Thallium 201 Kinetics in Stunned Myocardium Characterized by Severe Postischemic Systolic Dysfunction

Carl A. Moore, MD, James Cannon, MS, Denny D. Watson, PhD, Sanjiv Kaul, MD, and George A. Beller, MD

The hypothesis tested in this study was that despite the presence of severe postischemic myocardial dysfunction (“stunning”), the extraction and subsequent intracellular washout of thallium 201 should be preserved as long as irreversible sarcolemmal membrane injury was avoided. To produce myocardial stunning, 19 open-chested dogs with a critical left anterior descending coronary artery (LAD) stenosis underwent 10 5-minute periods of total LAD occlusion, each interspersed by 10 minutes of reperfusion by reflow through the critical stenosis. In another 12 control dogs observed for the same time period, no LAD occlusions were performed after placement of the critical stenosis. Hemodynamics, regional myocardial thickening by quantitative two-dimensional echocardiography, and microsphere-determined regional blood flows were serially measured. In 18 stunned dogs, systolic thickening in the LAD zone was markedly reduced to 0.4±2.4% at 40 minutes after the 10th reperfusion period compared with 32.5±2.2% thickening (p<0.001) in 12 control dogs at a matched time. The 201Tl first-pass extraction fraction determined by a double-isotope method using intracoronary 201Tl administration was comparable after the 10th reflow in a subgroup of 13 stunned (0.78) and six control (0.79) dogs. The T1// for the intracellular washout rate was also not significantly different in another group of six stunned (60±13 minutes) and six control (53±14 minutes) dogs, nor was the percentage of the 201Tl dose initially distributed in the interstitial compartment (11±3% vs. 7±2%). Systemic hemodynamics and regional flows were comparable in the two groups at 40 minutes after the 10th reflow. No dog had evidence of myocardial necrosis by triphenyl tetrazolium chloride staining. Thus, normal myocardial 201Tl extraction and washout kinetics are observed in a canine model of severe postischemic dysfunction (stunning) produced by repetitive brief LAD occlusions. These findings might have important clinical implications concerning the application of rest 201Tl scintigraphy for evaluation of perfusion and viability in patients with coronary artery disease and regional myocardial asynergy that is ultimately reversible. (Circulation 1990;81:1622–1632)

Myocardial perfusion imaging has been used to assess myocardial blood flow and viability in patients with chronic stable coronary artery disease, in patients with unstable angina, and in patients with acute myocardial infarction, particularly after coronary reperfusion. The initial myocardial uptake of thallium 201 after intravenous injection is directly proportional to nutrient coronary blood flow and the myocardial extraction fraction for 201Tl.1–4 In the presence of irreversible myocardial injury, the intracellular transport and concentration of 201Tl is markedly impaired.5,6 There are, however, scant data in the literature concerning what alterations, if any, are in myocardial 201Tl uptake or clearance kinetics in “stunned” myocardium, which is characterized by reversible severe postischemic systolic dysfunction. This is of significant clinical relevance because 201Tl rest imaging is often used to differentiate viable from necrotic myocardium. If 201Tl transport kinetics were reversibly altered in stunned myocardium, 201Tl imaging would tend to underestimate the degree of viability in regions of myocardial asynergy.

From the Cardiology Division, Department of Internal Medicine, University of Virginia Health Sciences Center, Charlottesville, Virginia.

Supported by grant R01-HL-26205 from the National Heart, Lung, and Blood Institute of the National Institutes of Health, Bethesda, Maryland. S.K. is the recipient of the FIRST (R29-HL-38345) award from the National Heart, Lung, and Blood Institute.

Address for reprints: George A. Beller, MD, Division of Cardiology, University of Virginia Health Sciences Center, Box 158, Charlottesville, VA 22908.

Received July 20, 1989; revision accepted January 4, 1990.
In recent years, evidence has accumulated demonstrating that under various experimental conditions and in certain clinical situations, postischemic myocardial dysfunction (stunning) can occur. Severe and prolonged regional systolic dysfunction despite restoration of coronary blood flow has been observed. The precise pathophysiology of the stunning phenomenon is not entirely understood. Mechanisms proposed have included impairment of myocardial energy production, disruption or inefficient transfer of energy into myocyte contraction, injury to the contractile proteins, "functional sympathectomy" that is secondary to ischemic damage to sympathetic nerves, impaired sarcolemmal Na⁺,K⁺-ATPase activity, altered calcium sensitivity at the myofilament level, calcium overload, microvascular capillary obstruction by neutrophils or platelet aggregates, ischemic damage to the extracellular collagen matrix, and detrimental effects of oxygen free radicals liberated during reperfusion, which can cause membrane lipid peroxidation and inactivation of enzymes. Clinically, myocardial stunning probably occurs after reperfusion in acute myocardial infarction because regional and global left ventricular function demonstrate delayed improvement during days or weeks after flow restoration. Stunning might also be manifested in some patients with unstable angina who experience repeated episodes of coronary flow decrement secondary to coronary vasospasm or intermittent luminal obstruction by platelet thrombi. Postischemic dysfunction can also be manifested for prolonged periods after termination of exercise testing in patients with coronary artery disease.

It can be important in clinical decision-making to be able to identify severe regional myocardial asynergy due to stunning of the myocardium and to distinguish this state from irreversible cellular injury. This would be particularly relevant when a high-grade coronary stenosis is detected in the epicardial coronary artery perfusing an asynergic zone. Because it has been shown experimentally that ischemic dysfunction can be improved by enhancing coronary flow in such a situation, it would be beneficial to determine the prospect of such reversibility by a conventional noninvasive technique that could identify intact cellular function despite the presence of severe resting asynergy. Because Tl requires energy availability for active intracellular transport and intact sarcolemmal membrane function, we investigated the potential alterations in Tl uptake and washout kinetics in a canine model of stunned myocardium. The hypothesis tested was that despite the presence of severe postischemic systolic dysfunction induced by the stunning protocol, the first-pass extraction and subsequent intracellular washout of Tl should remain intact as long as irreversible cellular injury was avoided.

Methods

Animal Preparation

Forty-five fasted adult mongrel dogs (20–30 kg) were anesthetized with sodium pentobarbital (30 mg/kg), intubated, and placed on a Harvard Apparatus respirator (Harvard Apparatus, South Natick, Massachusetts) set at a rate of 13 respirations per minute and a tidal volume of 500 ml. Arterial blood gases were monitored to confirm a physiological pH and Po2. A single-channel electrocardiogram was monitored throughout the experiment. A polyethylene catheter (Intramedic, Parsippany, New Jersey) was inserted through a cutdown into the right femoral vein for administration of fluids. Another catheter was placed into the right femoral artery and advanced to the central aorta for continuous monitoring of central aortic pressure. A separate catheter was placed through a cutdown into the left femoral artery and advanced to the central aorta for withdrawal of reference samples for microsphere flow determinations.

A thoracotomy was performed in the fifth left intercostal space. The heart was suspended in a pericardial cradle. A segment of the left anterior descending coronary artery (LAD) usually distal to the first diagonal branch was dissected free of the epicardium. In our model, occlusion at this site yields a risk area comprising approximately 35% of the left ventricular mass. A hydraulic occluder (model VO-3, Rhodes Medical Instruments, Woodland Hills, California) was placed around the LAD, and an appropriately sized electromagnetic flow probe (Carolina Medical Electronics, Inc., King, North Carolina) was fitted distal to the occluder. A Deseret 22-gauge angiographic catheter was inserted into the distal LAD for continuous monitoring of the distal perfusion pressure by a Hewlett-Packard 1280 pressure transducer (Hewlett-Packard Co., Palo Alto, California). This catheter also allowed intracoronary administration of thallium at specified times. A flared polyethylene tube was placed in the left atrial appendage for injection of radiolabeled microspheres and pressure measurement. The coronary sinus was catheterized in a retrograde manner with a Cordis 7F brachial A1 angiographic catheter through the right internal jugular vein. The tip of the coronary sinus catheter was positioned at the mouth of the great cardiac vein for sampling of thallium activity in coronary (LAD) venous blood after intracoronary injection of Tl. A thermocoupling right heart Cordis catheter was advanced to the pulmonary artery through a cutdown on the right internal jugular vein for monitoring central temperature.

Experimental Protocol

Baseline hemodynamic and echocardiographic measures were obtained in all dogs after instrumentation. The balloon hydraulic occluder was then progressively inflated to produce a critical LAD stenosis in all dogs as defined by the minimum stenosis required for abolition of the reactive hyperemic response to a transient 10-second total occlusion; this usually required a 45–55 mm Hg gradient across the stenosis. In 29 dogs, a silk ligature or snare was placed around the isolated segment of the LAD. Total LAD occlusion was achieved by periodic snar-
ing of the ligature. The protocol used to produce postischemic dysfunction (stunning) was accomplished by producing 10 5-minute periods of total LAD occlusion, each interspersed by 10 minutes of reperfusion by reflow through the critical stenosis. This is a modification of the method described by Nicklas et al.,26 who reperfused the LAD without the presence of a residual stenosis.

In 16 control dogs no LAD occlusions were performed after placement of the critical stenosis. Continuous perfusion by the critical stenosis was performed for 180 minutes before release of the stenosis, a time comparable in duration to the protocol for the stunned dogs. All hemodynamic, flow, echocardiographic, and radioisotope measurements were obtained at comparable times in both groups of dogs.

Wall Motion Analysis (Regional Myocardial Thickening)

Two-dimensional real-time imaging of myocardial function was obtained in all animals at baseline, after placement of a critical stenosis, during reperfusion periods 5 and 10, and 45 minutes after the last reflow.

In all dogs, an appropriate interface for optimum conduction of the ultrasonic signal was created by placing a cellophane sheet over the anterior half of the exposed epicardial surface of the left ventricle. The well was then filled with approximately 50–100 ml sterile saline. Imaging was performed by positioning a 5-mHz mechanical transducer within the fluid well overlying the heart. This transducer was connected to a Mark III Advanced Technology Laboratory two-dimensional real-time echocardiographic machine. Compression of the epicardial surface by the transducer was avoided. The transducer was positioned such that the two-dimensional ultrasonic plane transected the left ventricle at the level of the midpapillary muscles distal to the previously noted critical stenosis and perpendicular to the longitudinal axis of the left ventricle. Thus, endocardial and epicardial surfaces of both the LAD perfusion zone (ischemic) and the left circumflex zone (nonischemic) were easily visualized.

Several cardiac cycles at each reference point were recorded on 0.5-in. videotape. Wall motion analysis and determination of regional percentage of myocardial thickening was performed with the aid of a computerized image processing system (Mipron System, Kontron Electronics, Eching, FRG), which allows acquisition of still-frame, end-diastolic, and end-systolic images from prerecorded two-dimensional videotape.27 Myocardial thickening was assessed from analysis of 64 equally spaced chords extending from the epicardium to the endocardium, defined for end-diastolic and end-systolic images. Thickening in the ischemic and nonischemic regions was determined from analysis of two centrally placed subsets of eight chords.

This method of two-dimensional real-time echocardiographic imaging of systolic thickening has been previously validated by comparison to simultaneously measured systolic thickening by using implantable ultrasonic crystals.28,29 In our laboratory, this echocardiographic technique has been shown to be very sensitive because only a 20% reduction in flow was associated with a corresponding decrement in function.30 The flow-function relation reported by our laboratory using this echocardiographic approach is similar to what has been demonstrated by sonomicrometry.30

Determination of Regional Myocardial Blood Flow

Serial measurements of regional myocardial blood flow were determined by the radioactive microsphere technique as previously described.31 Microspheres (11–13 μm) were labeled with scandium 46, niobium 95, ruthenium 103, or tin 113 (Du Pont), and each aliquot was calibrated to contain approximately 2×10⁸ spheres. Each aliquot was diluted to a volume of 5 ml with normal saline containing 0.01% polysorbate 80 (Tween 80). Proper dispersion was accomplished by vigorously agitating each aliquot by injection between two 10-ml syringes connected by a stopcock. Microscopic examination of a drop of sphere suspension confirmed no significant clumping. Furthermore, duplicate reference arterial samples drawn simultaneously were similar in counts per milliliter per minute.

The microsphere suspension was injected as a bolus during 5–10 seconds into the left atrium followed by 0.9% saline flush with continuous monitoring of arterial pressure, coronary blood flow, distal coronary pressure, and heart rate. Duplicate timed withdrawals from the two femoral artery catheters were begun 10–15 seconds before the microsphere injection and continued for a total of 90 seconds. Blood samples from each withdrawal were divided among three or four tubes.

At the end of the experiment, the dog was killed by induction of ventricular fibrillation preceded by injection of monastral blue into the left atrium. The left ventricle and septum were dissected free of epicardial fat and vessels and divided into four rings from apex to base. Each ring was divided into eight segments that were further subdivided into epicardial, midwall, and endocardial sections. Segments within the LAD perfusion zone distal to the critical stenosis were easily demarcated by the absence of blue discoloration as a result of total occlusion of the LAD at the previously placed stenosis just before injection of monastral blue. Samples were weighed and counted with duplicate withdrawals and pure isotope samples for 500 seconds in a Packard Gamma Autoscintillation counter. A multichannel analyzer was used with the following windows: ⁴⁴Sc, 740–1,300 KeV; ⁹⁵Nb, 650–818 KeV; ¹⁰⁰Ru, 450–570 KeV; and ¹¹³Sn, 340–440 KeV.

Myocardial blood flow was calculated by the following equation: Qm=(Cm×100 Qr)/Cr, where Qm is myocardial blood flow (ml/min), Cm is tissue counts (counts/min), Qr is withdrawal rate of arterial samples (ml/min), and Cr is counts in a reference.
arterial sample. Flow per gram of myocardium was calculated by dividing blood flow by the sample weight. Separation of isotopes and myocardial blood flow calculations were computer-calculated by the method of Heymann et al.32 With this method, counts per minute recorded in each window from myocardial and reference blood samples were corrected for background activity and spill contributed by isotopes outside the window. 201TI activity in myocardial tissue samples was counted in the 50–100-KeV window. Samples were held for 2 weeks before counting to avoid excessive spill into microsphere windows as a result of the high 201TI activity.

Myocardial segments selected for determination of regional blood flow in the area perfused by the LAD were located at least 0.5–1.0 cm within margins denoted by blue discoloration to avoid significant interdigitation of normal myocardium at the border region.

**Histochemical Staining**

Representative myocardial rings, including the area of echocardiographically denoted dysfunction, were incubated in triphenyl tetrazolium chloride (TTC) dissolved in 3% Sorensen’s buffer at 38°C for 20 minutes. In no dog was an area of necrosis observed.

**Myocardial Extraction Fraction of 201TI**

The method for determining the first-pass extraction fraction for 201TI has previously been reported33 and represents a modification of the double-isotope method of Weich et al.4,34 Extraction fraction was determined in 13 dogs in the stunned group and six dogs in the control group. A Harvard infusion pump (Harvard Apparatus) was attached to the coronary sinus catheter and adjusted to withdraw blood at a rate of 4 ml/min. An isotope mixture containing 5–10 μCi 125I-albumin and 20–30 μCi 201TI/ml saline was prepared and diluted into approximately 18–20 ml saline. Aliquots of incremental volume were subsequently administered directly into the LAD perfusion bed through the distal LAD catheter. Identical aliquots were placed in individual plastic tubes as reference samples. Incremental volumes of the double isotope mixture were used to compensate for accumulation of background activity in the blood. Accordingly, the initial injectate volume of 0.4 ml administered at baseline was followed by volumes of 0.8, 1.22, 1.6, 2.0, and 2.4 ml, corresponding to times denoted on the protocol. Extraction fractions were determined after placement of the critical stenosis, during reperfusion 5, during reperfusion 10, and 40 minutes after reperfusion 10. Control dogs received identical volumes of injectant at comparable times with only the LAD stenosis in place.

Blood was withdrawn from the coronary sinus for 5 seconds before injection of the isotope mixture and continued while the isotope mixture was administered through the intracoronary catheter during a 10-second period. The catheter was flushed with 3 ml saline. Coronary sinus blood was withdrawn for another 20 seconds after each bolus injection. The entire sample was then transferred into preweighed plastic tubes for analysis. The collected samples were weighed and counted in a gamma well counter (model 9601, Packard Gamma Autoslotillation Spectrometer). Energy windows of 24–36 KeV were used for 125I-albumin and 130–180 KeV for 201TI. Energy spill from the 201TI into the 125I window was subtracted as was background radiation.

The extraction fraction was calculated using the following formula:

\[ E = 1 - \frac{[\text{Tl(coronary sinus)} - \text{bkgrd}] \times [\text{I(ref)} - \text{spill} - \text{bkgrd}]}{[\text{Tl(ref)} - \text{bkgrd}] \times [\text{I(coronary sinus)} - \text{spill} - \text{bkgrd}]} \]

where Tl is 201TI, I is 125I (125I-HSA) coronary sinus, Ref is reference pure sample, bkgrd is background radiation (in respective window), and spill is 201TI activity in 125I window.

This method for measuring extraction fraction is not influenced by some venous admixture from the left circumflex bed, occurring with coronary sinus sampling. Extraction fraction is determined by comparing the ratio of a nonextractable tracer (albumin) to an extractable tracer (201TI) before and after passage of the mixture through the coronary capillary bed. The venous sample must include venous drainage from the LAD bed but can be diluted by an unknown amount of venous drainage from the noninjected left circumflex bed without affecting the result. This happens because the same venous dilution factor will appear in both numerator and denominator and will be canceled in the result.

**Measurement of Intrinsic 201TI Washout Rate**

The intrinsic washout rate of 201TI was determined after direct intracoronary injection of the radionuclide as previously described.33 By this mode of administration, there is almost no systemic recirculation of 201TI back to the myocardium, thus permitting assessment of the true efflux rate of 201TI from the myocardium into the systemic pool. Previous work from our laboratory has shown a biphasic nature to the intrinsic 201TI washout rate.33 A rapid early component is attributed to the early clearance of 201TI from the interstitial compartment and comprises approximately 10% of the totally extracted 201TI dose. The slower component represents 201TI washout from the intracellular compartment.

The intrinsic 201TI washout rate was assessed in 12 dogs prepared and instrumented as previously described. These dogs did not include any that had extraction fraction measurements made in them but comprised a separate group. Six dogs with a critical LAD stenosis underwent the stunning protocol, and six other dogs with a critical LAD stenosis served as controls. After 150 minutes into the protocol, 80 μCi 201TI was injected directly into the LAD in both groups. Serial coronary sinus effluent samples were obtained by the previously inserted coronary sinus catheter. Blood samples (2.0 ml) were withdrawn at
1-minute intervals during 15 minutes and 5-minute intervals, thereafter, to a total of 40 minutes.

Collected coronary sinus samples were weighed and counted in the \( \gamma \)-scintillation counter at the energy window appropriate for \(^{201}\)TI. The intrinsic \(^{201}\)TI washout rate was calculated from the coronary sinus sample data by plotting counts versus time in a semilogarithmic manner.\(^{33}\) Coronary venous concentration of \(^{201}\)TI, \(C(t)\), was expressed as counts per 500 seconds per gram at each time point. The data was fit by a computer to a two-component exponential, as follows:

\[
C(t) = A_e^{-kt_1} + B_e^{-kt_2}
\]

where \(k_1\) is a rapid washout rate associated with interstitial washout, and \(k_2\) is the slow intracellular washout component. The percentage of the injected \(^{201}\)TI dose initially partitioned in the interstitial component was calculated as the ratio of the total area under the rapid component \(Q\), divided by the total area under the concentration curve \(Q\). The formula used was as follows: \(Q/Q_0=\text{Ak}_3/(\text{Ak}_3+\text{Bk}_2)\).

**Statistical Methods**

All computations were performed on a VAX computer. Data are expressed as mean±SEM. Baseline, occlusion, and reperfusion data were compared in control and stunned dogs by using a pooled \( t \) test, and differences were considered significant when \( p \) values were less than 0.05 (two sided). Different stages of the protocol in the same group were compared with one-way analysis of variance, and differences between stages were compared with the Newman-Keuls method, which is imbedded within the analysis of variance. Differences were considered significant when \( p \) values were less than 0.05.

**Results**

**Excluded Dogs**

Of 45 experiments conducted, 14 dogs were excluded. Ten died from refractory ventricular fibrillation at various times after placement of the critical stenosis or during the reperfusion periods after the transient coronary occlusions in the stunned protocol. In three dogs, significant wall motion abnormalities within the LAD zone were documented by the echocardiographic technique after either completion of the surgical preparation or placement of the critical stenosis. These dogs were excluded because regional ischemia might have resulted from the surgical preparation or instrumentation before the measurement of baseline values. Another dog was excluded because of excessive bleeding around the LAD dissection site after insertion of the distal LAD catheter.

**Hemodynamic Data**

Hemodynamic data were available for all 31 dogs included in subsequent analyses. As shown in Figure 1, heart rate and systemic arterial blood pressure were comparable in control and stunned dogs throughout the experimental protocol. After placement of the LAD stenosis, stenosis gradient was similar in both groups of dogs (stunned, 47±4 mm Hg; control, 49±6 mm Hg; \( p=\text{NS} \)). As shown in Figure 1, the mean distal LAD pressure was maintained constant throughout the experimental protocol in both groups of dogs with the exception being during the transient periods of LAD occlusion in the stunned dogs. When the LAD was totally occluded, the distal pressure fell significantly in the stunned dogs to a mean of 28±2 mm Hg. In stunned dogs, the LAD EMF flow (from electromagnetic flowmeter) was 34 ml/min compared with 35 ml/min in control
dogs. After creation of the stenosis, flow was reduced to 24 ml/min in both groups.

Myocardial Thickening

Figure 2 shows the serial changes of percentage of myocardial thickening in the LAD perfusion zone in stunned (n = 18) and control (n = 12) dogs during the experimental protocol. Creation of the stenosis resulted in a slight but not statistically significant diminution in systolic thickening in both groups of dogs. In control dogs, systolic thickening remained constant throughout the experimental protocol. In contrast, regional systolic thickening significantly diminished with serial LAD occlusions in the stunned dogs. During reperfusion 5 after the fifth LAD occlusion, systolic thickening was decreased to 6.7 ± 3.4% in the stunned dogs compared with systolic thickening in the LAD zone in the control dogs of 33.4 ± 3.1% (p < 0.001), at a comparable time. The decrease in regional systolic thickening was progressive, and 40 minutes after the 10th reflow period, systolic thickening in the LAD zone was markedly reduced to 0.4 ± 2.4% in the stunned dogs compared with thickening of the LAD zone in the control dogs, which was 32.5 ± 2.2% (p < 0.001), at a comparable time. Even 40 minutes after the 10th reflow (R-10E in Figure 2), systolic function was still markedly depressed.

Regional Myocardial Blood Flow

Figure 3 summarizes the regional myocardial blood flow results from control (n = 11) and stunned (n = 12) dogs in the endocardial layers of the LAD and left circumflex perfusion zones. Regional flow was not measured at baseline before creation of the LAD stenosis. Nonischemic flow in the left circumflex zone was comparable in control and stunned dogs throughout the experimental protocol. During LAD occlusion 5, flow was reduced in the endocardium to 0.18 ± 0.05 ml/min/g, reflecting the severity of ischemia. At the end of the experiment, 40 minutes after the 10th reperfusion, endocardial blood flow (ml/min/g) was still similar in stunned (0.71 ± 0.09) and control (0.75 ± 0.07) dogs at the same time, and was not significantly different from flows initially measured after creation of the stenosis. There was no evidence of 'no-reflow' in dogs undergoing myocardial stunning.

First-Pass Myocardial Extraction Fraction of 201Tl

The first-pass extraction fractions for 201Tl at the specified times in the protocol are summarized in Figure 4. The extraction fractions were similar for six control and 13 stunned dogs each of the five times measured. With the stenosis in place, the first-pass 201Tl extraction fraction was 0.83 ± 0.01 for stunned
and 0.82±0.01 for control dogs. Despite severe postischemic systolic dysfunction, the first-pass extraction fraction for 201Tl in the stunned dogs after the 10th reperfusion was 0.78±0.02, which was comparable with the value of 0.79±0.03 in control dogs.

**Intrinsic 201Tl Washout Rate**

Representative time-activity curves depicting intrinsic 201Tl washout from a dog in the stunned group and a dog in the control group are shown in Figure 5. Note that the configuration of the intrinsic washout curves is similar in both dogs, demonstrating an early rapid component followed by a later slow component. Figure 6 shows the mean washout rates calculated for the fast and slow components, respectively, for the control (n=6) and stunned (n=6) dogs. The T1/2 for the fast component was 1.8±0.18 minutes in the stunned dogs compared with 1.7±0.23 minutes for control dogs (p=NS). The slow washout component averaged 60±13 minutes for stunned dogs and 53±14 minutes for control dogs (p=NS).

The percentage of the 201Tl dose initially extracted in the interstitial compartment was 11±3% for stunned dogs and 7±2% for control dogs (p=0.38). There was no evidence of an expanded interstitial compartment in stunned dogs consequent to the production of posts ischemic regional dysfunction.

**Discussion**

In the present study, we demonstrated that despite severe postischemic myocardial dysfunction not associated with histochemical evidence of necrosis, 201Tl extraction fraction and intracellular washout kinetics are unaltered when compared with control dogs. The extraction fraction and intrinsic 201Tl washout values in stunned and control dogs in this study are similar to values in normal dogs in one of our previous studies.33

**Myocardial Extraction of 201Tl**

Studies in isolated heart and intact animal preparations have shown little or no effect of profound hypoxia on myocardial washout.6,35–37 Goldhaber et al.6 using a fetal mouse heart preparation in organ culture that does not depend on blood flow to provide metabolic substrate, found that deprivation of oxygen and oxidizable substrate with 1 hour of perfusion with 95% N2-5% CO2 resulted in no reduction in myocardial 201Tl content. Reduction in myocardial 201Tl content in this preparation was monotonically related to the extent of myocardial necrosis as measured by lactic dehydrogenase release. In an isovolumic isolated rabbit heart preparation, Leppo37 showed that extraction of 201Tl was not affected by hypoxia at constant flow. In intact dogs, Weich et al.4 demonstrated only a slight reduction in myocardial extraction fraction for 201Tl with a 30-minute period of sustained hypoxia where the Po2 was reduced to 30 mm Hg. Mean coronary blood flow increased by 70%, and the diminished extraction might have been secondary to the higher flow. It has been well demonstrated that the first-pass myocardial extraction for 201Tl, as well as for other monovalent cations, is reduced when flow is significantly increased above the physiological range.38

Krivokapich et al.36 reported that 20–40 minutes of anoxia in an isolated rabbit interventricular septum model caused a decrease in tissue uptake of 201Tl due to an increased efflux of the cation rather than inhibition of 201Tl influx. Interestingly, in this experiment, 60 minutes of reoxygenation preceded by 40–60 minutes of anoxia resulted in recovery of at least 95% of the 201Tl lost although mechanical recovery was still significantly depressed. Similarly, reperfusion accomplished after 20–60 minutes of total ischemia was
followed by a 90% resumption of $^{201}$TI uptake despite functional recovery of tension for only 53%. Thus, as observed in our study, these investigators showed recovery of $^{201}$TI kinetics with reperfusion after ischemia despite persistent mechanical dysfunction.

$^{201}$TI Uptake and Myocardial Necrosis

Intracellular $^{201}$TI uptake in experimental infarction models does not occur in zones of myocardial necrosis; however, initial $^{201}$TI defects with delayed distribution can be demonstrated in peri-infarction regions of diminished flow. Khaw et al$^{15}$ compared myocardial $^{201}$TI uptake with the distribution of cardiac-specific antimyosin antibody that is a marker for irreversible cellular necrosis. These investigators showed an inverse exponential relation between antimyosin antibody uptake and $^{201}$TI activity. Other experimental studies in anesthetized or intact animals have also demonstrated diminished $^{201}$TI uptake in areas of cellular necrosis.$^{2,39-43}$ Thus, myocardial uptake of $^{201}$TI is significantly impaired when irreversible cell membrane damage is present. Ischemic but hypoperfused myocardium will concentrate $^{201}$TI as the redistribution process progresses. In the present study, there was no evidence of myocardial necrosis in stunned dogs; thus, it was not surprising that extraction of $^{201}$TI was similar to what was seen in control dogs.

$^{201}$TI Transport and Na$^+$/K$^+$-ATPase

It has been suggested that both active and passive transport processes are involved in $^{201}$TI transport.$^{44,45}$ Active transport involves the sodium-potassium pump in the sarcolemma. Myung-Suk and Akera$^{12}$ reported that ischemia and reperfusion reduced Na$^+$,K$^+$-ATPase activity and specific $^3$H ouabain binding to the enzyme in guinea pig ventricular muscle homogenates as well as markedly lowering sodium pump activity estimated from ouabain-sensitive $^{86}$Rb$^+$ uptake by ventricular muscle slices. These effects were prevented to varying degrees by exogenous scavengers of oxygen radicals that reduced sarcoplasmatic membrane lipid peroxidation. One might expect altered $^{201}$TI extraction in stunned myocardium if oxygen radicals adversely affected the active sodium pump. Several investigators have shown that ouabain administration known to inhibit Na$^+$,K$^+$-ATPase failed to adversely affect early $^{201}$TI uptake; Melin and Becker,$^{38}$ Krivokapich and Shine,$^{45}$ and Weich et al$^{34}$ could not demonstrate an inhibition of $^{201}$TI extraction with cardiac glycosides. Thus, even if myocardial stunning resulting from reperfusion caused a reduction in sarcoplasmatic Na$^+$,K$^+$-ATPase activity, $^{201}$TI extraction might not be affected as long as irreversible sarcoplasmatic membrane injury did not occur. This supposition is consistent with a previous study in a canine infarct model that showed a significant loss of Na$^+$,K$^+$-ATPase activity and altered in vitro ouabain binding to the enzyme did not occur unless ischemia was prolonged and resulted in myocardial creatine kinase loss.$^{40}$ In our canine model, the protocol producing myocardial stunning probably did not significantly affect Na$^+$,K$^+$-ATPase activity because necrosis was not evident histologically.

Myocardial $^{201}$TI Washout

In the present study, despite profound systolic dysfunction, the intrinsic $^{201}$TI washout rate measured after intracoronary $^{201}$TI injection was not different from that in control dogs. Also, we found no significant increase in the fraction of the $^{201}$TI dose extracted in the interstitial compartment (11%) compared with control dogs (7%), and there was no evidence of no-reflow. Thus, these observations lend further support to the contention that $^{201}$TI kinetics are unaltered despite significant ischemic dysfunction and suggest further that sarcolemmal membrane integrity is intact.

When reperfusion is instituted in the presence of myocardial necrosis, there might be some enhanced uptake and faster early $^{201}$TI clearance from the damaged reperfused area compared with nonischemic myocardium.$^{41,43,44,47-49}$ This can be secondary to administration of $^{201}$TI during the hyperemic phase of reflow or represent tracer washout from an expanded interstitial compartment, or both. Interstitial $^{201}$TI washout is faster than intracellular washout. Myocardial hemorrhage and interstitial edema are consequences of reperfusion after prolonged coronary occlusion. In the present study, there was no evidence of faster early $^{201}$TI washout in the stunned dogs.

Admixture in coronary sinus sampling by a constant but unknown amount of left circumflex bed venous drainage should not have influenced measurement of the intrinsic $^{201}$TI washout rate from the injected LAD bed. The washout rates are related only to time dependence of tracer concentration and are valid for any arbitrary venous dilution if the dilution factor is not time dependent. This requirement was satisfied for the measurements made in these experiments because coronary flow distribution was stable when $^{201}$TI washout rates were being assessed. As with the extraction fraction measurement, determination of the fractional volume distribution between the slow and fast washout components similarly provides for cancellation of the overall dilution of the samples and thus is independent of venous admixture.

Experimental Model for Myocardial Stunning

The dog model used for myocardial stunning in this study was similar to the one described by Nicklas et al.$^{26}$ In that model, reperfusion was instituted by totally releasing the serial 5-minute coronary occlusions through a patent vessel rather than through a persistent stenosis as undertaken in our study. They showed that when the LAD was occluded for 5 minutes, followed by 10 minutes of reflow and repeated 16 times, the average systolic shortening decreased by 82% after the eighth transient occlusion, and 91% after the 16th transient occlusion. Niklas et
al26 did not detect any histochemical or ultrastructural evidence of myocardial necrosis in the stunned region. Furthermore, subsequent studies by this group demonstrated that the posts ischemic function produced by repetitive occlusion was reversible by augmenting coronary flow50 or infusion of intravenous epinephrine.51 Our 201TI kinetic data support the potential for reversibility of posts ischemic dysfunction in this model. The degree of systolic dysfunction was greater, perhaps, in our experiments because of the presence of a persistent residual stenosis.

Clinical Significance

Extrapolation of the results of this experimental study to the clinical setting must be done carefully. Some speculation, however, with respect to the relevancy of our findings in patients with ischemic heart disease and myocardial dysfunction might be justified. For example, in a study by Bulkley et al,52 some postinfarction patients who had large resting 201TI scintigraphic defects during the course of hospitalization and who subsequently died had significantly smaller areas of necrosis at postmortem analysis. It was suggested that a “surrounding area of reversibly ischemic myocardium” contributing to the size of the scintigraphic defect must have been present at the time of imaging. These patients, however, seemed to have had severe residual stenotic lesions in the infarct-related artery, which might have reduced resting flow and contributed to a larger extent of hypoperfusion than what ultimately became necrotic. This might be a more plausible explanation than postulating that a metabolically deranged 201TI transport system in the perinfarction area produced a large defect that was out of proportion to the extent of necrosis. Our data suggest that ischemic but viable tissue should be able to concentrate 201TI intracellularly as long as there is adequate residual perfusion permitting delivery of the radionuclide. Reduction in defect size during 10 days after acute infarction as reported by Wackers et al53 could also be attributed to improved perfusion rather than reversal of an abnormality in 201TI extraction in the perinfarction zone.

In the present experimental study, 201TI extraction was unaltered in stunned myocardium characterized by akinesis. In patients with coronary artery disease, normal 201TI uptake or delayed redistribution also occurs in some areas of regional akinesis.24,54–61 When vessels perfusing such regions are revascularized, significant improvement in early 201TI uptake and systolic function occurs.61 Intact 201TI uptake has even been observed in dysskinetic aneurysmal regions associated with high-grade coronary arterial lesions55 that show improved function after revascularization. 201TI uptake is normal between episodes of rest pain in patients with unstable angina.62 Most patients in that study were imaged within 12 hours after the last anginal attack when posts ischemic dysfunction must have been present. Berger et al61 reported that 27% of myocardial segments showing normal 201TI uptake or delayed redistribution on serial rest images in patients with severe angina were akinetic and dyskinetic. Stratton et al59 showed that 17% of myocardial segments with normal 201TI uptake were akinetic or hypokinetic.

Thus, data from the clinical studies cited above show that many patients with severe coronary artery disease will demonstrate normal or delayed 201TI uptake in areas of severe myocardial asynery. Demonstration of preserved 201TI uptake on myocardial scintigraphy supports viability in such areas of regional asynery and predicts a favorable response to revascularization with an expected postoperative improvement in perfusion and function.24,63

Conclusion

We have demonstrated normal myocardial 201TI extraction and 201TI washout kinetics in a canine model characterized by severe posts ischemic dysfunction despite restoration of regional myocardial blood flow to baseline levels. These findings can have important clinical implications concerning the application of rest 201TI scintigraphy for evaluation of perfusion and viability in patients with severe coronary artery disease and regional myocardial asynery that is ultimately reversible.

Acknowledgments

We are grateful for the superb editorial assistance provided by Mr. Jerry Curtis in the preparation of this manuscript. The 201TI and radiolabeled microspheres were generously provided by E.I. Du Pont de Nemours & Co., Medical Products Division, North Billerica, Massachusetts.

References

9. Greenfield RA, Swain JL: Disruption of myofibrillar energy use: Dual mechanisms that may contribute to post-ischemic dysfunction in stunned myocardium. Circ Res 1987;60:283–289
29. Pandian NG, Kieso RA, Kerber RE: Relationship between myocardial blood flow by layer and abnormalities of wall thickening on two-dimensional echocardiography: What is the initial perfusion threshold below which systolic thickening is replaced by systolic thinning (abstract)? Am J Cardiol 1982;49:918

Key Words • regional myocardial perfusion • myocardial ischemia • thallium 201
Thallium 201 kinetics in stunned myocardium characterized by severe postischemic systolic dysfunction.
C A Moore, J Cannon, D D Watson, S Kaul and G A Beller

Circulation. 1990;81:1622-1632
doi: 10.1161/01.CIR.81.5.1622

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/81/5/1622