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Myocardial Imaging with Technetium-99m CPI: Initial Experience in the Human

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The hexakis(isonitrile)technetium(I) analog [^{99m}Tc]carbomethoxyisopropyl isonitrile (CPI) has high myocardial uptake and rapid lung and liver clearance in most animal species. To evaluate [^{99m}Tc]CPI as a myocardial imaging agent in the human, we evaluated this tracer in three normals and in six patients with coronary artery disease (CAD). In normals, [^{99m}Tc]CPI cleared quickly from the lungs and accumulated in the liver and heart. The liver activity peaked at 10-15 min and cleared through the hepatobiliary system. Planar images were of excellent technical quality with high myocardial to background ratios as early as 10 min after injection. Myocardial activity fell gradually to 76.1 ± 2.9 (s.d.)% of initial activity by 60 min after injection. In six patients with CAD, myocardial defects were present on planar images up to 2 hr after exercise and injection. In one out of six patients, the defect was not seen 3 hr after injection. In five of the six patients, normal perfusion patterns were observed 1 hr after reinjection of CPI at rest (4 hr after the initial injection). In one patient who developed spontaneous angina prior to reinjection, the perfusion defects persisted. The repeat study 5 days later with injection of [^{99m}Tc]CPI at rest was normal. Technetium-99m CPI appears to have excellent physical and biologic properties for use in association with myocardial imaging with exercise.

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Myocardial perfusion imaging with thallium-201 (^{201}Tl) has become a routine part of the clinical evaluation of patients with coronary artery disease (CAD) (*1*). While the initial distribution of ^{201}Tl reflects blood flow, it is not an ideal radiotracer. Rapid serial evaluation of perfusion is not possible because of its long physical half-life and slow myocardial clearance. Image quality is marginal because of its low-energy radiation. Furthermore, its myocardial distribution reflects flow for only a short time after stress because of redistribution (*2,3*).

Recently, a number of hexakis(isonitrile)technetium analogs have been labeled with technetium-99m (^{99m}Tc) (*4*). One of these, [^{99m}Tc]TBI, distributes in a pattern which reflects myocardial blood flow and accumulates with sufficient avidity in the human heart so that planar, tomographic, and gated images of high technical quality can be obtained (*5*). Unfortunately, its high lung and liver uptake and rapid redistribution preclude its use during stress. Based on preliminary data derived from animal studies, [^{99m}Tc]carbomethoxyisopropyl isonitrile ([^{99m}Tc]CPI) has more favorable biologic characteristics, with avid accumulation by the normal myocardium and rapid clearance from the lung and liver (*6*).

We report the first application of this new myocardial imaging agent, [^{99m}Tc]CPI, in normal subjects and in patients with coronary artery disease.

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MATERIALS AND METHODS

Preparation of [^{99m}Tc]CPI

Sterile, pyrogen-free kits were prepared by dissolving 3.125 g of $Zn(CPI)_2Br_2$ in 100 ml of sterile, nonpyrogenic saline. Using aseptic technique, 1-ml aliquots were dispensed through a 0.22-μm Millex GV sterile filter,* into 10-ml sterile vials that were pre-cooled with liquid nitrogen. The kits were stored frozen until required. The [^{99m}Tc]CPI was prepared by adding TcO_4^- solution (75–100 mCi in 0.2–0.8 ml) to a Glucosan kit† followed by 0.8 ml of $Zn(CPI)_2Br_2$ solution from a thawed kit. The mixture was incubated at room temperature for 15 min. The contents of the vial were withdrawn and discarded and the vial was rinsed twice with 10 ml of sterile water. Sterile ethanol 0.5 ml was added to the vial and swirled around all inside surfaces to dissolve the [^{99m}Tc]CPI absorbed on the walls. Finally, 1.5 ml of sterile saline was added to the vial. The 25% ethanol solution containing ~20% of the original activity was then tested for radiochemical purity by TLC using Whatman KC-18 reverse phase plates and methanol:acetonitrile:0.5*M* ammonium acetate, tetrahydrofuran (3:3:2:2) as the solvent. Under these conditions the Rf of [^{99m}Tc]CPI, TcO_4^-, technetium-glucoheptonate and $TcO_2 \cdot xH_2O$ is 0.65–0.75, 0.9–1.0, 0–0.15 and 0, respectively. The radiochemical purity was >95% in all preparations used in this study.

Imaging Studies

Three male volunteers (ages 45, 57, and 58 yr old) without clinical evidence of cardiopulmonary disease and with normal stress electrocardiography and six patients with typical angina pectoris, with strongly positive exercise stress tests and with either evidence of transient ischemia on standard planar ^{201}Tl or evidence of CAD by coronary angiography were studied during stress and at rest. All subjects were studied in the fasting state and underwent upright bicycle or treadmill ergometry either to 85% of predicted heart rate (normal subjects) or to the level of exercise reached with the initial exercise stress test. [^{99m}Tc]CPI (5 mCi) was injected intravenously and exercise was continued for an additional 30–60 sec.

In the normal subjects, imaging began at 10 min after injection in the 30° left anterior oblique (LAO) projection using a large field-of-view Anger scintillation camera positioned over the myocardium, lungs, and liver. Dynamic imaging in the normal was performed for 50 min collecting 1 frame/30 sec with a 128 × 128 matrix. At 1, 2, and 3 hr, 5-min planar myocardial images were performed in the anterior and 30°, 45°, and 70° LAO projections collecting ~400–500 thousand counts per image and ~100 thousand counts from the myocardium.

In the patients with coronary artery disease, 5-min planar myocardial images were performed in the anterior and 30°, 45°, and 70° LAO projections at 10–30 min, 1, 2, and 3 hr after exercise. An additional 5 mCi of [^{99m}Tc]CPI were injected 4 hr after the initial injection with the patient at rest and repeat myocardial images were obtained 60 min after injection. No attempt was made to subtract the activity from the first injection.

Clearance of the radiotracer was determined in the normal subjects from the lung, heart, and liver for the first hour after injection by taking an average activity per pixel from the three regions of interest (heart, lungs, and liver).

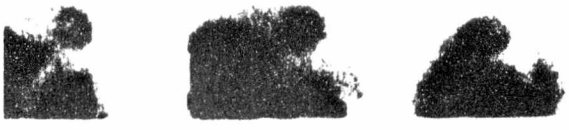

FIGURE 1
Normal myocardial images obtained 1 hr after injection of [^{99m}Tc]CPI during peak exercise in a normal volunteer. Intense hepatic activity is focused in the central portion of the liver and gallbladder with substantial clearance from the periphery.

The [^{99m}Tc]CPI scintigraphic images were interpreted independently by three trained observers. For the CAD patients the images were then compared with the exercise ECG (six patients) and the corresponding ^{201}Tl images (five patients) as to presence and location of transient ischemia.

RESULTS

Following i.v. injection in the normal subjects, the radiotracer cleared quickly from the lung and accumulated in the liver and heart (Fig. 1). The heart to lung activity ratio was 1.7 ± 0.3 s.d.:1, 1.9 ± 0.1:1; and 2.4 ± 0.2:1 at 10, 30, and 60 min after injection, respectively. The liver activity peaked at ~10 –15 min after injection and cleared slowly through the hepatobiliary system (Fig. 2). Gallbladder activity was present by 15 min and liver activity was reduced below its peak value by 1 hr; because of myocardial clearance, the

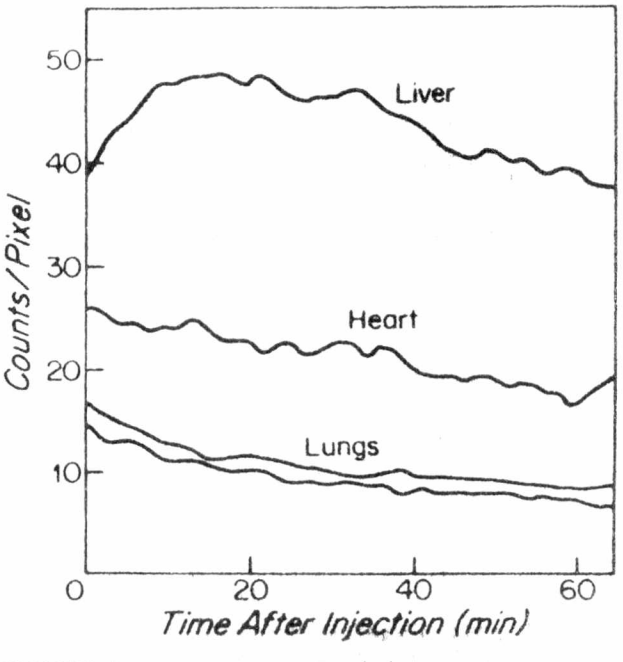

FIGURE 2
The clearance of [^{99m}Tc]CPI from one of the normal subjects following injection during exercise.

heart to liver activity ratio was unchanged at 60 min compared with the time of maximum liver activity, (heart to liver activity ratio: 0.6 ± 0.1:1 at 1 hr compared with 0.6 ± 0.2:1 at maximum liver activity). Liver activity fell further by 2 and 3 hr after injection. Myocardial activity was uniformly distributed throughout the left ventricle with less activity seen in the right ventricle. Myocardial activity fell slowly with 76.1 ± 2.9% of the initial activity remaining in the heart 60 min after injection.

None of the patients with CAD had resting ECG abnormalities or previous myocardial infarctions by history. In four patients, exercise was stopped because of chest pain; in two patients exercise was stopped because of fatigue. All of the patients developed ST segment depression of >2 mm during their exercise test.

Focal defects were present on [^{99m}Tc]CPI images obtained after exercise in all six patients (Fig. 3). In the five patients with reversible myocardial perfusion defects on ^{201}Tl imaging, the defects on the [^{99m}Tc]CPI images were in the same location. In the sixth patient, coronary angiography 1 mo prior to the [^{99m}Tc]CPI study showed that a dominant right coronary artery was 100% occluded with left to right collateralization. A 90% stenosis was present in the left anterior descending artery. Left ventriculography showed that the inferior wall and apex were contracting normally. An inferior wall perfusion defect was present on [^{99m}Tc]CPI after exercise (Fig. 4).

In five of the six patients, the perfusion defects persisted on planar images obtained up to 3 hr after exercise and injection. In one patient, the defect was indistinct by 3 hr, but was clearly defined on images obtained 1 and 2 hr after exercise. In five of six patients, the images obtained 1 hr after reinjection of 5.0 mCi of [^{99m}Tc]CPI (4–5 hr after the first injection) were normal with uniform distribution of the tracer throughout the left ventricular wall.

One of the patients (Patient 3, Table 1) sustained spontaneous anginal pain accompanied by 2 mm ST segment depression beginning 3.5 hr after the initial injection. He was reinjected with [^{99m}Tc]CPI during the chest pain (Fig. 5). A perfusion defect involving the inferior wall of the left ventricle similar, but more intense, than the one observed after exercise was present on images obtained 1 hr after reinjection. Myocardial uptake was normal on images obtained 1 hr after a third injection of [^{99m}Tc]CPI 3 days after the initial studies.

DISCUSSION

The current radiotracers of choice for single photon myocardial perfusion studies is ^{201}Tl. While this tracer has performed well, it is not ideal. For example, while myocardial redistribution of ^{201}Tl has been used to distinguish infarction from ischemia (7), rapid tracer

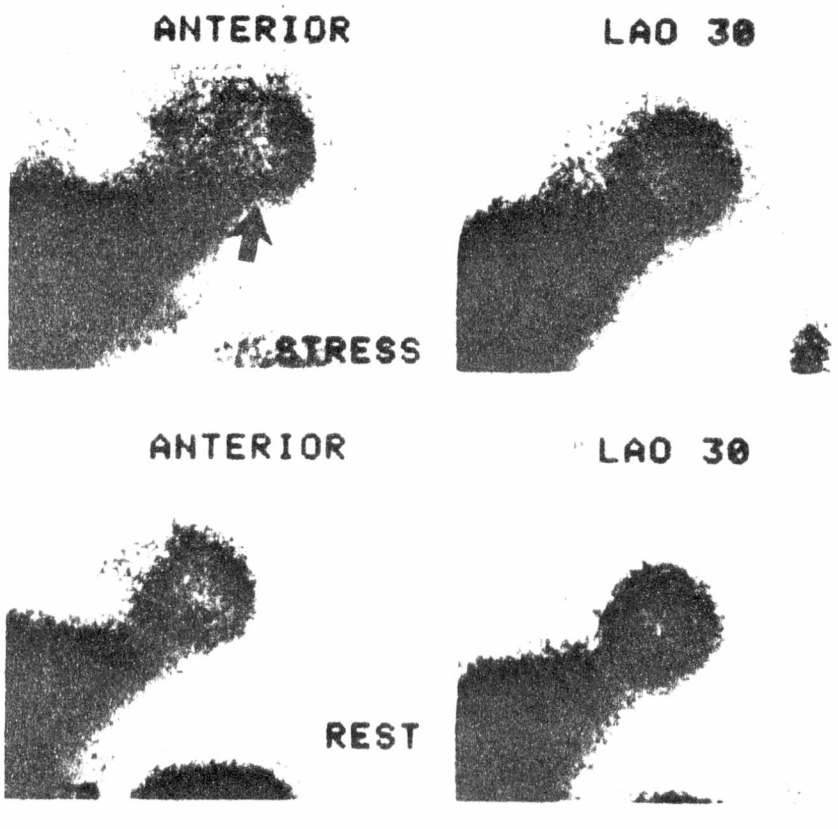

FIGURE 3
Extensive inferoapical defect (arrow) on myocardial images obtained one hour after injection of [^{99m}Tc]CPI during peak exercise in Patient 5. Images obtained 4 hr later and 1 hr after reinjection at rest are normal.

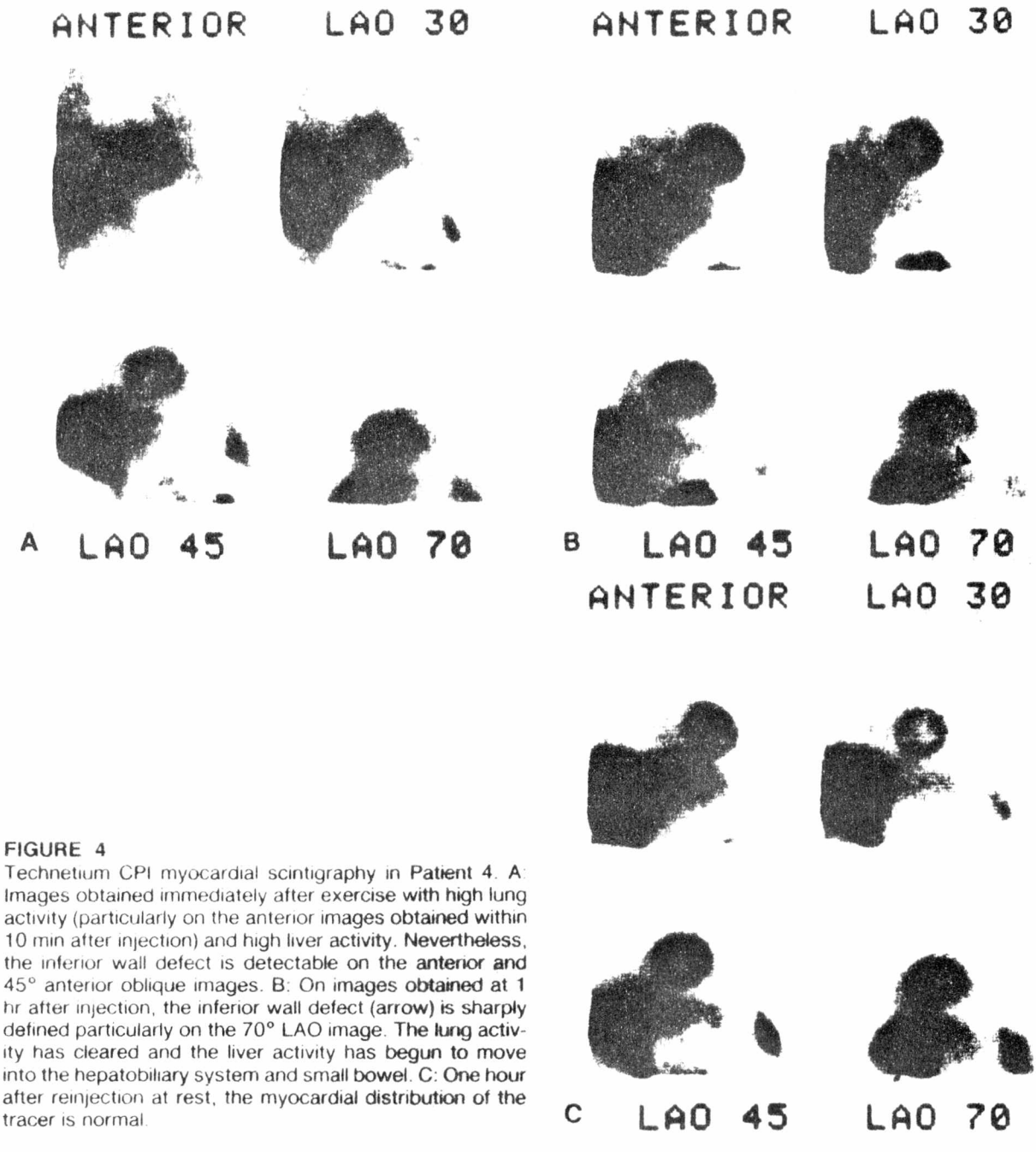

FIGURE 4
Technetium CPI myocardial scintigraphy in Patient 4. A: Images obtained immediately after exercise with high lung activity (particularly on the anterior images obtained within 10 min after injection) and high liver activity. Nevertheless, the inferior wall defect is detectable on the anterior and 45° anterior oblique images. B: On images obtained at 1 hr after injection, the inferior wall defect (arrow) is sharply defined particularly on the 70° LAO image. The lung activity has cleared and the liver activity has begun to move into the hepatobiliary system and small bowel. C: One hour after reinjection at rest, the myocardial distribution of the tracer is normal.

redistribution may occur following injection during stress, particularly if hyperemia occurs during reperfusion in areas of transient ischemia (*2*, *3*). The rate of redistribution may be rapid and is variable so that the myocardial distribution of ^{201}Tl may reflect blood flow for only a short time after injection. While standard imaging techniques have been particularly successful in identifying CAD (*7*), the redistribution phenomenon may result in underestimation of the total extent and severity of ischemia (*3*).

The physical characteristics of ^{201}Tl are also less than ideal. Its low-energy characteristic x-rays are not ideal for Anger camera imaging. Their attenuation by soft tissues is high, markedly reducing the efficiency with which activity in deep structures is measured. The long half-life of ^{201}Tl coupled with its long biologic half-life in the myocardium limits serial studies to frequencies of a day or more.

In our preliminary experience in the human, [^{99m}Tc] CPI, a member of the hexakis(isonitrile)technetium family, demonstrates high myocardial uptake with no evidence of myocardial redistribution into zones of transient ischemia for several hours after exercise. Only after reinjection during rest do the transiently ischemic areas appear normal. The myocardial activity clears from the heart, however, so that repeat imaging is

TABLE 1
Comparison of [^{99m}Tc]CPI Myocardial Scintigraphy with Exercise ECG and ^{201}Tl Tests

Patient no	ECG	^{201}Tl		[^{99m}Tc]CPI			
			Rest	15–30 min	1 hr	2 hr	3 hr	Rest
1	+[*]	- (inferior)	–	+ (Anterior)	+	+	+	–
2	+	- (apical)	–	+ (Inferoapical)	+	+	+	–
3	+	- (posterior)	–	+ (Inferoposterior)	+	+	+	–
4	+	- (Apical)	–	+ (Apical)	+	+	±	–
5	+	- (apical)	–	+ (Inferoapical)	+	+	+	–
6	+	[‡]		+ (Inferior)	+	+	+	–

[*] Time after exercise
[†] + indicates >2.0 mm ST depression.
[‡] Patient 6 underwent coronary angiography (see text).

possible by 3 or 4 hr after the stress injection. We postulate that the tracer is metabolized by the myocardium and that these metabolites are not reaccumulated by the heart following washout.

The rapid myocardial clearance of [^{99m}Tc]CPI permits reinjection of the tracer up to 4 hr after the first injection and completion of the stress and rest studies within the same day. We had intended to perform a second rest study 24 hr after the first, but found it unnecessary in all but one patient (who developed spontaneous angina) because left ventricular tracer uptake on the rest study obtained 4 hr after the initial

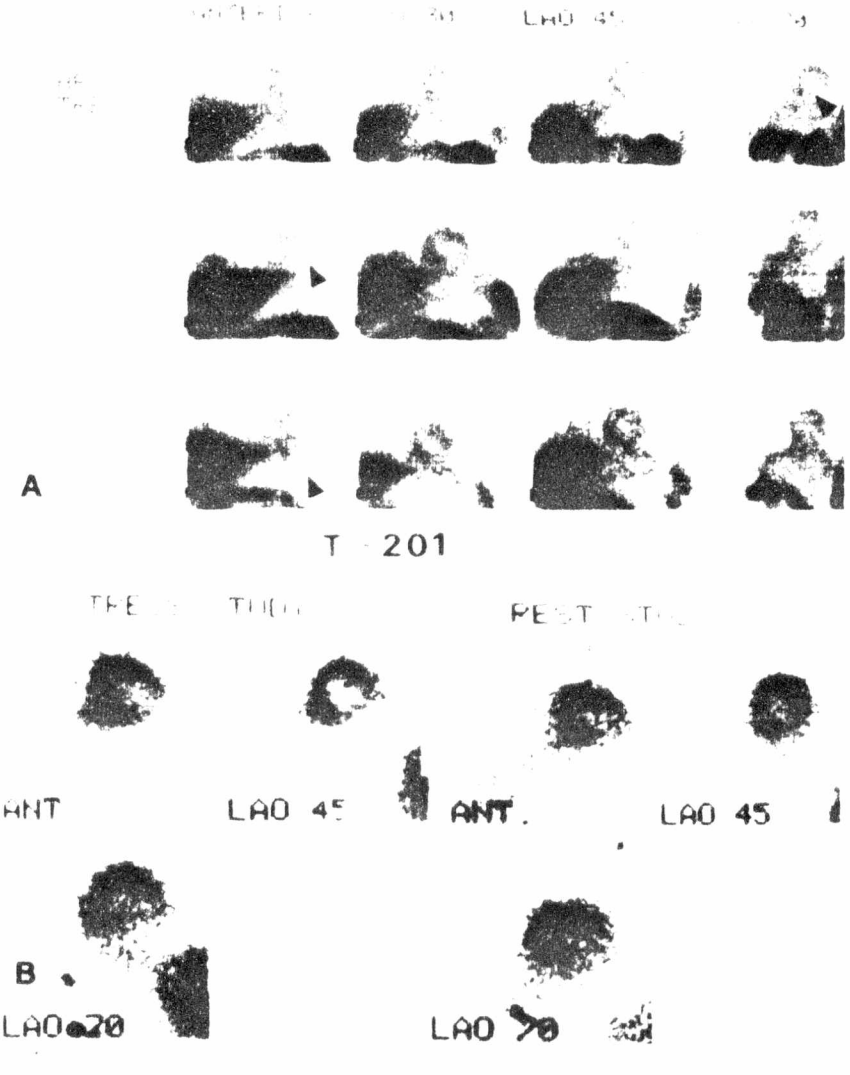

FIGURE 5
A: [^{99m}Tc]CPI images in Patient 3. Images obtained 1 hr after injection during exercise (upper panel) with inferoposterior perfusion defect (arrow). Images obtained 4 hr later and 1 hr after injection during spontaneous angina (middle panel) with more extensive defect extending to apex (arrow). Normal study 3 days later and 1 hr after injection of [^{99m}Tc]CPI at rest (lower panel). Note loop of small bowel (arrow). B: Thallium-201 images obtained in the same patient with reversible exercise induced inferoposterior perfusion defect.

injection and 1 hr after the second injection at rest was uniform and homogeneous. Thus, the background myocardial activity from the first injection, reduced by clearance and decay, did not affect subsequent interpretation of the rest injection. The rapid clearance of [^{99m}Tc]CPI from the myocardium will be useful in the serial assessment of patients undergoing procedures such as angioplasty or with unstable angina, myocardial infarction, or spontaneous angina.

Other advantages of [^{99m}Tc]CPI arise from the physical characteristics of ^{99m}Tc. Its gamma emissions are better suited to standard imaging equipment than ^{201}Tl, resulting in better image quality with less attenuation of photons from deeper tissues. The higher photon flux resulting from the 140-keV photons and the higher administered dose will result in improved single photon emission computed tomographic imaging and should result in high quality gated and first-pass studies to assess global and region ventricular performance. Because it is obtained from a generator system, [^{99m}Tc]CPI can be prepared on site, so that myocardial imaging can be applied to emergency situations such as acute myocardial infarction.

At the present time, the nature of [^{99m}Tc]CPI uptake within the myocardium is unknown. Animal studies have shown that its sister compound, [^{99m}Tc]TBI, distributes proportionately to myocardial blood flow but, because of the slow lung clearance, its redistributes into zones of transient hyperemia with time (*8*). Furthermore, its myocardial uptake is not inhibited by oubain, so that [^{99m}Tc]TBI probably is not a potassium analog. Based on our clinical data, [^{99m}Tc]CPI differs significantly from [^{99m}Tc]TBI in that [^{99m}Tc]CPI does not redistribute into zones of ischemia for at least several hours after injection and clears rapidly through the lung and liver. Nevertheless, application of this interesting isonitrile analog will require a very careful characterization of its mechanism of uptake and the relationship of that uptake to changes in myocardial blood flow and to the applications of various classes of pharmaceuticals.

NOTES

[*] Millipore Bedford, MA

[†] Du Pont Company No Billerica MA

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