Effects of No Flow and Reperfusion on Technetium-99m-Q12 Kinetics

Robert D. Okada, Kiem N. Nguyen, Michael Lauinger, Iantha L. Allton, Kristy Spreitzer, Delia Beju and Gerald Johnson III

William K. Warren Medical Research Institute, University of Oklahoma Health Sciences Center and Cardiology of Tulsa, Tulsa, Oklahoma

The purpose of this study were to determine if ^{99m}Tc-Q12 tracer kinetics could be affected by the insult of total no flow followed by reflow and the effects of viability on clearance. **Methods:** In six control buffer perfused rat hearts, flow was maintained at 12 ml/min throughout uptake and clearance. In six hearts (IR30), 30 min of no flow was followed by 60 min of reflow. In six hearts (IR60), 60 min of no flow was followed by 60 min of reflow. One millicurie ^{99m}Tc-Q12 was injected in control hearts or during reflow in the IR30 and IR60 hearts and myocardial clearance was monitored for 1 hr using a NaI detector. **Results:** Control hearts demonstrated biphasic ^{99m}Tc-Q12 myocardial clearance with an early rapid clearance phase ending 5–10 min after injection (73.5% ± 1.5% retention) followed by a late slow clearance phase (90.5% ± 0.2% retention). IR30 hearts demonstrated a near identical clearance curve (74.3% ± 0.9% early retention, 90.9% ± 0.6% late retention). IR30 heart electron micrographs demonstrated predominantly ischemia insulted but viable cells. IR60 hearts also demonstrated a biphasic myocardial clearance, with a late slow phase similar to controls (91.9% ± 0.6% retention). The early rapid phase was significantly faster than controls (61.1% ± 3.4%). IR60 heart electron micrographs demonstrated predominantly injured nonviable cells. Well counting confirmed decreased retention in the IR60 rats compared to controls and IR30 rats. **Conclusion:** Technetium-99m-Q12 myocardial clearance is normally biphasic, with an early rapid phase ending after 5–10 min and a late slow phase. Ischemicaly insulted but viable myocardium created by 30 min of no flow followed by reflow has no effect on either clearance phase. This tracer warrants further study to determine its potential utility in assessing myocardial viability.

J Nucl Med 1995; 36:2103–2109

Technetium-99m-Q12 is a new myocardial perfusion imaging agent that is in the Schiff base/phosphine class. This compound, trans(1,2-bis(dihydro-2,2,5,5-tetramethyl3(2H)-furanonato-4-methyleneimino)ethane) bis(tris(3-methoxy-1-propyl)phosphine)^{99m}Tc(III) is both cationic and lipophilic (*1*). Canine studies have demonstrated that initial uptake is related to blood flow for flows up to 2 ml/min/g and that subsequent clearance is the same from normal and ischemic myocardium (*2*). Human volunteer studies have shown high myocardial uptake and minimal 5-hr clearance, allowing for imaging several hours after administration (*3–7*). Our laboratory has demonstrated that myocardial clearance is only minimally affected in viable myocardium despite hypoxia or low flow over a 60-min period (*8*).

The current study utilized a buffer-perfused, isolated rat heart preparation to study the effects of no flow followed by reperfusion on ^{99m}Tc-Q12 myocardial kinetics. One group of hearts had 30 min of no flow followed by reperfusion, and another group had 60 min of no flow followed by reperfusion. The purposes of the study were to determine if ^{99m}Tc-Q12 myocardial kinetics are affected by the insult of total no flow followed by reperfusion and the effects of viability on ^{99m}Tc-Q12 clearance.

METHODS

Apparatus

The experimental apparatus used is shown in Figure 1. Hearts were perfused with Krebs-Henseleit buffer containing (m*M*) 127 NaCl, 5.8 dextrose, 0.83 EDTA, 1.25 KH_2PO_4, 1.51 $CaCl_2$, 4.88 KCl, 0.56 $MgSO_4$ and 20 $NaHCO_3$, and oxygenated throughout the experiments with 95% O_2/5% CO_2. Coronary perfusion pressure was monitored by a Gould Statham P23 ID transducer (A). Temperature (B), oxygen saturation (C) and pH (C) of the perfusate were measured continuously by in-line probes. Hearts were vented and paced at 300 bpm. Left ventricular diastolic and systolic pressures were monitored by a Gould Statham P23 ID pressure transducer connected by a rigid catheter to a latex balloon (D). The balloon was inserted into the hearts through a slit made in the left atrial appendage and was filled with 0.9% saline solution. Left ventricular performance variables and conditions of the Krebs-Henseleit buffer were recorded continuously on a Gould stripchart recorder and displayed on a computer monitor. Lead shielding (not shown in Fig. 1) separated the sidearm and perfusion tubing from the sodium iodide crystal. Teflon tubing was used in construction of the sidearm apparatus for bolus delivery.

Radiopharmaceutical Preparation

A vial of Q12 was injected with 2–3 ml sterile sodium pertechnetate solution containing approximately 25 mCi ^{99m}Tc. The vial was placed in a boiling water bath for 20 min and then cooled to room temperature. Quality control procedures to determine the purity of the ^{99m}Tc-Q12 complex were carried out using Sep-Pak R Alumina cartridges (Millipore Corp., Milford, MA). A 0.1-ml

Received Sept. 8, 1994; revision accepted Feb. 14, 1994.

For correspondence or reprints contact: Gerald Johnson III, PhD, William K. Warren Medical Research Institute, 6465 South Yale, Suite 1010, Tulsa, OK 74136.

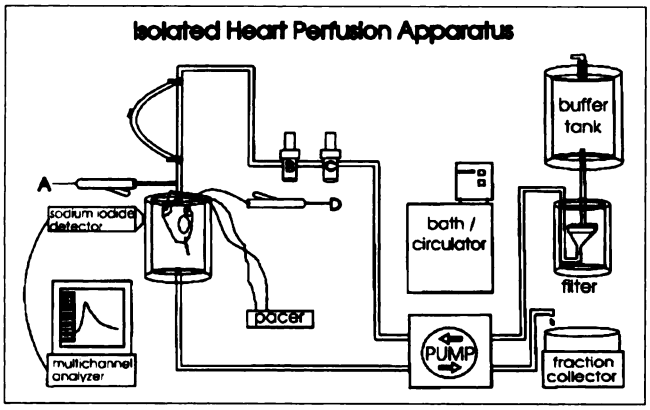

FIGURE 1. The isolated buffer-perfused rat heart apparatus.

sample of ^{99m}Tc-Q12 was injected into the long end of the cartridge. Ten milliliters 200 proof ethanol were injected into the cartridge and the elution was collected. Ten milliliters 0.9% NaCl solution were injected next followed by 10 ml of room air and the elution from these two steps was collected separately from the ethanol-based elution. The activity of each of the two elutions and the cartridge were measured separately. The first elution contained pure ^{99m}Tc-Q12. The second elution and the cartridge contained impurities. Purity of the sample was calculated by dividing the activity of the first elution by the sum of the activities of the two elutions and the cartridge. Radiochemical purity values ranged from 92% to 96%.

Protocol

Male Sprague-Dawley rats, 375–400 g, were anesthetized with 1 ml sodium pentobarbital solution (65 mg/ml). Heparin (400 units) was injected into the femoral vein upon reaching deep anesthesia. Rapid excision of the hearts was followed immediately by suspension of the hearts by the aortic stump from the glass cannula of the perfusion apparatus. Pacing wires were then attached to the right atrium, and the intraventricular balloon was inserted into the left ventricle. Following instrumentation, hearts were randomly assigned to groups and subjected to the protocols illustrated in Figure 2. Hearts were perfused in a retrograde manner with nonradioactive Krebs-Henseleit during a 20-min baseline period at 12 ml/min using the Langendorff technique. Myocardial uptake and clearance of ^{99m}Tc-Q12 were monitored by a NaI probe. Three groups of hearts were used in this study as follows: a control group (n = 6), a 30-min no flow group followed by reflow (n = 6) and a 60-min no flow followed by reflow group (n = 6). All experimental animals were handled in accordance with the "Position of the American Heart Association on Research Animal Use" and with the approval of the Institutional Animal Care and Use Committee of the University of Oklahoma Health Sciences Center.

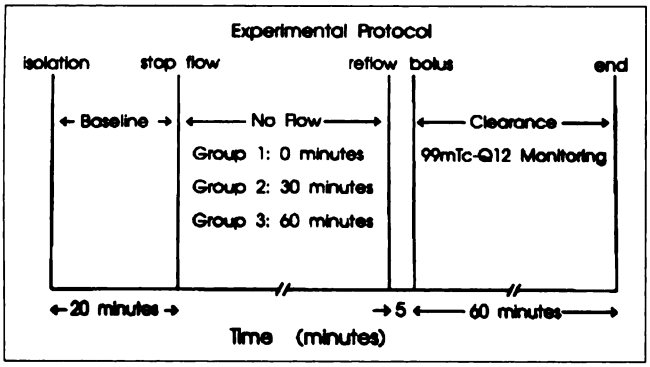

FIGURE 2. Experimental protocol. Group 1 = controls, Group 2 = 30 min no flow followed by reflow and Group 3 = 60 min no flow followed by reflow.

Group 1 (Control). Six control hearts were given the bolus injection of 1 mCi ^{99m}Tc-Q12 at the end of baseline. There was no interruption of flow. Control hearts were perfused for 60 min of clearance after the bolus at 12 ml/min.

Group 2 (Thirty Minute No Flow). This group consisted of six hearts which received 30 min of no flow beginning at the conclusion of baseline. At the end of the no flow period, the hearts were reperfused at the normal rate of 12 ml/min and given 5 min to stabilize before the bolus injection. Clearance was monitored for 60 min following peak uptake.

Group 3 (Sixty Minute No Flow). This group consisted of six hearts which received 60 min of no flow beginning at the end of baseline. At the end of the no flow period, the hearts were reperfused at the normal flow rate of 12 ml/min. Just as with Group 2, each heart in this group was given 5 min to stabilize after reperfusion before the ^{99m}Tc-Q12 bolus injection. Clearance was monitored for 60 min following peak uptake.

Technetium-99m-Q12 Monitoring

Activity in the hearts was measured at 1-min intervals by a NaI detector positioned 3 cm from the left side of the heart. The probe was interfaced with a discriminator and the data were transferred to a multichannel analyzer which recorded and displayed the time-activity curve for each minute throughout the experimental protocol.

Data Analysis

Background counts taken for 5 min at the end of clearance after the heart had been removed were averaged and the average was subtracted from the activity recorded on the multichannel analyzer for each minute of clearance. The background-subtracted counts were corrected for decay of ^{99m}Tc. The background-subtracted, decay-corrected counts for each experiment were used to calculate total fractional washout of ^{99m}Tc-Q12 by subtracting the 60-min activity from the 2-min activity and then dividing by the 2-min activity. Fractional clearances for 2–10 min and 10–60 min were similarly calculated. Then, data from each individual experiment were averaged to obtain a mean curve for each group. The first 2 min of data were omitted to eliminate the bolus effect.

Statistical Analysis

A one-way analysis of variance procedure (ANOVA) was conducted to determine whether differences were present among the groups. Student's t-tests along with the Bonferroni correction for multiple comparisons were used to test specific pairs of means. Analysis of variance with repeated measures was used to compare multiple time points within a group for significant differences. A value was considered to be statistically significant when $p < 0.05$. Results are reported as mean ± s.e.m.

Curve Fitting

Individual clearance curves were fit using nonlinear regression procedures available in Tablecurve 2D software (Jandel Scientific, San Rafael, CA). Planned comparisons of group means were conducted by Student's t-test.

TABLE 1
Hemodynamic Parameters

	Baseline	15 min	30 min	45 min	60 min
Coronary perfusion pressure (mmHg)					
Control	50.8 ± 3.5	51.0 ± 3.6	50.3 ± 4.3	48.4 ± 4.6	47.7 ± 4.9
IR30	46.7 ± 1.7	54.0 ± 5.6	53.8 ± 5.7	53.2 ± 5.4	53.5 ± 6.1
IR60	45.7 ± 2.0	51.8 ± 2.9	53.1 ± 4.0	54.0 ± 4.2	54.0 ± 4.4
Systolic pressure (mmHg)					
Control	80.7 ± 3.7	81.0 ± 3.6	80.9 ± 3.6	74.7 ± 4.1	72.3 ± 4.6
IR30	74.5 ± 8.2	86.3 ± 5.1	87.0 ± 6.0	85.8 ± 6.3	82.8 ± 7.2
IR60	94.5 ± 4.0	119.3 ± 13.5*†	118.3 ± 13.4*†	116.7 ± 13.1*†	114.5 ± 13.0*†
Diastolic pressure (mmHg)					
Control	8.1 ± 0.82	7.6 ± 0.7	6.7 ± 1.0	5.8 ± 1.1	5.3 ± 1.1
IR30	8.7 ± 0.76	9.0 ± 1.0	7.8 ± 1.2	7.3 ± 1.1	6.8 ± 1.1
IR60	7.5 ± 1.0	44.3 ± 12.0*†	43.5 ± 12.0*†	43.0 ± 11.7*†	42.8 ± 11.8*†
Heart rate (bpm)					
Control	296.4 ± 1.2	296.7 ± 1.2	295.9 ± 1.3	295.4 ± 1.4	295.3 ± 1.5
IR30	297.8 ± 1.2	295.0 ± 1.6	296.5 ± 1.2	295.3 ± 1.5	295.3 ± 1.5
IR60	300.0 ± 0.0	200.0 ± 63.2	200.0 ± 63.2	200.0 ± 63.2	200.0 ± 63.2

*$p < 0.05$ versus controls.
†$p < 0.05$ versus baseline.
IR30 = 30-min no flow/reflow, IR60 = 60-min no flow/reflow. Note: two hearts in the IR60 group did not recover function after reflow. All values are mean ± s.e.m.

Assessment of Ultrastructural Injury

At the end of the experiment, hearts from each group were fixed and prepared for electron microscopy studies to document tissue injury. These hearts were perfused with 2% gluteraldehyde in 0.1 *M* cacodylate buffer at pH 7.4, postfixed in 1% osmium tetroxide, bloc stained with 0.5% aqueous uranyl acetate, dehydrated in graded ethanol and embedded in PolyBed 812. Thin sections were obtained with MT-6000 and MT-2B ultramicrotomes equipped with diamond knives. The sections were contrasted with uranyl acetate and lead citrate and were examined in a Zeiss 109 electron microscope operated at 80 kV.

RESULTS

Hemodynamic Data

Table 1 lists the hemodynamic data for all three groups. There was no significant difference among the groups in any hemodynamic parameter during the baseline period. The control group of hearts demonstrated no significant changes in coronary perfusion pressure, systolic and diastolic pressure and heart rate during the study period. The 30-min no flow-reflow group of hearts also demonstrated no significant change in these parameters during the reflow period. The 60-min no flow-reflow group of hearts demonstrated a significant increase in diastolic and systolic pressures and a decline in heart rate despite pacing during the reflow period.

Myocardial Technetium-99m-Q12 Clearance

Figure 3 demonstrates the ^{99m}Tc-Q12 clearance curves for the three groups of hearts. The control hearts demonstrated a biphasic clearance curve. The early phase demonstrated rapid clearance, ending 5–10 min after tracer administration (73.5% ± 1.5% retention at 10 min, as shown in Fig. 4). The late phase demonstrated slow clearance (90.5% ± 0.2% retention for 10–60 min). Final retention at the end of the 60-min period was 61.2% ± 1.7% in the control hearts.

The 30-min no flow-reflow group demonstrated a clearance curve which was indistinguishable from the control hearts (Fig. 3). Clearance was also biphasic with an early

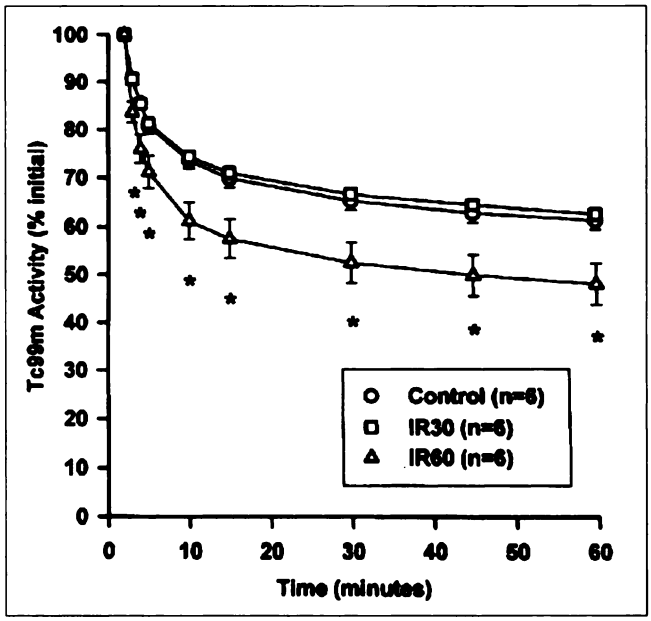

FIGURE 3. Mean background-subtracted, decay-corrected ^{99m}Tc-Q12 myocardial clearance from the controls, 30-min no flow followed by reflow group (IR 30) and 60-min no flow followed by reflow group (IR 60). Activity is plotted as a percentage of activity from the second minute post-peak uptake. *$p < 0.05$ compared to the control and IR 30 groups.

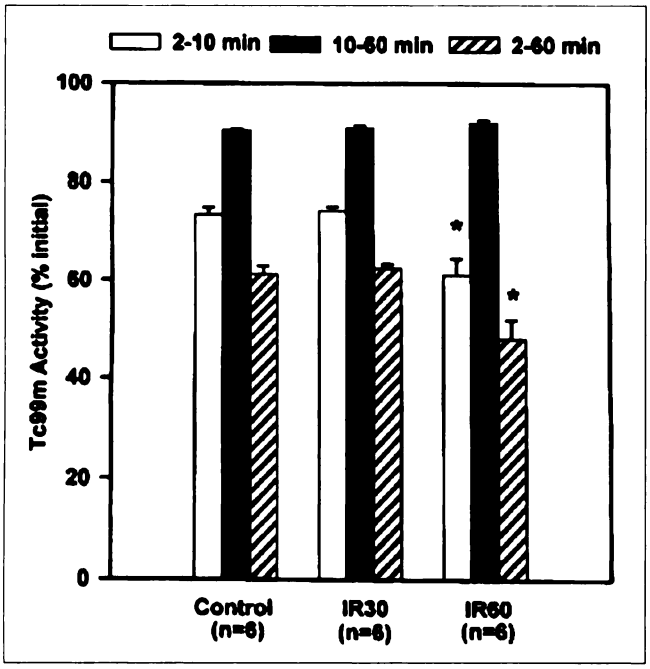

FIGURE 4. Fractional ^{99m}Tc-Q12 myocardial retention for the three groups of hearts over three time periods. Time intervals are from time of tracer administration. *p < 0.05 compared to control and IR 30 groups.

rapid clearance phase (74.3% ± 0.9% retention, 2–10 min, p = ns, compared to controls) followed by a late slow clearance phase (90.9% ± 0.6% retention, 10–60 min, p = ns, compared to control), as shown in Figure 4. Total retention for the 60-min period was 62.5% ± 1.0% (p = ns, compared to controls).

The 60-min no flow-reflow group of hearts demonstrated a biphasic myocardial clearance curve (Fig. 3). The early rapid clearance phase, however, demonstrated significantly faster clearance compared to the control and 30-min groups (61.1% ± 3.4% 2–10 min retention, p < 0.05 compared to the control and 30-min group), as displayed in Figure 4. The later slow clearance phase (91.9% ± 0.6% 10–60 min retention) was not significantly different than that for the control and 30-min groups. Final fractional myocardial retention in this group was 48.0% ± 3.9%, which was significantly different from both other groups (p < 0.01).

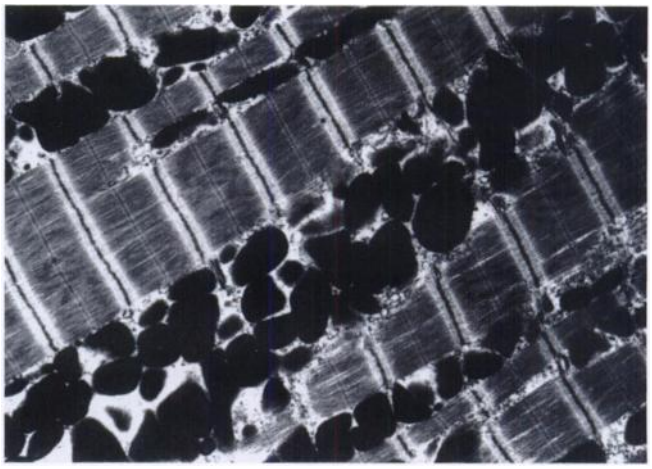

FIGURE 5. Electron micrograph taken from a normal control heart (12,600×). The cytoarchitecture is normal in appearance.

Myocardial Clearance Curve Fitting

Biexponential equations were found to be the best fits to the clearance curves for each group in the study. The best fit equation was: $y = a * \exp(-bx) + c * \exp(-dx)$. The parameters derived for these fits are presented in Table 2. The half-time for the rapid clearance phase was significantly faster for the IR 60 group (1.58 ± 0.12 min) compared to controls (1.95 ± 0.08 min, p = 0.02). There were no significant differences in the half-time values for the second slower clearance phase among the three groups.

Electron Microscopy

Figure 5 demonstrates an electron micrograph from a normal control rat heart (12,600×). The cytoarchitecture in the control hearts was uniformly found to be normal with occasional artifacts most probably related to processing.

Figure 6 shows a representative electron micrograph from a 30-min no flow-reflow rat heart (25,900×). These hearts had a predominantly normal appearance with some evidence of minor abnormalities, including blebs and vacuolization. Sarcolemmal and mitochondrial membranes were intact. Some variation in mitochondrial size was observed. There were no differences between endocardial and epicardial samples. These findings suggested predominantly ischemically injured but viable cells.

Figure 7 depicts a representative electron micrograph

TABLE 2
Biexponential Myocardial Clearance Parameters

	First Component		Second Component		
	Constant (cpm × 1000)	$t_{1/2}$ (min)	Constant (cpm × 1000)	$t_{1/2}$ (min)	r^2
Group 1: Control (n = 6)	85.7 ± 8.9	1.95 ± 0.08	85.1 ± 20.0	203.79 ± 21.22	0.996
Group 2: No flow (30 min) (n = 6)	87.2 ± 13.4	1.78 ± 0.15	83.7 ± 13.4	217.01 ± 19.03	0.997
Group 3: No flow (60 min) (n = 6)	102.2 ± 14.8	1.58 ± 0.12*	64.2 ± 2.5	159.58 ± 22.89	0.997

*p < 0.05 from control group.
$t_{1/2}$ = time to reach half of initial activity. All values are mean ± s.e.m.

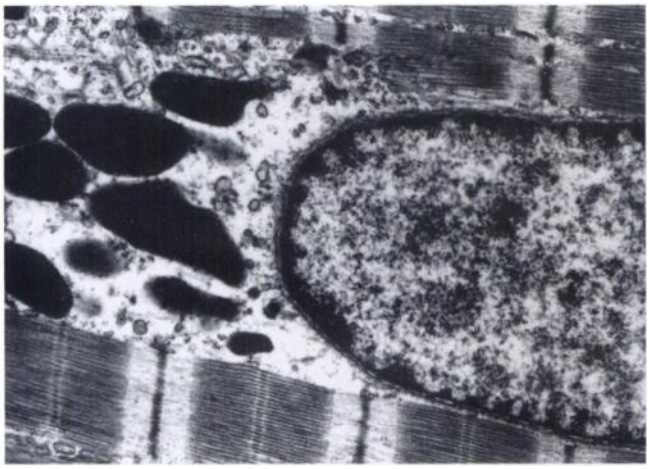

FIGURE 6. Electron micrograph taken from 30-min no flow followed by reflow heart (25,900×). There is a predominately normal appearance with some evidence of vacuolization. Sarcolemnal and mitochondrial membranes are intact. There is variation in mitochondrial size.

from a 60-min no flow-reflow rat heart (25,900×). More severe injury was noted in this group of hearts, including disruption of myofibrillar bands and presence of fibers in contracture. Focal mitochondrial injury was also present as demonstrated by breaks in mitochondrial membranes and disruption of cristae. There were no significant differences between endocardial and epicardial samples. These findings indicated predominantly injured nonviable cells.

DISCUSSION

Technetium-99m-Q12 is a cationic and lipophilic myocardial perfusion imaging agent that belongs to the phosphine class of agents and is available in a kit form (*1,9*). Gerson et al. found that canine myocardial uptake related to flows between 0 and 2 ml/g/min in dogs (r = 0.88). The uptake rolled off at flows greater than 2 ml/g/min and overestimated flows in the low range (*2*). These investigators also found a biexponential blood clearance curve. Rossetti et al. (*3,4*) reported good myocardial uptake in human volunteers (2.0% at rest and 2.6% with exercise). They also reported excellent image quality. There was rapid hepatobiliary clearance with only 30% renal excretion, thus allowing early imaging. Rossetti et al. (*5*) also studied 47 patients with coronary artery disease who underwent exercise ^{99m}Tc-Q12 imaging and found an accuracy of 98%; Gerson et al. (*6*) studied 20 patients with coronary artery disease and 12 normal subjects who had exercise ^{99m}Tc-Q12 imaging 15 min postinjection and found sensitivity and specificity of 85% and 80%, respectively.

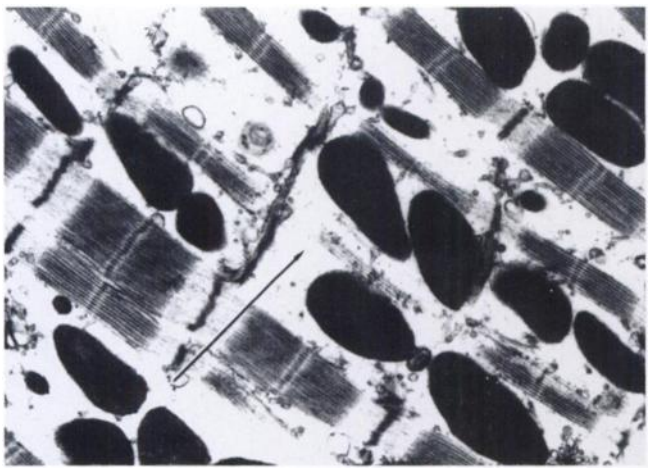

FIGURE 7. Electron micrograph taken from 60-min no flow-reflow hearts. Myofibrillar injury (arrow) is notable in this photomicrograph (25,900×).

Hemodynamics

The current study demonstrated no significant changes in coronary perfusion pressure, systolic, diastolic pressure and heart rate during the study period for the control and 30 min groups. These data indicate that the 30-min no flow-reflow hearts were hemodynamically stable despite the insult of 30 min without flow. This also supports the electron micrographic findings of predominantly ischemically insulted but viable myocardium.

The 60-min no flow-reflow hearts demonstrated elevated diastolic pressures, which is consistent with hemodynamically significant myocardial injury. Systolic pressure rose in this group of hearts following reperfusion, most probably as a result of the presence of excessive intracellular free ionic calcium (*9*).

Normal Technetium-99m-Q12 Myocardial Clearance

The current study demonstrates a biphasic myocardial ^{99m}Tc-Q12 clearance curve for the control hearts. The early phase demonstrated rapid clearance, and the second phase demonstrated slower clearance. This biphasic clearance curve pattern is similar to that previously reported by our laboratory (*8*).

The rapid, early myocardial ^{99m}Tc-Q12 clearance observed in this study was not observed by Gerson et al. in their canine study (*2*). These investigators reported minimal clearance from 30 to 240 min using serial endocardial biopsies. Furthermore, they reported constant ischemic-to-normal zone scan counts from 5 to 240 min after tracer administration. These latter results are not inconsistent with the current results because our clearance curves also demonstrated flat clearance by 30 min. Furthermore, constant ischemic-to-normal zone ratios are not inconsistent with rapid but equivalent clearance from both zones.

The rapid, early myocardial ^{99m}Tc-Q12 clearance observed in the current study has not been reported in human studies (*3–7*), but only one study has been fully published (*6*), the rest are abstracts and the details of the imaging protocols used are unknown. If imaging in these studies began 5–10 min after tracer administration, it is possible the the early clearance phase observed in the current study may have been missed. Gerson et al. (*6*) started imaging 15 min postinjection.

Meerdink et al. (*11*) estimated the myocardial transcapillary exchange of ^{99m}Tc-Q12 using bolus indicator-dilution

studies in isolated perfused rabbit hearts. They found a linear relationship between the capillary permeability-surface area product versus blood flow, suggesting that tracer uptake should mirror blood flow. Maximum fractional extraction for ^{99m}Tc-Q12, however, was less than that for thallium. Furthermore, net tissue extraction was relatively low, suggesting diminished retention. Thus, these blood perfused data are consistent with the buffer-perfused retention data observed in the current study. Furthermore, in a preliminary report, McGoron et al. (*12*) also found rapid, early myocardial clearance phase in perfused rat hearts, with a 24% 15-min retention (maximal extraction minus 15 min net extraction).

No Flow-Reflow Myocardial Technetium-99m-Q12 Clearance

In the current study, the 30-min no flow-reflow hearts demonstrated a biphasic ^{99m}Tc-Q12 myocardial clearance curve indistinguishable from the control curve. Electron micrographs from this group depicted only minor abnormalities, including blebs and vacuolization with minor variation in mitochondrial size. These findings indicate that ischemically insulted but predominantly viable cells demonstrate normal myocardial clearance kinetics.

In contrast, the 60-min group demonstrated accelerated early phase ^{99m}Tc-Q12 myocardial clearance when compared to control and 30-min groups. There was no change in the second and longer, slow clearance phase. Electron micrographs from this group demonstrated evidence for severely damaged, predominantly nonviable myocardium, including myofibrillar and focal mitochondrial injury. These data suggest at least a two-compartment model of myocardial ^{99m}Tc-Q12 uptake. One compartment contains loosely bound ^{99m}Tc-Q12 and is unaffected by severe but potentially reversible ischemic injury. This compartment, however, is affected by more severe irreversible injury. The second compartment contains tightly bound ^{99m}Tc-Q12, which normally clears slowly from the heart, and is unaffected by even severe irreversible damage caused by 60 min of no flow followed by reflow.

Comparison to Other Technetium-Labeled Agents

The current study reports biphasic myocardial ^{99m}Tc-Q12 clearance in normal and ischemic myocardium. The early clearance phase is accelerated in irreversibly insulted myocardium. Teboroxime also demonstrates biexponential myocardial clearance in normal and reperfused myocardium (*13,14*). Like ^{99m}Tc-Q12, teboroxime clearance was not altered by 30 min of no flow followed by reflow in a perfused rat heart model (*13*). Furthermore, teboroxime clearance was accelerated by 2 hr of occlusion followed by reperfusion (*14*). The rapid clearance of teboroxime, however, makes imaging studies technically demanding in patients. Technetium-99m-sestamibi demonstrates monophasic clearance from normal and reperfused myocardium (*15*). Furthermore, unlike ^{99m}Tc-Q12 and ^{99m}Tc-teboroxime, ^{99m}Tc-sestamibi clearance is altered in a similar perfused rat model of 30 min of no flow followed by reflow when compared to normal controls (*15*). Thus, although ^{99m}Tc-Q12 and ^{99m}Tc-sestamibi are both cationic and lipophilic, their kinetics appear to differ in this no-flow/reflow model.

Study Limitations

The current study used a bolus injection of ^{99m}Tc-Q12. Thus, the exact magnitude of the rapid clearance phase is difficult to determine with certainty. Some of the initial decline in counts could have been due to intravascular ^{99m}Tc-Q12, thus artificially magnifying the early fall in counts. The biphasic myocardial clearance reported in the current study was not observed by Gerson et al. in dogs (*1*) and Rossetti et al. and Gerson et al. in humans (*2–5*). As previously discussed, these studies could potentially have missed the first rapid clearance phase by starting imaging or biopsy too late. It is also possible, however, that the differences in results are due to species differences between rats versus dogs and humans.

Clinical Implications

The current study indicates that early phase ^{99m}Tc-Q12 myocardial clearance kinetics may be a marker of myocardial viability. It may be possible to assess viability after only 5–10 min of clearance. This could prove useful in assessing viability in patients presenting with acute myocardial infarction treated with reperfusion therapy to distinguish stunned from nonviable myocardium. This could also prove useful in assessing patients with ischemic cardiomyopathies to distinguish hibernating myocardium from scar.

The current study used an isolated perfused rat heart model. This model has the advantages of: (a) strictly controlling heart rate, blood flow, temperature and metabolic substrate, (b) eliminating recirculation of isotope and (c) eliminating background due to the lung and liver. Direct extrapolation from the rat data to clinical situations should be done with caution. Validation of the current rat results in larger intact animal models is first indicated.

CONCLUSION

Technetium-99m-Q12 myocardial clearance is biphasic in normal buffer-perfused rat myocardium. Clearance consists of an early rapid phase and a late slow phase. Ischemically insulted but viable myocardium demonstrates normal clearance kinetics. Injured nonviable myocardium, however, demonstrates an accelerated early rapid clearance phase but no difference in the late slow phase. Thus, ^{99m}Tc-Q12 warrants further study to determine the potential utility of this compound in assessing myocardial viability. Furthermore, the results of the current study need confirmation in whole animal models and patients studied with early imaging protocols.

ACKNOWLEDGMENTS

The authors thank Drs. Karen Deutsch and Mary Marmion and Mallinckrodt Medical for supplying the Q12 kits. The authors also thank Andrea Lightfoot for her secretarial assistance and Dianne Knox and Dianna Yates for their expertise in preparing tissues for

electron microscopy. This study is dedicated to the William K. Warren Family for their continuing support of medical research.

REFERENCES

1. Deutsch E, Kwiathowski M, Nosco D, et al. Synthesis and biodistribution of a new class of ^{99m}Tc myocardial perfusion agents with optimized imaging properties [Abstract]. *Eur J Nucl Med* 1991;18:537.
2. Gerson MC, Millard RW, Roszell NJ, et al. Kinetic properties of ^{99m}Tc-Q12 in canine myocardium. *Circulation* 1994;89:1291–1300.
3. Rossetti C, Vanoli G, Paganelli G, et al. Biodistribution and preliminary clinical evaluation of a kit formulation for the new myocardial imaging agent ^{99m}Tc-Q12 [Abstract]. *Eur J Nucl Med* 1992;19:596.
4. Rossetti C, Paganelli G, Vanoli G, et al. Biodistribution in humans and preliminary clinical evaluation of a new tracer with optimized properties for myocardial perfusion imaging: ^{99m}Tc-Q12. *J Nucl Biol Med* 1992;36(suppl): 29–31.
5. Rossetti C, Vanoli G, Paganelli G, et al. Human biodistribution, dosimetry and clinical use of technetium (III)-99m-Q12. *J Nucl Med* 1994;35:1571–1581.
6. Gerson MC, Lukes J, Deutsch E, et al. Comparison of Tc-99m Q12 and Tl-201 for detection of angiographically documented coronary artery disease. *J Nucl Cardiol* 1994;1:499–508.
7. Hendel RC, Gerson, MC, Verani MS, et al. Perfusion imaging with Tc-99m furifosmin (Q12): multicenter phase III trial to evaluate safety and comparative efficacy [Abstract]. *Circulation* 1994;90:I-449.
8. Johnson G III, Nguyen KN, Okada RD. Myocardial Tc-99m Q12 (TechneCardTM) clearance is not affected by hypoxia or low flow in an isolated perfused rat heart model [Abstract]. *Circulation* 1993;88:I-249.
9. Bugaj JE, DeRosch MA, Marmion ME, Quint RH, Deutsch KF, Deutsch E. Novel chemistry used in the cyclodextrin-stabilized technescan(R) Q12 kit [Abstract]. *J Nucl Med* 1994;35:139.
10. Schouten VJA, Los GJ, Kuypers PDL, Brinkmann CJJ, Huysmans HA. Paradox of enhanced contractility in post-ischemia rat hearts with depressed function. *Am J Physiol* 1991;260:H89–H99.
11. Meerdink DJ, Dahlberg ST, Gilmore M, Leppo JA. Transcapillary exchange of Q12 and thallium-201 in isolated rabbit hearts [Abstract]. *Circulation* 1993;88:249.
12. McGoran A, Millard RW, Biniakiewicz D, Washburn LC, Gerson M. Ouabain-resistant myocardial ^{99m}Tc-Q12 extraction and sustained retention [Abstract]. *Circulation* 1994;90:I-368.
13. Glover DK, Okada RD, Hebert CB. Technetium-99m-teboroxime (SQ30217, CardioTec) kinetics in normal and ischemic canine myocardium [Abstract]. *Circulation* 1990;82:III–486.
14. Johnson G III, Okada RD, Hebert CB. Myocardial clearance kinetics of technetium-99m teboroxime in normal and reperfused myocardium [Abstract]. *Circulation* 1991;84:II-302.
15. Okada RD, Glover DK, Hebert CB. Is there life after death? Technetium-99m-MIBI uptake and clearance kinetics in "stunned" myocardium [Abstract]. *J Am Coll Cardiol* 1990;15:7A.