Myocardial Extraction of Technetium-99m-[2-(1-Methoxybutyl) Isonitrile] in the Isolated Rabbit Heart: A Myocardial Perfusion Agent with High Extraction and Stable Retention

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Technetium-99m-[2-(1-methoxybutyl) isonitrile] (MBI) is a potential new compound for the scintigraphic imaging of coronary flow. Evaluation in the blood-perfused isolated rabbit heart model showed this compound to have a myocardial uptake comparable to ^{201}Tl and higher than sestamibi. Although the mean ± s.d. maximum extraction (E_{max}) and capillary permeability-surface area product (PS_{cap}) of ^{99m}Tc-MBI (E_{max} = 0.45 ± 0.10, PS_{cap} = 1.07 ± 0.47 ml/min · g) were much less than ^{201}Tl (E_{max} = 0.71 ± 0.07, PS_{cap} = 2.21 ± 0.76 ml/min · g, $p < 0.0001$), the net extraction of ^{99m}Tc-MBI (E_{net} = 0.52 ± 0.10) was only slightly less than the value for ^{201}Tl (E_{net} = 0.56 ± 0.10, $p < 0.05$). There was no significant difference in the myocardial uptake versus flow between ^{99m}Tc-MBI and ^{201}Tl. These data indicate that assessment of relative coronary flow based on the myocardial uptake of ^{99m}Tc-MBI should give results comparable to ^{201}Tl. Therefore, ^{99m}Tc-MBI may have clinical potential as a radiolabeled myocardial perfusion agent.

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The ideal scintigraphic myocardial perfusion agent should have two basic properties: the compound's myocardial uptake versus coronary flow should be linear with a slope of 1, and the compound should be labeled with a radionuclide that has favorable physical imaging properties (*1*). Thallium-201 is the most widely used isotope for myocardial perfusion imaging. Although it has a high myocardial uptake and relatively stable myocardial retention, its low photon energy and long half-life are disadvantages for Anger camera imaging. Technetium-99m-labeled perfusion agents offer favorable imaging characteristics, but the physiologic properties of current ^{99m}Tc-labeled myocardial perfusion agents are not ideal. Sestamibi has a stable myocardial retention, but its uptake is lower than that of ^{201}Tl, particularly at higher levels of coronary flow (*1,2*). Teboroxime has a very high myocardial uptake, but its rapid myocardial clearance presents a challenge for the development of practical imaging protocols (*3,4*). A ^{99m}Tc-labeled perfusion agent with both a high myocardial uptake and a stable retention would be quite desirable.

In this report we present data on the myocardial extraction of ^{99m}Tc-[2-(1-methoxybutyl) isonitrile] (MBI) in the isolated rabbit heart. This compound has a myocardial uptake comparable to ^{201}Tl and a retention comparable to sestamibi.

METHODS

Surgery and Perfusion

Isolated, isovolumically-contracting rabbit hearts were perfused using established methods (*2*). Male New Zealand white rabbits (1.5–2.5 kg) were heparinized (600 IU/kg i.v.) and anesthetized (sodium pentobarbital, 40 mg/kg i.v.) briefly. Hearts were quickly removed, mounted on a perfusion apparatus and retrogradely perfused via the aorta with bovine red blood cell- (RBC) enriched Krebs-Henseleit buffer using a constant flow pump. A pacing catheter and temperature probe were placed in the right ventricle through the right atrium, and a vinyl catheter was placed in the right ventricle through the pulmonary artery to determine coronary flow and collect coronary sinus drainage for indicator dilution experiments. A plastic tube in the left ventricular apex was used to collect Thebesian vein flow and aortic valve leakage. Left ventricular pressure and its first derivative were constantly monitored with a saline-filled latex balloon inserted into the left ventricle via the left atrium. The heart was placed in a water-jacketed chamber filled with saline, maintained at 37 ± 1°C, and paced to at least 180 bpm.

The RBC and buffer perfusate was oxygenated with 4% CO_2/96% air as it passed through a membrane oxygenator. Oxygen was supplemented as needed, and appropriate adjustments were made to maintain blood Ph, P_{O2} and P_{CO2} in the physiologic range. Lactate and glucose were provided as substrate for myocardial metabolism.

Indicator Cocktail

The injected indicator cocktail consisted of 6 μCi of ^{111}In-albumin (*5*), 20 μCi of ^{201}TlCl and 40 μCi of ^{99m}Tc-MBI diluted in

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perfusate. The ^{99m}Tc-MBI was prepared by adding 20–40 mCi [^{99m}Tc] pertechnetate to kits supplied by Du Pont-Merck, North Billerica, MA. Labeling efficiency was assessed using Whatman KC18 20-cm thin layer chromatography plates developed in a 4:3:2:1 mixture of acetonitrile, methanol, 0.5 *M* ammonium acetate and tetrahydrofuran, respectively. The ^{99m}Tc-MBI represented greater than 90% of the total measured activity. The R and S optical isomers of MBI (7 and 11 injections, respectively), as well as the racemic mixture (4 injections), were studied separately. Analysis of variance of the regression lines [BMDP 1R, (*6*)] showed no difference in the myocardial uptake versus flow of the isonitrile enantiomers. Therefore, all injections of ^{99m}Tc-MBI were grouped together for comparison with ^{201}Tl. A total of 11 hearts received 22 tracer injections at variable levels of coronary flow.

Isotope Injection and Collection

The isotope cocktail was thoroughly mixed and a 0.3-ml bolus quickly loaded into an injection loop that ran parallel to and joined with the aortic inflow with three-way valves. The cocktail was injected by turning the three-way valves so that the bolus was distributed as homogeneously as possible to both coronary arteries. Collection of the coronary venous effluent into preweighed plastic tubes (1–3 sec each, 3–4 min total) was timed so that each tube contained ~0.2 ml. After weighing each tube, the activities in the samples and in a 0.1-ml aliquot of injectate were determined in a gamma well counter. Appropriate corrections for energy crossover, background and decay were made for each isotope and activities were expressed as counts/min · ml.

Experimental Protocol

After temperature, coronary flow and pressure and ventricular pressure were stabilized (~15 min after beginning the perfusion), the first isotope-dilution study was conducted. Following this initial injection, coronary flow was either increased or decreased by ~50%–70%. After stabilization at each new flow (5–10 min), another bolus injection of isotopes was made and samples collected as described above.

Myocardial extraction and retention of ^{99m}Tc-MBI and ^{201}Tl were compared using the multiple indicator-dilution technique (*7–9*). With this method, diffusible compounds (^{201}Tl and ^{99m}Tc-MBI) are coinjected into the aorta with a reference tracer (^{111}In-albumin) that remains in the vascular space. Samples of venous flow are then collected from the coronary sinus, and the measured isotope activities are used to plot indicator-dilution venous outflow curves for each isotope (Fig. 1A and B). For every injection, normalized outflow dilution curves, h(t), were calculated for each of the coinjected tracers: ^{111}In-albumin (reference), $h_R(t)$; ^{201}Tl and ^{99m}Tc-MBI (diffusible), $h_D(t)$ using the equation:

$$h(t) = F \cdot C(t)/q_0,$$

where F is coronary flow (ml/min), t is time (sec) after injection, C(t) is isotope activity (cpm/ml) and q_0 is injected dose (cpm); the units of h(t) are sec^{-1} (*10,11*). Therefore, h(t) is the fraction of the injected tracer activity that is collected from the coronary sinus at time t.

Instantaneous extractions, E(t), of the diffusible tracers were then calculated as:

$$E(t) = 1 - h_D(t)/h_R(t),$$

where $h_D(t)$ is the venous outflow dilution curve of the diffusible tracer, ^{201}Tl or ^{99m}Tc-MBI, and $h_R(t)$ is the transport function of albumin, the intravascular reference. E_{max} was taken as the highest value of E(t) up to the peak of the albumin h(t) curve and is the best estimate of fractional tissue extraction for each diffusible tracer.

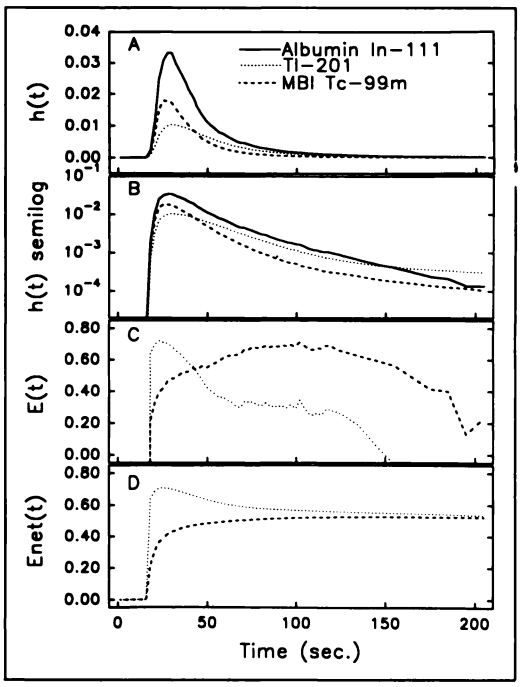

FIGURE 1. (A) Outflow dilution curves, h(t), for ^{111}In-albumin, ^{201}Tl and ^{99m}Tc-MBI. (B) Semilog plot of h(t) emphasizes tails of the curves. (C) E(t) for ^{201}Tl and ^{99m}Tc-MBI illustrates the higher maximum extraction for ^{201}Tl. (D) $E_{net}(t)$ for ^{201}Tl and ^{99m}Tc-MBI illustrates the similar final E_{net} for both compounds despite lower initial extraction of ^{99m}Tc-MBI.

The Crone-Renkin capillary permeability-surface area product was calculated as:

$$PS_{cap} = -F \cdot \ln(1 - E_{max}),$$

where PS_{cap} is the permeability-surface area product in ml/min · g, F is coronary flow in the same units and E_{max} is the maximum extraction as defined above (*12*).

Net tissue extraction, $E_{net}(t)$, of a diffusible compound reflects the integral balance of both extraction and clearance up to the time t. E_{net} was calculated as:

$$E_{net} = \int_0^t [h_R(\lambda) - h_D(\lambda)]\, d\lambda \div \int_0^t h_R(\lambda)\, d\lambda,$$

where λ is a dummy variable for integration. $E_{net}(t)$ was determined at the time t (sec) when 99.99% of the reference albumin had emerged in the collected coronary sinus flow.

Myocardial uptake of a tracer is a function of both the quantity of tracer delivered by coronary flow and the extraction fraction of that tracer. Myocardial uptake of the diffusible compounds was determined as:

$$\text{Uptake} = E_{net}(t) \cdot F,$$

where $E_{net}(t)$ is net extraction and F is coronary flow. Uptake, therefore, has the same units as flow, ml/min · g. It is also referred to as uptake by Marshall (*1*), as clearance by Renkin (*13*), as deposition by Caldwell (*14*) and as net extraction by Phelps (*15*).

TABLE 1

Hemodynamics	
Coronary flow (ml/min · g)	1.86 ± 0.83
Heart rate (bpm)	184 ± 11
Aortic pressure (mmHg)	115 ± 40
Left ventricular systolic pressure (mmHg)	95 ± 25
Left ventricular diastolic pressure (mmHg)	7.4 ± 3.9

We use E_{net} in our calculation of uptake because it corresponds most closely to extraction as it would be measured in an in vivo experiment. Also, most single-photon perfusion agents are not imaged before the 3–4 min postinjection when E_{net} is determined.

All data are expressed as mean ± s.d. Continuous data were compared using t-tests, and significant differences between regression lines were assessed using analysis of variance with BMDP 1R (*6*).

RESULTS

The mean weight of the 11 hearts was 4.71 ± 0.83 g. Coronary sinus flow was collected for 236 ± 111 sec after isotope injections. The hemodynamics from the 22 injections are summarized in Table 1. Figure 1 shows an example of venous outflow dilution curves, h(t), on linear (Fig. 1A) and semilog plots (Fig. 1B) from a single injection into a rabbit heart with a coronary flow of 1.60 ml/min · g. Calculated instantaneous and net extractions (E(t), Fig. 1C and E_{net}(t), Fig. 1D) for ^{201}Tl and ^{99m}Tc-MBI, are also shown. The lower peak heights of the ^{201}Tl and ^{99m}Tc-MBI h(t) curves relative to the peak height of the albumin curve (Fig. 1A) reflect the capillary permeabilities of the imaging tracers. The lower tail of the ^{99m}Tc-MBI curve relative to the albumin curve (Fig. 1B) reflects the avid myocardial retention and relatively slow backdiffusion of the isonitrile. In contrast, the higher tail of the ^{201}Tl curve, which crosses above the albumin curve, reflects myocardial washout (backdiffusion) of ^{201}Tl. E_{max}, the early peak of the E(t) curves (Fig. 1C), reflects the peak capillary flux of ^{201}Tl and ^{99m}Tc-MBI, while E_{net} (Fig. 1D) assesses both initial extraction and cellular retention. If one accepts that the same capillary surface area was available to both tracers, then capillary permeability for ^{201}Tl was significantly greater than ^{99m}Tc-MBI as reflected by the E_{max} and PS_{cap} data in Table 2. However, myocardial retention of ^{99m}Tc-MBI, as determined by E_{net} (Table 2) was only slightly lower than that of ^{201}Tl.

TABLE 2
Myocardial Extraction of ^{201}Tl and ^{99m}Tc-MBI at Variable Flow

	^{201}Tl	^{99m}Tc-MBI
E_{max}	0.71 ± 0.07	0.45 ± 0.10*
PS_{cap} (ml/min · g)	2.21 ± 0.76	1.07 ± 0.47*
E_{net}	0.56 ± 0.10	0.52 ± 0.10†

*$p < 0.0001$ vs. ^{201}Tl.
†$p < 0.05$ vs. ^{201}Tl.

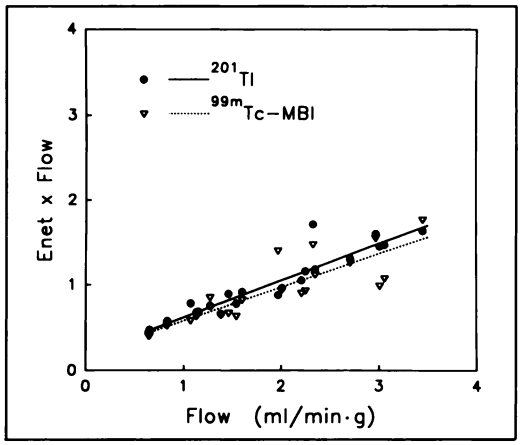

FIGURE 2. Myocardial uptake (E_{net} · Flow) of ^{99m}Tc-MBI (open triangles) and ^{201}Tl (closed circles) versus coronary flow. The regression lines for ^{201}Tl (solid line) and ^{99m}Tc-MBI (dashed line) are also shown. There is no significant difference between the regression lines of ^{201}Tl and ^{99m}Tc-MBI.

Myocardial uptake of each tracer versus coronary flow (E_{net} · flow versus flow) is shown in Figure 2. The data for ^{201}Tl and ^{99m}Tc-MBI were compared using linear regression. The regression for ^{201}Tl is: uptake = 0.43 · flow + 0.20, r = 0.94; while for ^{99m}Tc-MBI: uptake = 0.39 · flow + 0.19, r = 0.86. Comparison of these regression lines using analysis of variance showed no significant difference in the myocardial uptake versus flow between ^{201}Tl and ^{99m}Tc-MBI.

DISCUSSION

The ideal myocardial perfusion agent should show a myocardial uptake that is linearly related to coronary flow. If a quantitative assessment of flow is to be achieved, then a doubling of coronary flow should result in a doubling of uptake, and the slope of uptake versus flow should approximate the line of identity (slope = 1). Although desmethylimipramine is an example of a nearly ideal perfusion agent for experimental use (*16,17*), current radiolabeled single-photon agents for clinical use all show slopes of less than 1 due to impaired diffusion and reduced extraction of these compounds at higher levels of coronary flow (*1,18*).

Comparison to Other ^{99m}Tc-Labeled Agents

Technetium-99m-teboroxime does have a very high myocardial uptake immediately after intravenous injection. The E_{net} · flow versus flow slope of this compound is 0.52, which is higher than that of ^{201}Tl or ^{99m}Tc-sestamibi (*18*). This high extraction of ^{99m}Tc-teboroxime should allow more accurate assessment of variable levels of coronary flow (especially with hyperemia). However, the rapid differential myocardial washout of ^{99m}Tc-teboroxime results in a more rapid loss of activity from high flow versus low flow regions (*19*). Thus, within several minutes after injection, the initial pattern of myocardial ^{99m}Tc-teboroxime uptake is lost (*20,21*). Although this rapidly changing ac-

tivity can be imaged with some planar or SPECT protocols (*4,22*), a compound with stable retention allows longer imaging protocols that are better suited to many SPECT systems.

Technetium-99m-labeled isonitrile compounds have the advantage of a stable myocardial uptake after intravenous injection. After promising initial studies of t-butyl isonitrile, its clinical use was limited by high pulmonary and hepatic uptake (*23*). More recently, ^{99m}Tc-sestamibi has achieved wide clinical use, in part because its stable myocardial uptake (*24,25*) is well suited for imaging with current SPECT cameras. One disadvantage of the compound is that its myocardial extraction and its uptake versus flow are lower than those of ^{201}Tl (*1,2,18*). Therefore, despite the improved physical imaging properties of ^{99m}Tc, accurate assessment of regional coronary flow may be impaired.

Myocardial Transport of ^{99m}Tc-MBI

Technetium-99m-MBI is a new myocardial perfusion agent. Although its capillary permeability (as reflected in its PS_{cap} and E_{max}) is much less than that of ^{201}Tl, ^{99m}Tc-MBI is so avidly retained in the myocardium that its E_{net} is only slightly less than that of ^{201}Tl. An ideal myocardial perfusion agent should have both a high capillary permeability (PS_{cap} and E_{max}) and myocardial retention (E_{net}).

However, E_{net}, in this model, is the parameter that most closely reflects the fraction of the injected tracer remaining in the heart, as determined by gamma well counting (*1*). Since E_{net} reflects net tracer washin as well as washout, it is the more relevant parameter for calculation of total myocardial uptake, as opposed to E_{max}, which has no correction for back diffusion. Therefore, the E_{net} · flow estimate of relative uptake is most likely to reflect the characteristics of the myocardial transport of a radiopharmaceutical as it is imaged in vivo. E_{max}, measured at 20–40 sec, would also occur during clearance of blood-pool activity before imaging has begun. Myocardial uptake versus flow of ^{99m}Tc-MBI is similar to ^{201}Tl (Fig. 2) and higher than ^{99m}Tc-sestamibi (*18*). As with ^{99m}Tc-sestamibi, the stable myocardial retention of ^{99m}Tc-MBI results in only minimal myocardial washout.

Limitations

One limitation of the current study is the relatively short collection time after isotope injection (mean time = 3.9 min); studies focusing on myocardial clearance and differential washout (redistribution) might benefit from longer collections. However, previous studies of the early extraction and washout of other radiolabeled perfusion agents using the present model have correlated with their clinical properties and aided in developing clinical imaging protocols (*2,3,26*). The rapid planar imaging protocol for ^{99m}Tc-teboroxime described by Hendel (*27*) was based in part on evidence of rapid myocardial washout obtained from basic studies in the isolated rabbit heart model. Basic studies of ^{99m}Tc-sestamibi, showing stable myocardial retention, also correlated with the stable myocardial distribution and lack of redistribution observed in clinical studies.

Another limitation of this study is that even a compound with a high myocardial extraction and stable retention may find its clinical use limited by extracardiac factors such as high lung or liver uptake or delayed clearance from the blood (*23,28*). Such extracardiac factors must be evaluated with in vivo animal experiments or human clinical studies.

CONCLUSION

Technetium-99m-MBI has a myocardial uptake that is comparable to that of ^{201}Tl. The combination of high myocardial uptake, stable retention and the favorable imaging characteristics of ^{99m}Tc make ^{99m}Tc-MBI a promising compound for myocardial perfusion imaging that warrants further basic and clinical studies.

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