_{1/2} = 84.2$ minutes). The myocardial decay constant after intracoronary administration was significantly greater than that after i.v. administration. The total intrinsic clearance $T_{1/2}$ of 83 minutes is similar to the value of 75 minutes reported by Watson and associates.$^{19}$ In the present study, blood $^{201}$Tl ac-

![Figure 3](image-url) Multi-channel analyzer display of $^{201}$Tl activity (counts/minute) vs time after i.v. administration of $^{201}$Tl (dog 1).

![Figure 4](image-url) Thallium-201 activity on semilogarithmic scale vs time after i.v. administration. Values represent mean ± SD for nonlinear least-squares estimation of $^{201}$Tl decay constants for myocardium ($\lambda$ myo) and blood ($\lambda$ bld).

### Table 2. Data for Dogs Given Intracoronary Thallium

<table>
<thead>
<tr>
<th>Dog</th>
<th>Duration of experiment (min)</th>
<th>Time to peak myocardial activity (min)</th>
<th>$\lambda$ Myo (min$^{-1}$)</th>
<th>$T_{1/2}$ Myo (min)</th>
<th>$\lambda$ Bld (min$^{-1}$)</th>
<th>$T_{1/2}$ Bld (min)</th>
<th>$\lambda_3$ Bld (min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>160</td>
<td>2</td>
<td>0.0991 ($r = 0.98$)</td>
<td>[76.1]</td>
<td>0.01927</td>
<td>[3.6]</td>
<td>0.0011</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0001 ($r = 1.00$)</td>
</tr>
<tr>
<td>2a</td>
<td>160</td>
<td>2</td>
<td>0.0683 ($r = 0.98$)</td>
<td>[101.9]</td>
<td>0.1331</td>
<td>[5.2]</td>
<td>0.0081</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0003 ($r = 1.00$)</td>
</tr>
<tr>
<td>3a</td>
<td>113</td>
<td>3</td>
<td>0.0082 ($r = 0.97$)</td>
<td>[84.5]</td>
<td>0.1427</td>
<td>[4.8]</td>
<td>0.0092</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0006 ($r = 0.99$)</td>
</tr>
<tr>
<td>4a</td>
<td>290</td>
<td>1</td>
<td>0.0093 ($r = 0.94$)</td>
<td>[74.5]</td>
<td>0.2253</td>
<td>[3.1]</td>
<td>0.0772</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0009 ($r = 1.00$)</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>181 ± 76</td>
<td>2.0</td>
<td>0.00833</td>
<td>[84.2 ± 12.5]</td>
<td>0.17345</td>
<td>[4.1 ± 1.0]</td>
<td>0.02350</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>± 0.00115</td>
<td></td>
<td>± 0.04333</td>
<td>± 0.03571</td>
<td>± 0.00035</td>
</tr>
</tbody>
</table>

Abbreviations: See table 1.
tivity decreased at least triexponentially after intracoronary administration. Although the blood decay constant \( \lambda_3 \) was significantly smaller after intracoronary \(^{201}\text{Tl} \), \( \lambda_1 \) and \( \lambda_3 \) decay constants did not differ for intracoronary compared with i.v. administration of \(^{201}\text{Tl} \). The early blood clearance of \(^{201}\text{Tl} \) probably represents the initial distribution of the tracer throughout the body, and thus would be expected to be rapid after both intracoronary and i.v. injection.

The myocardial uptake kinetics of \(^{201}\text{Tl} \) have been studied. Strauss and associates\(^{29} \) and Nielsen and associates\(^{30} \) have shown that the initial myocardial distribution of \(^{201}\text{Tl} \) has a close linear relationship to regional myocardial blood flow. The myocardial extraction fraction of \(^{201}\text{Tl} \) has been reported to be 88%.\(^{23} \) Zimmer and associates\(^{29} \) showed in a model independent of flow that the uptake of \(^{201}\text{Tl} \) by cultured myocardial cells is described by a single exponential. Ingwall and associates\(^{34} \) showed that this uptake rate of \(^{201}\text{Tl} \) by fetal mouse myocardial cells was unrelated to the extent of reversible injury. Zimmer and associates\(^{20} \) and Ku and associates\(^{25} \) reported data supporting the use of the sodium-potassium pump in the myocardial uptake of \(^{201}\text{Tl} \). However, other investigators have reported data supporting a passive transport mechanism for \(^{201}\text{Tl} \), which follows an electropotential gradient across the cell membrane.\(^{26, 27} \)

The myocardial clearance phase of \(^{201}\text{Tl} \) has been studied under various myocardial blood flow conditions. To determine myocardial clearance of \(^{201}\text{Tl} \) when myocardial blood flow was normal, we used an implantable miniature cadmium telluride radiation detector to monitor \(^{201}\text{Tl} \) activity continuously. In the present study the mean final decay constant for blood \(^{201}\text{Tl} \) was almost identical to the mean decay constant for myocardial \(^{201}\text{Tl} \) after i.v. administration. The myocardial \(^{201}\text{Tl} \) decay constant was significantly greater (shorter \( T_1/2 \)) after intracoronary than after i.v. \(^{201}\text{Tl} \). Thus, the rate of \(^{201}\text{Tl} \) clearance from non-ischemic, normally perfused myocardium is related to the rate of \(^{201}\text{Tl} \) clearance from the blood if injected intravenously, but is not related to blood clearance if injected via the intracoronary route. To determine myocardial clearance of \(^{201}\text{Tl} \) when myocardial blood flow was higher than normal, L’Abbate and associates\(^{28} \) used the frequency function of transit times in human subjects without coronary artery disease. These investigators showed that myocardial clearance of \(^{201}\text{Tl} \) was unaffected by higher-than-normal myocardial blood flows. Leppo and associates\(^{29} \) confirmed that clearance of \(^{201}\text{Tl} \) is not affected by high myocardial blood flow in a canine model. To determine myocardial clearance of \(^{201}\text{Tl} \) when myocardial blood flow was reduced, Gewirtz and associates\(^{19} \) injected \(^{201}\text{Tl} \) intravenously before coronary occlusion and determined myocardial \(^{201}\text{Tl} \) activity in serial biopsies. They reported normal myocardial clearance of \(^{201}\text{Tl} \) in a severely ischemic canine model. However, Beller and associates\(^{20, 31} \) derived a multicompart model for myocardial \(^{201}\text{Tl} \) whereby myocardial clearance of \(^{201}\text{Tl} \) could be altered by very severe reductions in regional myocardial blood flow. Grunwald and associates\(^{22} \) reported an ischemia-induced reduction in
the intrinsic clearance rate of $^{201}\text{TI}$ from the severely ischemic myocardium. These investigators administered intracoronary $^{201}\text{TI}$ after coronary stenosis and determined myocardial $^{201}\text{TI}$ activity using an external detector. Their results suggest that clearance of $^{201}\text{TI}$ from ischemic myocardium may depend on factors in addition to blood $^{201}\text{TI}$ concentration, such as myocardial blood flow. The differences in the results reported by Gewirtz et al. and by Grunwald et al. may be partially explained by the different techniques used.

Thus, the kinetics of $^{201}\text{TI}$ in nonischemic myocardium can be summarized as follows. The initial distribution of $^{201}\text{TI}$ to nonischemic myocardium is related to both cellular extraction and regional perfusion. A process of continuous extraction and release of ionic thallium by myocardial cells is initiated. First, the cells accumulate more thallium than they release, resulting in a net accumulation of the ion. The rate at which a region of myocardium reaches its peak activity is related to the amount of $^{201}\text{TI}$ presented to the region per unit of time, which in turn is determined by the product of the concentration of thallium in the blood and the blood flow. After peak activity is achieved, the rate of $^{201}\text{TI}$ clearance from the myocardium is related to the rate of $^{201}\text{TI}$ clearance from the blood.

Thallium-201 is taken up rapidly by the nonischemic myocardium after i.v. injection. Thallium-201 is then monoexponentially cleared from the myocardium at a rate determined by the rate of $^{201}\text{TI}$ clearance from the blood after i.v. administration. Clinically, this implies that the resolution rate of ischemia-induced defects on $^{201}\text{TI}$ images may be altered by factors that affect the clearance rate of $^{201}\text{TI}$ from the blood, thereby affecting the clearance rate of $^{201}\text{TI}$ from the nonischemic myocardium.

Acknowledgment

The authors are grateful to Betty LaMarca and Katherine Hogan for their secretarial assistance and to Luis Guerrero, James Titus and James Hickey for their technical assistance. We also thank Dr. Irwin Gruverman, Dr. Allen Green and Marilyn Sheeham from the New England Nuclear Corporation for supplying thallium-201 and microspheres.

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Effect of Propranolol on Myocardial Perfusion Images and Exercise Ejection Fraction in Men with Coronary Artery Disease

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SUMMARY  Propranolol increases exercise performance in association with a decrease in exercise heart rate and blood pressure. In 30 men with coronary disease and exercise limited by angina, 15 without prior infarction and 15 with infarction, we measured left ventricular ejection fraction (LVEF) (scintillation probe) at rest and during supine bicycle exercise and myocardial blood flow distribution (MBF) (thallium-201 imaging) during treadmill exercise. Exercise was performed as control and after 1 week of treatment with propranolol (40 mg orally four times daily). Propranolol improved exercise LVEF (at the same work load) (men without infarction: control 0.37 ± 0.02, average ± SEM; propranolol 0.45 ± 0.01; n = 15, p < 0.01; and with infarction: control 0.36 ± 0.01, propranolol 0.36 ± 0.01; n = 15, p < 0.05). Propranolol also improved MBF during exercise to the same work load in men without infarction (comparison of integrated normalized count-rate differences, 607 normalized counts). In men with infarction, propranolol did not alter MBF (15 normalized counts). Placebo did not alter normalized counts by more than ± 150. Changes in exercise LVEF and MBF were related. MBF improved in 17 men with propranolol treatment and LVEF was increased in 15. Of six men who had no change in MBF, exercise LVEF increased in three and did not change in three. Propranolol was associated with a worsening of MBF in five men and all had no change in exercise LVEF. Results suggest that propranolol favorably alters MBF and LVEF in men with coronary disease, particularly in men without prior myocardial infarction.

PROPRANOLOL is an effective drug for the treatment of angina in patients with coronary disease. Increased sympathetic nervous system activity during exercise may contribute to an increase in cardiac output and heart rate. In normal dogs, propranolol decreases cardiac output, stroke volume and heart rate during dynamic exercise. Similar changes occurred during exercise in normal subjects who were given propranolol.

Studies in animals suggest that propranolol favorably alters myocardial blood flow to ischemic areas and improves performance of ischemic regions. In dogs with a chronic coronary obstruction, propranolol lessened regional performance abnormalities during exercise. That these favorable changes with propranolol were due to alteration of myocardial oxygen requirements appears to be supported by the work of Swain and associates. These investigators found that propranolol had no effect on myocardial blood flow when administered in a dose that did not alter hemodynamics.

We studied the effects of propranolol on left ventricular ejection fraction (LVEF) and myocardial blood flow during exercise in men with coronary disease. In these men, exercise was limited by angina.

Patients and Methods
Thirty men with arteriographically defined coronary artery disease were informed of the risks of the study and agreed to participate. They were selected to include men with and without prior infarction and to provide a spectrum of disease severity. Each man had...
Thallium-201 kinetics in nonischemic canine myocardium.

Circulation. 1982;65:70-77
doi: 10.1161/01.CIR.65.1.70

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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