Effect of glucose-insulin-potassium infusion on thallium myocardial clearance

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ABSTRACT Factors influencing the rate of $^{201}$Tl clearance from the myocardium have not been clearly defined. This study determined the effect of an intravenous infusion of glucose-insulin-potassium (GIK) on the net $^{201}$Tl clearance rates from myocardium with and without initial $^{201}$Tl loading. Anesthetized open-chest dogs underwent 5 min of left anterior descending coronary artery occlusion and intravenous $^{201}$Tl was injected and the occlusion released 5 min later. Thirty minutes after $^{201}$Tl injection, 30 ml of either GIK (nine dogs) or saline (five dogs) was infused intravenously. The clearance rates of $^{201}$Tl from the anterior wall (without initial $^{201}$Tl loading) and from the posterior wall (with initial $^{201}$Tl loading) were monitored with miniaturized cadmium telluride detectors placed on the myocardium. Calculation of net myocardial clearance rates was performed by linear regression analysis from serial 1 min counts. Compared with saline infusion, GIK increased the net clearance of $^{201}$Tl from both myocardial regions with and without initial loading. The most marked change induced by GIK infusion was in the myocardial region without initial $^{201}$Tl loading; a net increase in $^{201}$Tl activity (72 ± 42 cpm/30 min) was converted into a net loss (−594 ± 228 cpm/30 min). There was no significant change in $^{201}$Tl clearance after the saline infusion. Heart rate, aortic and left atrial pressure, sonomicro-meter-measured transmural myocardial wall thickness, microsphere-determined myocardial blood flow, and blood glucose and potassium concentrations did not change significantly during GIK or saline infusions. Thus, GIK infusion appears to increase net $^{201}$Tl clearance from myocardial zones with and without initial $^{201}$Tl loading.


ALTHOUGH previous studies have defined the relationship of initial $^{201}$Tl distribution in the myocardium to regional myocardial blood flow,1 relatively little information is available regarding the factors influencing the rate of $^{201}$Tl loss in normal and ischemic myocardium. Results of recent studies2–4 suggest that the rate of $^{201}$Tl loss from the myocardium can be used as a criterion for the detection of myocardial ischemia. Approximately 20% of $^{201}$Tl should be lost by the myocardium over a minimum 4 hr period in normal individuals.2 Some patients have an unusually rapid loss of $^{201}$Tl from the myocardium, with a decrease of over 60% in $^{201}$Tl activity in normal myocardium in the time between the recording of initial and delayed images (recorded 4 hr later). Preliminary investigations have suggested that rapid loss of $^{201}$Tl is associated with the ingestion of a high-carbohydrate meal between initial and delayed imaging sessions. Since many investigators believe the kinetics of $^{201}$Tl in the myocardium are similar to those of potassium,5,6 we investigated the possibility that the myocardial $^{201}$Tl clearance time is influenced in part by insulin. Results of previous studies by Weich et al.7 suggested that the initial extraction of $^{201}$Tl by the myocardium was not influenced by insulin. However, that study did not determine whether the myocardial release rate of $^{201}$Tl was influenced by the hormone. Accordingly, our purpose was to define the impact of an intravenous infusion of glucose-insulin-potassium (GIK), with and without initial $^{201}$Tl loading, on the clearance of $^{201}$Tl from myocardium in dogs.

Methods

Fourteen adult mongrel dogs (mean weight 22 kg, range 18 to 27) were anesthetized with chloralose (140 mg/kg) and urethane (1400 mg/kg iv), intubated, and ventilated with a Harvard respirator apparatus with 5 cm of positive end-expiratory pressure. The heart was exposed by a left thoracotomy and was suspended in a pericardial cradle. Supplemental oxygen was used to maintain an arterial Po2 greater than 70 mm Hg. Miniature cadmium
telluride (CdTe) radiation detection probes were placed through the left ventricular apex and positioned against the endocardial surface of the anterior and posterior walls to measure regional myocardial 201Tl activity.8,9 In the anterior wall the detector was positioned to face toward the open thoracotomy, thus markedly reducing the detection of background activity. A lead sheet was placed between the posterior wall and pericardium to reduce the background activity detected by the posterior wall probe. Previous validation studies have shown that the lead shielding around the crystal effectively reduces contamination from blood pool activity.8 The probes were connected via a preamplifier to a multichannel analyzer (Canberra Corp., Meriden, CT) to continuously monitor and display 201Tl activity in the anterior and posterior walls. Probe background activities were determined before 201Tl injection as the average of three 1 min collections. The 201Tl activity data were acquired as serial 1 min collections. These count vs time data were displayed on the multichannel analyzer screen and recorded on paper tape. The CdTe radiation probe consisted of a 2 mm2 CdTe crystal surrounded by lead foil that was housed in a steel (4 mm od) cylinder attached to an arterial clamp. In addition, sonomicrometer crystals (3 mm in diameter) were attached to both arms of the arterial clamp and connected to a sonomicrometer (Norland Instruments model NL-202-4R, Fort Atkinson, WI). These ultrasonic crystals permitted frequent determination of anterior and posterior left ventricular wall thickness. The monitoring of wall thickness changes was performed to exclude changes in wall thickness as a cause of changes in 201Tl activity recorded by the CdTe probe.9 Care was taken not to position the probe over a coronary artery branch. To induce myocardial ischemia at the time of 201Tl injection, the left anterior descending coronary artery was dissected free and a ligature was loosely placed around the vessel. Aortic and left atrial pressures were monitored by 20 cm vinyl catheters attached to Statham P23Db pressure transducers and were recorded on paper with a Sandborn 7700 series recorder. To sample coronary sinus 201Tl activity, a coronary sinus catheter (No. 7F modified NIH catheter) was placed through the right atrial appendage.

The experimental protocol is illustrated in figure 1. Baseline blood gas, aortic and left atrial pressure, heart rate, and wall thickness measurements were obtained. The left anterior descending coronary artery was then ligated. After 5 min of occlusion, 201Tl (1.2 to 1.4 mCi) and approximately 4.5 million 113Sn-labeled microspheres (15 μm diameter, 30 μCi total activity, New England Nuclear Corp., North Billerica, MA) were simultaneously injected intravenously and into the left atrium, respectively.9 Aortic blood was drawn from a Holter pump to obtain reference samples for microsphere determination of regional myocardial blood flow. Five minutes after the 201Tl administration, the coronary artery ligation was released. Serial 1 min regional counts were acquired with the CdTe detectors from the time of 201Tl injection and this was continued for the duration of the study (2 hr). In all dogs, the probe-recorded 201Tl activity was at least 1000 cpm (mean ± SEM = 4929 ± 466). Thirty minutes after 201Tl injection (25 min after ligature release) the intravenous infusion of 30 ml GIK (glucose 10% dextrose in water), regular insulin [12 U, and potassium (16 mEq)] was begun in nine dogs at a rate of 1 ml/min for 30 min. Five additional control dogs were given an intravenous infusion of normal saline instead of GIK. Just before, during (after 20 to 30 min of the infusion), and 1 hr after the infusion of GIK (or saline), venous blood samples for glucose and potassium and arterial blood samples for pH, PO2, and PCO2 were obtained. In addition, serial aortic and coronary sinus blood samples (1 ml) for 201Tl were obtained simultaneously at specific times before, during, and after the GIK or saline infusion (2, 4, 6, 8, 10, 15, 20, 25, 28, 30, 31, 32, 33, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 110, and 120 min after 201Tl injection, figure 1). 103Ru- and 46Sc-labeled microspheres were injected during GIK or saline infusion, respectively, and at the end of the study. The total number, mean size, and total radioactivity of the 103Ru- and 46Sc-microspheres were the same as for the 113Sn-microspheres. No changes in probe counts were detected during microsphere administration. During the 120 min of the experiment, no bicarbonate, heparin, or fluid boluses were administered. The dogs were killed 120 min after 201Tl injection.

Myocardial regions around the CdTe probes in the areas with and without 201Tl loading were excised and later divided into 48 transmural sections (of approximately 1 g each). Microsphere and 201Tl activities were determined in the different sections of myocardium by well counting (Auto-Gamma Scintillation Spectrometer, Packard Instruments Company, Downers Grove, IL) for 5 min to collect at least 10,000 counts for each isotope. The myocardial and blood microsphere reference samples were counted after 201Tl activity had decayed one to two half-lives. Serial aortic and coronary sinus blood samples were analyzed for 201Tl in the well counter within 24 hr. The 113Sn was counted within a 350 to 435 keV window, the 103Ru within a 460 to 760 keV window, the 46Sc within a 800 to 1200 keV window, and the 201Tl within a 60 to 110 keV window. Appropriate corrections were made for higher energy contamination of the 201Tl and microsphere energy windows. Regional myocardial blood flow was calculated by a computer program from the sample activity and the activity in the reference blood samples was determined simultaneously with the administration of each isotope.9 Regional myocardial blood flows determined during left anterior descending coronary artery ligation (113Sn), during GIK or saline infusion (103Ru), and immediately before the dogs were killed (46Sc) were expressed as milliliters per minute per gram. Blood and myocardial 201Tl activities were expressed as counts per minute per milliliter and counts per minute per gram, respectively. To correct for differences in sensitivity between the two CdTe probes, the serial background-corrected 1 min counts from the CdTe probes were normalized to the average 201Tl activity, as determined by well counting in their respective myocardial regions at the end of the study. The 201Tl clearance curves were also normalized to the highest 201Tl activity recorded for each CdTe probe.

Statistics. The rates of 201Tl clearance before, during, and after GIK or saline infusion were calculated by linear regression analysis from the serial 1 min counts and expressed as counts per minute per 30 minutes. Group values were expressed as a mean ± SEM. Difference in clearance rates and transmural wall thickness parameters were assessed by one-way analysis of variance. Differences between coronary sinus and aortic blood 201Tl activities before and during infusion were determined by paired t test.

Results

Plots of 201Tl activity in myocardium with and without 201Tl loading in a representative control dog and in a dog that received a GIK infusion are illustrated in
figures 2 and 3, respectively. GIK infusion increased the net clearance of 201Tl from both myocardial regions. The most marked change induced by the infusion occurred in the region without initial 201Tl loading, where the small increase in 201Tl activity was converted into a release of 201Tl. The rate of 201Tl release rapidly decreased toward baseline after the infusion was stopped.

In all nine dogs that received the GIK infusion, the net clearance of 201Tl from myocardium increased during the infusion in both the area with initial 201Tl loading (−591 ± 228 to −1107 ± 291 cpm/30 min, p ≤ .01) and that without (72 ± 42 to −594 ± 228 cpm/30 min, p ≤ .01; figures 4 and 5). In all dogs, the net clearance decreased in areas with (−1107 ± 291 to −174 ± 81 cpm/30 min, p ≤ .01) and without loading (−594 ± 228 to 18 ± 45 cpm/30 min, p ≤ .01) when the GIK infusion was stopped.

Initially, 201Tl-loaded regions (figure 4) showed an increase in the net rate of 201Tl clearance during GIK, but no significant increase with saline (−501 ± 252 to −333 ± 210 cpm/30 min). In the regions without initial 201Tl loading (figure 5) GIK infusion changed the net 201Tl accumulation into a net loss. However, saline had no effect on the 201Tl time-activity curve (306 ± 171 to 372 ± 132 cpm/30 min). After the GIK infusion was stopped, the rate of 201Tl clearance decreased abruptly in both regions. However, there was a significant decrease in net 201Tl uptake that was associated with cessation of the saline infusion in the myocardium without initial 201Tl loading (372 ± 132 to 75 ± 108 cpm/30 min, p < .05). This change was in the opposite direction of the change that occurred when the GIK infusion was stopped and represents the change from net 201Tl uptake to net 201Tl clearance that occurs over time in transiently ischemic myocardium without initial 201Tl loading.10 With cessation of the saline infusion, net 201Tl clearance from the loaded region did not change significantly (−333 ± 210 to −336 ± 213 cpm/30 min).

FIGURE 3. Representative examples of myocardial 201Tl time-activity curves in myocardium with and without initial 201Tl loading during infusion of GIK.

FIGURE 2. Representative example of myocardial 201Tl time-activity curves in myocardium with and without 201Tl loading during infusion of saline. Serial 1 min counts were corrected for background activity and differences in CdTe probe sensitivities and normalized to maximal 201Tl activity.
The infusion of either GIK or saline was not associated with significant changes in heart rate, mean aortic or left atrial pressure, sonomicrometer-measured transmural myocardial wall thickness, or anterior/posterior myocardial blood flow ratio (table 1). Serum glucose and potassium concentrations and arterial pH, PCO₂, and PO₂ did not change significantly during the experiment (table 2).

To further evaluate changes in myocardial ²⁰¹Tl during GIK infusion, coronary sinus blood ²⁰¹Tl activity was measured serially before and during GIK or saline infusion (figure 6). GIK infusion was associated with a
TABLE 1
Hemodynamic variables for two groups of dogs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before infusion</th>
<th>During infusion</th>
<th>After infusion</th>
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<tbody>
<tr>
<td>Heart rate (bpm)</td>
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<tr>
<td>GIK (n = 9)</td>
<td>154 ± 6.4</td>
<td>149 ± 6.8</td>
<td>151 ± 7.0</td>
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<tr>
<td>Saline (n = 5)</td>
<td>176 ± 3.7</td>
<td>166 ± 6.8</td>
<td>161 ± 10.5</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>GIK</td>
<td>88 ± 7.6</td>
<td>86 ± 7.7</td>
<td>86 ± 4.1</td>
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<tr>
<td>Saline</td>
<td>110 ± 2.0</td>
<td>105 ± 2.2</td>
<td>103 ± 3.7</td>
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<tr>
<td>Mean left atrial pressure (mm Hg)</td>
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<tr>
<td>GIK</td>
<td>4.4 ± 0.8</td>
<td>3.9 ± 0.9</td>
<td>4.5 ± 0.8</td>
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<tr>
<td>Saline</td>
<td>5.8 ± 1.1</td>
<td>4.6 ± 0.9</td>
<td>3.8 ± 0.9</td>
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Anterior wall transmural diastolic thickness (mm)

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<tr>
<td>GIK</td>
<td>8.0 ± 0.5</td>
<td>8.1 ± 0.5</td>
<td>8.1 ± 0.5</td>
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<tr>
<td>Saline</td>
<td>7.7 ± 0.7</td>
<td>7.7 ± 0.6</td>
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Posterior wall transmural diastolic thickness (mm)

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<tr>
<td>GIK</td>
<td>9.4 ± 0.8</td>
<td>9.5 ± 0.8</td>
<td>9.3 ± 0.8</td>
</tr>
<tr>
<td>Saline</td>
<td>8.4 ± 0.6</td>
<td>8.5 ± 0.7</td>
<td>8.5 ± 0.8</td>
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Anterior/posterior wall myocardial blood flow ratio

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<tr>
<td>GIK</td>
<td>0.06 ± 0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.85 ± 0.15</td>
<td>0.82 ± 0.37&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Saline</td>
<td>0.07 ± 0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.79 ± 0.14</td>
<td>0.85 ± 0.10&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup>Preinfusion values are those for the period during left descending coronary artery occlusion. During and postinfusion values are those for the period after coronary artery reperfusion.

<sup>b</sup>p < .05 compared with "during infusion" value.

29% rise in coronary sinus blood 201TI activity (p < .01), while no significant change occurred in coronary sinus blood 201TI activity during saline infusion. After the GIK infusion was stopped, coronary sinus blood 201TI activity decreased abruptly. Serial aortic blood samples were also obtained before and during GIK or saline infusion. A 27% increase in aortic blood 201TI activity was found with GIK infusion, but not with saline infusion, suggesting that in addition to loss from the myocardium, 201TI loss from other sites occurred.

**Discussion**

The results of this study suggest that an infusion of GIK is associated with an increase in net myocardial 201TI clearance in myocardium with and without initial 201TI loading. In addition, GIK infusion not only decreased net 201TI uptake in a region without 201TI loading, but also caused a net washout of 201TI for the duration of the infusion. Although our study was performed in anesthetized open-chest dogs and therefore the results may not be directly applicable to the conscious patient, the results suggest that a GIK infusion might affect the rate at which such regions "fill-in" in a serial 201TI imaging study. If this effect occurs in man, food ingestion (especially foods rich in carbohydrates and potassium) may cause similar changes in 201TI kinetics and redistribution rates. A single 550 g (1/4 lb) hamburger with a bun would contain more carbohydrate (approximately 23 vs 30) and more potassium (23 vs 16 mEq) than the GIK infusion used in this study. Thus, 201TI clearance rates from myocardium with and without 201TI loading could initially be significantly increased if patients are allowed to eat in

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The myocardial clearance of $^{201}$TI is not known, but it is known that insulin stimulates potassium transport into muscle cells. It is possible that stimulation of this transport system rapidly increases transport of potassium intracellularly and displaces $^{201}$TI from its intracellular location, resulting in a net loss of $^{201}$TI. Investigators have reported an insulin-induced increase in myocardial blood flow, and it could be questioned whether such an increase in flow could have contributed to the increased myocardial $^{201}$TI clearance directly. We were unable to determine if insulin increased myocardial blood flow in the current study since the flows determined during GIK infusion and at the end of the experiment were separated by several hours. However, even if an increase in flow did occur after insulin, previous data from our laboratory indicate that it is unlikely that this affected myocardial $^{201}$TI kinetics. We have found that doubling myocardial blood flow after $^{201}$TI loading has no effect on its myocardial clearance.

Since $^{201}$TI redistribution has been shown to be due to clearance in normal myocardium and to slow uptake in ischemic myocardium, the reversal of the ischemic myocardium uptake curve to a clearance curve might be expected to decrease the rate and extent of redistribution. In a preliminary study, 59 patients were prospectively randomized into two groups; 32 patients ate a high-carbohydrate meal between initial and delayed imaging sessions and 27 fasted. Myocardial $^{201}$TI clearance in the time between initial and delayed imaging was significantly faster for both anterior and posterior walls in the patients who ate. In addition, the patients who ate had a significantly lower incidence of isolated transient defects compared with those in the fasting group.

Since changes in the volume of myocardium (and apparent $^{201}$TI activity) under the CdTe radiation detector would be decreased if ventricular wall thinning occurred during the experiment, transmural wall thickness was measured to exclude wall thinning as a possible cause for the change in net $^{201}$TI clearance rate observed. The absence of a change in transmural wall thickness discernible by ultrasonography during GIK infusion confirmed that the apparent increase in net $^{201}$TI clearance was not due to wall thinning during GIK infusion. In addition, the increase in coronary sinus blood $^{201}$TI activity during GIK infusion also suggests that net clearance of the agent had increased in response to the GIK infusion. It is possible, however, that the increased coronary sinus blood $^{201}$TI activity was exclusively due to higher aortic blood $^{201}$TI activity from noncardiac sources.

![Graph showing coronary sinus blood $^{201}$TI activity (cpm/ml) before and during (peak value) infusion of GIK or saline. Values are expressed as mean ± SEM.](image-url)
The addition of potassium to the infusion mixture of glucose and insulin was believed to be necessary to prevent hypokalemia. The substantial amount of potassium (16 mEq) infused may have had a direct effect on $^{201}$TI kinetics independent of the effect of insulin. Recent work by Krivokapich and Shine\textsuperscript{1} suggests that potassium infusion does increase $^{201}$TI myocardial efflux in an isolated, arterially perfused rabbit interventricular septum preparation when the concentration of potassium in the perfusate is increased from 5 to 10 mm. This change in potassium in the perfusate is much higher than that induced by the intravenous GIK infusion in this study, which did not significantly change serum potassium concentration. Moreover, since potassium infusion itself may stimulate insulin secretion,\textsuperscript{21, 22} it was not possible for us to distinguish between an insulin effect and a potassium effect on $^{201}$TI myocardial clearance. It should be noted that although the changes were not significant, there was a small increase in mean serum potassium level during the GIK infusion. A statistically significant change may have been demonstrated in a larger group of dogs.

In conclusion, the results of our study demonstrate that an intravenous infusion of GIK significantly increases the rate of net $^{201}$TI myocardial clearance in myocardium with and without initial $^{201}$TI loading. Although the data were obtained in anesthetized open-chest dogs and therefore may not be directly applicable to conscious patients, this possible interaction must be considered when interpreting clearance data derived from clinical serial $^{201}$TI imaging studies. Furthermore, GIK may significantly alter the rate of $^{201}$TI redistribution in myocardium without initial $^{201}$TI loading. Our study also provides a rationale for determining whether patients should fast between initial and delayed $^{201}$TI imaging sessions. Other factors that could affect myocardial $^{201}$TI clearance rates must be examined before such criteria can be applied to the interpretation of clinical $^{201}$TI study results.

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