Comparison of Technetium-99m MIBI and Thallium-201 Chloride Myocardial Scintigraphy in Infants

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Myocardial perfusion scintigraphy was performed with both ^{201}Tl and a new six coordinate monocationic isonitrile complex of ^{99m}Tc, [^{99m}Tc]2-methoxyisobutylisonitrile (MIBI), on 11 infants who had undergone the arterial switch procedure for transposition of the great arteries. Unlike ^{201}Tl which can show rapid and variable rates of washout from myocardium, 73% of the initial first-pass activity of the isonitrile complex in the myocardium remains 1 hr after intravenous administration. The images obtained with [^{99m}Tc]MIBI required a shorter recording time, entailed less radiation exposure to the patient, and were qualitatively at least as good as those obtained with ^{201}Tl. No infant had perfusion abnormalities. The potential applications of the isonitrile complexes for myocardial perfusion scintigraphy in children are discussed.

J Nucl Med 30: 1176–1181, 1989

Although thallium-201 (^{201}Tl) has been regarded as the radiopharmaceutical of choice for myocardial perfusion scintigraphy, it is widely recognized that its physical and biologic characteristics make it less than an ideal substance for imaging with the gamma camera. The majority of its emissions, which consist of low-energy characteristic x-rays, undergo significant attenuation and scatter by tissues and are suboptimal for external detection. The relatively long physical half-life of ^{201}Tl and its decay scheme result in an absorbed radiation dose to the patient which restricts the acceptable administered dose. In addition, redistribution of the agent to areas of ischemia following intravascular administration during stress may be quite variable. Alternatively, technetium-99m (^{99m}Tc) has a relatively short half-life and emits almost exclusively gamma photons of an energy ideal for imaging by the gamma camera. In addition, the absorbed radiation dose to the patient is far less for ^{99m}Tc-containing radiopharmaceuticals than for ^{201}Tl. Thus, the potential advantages of a ^{99m}Tc myocardial perfusion agent have long been recognized. The difficulty in developing such an agent is that not only must such a substance localize in the myocardium in proportion to regional blood flow, but it must also exhibit relatively low lung and liver uptake and must redistribute from the myocardium relatively slowly. Since the report in 1981 that certain lipophilic six coordinate monocationic complexes of technetium(I) could localize in myocardial tissue (*1*), efforts have been expanded to find such a complex showing the necessary biologic behavior in humans required of a myocardial perfusion agent (*2–5*). To date, only two substituted isonitrile complexes, [^{99m}Tc]carbomethoxyisopropyl isonitrile (CPI) and [^{99m}Tc]methoxyisobutylisonitrile (MIBI) have reached clinical trials. One recent report studied the myocardial imaging properties of [^{99m}Tc]CPI in three normal adults and six patients with coronary artery disease (*6*).

Although myocardial perfusion studies are less often utilized in the pediatric population than the adult population, they may be extremely helpful in some clinical settings (*7–9*). Adequate myocardial imaging in pediatrics often requires sedation to eliminate movement artifact, and absorbed radiation doses often limit the administered dose that can be given. No prior report has demonstrated the use of [^{99m}Tc]MIBI in infants. In this study we compared [^{99m}Tc]MIBI and ^{201}Tl with

Received Nov. 30, 1987; revision accepted Apr. 6, 1989.

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respect to imaging characteristics, scanning times and dosimetry in a group of pediatric patients following surgical repair of transposition of the great arteries (TGA) by the arterial switch procedure.

METHODS

Patients

Following approval from the Committee on Clinical Investigation of the Children's Hospital and after obtaining the informed consent of the parents, 11 infants were studied with ^{201}Tl and [^{99m}Tc]MIBI. All patients had undergone the arterial switch procedure for correction of transposition of the great arteries. Patient ages at the time of study ranged from 13 days to 8 mo (mean 17 wk). There were five males and six females. Eight patients were imaged within 1 wk of surgery and the remaining three patients were studied 6 mo following surgery. In all cases the [^{99m}Tc]MIBI studies were obtained on the same day as the ^{201}Tl studies.

Radiopharmaceuticals

The [^{99m}Tc]MIBI was prepared according to the instructions supplied by the manufacturer (E.I. du Pont de Nemours and Co., No. Billerica, MA). The labeling efficiency averaged 98.3% (range 94.6–99.6). The specific activity of the resulting solutions averaged 53.9 mCi/ml (range 20.6–88.6).

Imaging Studies

All patients were imaged in the fasting state after administration of chloral hydrate (50–100 mg/kg).

Thallium imaging, which was performed prior to the administration of [^{99m}Tc]MIBI, was initiated 5 min after the i.v. administration of [^{201}Tl]thallous chloride (E.I. du Pont de Nemours and Co.). The administered dose was adjusted for body weight at 0.03 mCi/kg with a minimum dose of 0.15 mCi (range 0.15–0.36). Images were obtained for 150,000 counts in the anterior, left anterior oblique (LAO) (45° and 60°), and left lateral projections using a large field-of-view gamma camera equipped with a 3-mm aperture pinhole collimator. Images were obtained using both the characteristic 68–80 keV x-ray emissions of mercury-201 and the 135-keV photopeak associated with electron capture decay of ^{201}Tl and were recorded on a computer using a 128 × 128 matrix.

After the above images were obtained, [^{99m}Tc]MIBI was administered intravenously using a dose adjusted for body weight of 0.20 mCi/kg (range 0.77–2.5 mCi). Immediately after the administration of the radiopharmaceutical, the patient was positioned anteriorly under a large field-of-view Anger scintillation camera equipped with a high-resolution, parallel hole collimator and sequential images were obtained for 1 hr at a rate of 1 frame/30 sec and stored on a computer using a 64 × 64 matrix. Static images using the pinhole with time collimator were then obtained using the same gamma camera and conditions as employed for the ^{201}Tl images.

Disappearance of [^{99m}Tc]MIBI from lung, heart, and liver with time was monitored for the first hour after injection by taking an average activity per pixel obtained from the anterior images using the parallel hole collimator, from the three regions of interest (ROIs).

Cardiac target to lung background activity was compared for the ^{201}Tl and [^{99m}Tc]MIBI static images from average counts per pixel obtained from ROIs over the left ventricular free wall and the lung from the 45° LAO images. The LAO projection was used for this comparison since there is considerable overlap of activity from the large, hypertrophied right ventricle observed in infants with TGA. The region of interest over the left ventricle spanned the entire myocardial width; the pulmonary ROI was placed at a fixed distance from the myocardial edge. In addition, horizontal profiles 9 pixels wide were obtained from the 45° LAO ^{201}Tl and [^{99m}Tc]MIBI static images. For neither ROIs nor the horizontal slices was an attempt made to subtract residual ^{201}Tl activity from the [^{99m}Tc]MIBI images. All static scintigrams were further evaluated blindly for perfusion defects by two experienced observers.

Absorbed radiation doses for [^{99m}Tc]MIBI were calculated by the Dose Information Center of Oak Ridge Associated Universities using biodistribution data obtained from animal studies.

RESULTS

Myocardial uptake of [^{99m}Tc]MIBI was evident within the first few seconds following injection and persisted at approximately the same level for the 1 hr observation period. Similarly, little variation in lung activity was observed during this period (Fig 1A,B). The average heart-to-lung activity ratio as determined from anterior projections was 2.1 (range 1.8–2.4) 1 hr after administration. Excretion of the isonitrile complex was observed to occur through both hepatic and renal routes; 1 hr after administration hepatic activity was sufficiently low to permit imaging (Fig 1B,C). Frequently there was a high concentration of the agent in the gallbladder at that time, and care had to be taken to exclude it from the field-of-view when obtaining images with the pinhole collimator.

The myocardium to pulmonary activity ratios as determined from the static, pinhole images obtained 10–20 min after injection of the ^{201}Tl and ~75 min after injection of the [^{99m}Tc]MIBI averaged 3.6 (range 2.4–4.7) for the isonitrile complex and 2.7 (range 1.6–3.6) for ^{201}Tl (p, 0.001) (Table 1). The average time required to obtain 150,000 count static pinhole images was 12 min with ^{201}Tl and 8 min with [^{99m}Tc]MIBI. In all 11 patients the images obtained from the administration of [^{99m}Tc]MIBI were subjectively felt to be equivalent or superior to those obtained with ^{201}Tl (Fig. 2); evaluation of the horizontal slices in all cases suggested a sharper definition of the myocardium with [^{99m}Tc]MIBI than with ^{201}Tl (Fig. 3).

No myocardial perfusion abnormalities were identified with the isonitrile complex. Similarly, ^{201}Tl scanning demonstrated no perfusion abnormalities except for one patient in whom a single area of possibly decreased perfusion was detected at the apex.

Absorbed radiation doses for representative organs for both ^{201}Tl and [^{99m}Tc]MIBI are given in Table 2.

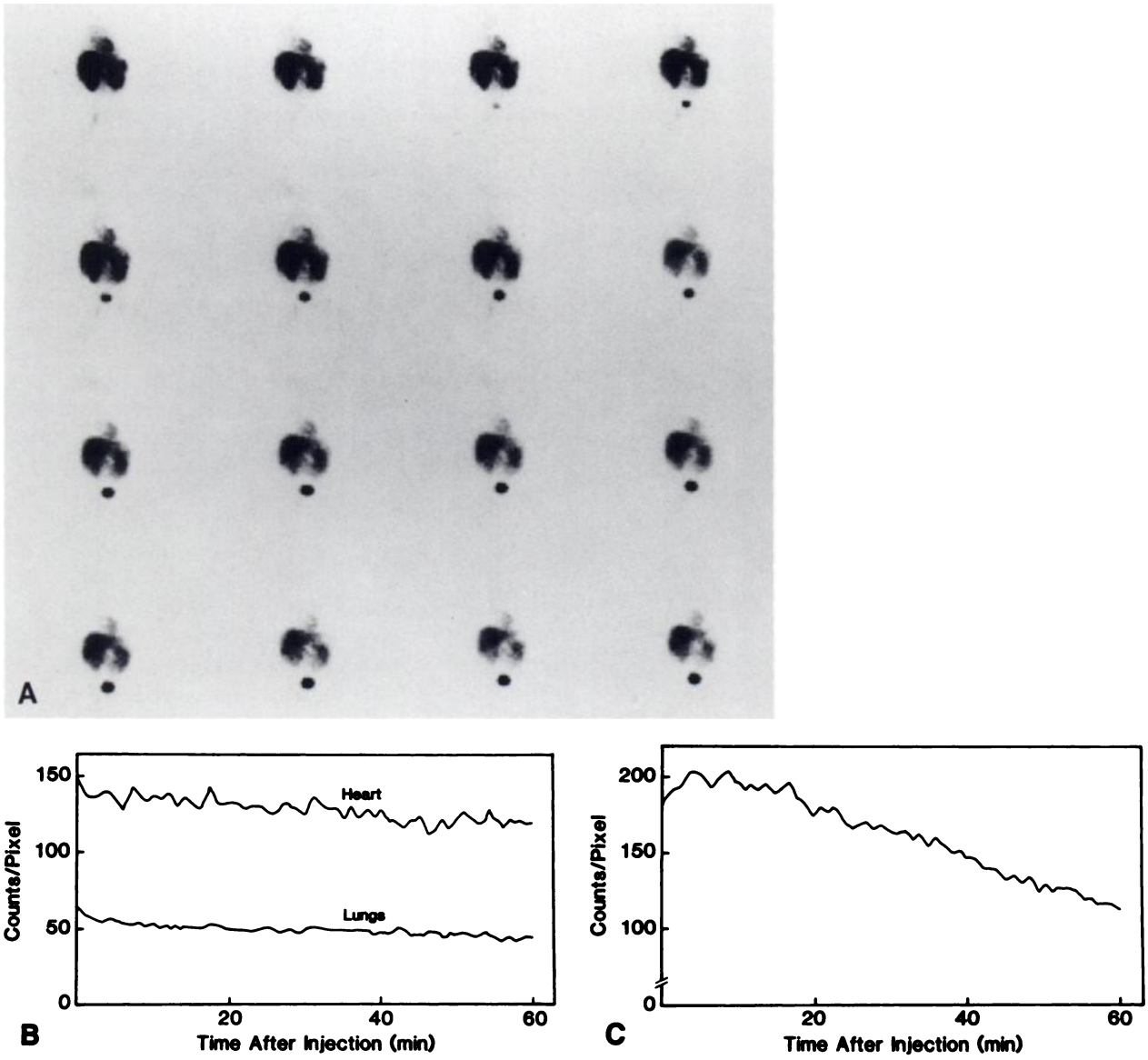

FIGURE 1
A: Anterior images (1 frame/min) obtained with a parallel hole collimator for the first 16 min after the injection of [^{99m}Tc]MIBI. B: Washout of activity, corrected for decay of ^{99m}Tc, contained in ROIs of heart and lungs for 1 hr after the administration of [^{99m}Tc]MIBI to an infant. C: Clearance of activity from ROI of liver from same infant as in B.

DISCUSSION

In pediatrics, myocardial perfusion scintigraphy with ^{201}Tl has proven useful in evaluating myocardial perfusion abnormalities associated with anomalous origin of the left coronary artery from the pulmonary artery (*7*), the mucocutaneous lymph node (Kawasaki's syndrome) (*8*), the cardiomyopathies, and a variety of congenital cardiac disorders including postoperative evaluation of patients undergoing the arterial switch procedure for transposition of the great arteries (*9*). The low administered pediatric dose (0.03 mCi/kg) of ^{201}Tl, required by the relatively high absorbed radiation dose, and the need for pinhole collimation when studying infants results in images taking up to 15 min to acquire and yields images of poorer quality than usually obtained in adults. The introduction of the [^{99m}Tc]isonitrile complexes offers the potential of obtaining images of similar or superior quality to those of ^{201}Tl with a shorter imaging time and with a significantly reduced absorbed radiation dose to the patient. This study was undertaken to determine if adequate images could be obtained in infants.

Comparison of the images obtained with both myocardial perfusion agents in this patient population indicates that at the administered dose levels, images of myocardium obtained after the administration of [^{99m}Tc]MIBI were at least equivalent to and often superior to those obtained with ^{201}Tl. Comparison of myocardial to lung activity ratios determined from 45°

TABLE 1
Myocardium to Pulmonary Background Ratios in the LAO Projection in 11 Patients

Patient	^{201}Tl	[^{99m}Tc]MIBI
1	3.0	3.1
2	2.2	3.0
3	2.8	4.3
4	2.2	4.4
5	2.9	3.7
6	2.3	3.0
7	3.4	4.2
8	3.6	3.6
9	3.6	4.7
10	2.2	3.5
11	1.6	2.4
Average	2.7	3.6

LAO images obtained with the pinhole collimator ~15 and 75 min after injection of ^{201}Tl and [^{99m}Tc]MIBI, respectively, showed consistently higher target to background ratios with the technetium agent. The LAO projection was chosen because of the great deal of overlap of the enlarged, hypertrophied right ventricle in newborns with TGA. Such improved target to background ratios were obtained with [^{99m}Tc]MIBI using a shorter imaging time than required with ^{201}Tl and entailed a significantly lower absorbed radiation dose to the patient. This can be readily seen from Table 2, recognizing that the administered dose of [^{99m}Tc]MIBI in this study was approximately seven times that of ^{201}Tl. The absorbed radiation dose calculations indicate that an even greater administered dose could be used and would further reduce the time required to obtain adequate images.

Comparing the myocardial perfusion studies performed with [^{99m}Tc]CPI as reported in adults by Holman and co-workers (*6*) and the results obtained with [^{99m}Tc]MIBI in infants, it can be seen that there are definite similarities in the biologic behavior of the two complexes in that both compounds rapidly accumulate in heart and lungs and show slow rates of clearance from these organs over the ensuing hour. The heart to lung activity ratio obtained from the LAO projection 10, 30, and 60 min after injection were reported as 1.7, 1.9, and 2.4, respectively, for [^{99m}Tc]CPI; ratios obtained at the same time intervals in this study from anterior projections were 1.9, 2.0, and 2.1, respectively. Holman and co-workers report 76.1% of the maximum cardiac activity of [^{99m}Tc]CPI remaining in the heart at 1 hr; the value obtained in this study, corrected for decay, is 73%.

Since there were no unequivocal myocardial perfusion defects seen on images obtained with either ^{201}Tl or [^{99m}Tc]MIBI, no comparison of the relative ability of the two agents to detect myocardial perfusion defects could be made from this study. Further, since these studies were performed at rest, no assessment of the

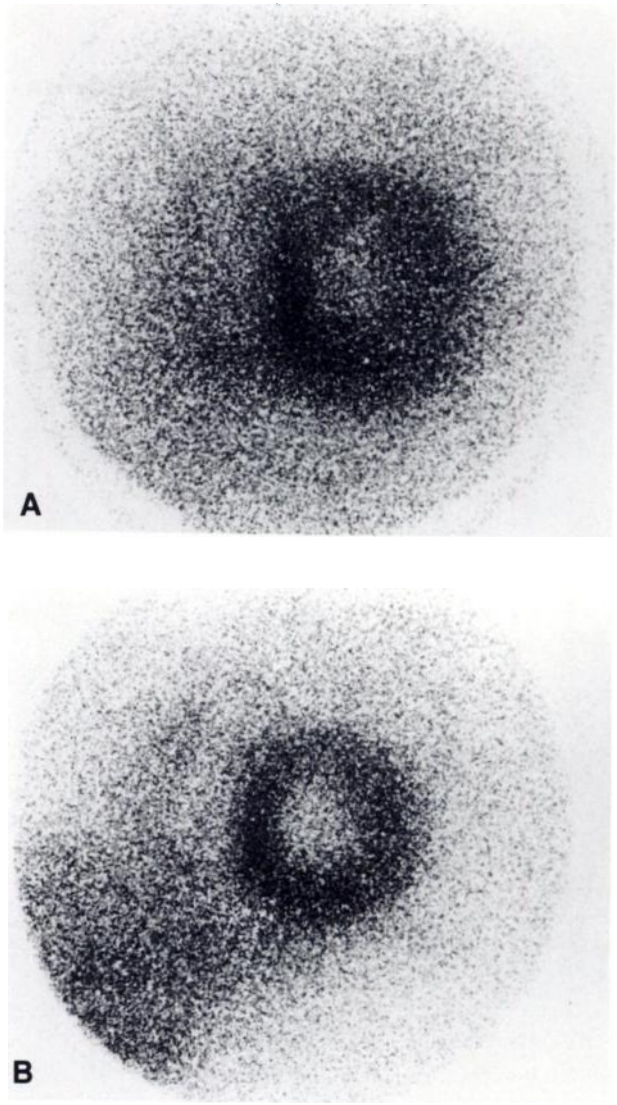

FIGURE 2
LAO (45°) views obtained with a pinhole collimator of the same patient shown in Figure 1, obtained with (A) ^{201}Tl and (B) [^{99m}Tc]MIBI demonstrating the relative quality of the images obtained with the two radiopharmaceuticals.

biodistribution of the radiopharmaceutical with time after stress could be made. Comparison of the two myocardial perfusion agents in the assessment of ischemic or infarcted myocardium in children other than with TGA will be difficult because compromised coronary arterial circulation is otherwise rare in the pediatric population. However, a recent comparative study (*12*) in adults with coronary artery disease showed MIBI to be as sensitive as thallium in detecting the presence and severity of perfusion defects and in the assessment of defect reversibility.

Finally, recent investigations with the isonitrile complexes have shown them to undergo a pattern of biologic distribution different from that of ^{201}Tl. Animal studies involving the simultaneous injection of [^{99m}Tc]MIBI,

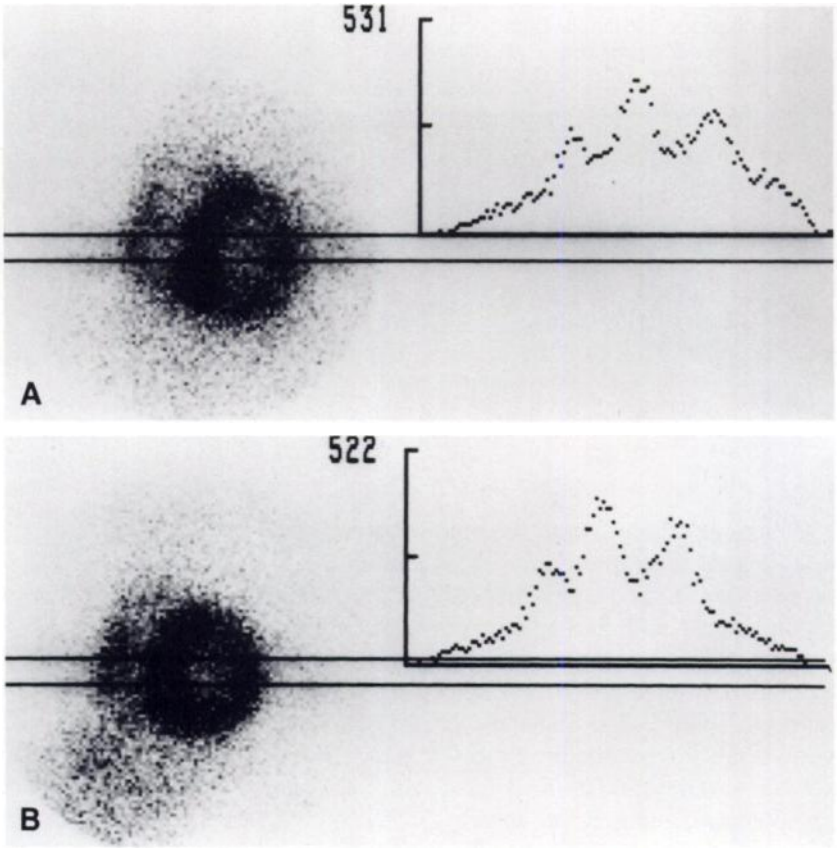

FIGURE 3
Computer generated profiles of horizontal slices 9 pixels thick obtained from 45°LAO images with (A) ^{201}Tl and (B) [^{99m}Tc]MIBI.

^{201}Tl, and radiolabeled microspheres indicate that the isonitrile complex, like the thallous ion, is taken up by the myocardium proportional to regional blood flow (*10*). Unlike the thallous ion, however, redistribution with time of the isonitrile complex does not occur. The mechanisms of this prolonged retention are still uncertain, however preliminary data from cultured chick embryo myocardium suggest that localization of the isonitrile complexes in the myocardium occurs by membrane adherance rather than through active cellular uptake as occurs with ^{201}Tl (*5,11*). The distribution of the isonitrile complexes in the myocardium therefore represents myocardial perfusion and not a combination of perfusion and metabolically influenced redistribution as is observed with the thallous ion. This unique property of the isonitrile complexes would permit the assessment of regional cardiac blood flow during exercise, drug trials, or rapid cardiac pacing during catheterization; while permitting imaging to occur after other hemodynamic and angiographic assessments have been made. The distribution of the tracer will reflect regional blood flow at the time of injection.

In conclusion, we believe that the isonitrile complexes of ^{99m}Tc, such as [^{99m}Tc]MIBI, have many poten-

TABLE 2
Radiation Absorbed Doses for [^{99m}Tc]MIBI and ^{201}TlCl (rad/mCi)

	Newborn		1-yr-old		5-yr-old		10-yr-old	
Organ	MIBI	TlCl	MIBI	TlCl	MIBI	TlCl	MIBI	TlCl
Heart	0.18	5.1	0.09	2.3	0.49	1.4	0.03	1.0
Testes	0.038	5.5	0.017	2.0	0.011	1.3	0.011	1.0
Ovaries	0.056	5.5	0.032	0.54	0.024	0.35	0.017	0.24
Whole body	0.058	0.86	0.018	0.28	0.011	0.16	0.007	0.12
Thyroid*	1.4	9.5	0.98	6.6	0.52	3.4	0.24	1.6
Kidney‡	0.89	10.2	0.36	4.4	0.20	2.5	0.14	1.8

* Critical organ for [^{99m}Tc]MIBI.
‡ Critical organ for ^{201}Tl.
Courtesy of Mr. Michael Sabin, Radiopharmaceutical Internal Dose Information Center, Oak Ridge Associated Universities, Oak Ridge, TN.

tial benefits as myocardial perfusion agents in children and hold the promise of replacing ^{201}Tl as the agent of choice for performing myocardial imaging in the pediatric population.

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