# The Kinetics of Copper-62-PTSM in the Normal Human Heart

Rob S.B. Beanlands, Otto Muzik, Mark Mintun, Thomas Mangner, Kien Lee, Neil Petry, Gary D. Hutchins, and Markus Schwaiger

*Division of Nuclear Medicine, Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan*

Copper-62-labeled pyruvaldehyde bis(N-4-methylthiosemicarbazone) copper(II) (PTSM) is a generator-produced myocardial perfusion tracer. Animal studies have shown high myocardial tissue extraction and prolonged retention. The aim of this study was to define myocardial kinetics of $^{62}$Cu-PTSM and to determine its suitability for evaluating myocardial perfusion at rest and during pharmacological vasodilation in human subjects. In six healthy volunteers, $^{62}$Cu-PTSM was administered at baseline and during a 6-min adenosine infusion (140 μg/kg/min). Dynamic PET imaging with high temporal resolution was performed over 20 min. Good image quality was observed at rest and following adenosine. Myocardial kinetics demonstrated prolonged tissue retention with a clearance half-life of 105 ± 49 min at rest and 101 ± 65 min following adenosine (p = ns). Copper-62-PTSM tissue retention was quantified and showed only a 1.97-fold increase from rest to adenosine studies. This suggests attenuation of tracer retention at high flow rates. Copper-62-PTSM represents a promising new radiopharmaceutical for the evaluation of myocardial perfusion in the human heart.

**J Nucl Med 1992; 33:684–690**

The evaluation of myocardial blood flow and flow reserve in the assessment of coronary artery disease continues to be the most important aspect of myocardial imaging. Qualitative evaluation of blood flow using positron emission tomography (PET) has been shown to be highly accurate in coronary artery disease detection (*1–5*) and superior to standard $^{201}$Tl SPECT imaging (*4,5*). In addition, the accurate quantification of myocardial blood flow can be achieved using cyclotron-produced PET agents: $^{13}$N-ammonia (*6–8*) or $^{15}$O-water (*9,10*).

Onsite cyclotron facilities are still limited to a small number of centers. The use of the generator-produced agent $^{82}$Rb has fostered the development of cardiac PET centers independent of cyclotron support. Rubidium-82 has been shown to be of value in the detection of coronary artery disease using qualitative estimation of myocardial flow (*3–5*). Although a practical radiopharmaceutical, $^{82}$Rb has a very short half-life ($t_{1/2}$ = 76 sec). Data must be acquired rapidly over a short period of time. As a result, depending on the instrumentation used, image quality may be suboptimal (*11,12*). In addition, generation of $^{82}$Sr requires a high-energy cyclotron, which makes the generator expensive. In light of the limitations of $^{82}$Rb, other generator-produced PET flow tracers are being investigated.

The lipophilic perfusion tracer, $^{62}$Cu-labeled pyruvaldehyde bis(N-4-methylthiosemicarbazone)copper(II) (PTSM) may represent such a development. The $^{62}$Cu isotope has 100% positron decay with a physical half-life of 9.7 min, making it ideal for most PET instrumentation. It can be produced rapidly and efficiently from a $^{62}$Zn/$^{62}$Cu generator (parent $t_{1/2}$ = 9.13 hr) (*12–15*). Kinetic studies in animals have shown that $^{67}$Cu-PTSM has a single-pass extraction similar to $^{13}$N-ammonia, with a markedly prolonged myocardial retention (*11*) and rapid blood-pool clearance (*12*). The myocardial activity appears to correlate with microsphere determined blood flow in a canine model, although there is a plateau in the net extraction above 2.5 ml/min/g (*12*). Given these characteristics, it is not surprising that images obtained from dogs are of high quality (*12*). The applications of this tracer in animal studies are promising, however, it is necessary to evaluate the kinetic properties of $^{62}$Cu-PTSM in human subjects.

The purpose of this study was to define the myocardial kinetics of $^{62}$Cu-PTSM in healthy human subjects and to determine the suitability of this tracer for evaluating myocardial perfusion at rest and after pharmacological vasodilation.

## METHODS

Before any subjects were enrolled in the study, the study protocol was reviewed by the Internal Review Board and the Radiation Safety Committee at the University of Michigan Medical Center.

### Subjects

Six healthy male volunteers (mean age 30.3 ± 2.3) participated in the study. There was no evidence of cardiovascular disease in

Received Sept. 18, 1991; revision accepted Dec. 14, 1991.

For reprints contact: Dr. Markus Schwaiger, Director of Cardiovascular Nuclear Medicine, Division of Nuclear Medicine, UH B1G505, University of Michigan Medical Center, 1500 East Medical Center Dr., Ann Arbor, MI 48109-0028.

any of the volunteers, as assessed by history and physical and ECG examination.

All subjects were studied under fasting conditions (>6 hr) and had abstained from caffeine for 24 hr. Informed written consent was obtained in each case prior to the PET study.

### Tracer Preparation

Copper-62-PTSM was prepared according to the method of Green et al. (*15,16*). The $^{62}$Zn parent was obtained as a solution in 2 N HCl from Mallinckrodt Medical Inc. (St. Louis, MO) and applied to a Dowex 1 × 8 generator column, previously equilibrated with 2 N HCl. The $^{62}$Cu was eluted in 3 ml of 2 N HCl and neutralized with 4 ml of 3 N sodium acetate. To this solution 3 μg of H2(PTSM) was added in 200 μl of ethanol and the resulting mixture was stirred for 2 min. The crude PTSM solution was then purified by passing through a C-18 Sep-Pak. The Sep-Pak was rinsed with water to remove unbound $^{62}$Cu, and the PTSM was eluted with 0.5 ml of ethanol according to Green (*15, 16*). The product was formulated by adding 7.5 ml of normal saline and sterilized by passing through a Millex-FG filter. Radiochemical purity was determined by radio-HPLC with a Hamilton PRP-1 reverse-phase column using a gradient elution of water followed by methanol. (Flow rate = 2 ml/min, initial solvent = water; gradient from 100% water to 100% methanol in 1 min). With this system, unbound $^{62}$Cu elutes with a retention time of 2.2 min and $^{62}$Cu-PTSM elutes in 6.8 min. Typical radiochemical purity was greater than 95% as $^{62}$Cu-PTSM.

### PET

Each subject was positioned in the ECAT 931 (Siemens, Hoffman Estates, IL) body scanner. In order to verify the correct position of the detectors over the heart, a 2-min scout scan was performed. Subsequently, a 15-min transmission scan was acquired and the data used to determine attenuation correction factors. Copper-62-PTSM (14.0 ± 2.5 mCi) was administered intravenously. Simultaneously, 20-min dynamic PET image acquisition was initiated with varying frame duration (10 × 6 sec/ 4 × 15 sec/2 × 30 sec/ 2 × 60 sec/ 2 × 150 sec/ 2 × 300 sec). After images were acquired under resting conditions, 40 min were allocated for the decay of $^{62}$Cu (physical $t_{1/2}$ = 9.7 min).

Adenosine (140 μg/kg/min) was infused intravenously over 6 min to induce maximal coronary vasodilation. At the 3-min mark of the infusion, a second injection of $^{62}$Cu-PTSM was administered. The dynamic PET image acquisition protocol was the same as that of the resting study.

The reconstructed transaxial images were reoriented along the long-axis of the left ventricle in order to yield resliced images along the horizontal, vertical, and short-axes of the heart using a Sun 4 Workstation (Sun Microsystems Inc., Mountain View, CA) and software developed at our institution (*17*).

### Data Analysis

*Determination of Image Quality and $^{62}$Cu-PTSM Kinetics.* Activity ratios were used as an objective measure of contrast between the myocardium and blood, myocardium and lung, and the myocardium and liver. In each study, the last time frame of a mid-ventricular short-axis image plane was used for region definition. Regions of interest were placed over the entire myocardium, the left lung field, the center of the left ventricular cavity (representing the blood) and the liver. Time-activity curves were subsequently determined from the dynamic image sequence. The peak activity of the blood in each study was assigned an arbitrary value of 100%. Subsequent regional tissue activities were expressed as a percent of this maximum. Activity ratios were determined from the time-activity data at selected time points after injection.

For each study, myocardial time-activity data after the myocardial peak were fitted to a biexponential function. The myocardial clearance half-life ($t_{1/2}$) was calculated by dividing the natural logarithm of 2 by the rate constant ($k_2$) of the second phase of the biexponential function ($t_{1/2} = \ln 2/k_2$).

*Regional Myocardial $^{62}$Cu-PTSM Distribution.* The regional distribution of $^{62}$Cu-PTSM in the normal myocardium was evaluated at rest and after pharmacological vasodilation. A semi-automated regional analysis program developed at our institution (*17*) was applied to images combined from three time frames (between 5 and 15 min postinjection). In seven to eight short-axis images, the edges of the myocardium were defined by inner and outer ellipses chosen by the operator. The posterior intersection of the right and left ventricles was also defined and a radius automatically interpolated between the center of the ellipse and this point. A circumferential profile was then defined for each plane with the radius as the starting point. The program searches for the maximum average activity in a 3 × 3 pixel area in each of 60 sectors within the defined myocardial boundaries of each plane. The data were then displayed in a polar coordinate map. The heart was subsequently divided into the five major segments (inferior, anterior, lateral, septum and apex). The regions were further subdivided into proximal and distal planes yielding nine segments in each study. The regional data were expressed as a mean percent of the maximum myocardial activity ± one standard deviation for each study.

*Myocardial $^{62}$Cu-PTSM Retention.* For the determination of $^{62}$Cu-PTSM myocardial retention, separate time-activity curves for the myocardium and ventricular blood pool were determined. An automatic program developed at our institution was first used to define the left ventricular myocardial region of interest. Again, a mid-ventricular short-axis image from the last time frame of each acquisition was used. The mid-myocardium was denoted by a continuous line drawn by the operator. This line defined the center of multiple adjacent circular regions of interest of 2 pixel radius within the myocardial boundaries. The global myocardial activity was defined by the mean of all the myocardial regions. Decay-corrected myocardial time-activity curves were then reconstructed.

A basal short-axis image from the last time frame was used to define the left ventricular blood-pool region of interest for each study. Decay-corrected time-activity curves were then reconstructed for the left ventricular blood pool.

The absolute retention of $^{62}$Cu-PTSM was calculated as follows:

$$R = \frac{C_t}{C_b},$$

where R is retention in arbitrary units, $C_t$ is the activity in the myocardium at 5 min after injection and $C_b$ is the integral of the blood-pool activity corrected to 1 min. Previous studies by Mathias et al. have indicated that at about 1 min after administration of the tracer, all of the radioactivity in blood was due to metabolites (*18*). Thus, the available blood pool is effectively zero after 1 min.

### Statistical Analysis

All data were expressed as mean ± one standard deviation. Blood pressure and heart rate at baseline and during the adenosine

infusion were compared by paired t-testing. Myocardial clearance half-life and the retention at rest and during adenosine were also compared by paired t-testing, with $p \leq 0.05$ considered significant.

The percent of maximal activity data in the myocardial segments, the percent of peak blood activity data in the tissue regions and the activity ratios were compared by ANOVA and by subsequent post-hoc subgroup paired t-testing when differences were detected. In light of the multiple paired t-testing in this regional analysis, only data with $p \leq 0.01$ were considered statistically significant.

## RESULTS

### Hemodynamic and Symptomatic Responses to Adenosine

During the rest PET image acquisition, the systolic blood pressure and heart rate were 110 ± 7 mmHg and 58 ± 7 bpm, respectively. During the adenosine infusion, the systolic blood pressure was 108 ± 8 mmHg (p = ns), while the heart rate increased to 85 ± 13 bpm ($p < 0.005$). During the adenosine infusion, three of the six subjects developed chest discomfort, three developed dyspnea, three experienced flushing, two had nausea, two had headaches, and one had a mild burning sensation in his eyes. No treatment was required for any of these symptoms, and all resolved shortly after the end of the adenosine infusion. Only one subject was asymptomatic during the adenosine infusion. No subjects had bronchoconstriction, conduction abnormalities, or ST-segment changes.

### Copper-62-PTSM Kinetics

In Figure 1, typical time-activity curves are shown for the rest and adenosine studies of one healthy volunteer. Myocardial activity reached a peak within 40 sec. After 2 min, the tissue activity remained essentially constant. This was true for both the rest and adenosine curves, however, the plateau of tissue activity was clearly higher in the adenosine study. The blood-pool activity also peaked within 40 sec and cleared rapidly. This was comparable to the mean time-to-peak activity after injection, which was 41 ± 9 sec at rest and 40 ± 12 sec with adenosine (p = ns).

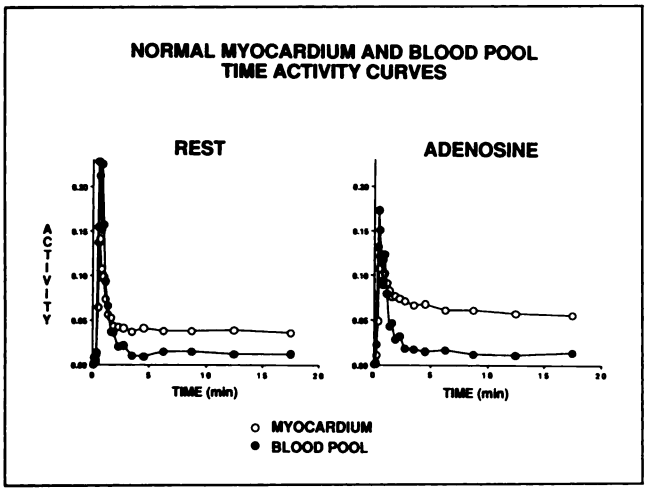


**FIGURE 1.** Examples of $^{62}$Cu-PTSM myocardial and blood time-activity curves in a healthy volunteer at rest and following adenosine infusion.

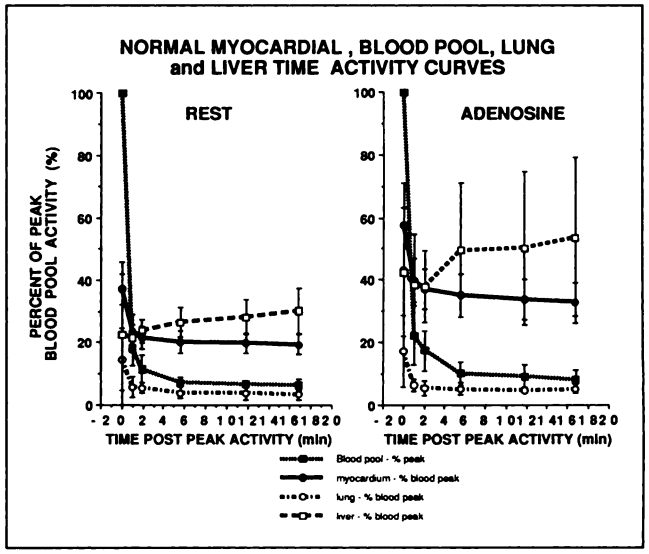


**FIGURE 2.** Means of the percent of peak blood-pool activity in blood, myocardium, lung and liver over time in healthy volunteers at rest and following adenosine. The time of the peak was assigned as time zero for each study. Standard deviation bars are shown for selected time points after the peak.

The means of the activities in the blood, myocardium, lung and liver expressed as a percent of the maximum blood-pool activity for each study are shown in Figure 2. Selected time points have been plotted after the time of peak activity. By 2 min after this peak, the activity in blood was 11.3% ± 4.3% at rest and 17.3% ± 6.6% during adenosine (p = ns). The activity in the myocardium on the other hand cleared gradually decreasing from 22% ± 4% at 2 min after the peak to 19% ± 3% at the end of the acquisition for the resting studies, and from 37% ± 6% to 33% ± 6% after adenosine. The increase in myocardial activity between rest and adenosine studies was significant at all time points after the 2-min mark ($p \leq 0.01$). The liver also showed substantial activity both at rest and after adenosine. However, the increase observed with adenosine over the resting studies did not reach statistical significance.

The myocardial clearance half-life was 105 ± 49 min at rest and did not change significantly with adenosine (clearance $t_{1/2}$ = 101 ± 65 min, p = ns). The overall range of the clearance half-life was 55–224 min.

### Image Quality and Activity Ratios

Figure 3 represents examples of rest and adenosine images obtained after injection with $^{62}$Cu-PTSM, which demonstrate good tissue:background and tissue:blood-pool contrast. There is, however, significant liver activity which may hinder the view of the inferior wall.

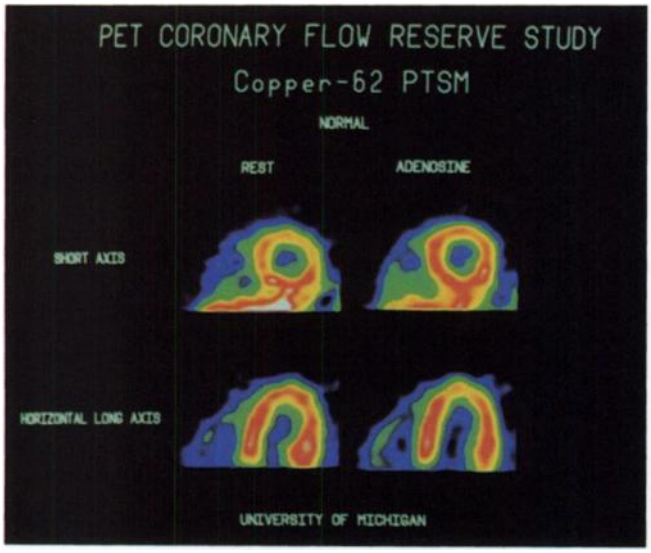


**FIGURE 3.** Example of $^{62}$Cu-PTSM studies in a normal volunteer in the short-axis and horizontal long-axis views at rest (left) and following pharmacological vasodilation with adenosine (right). Good image quality is noted, however, activity in the inferior wall appears greater than the remainder of the myocard (?). Prominent liver activity is apparent adjacent to the inferior region.

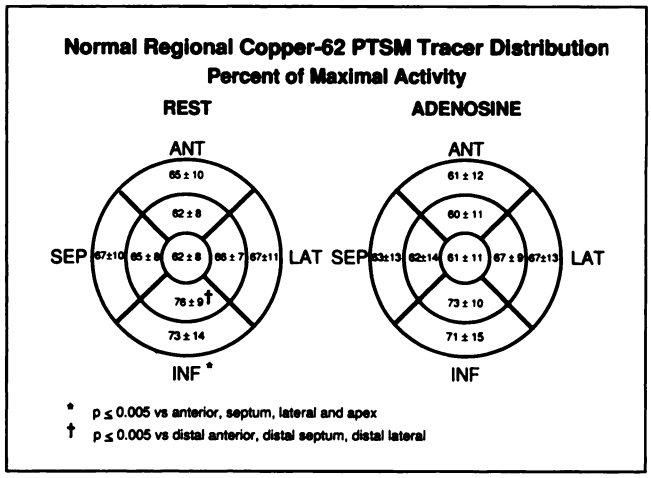


**FIGURE 4.** Mean regional myocardial $^{62}$Cu-PTSM tracer distribution. Regional activity was expressed as a percent of the maximal activity for each study. This polar representation of pooled activity data was obtained from analysis of short-axis images. Each heart is divided into the four standard ventricular walls. The outer segments represent basal planes, the middle segments represent distal planes and the inner most segment represents the apex.

By 5 min postinjection, the mean myocardium:lung, myocardium:blood and myocardium:liver ratios at rest were: 5.9 ± 1.7, 3.1 ± 0.9 at rest and 0.87 ± 0.35, respectively. Following adenosine, the ratios at 5 min postinjection were 6.9 ± 2.8, 3.4 ± 1.7 and 0.83 ± 0.21, respectively (p = ns versus resting studies). Over the remainder of the acquisition, the activity ratios did not change significantly. However, there was a tendency for the myocardium:liver ratios to reduce over time.

### Regional Myocardial $^{62}$Cu-PTSM Distribution

The regional myocardial distribution of $^{62}$Cu-PTSM activity is shown in Figure 4. The inferior wall demonstrated a slightly greater percent of maximal activity compared to the other principle regions of the heart both at rest and during adenosine. This difference reached statistical significance at rest (inferior: 74% ± 12% versus lateral: 67% ± 9%, anterior: 63% ± 8%, septum: 66% ± 9%, and apex: 62% ± 8%, $p \leq 0.005$) but not following adenosine (inferior: 72% ± 13%, lateral: 67% ± 11%, anterior: 61% ± 11%, septum: 62% ± 13%, and apex: 61% ± 11%). Analysis of the subdivisions of the four major walls revealed that these differences were principally confined to the distal segments where the distal inferior wall had significantly greater activity in comparison to the distal lateral, distal anterior and distal septal segments at rest ($p \leq 0.005$). A similar trend was also noted with adenosine but this did not reach statistical significance.

### Copper-62-PTSM Myocardial Retention

The mean myocardial retention of $^{62}$Cu-PTSM at rest was 0.41 ± 0.10 units. During adenosine this increased to 0.79 ± 0.24 ($p \leq 0.01$). Thus, the adenosine:rest retention ratio was 1.97 ± 0.71. The range of this ratio was from 1.45 to 3.37.

## DISCUSSION

Green et al. have previously presented myocardial images of good quality from a healthy volunteer at rest using $^{62}$Cu-PTSM (*15*). This study did not, however, evaluate tracer kinetics at rest or following pharmacological vaso-

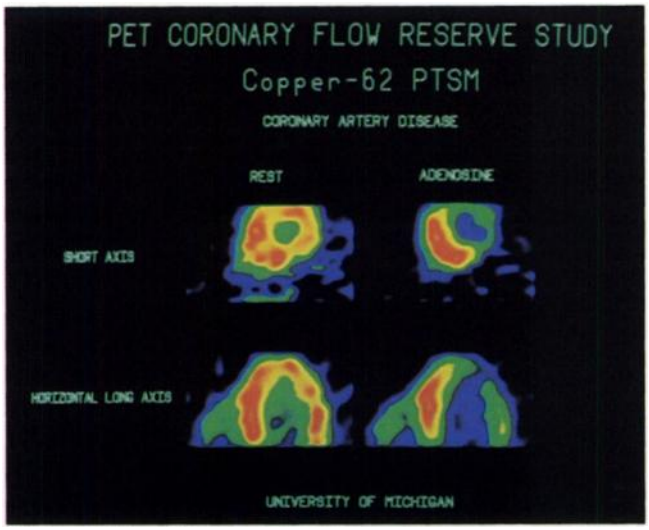


**FIGURE 5.** Example of $^{62}$Cu-PTSM PET studies in a patient with two-vessel coronary artery disease in the short-axis (SA) and horizontal long-axis (HLA) views at rest (left) and following adenosine (right). Note the adenosine-induced perfusion defect in the anterior, lateral and apical walls which is consistent with impaired coronary flow reserve in these regions. (See page 689 for further discussion).

dilation in the heart and other organs as was performed in this study.

The data from the present study confirm the good image quality reported by Green et al. (*15*). They also demonstrate that $^{62}$Cu-PTSM displays kinetic properties in humans that are suitable for myocardial perfusion imaging as has been suggested by animal data (*11,12*).

It has been proposed that $^{62}$Cu-PTSM could be used to establish satellite PET imaging centers without an onsite cyclotron (*15,18*). A central medium-energy cyclotron could be used for the production of the parent compound, $^{62}$Zn (*13,15*). This would require a 99.99% pure copper target designed to sustain a beam power density of ca. 300 W/cm$^2$ and be irradiated with protons at 27.5 MeV (*15*). In fact, high yields of $^{62}$Zn have been achieved with nominal 30 and 40 MeV cyclotron systems equipped with such targetry (*15*). Since the parent half-life is relatively short (9.13 hr), the generator could only be used for 1–2 days (*13,18*). This, however, may prove advantageous, since generators need only be synthesized for the days when they are needed. This would maximize the use of the generator, unlike other longer half-life systems where there may be significant periods of time when they are idle. Finally, the preparation scheme available for radiolabeled $^{62}$Cu-PTSM is rapid and simple (*15,16,19*). In our laboratory, the $^{62}$Cu-PTSM could be delivered to the PET suite in about 30 min from the time the radiochemist was notified. All these features could make this agent a suitable option for centers with cyclotron facilities.

### Activity Distribution and Image Quality

As can be seen in Figure 3, the image quality in human subjects is good. This is to be expected given the kinetics of this agent. The modest physical half-life of 9.7 min permits imaging with less sensitive PET systems over several minutes to acquire good counting statistics without compromising the ability for sequential studies (*15*). Rubidium-82 with its rapid decay ($t_{1/2}$ = 76 sec) allows sequential imaging, but yields poor counting statistics unless imaged with a high-sensitivity PET camera (*15*). Copper-62-PTSM also has a lower positron energy of 2.5 MeV compared to 3.3 MeV for $^{82}$Rb. This lower energy offers a theoretical advantage for better image resolution. This difference, however, may not be realized with the resolution limitations of present PET imaging systems.

In terms of tracer distribution, our data suggest that there is slightly increased activity in the inferior wall relative to the other myocardial regions. This is most likely related to cross-contamination of activity from the liver, whose activity was in fact greater than the myocardium at 5 min postinjection. This difference tended to increase with time. The close proximity of the liver to the inferior wall (Fig. 3) may lead to excessive scatter contribution in this region; or it may encroach upon the resolution limitations of the scanner. This could potentially lead to reduced sensitivity of disease detection in this region. The incorporation of a scatter correction into the reconstruction program may help overcome this potential problem but requires further development of image processing.

This problem with prominent liver activity is not unique to $^{62}$Cu-PTSM PET imaging. Difficulties with inferior wall interpretation related to liver activity have also been encountered with $^{99m}$Tc-labeled perfusion compounds that are excreted via the biliary tract. Such image distortion by liver activity represents a potential disadvantage for $^{62}$Cu-PTSM and other agents in comparison to potassium analogue tracers such as $^{201}$Tl and $^{82}$Rb where this has not been a significant problem.

### Copper-62-PTSM Kinetics

A potential anti-neoplastic effect of $^{62}$Cu-PTSM has led to an understanding of this tracer's extraction and retention at a cellular level. Data from tumor cell studies show that $^{62}$Cu-PTSM appears to be reduced within the cell by sulfhydryl groups liberating ionic copper. Tissue retention occurs because of subsequent binding of the liberated copper ion to intracellular macromolecules (*20–22*).

Radiolabeled copper-PTSM myocardial kinetics have now been well studied in animal models. In an isolated heart preparation, Shelton et al. found a residual fraction for $^{67}$Cu-PTSM of 45% ± 7%. This residual fraction had little change under variable flow conditions (flow range of 0.15–3.0 ml/min/g) and variable metabolic conditions. These investigators reported a prolonged myocardial retention with a clearance half-life of greater than 3,600 min (*11*). Prolonged retention was also demonstrated in a recent canine study (*12*) in which $^{62}$Cu-PTSM retention was measured over a wide flow range induced by ischemia, occlusion, dobutamine or dipyridamole. This study showed that copper retention correlated well with microsphere determined blood flow, although there was a plateau in this relationship at flows of 2.5 ml/min/g or greater. In addition, a rapid blood-pool clearance was noted to be less than 10% of the peak activity by 2 min postinjection. This rapid blood-pool clearance was also shown in the baboon by Mathias et al. (*18*). These investigators demonstrated that by 1 min after tracer injection, none of the radioactivity in blood was associated with PTSM (*18*), suggesting that the measured blood-pool activity may in fact overestimate the true arterial input function.

Our results on $^{62}$Cu-PTSM kinetics in humans support the animal data discussed above. We observed a prolonged tissue retention as noted in the time-activity curves of Figures 1 and 2. A long clearance half-life was noted at rest (105 ± 49 min) and with adenosine (101 ± 65 min). We also observed rapid blood-pool clearance with blood-pool activity being only 11.3% ± 4.3% at rest and 17.3% ± 6.6% with adenosine 2 min after the peak.

We also evaluated $^{62}$Cu-PTSM retention at rest and during maximal coronary vasodilation. We found the adenosine:rest retention ratio to be 1.97. This is much less than the expected normal coronary flow reserve, which is

between about 4 and 5 (*6,9,23,24*). In our present study, there was no direct invasive coronary flow measurement. However, the symptoms and hemodynamic responses observed are in keeping with large studies using adenosine (*25*) and would suggest that maximal vasodilation was achieved in our subjects. Our data thus suggest that retention is decreased relative to increased flow at high flow rates. This is consistent with the canine data which showed the plateauing of the retention blood flow relationship above 2.5 ml/min/g (*12*). In fact, if one assumes that a normal flow of 0.9 ml/min/g and a maximal flow reserve of 4, using the curve equation presented by Shelton et al. for the retention blood flow relationship in the dog, the maximum vasodilation to rest retention ratio for $^{62}$Cu-PTSM would be expected to be 2.3.

### Comparison to Other Perfusion Agents

The time-activity curves of $^{62}$Cu-PTSM bear a striking resemblance to those of $^{13}$N-ammonia (*6,26*) in that both have prolonged tissue retention. In fact, the single-pass extraction of radiolabeled Cu-PTSM measured in an isolated heart model was similar to $^{13}$N-ammonia single-pass extraction in the same model (radiolabeled Cu-PTSM extraction is equal to 45%, $^{13}$N-ammonia extraction is equal to 55%) (*11,27*). The clearance half-life of $^{13}$N-ammonia ranges from 110 to 642 min (*26*). While this is considerably shorter than the clearance half-life suggested for radiolabeled Cu-PTSM by isolated heart studies, (*11*), it is comparable to the range in man, demonstrated in this study, of 55–224 min with an overall mean (rest and adenosine studies) of 103 ± 55. In addition, preliminary animal work done in our laboratory demonstrated a clearance half-life for $^{62}$Cu-PTSM equal to 109 ± 6 min in the dog (*28*).

The retention of $^{62}$Cu-PTSM, as with most other myocardial perfusion agents, is flow-dependent and underestimates myocardial blood flow at high flow rates. Reducing retention with increasing flow has been demonstrated for $^{13}$N-ammonia (*29,30*), $^{82}$Rb (*31–33*), $^{201}$Tl (*34–36*), $^{99m}$Tc-sestamibi (*34*) and $^{99m}$Tc-teboroxime (*37*). In an attempt to overcome this non-linear relationship, tracer kinetic models have been successfully applied using the PET agent $^{13}$N-ammonia. Two fundamental approaches have been used (*6–8*). The first involves establishing values of retention over a wide range of blood flow in an animal model and determining a correction factor (*7*). Depending on the tracer's retention-blood flow relationship, there may be a significant amount of scatter in estimation of flow rates in the higher range. The second approach involves a three-compartmental model developed to separate tissue extraction and metabolic retention (*6*). This model depends upon a stable first-pass extraction over a wide flow range and determination of the true arterial input function of the tracer. For $^{62}$Cu-PTSM, further studies are needed to establish if either of these approaches can be applied to its kinetics to accurately quantify blood flow, or whether new methods will need to be developed. Preliminary work has been done, suggesting that radiolabeled Cu-PTSM PET imaging may allow quantification of myocardial flow (*38, 39*). The problem of rapid $^{62}$Cu-PTSM metabolism after intravenous injection (*18*), however, needs to be further addressed, and a simple method for determining the true input function established.

### Evaluation of Coronary Artery Disease

In addition to the healthy volunteers in this study, we have also evaluated one patient with angiographically proven two-vessel coronary artery disease using $^{62}$Cu-PTSM. Figure 5 shows this patient's images at rest and during adenosine infusion. There was an obvious adenosine-induced perfusion defect indicative of impaired coronary flow reserve in the lateral, anterior and apical walls. The ratio of activity in the normal:risk zone myocardium was 1.2 at rest, and increased to 2.0 with adenosine. Copper-62-PTSM retention was also measured in this patient. In the normal zone, retention increased from 0.42 at rest to 0.67 after adenosine, yielding an adenosine:rest ratio of 1.53. In contrast, the area at risk had a resting retention of 0.34, which did not change with adenosine (0.35), yielding a ratio of 1.03. Based on this case, $^{62}$Cu-PTSM appears to have some potential for coronary artery disease detection. Clearly, large scale trials involving patients with suspected coronary artery disease must now be undertaken to determine the ultimate diagnostic utility of $^{62}$Cu-PTSM as a myocardial perfusion tracer.

## CONCLUSIONS

Copper-62-PTSM represents a promising new PET tracer for qualitative evaluation of coronary flow reserve in the human heart. The prolonged tissue retention and rapid blood-pool clearance offer suitable kinetics to achieve good quality images. Scatter correction may be required, however, to overcome potential cross-contamination from high liver activity.

Accurate quantification of myocardial blood flow using $^{62}$Cu-PTSM tissue retention may be limited by the relative attenuation of tracer retention at higher flow rates. On the other hand, given its kinetic properties, tracer kinetic modeling may provide a quantitative index of myocardial blood flow with this new tracer.

## ACKNOWLEDGMENTS

The authors would like to express their gratitude to Jill Rothley, CNMT, Leslie Botti, CNMT, Christine Allman, CNMT, Edward McKenna, CNMT, Vincent McCormick, CNMT, and Andrew Weeden, CNMT of the PET center for technical assistance. The authors would also like to thank Tina Bennett for her assistance in preparing the manuscript.

This work was carried out during the tenure of an established investigator of the American Heart Association, Dr. Markus Schwaiger, and was supported in part by the National Institute of Health grant R01 HL41047-01. Dr. Rob Beanlands was a research fellow supported by the Heart and Stroke Foundation

of Canada until June 30, 1991 and by the Medical Research Council of Canada Centennial Fellowship from July 1, 1991 to the time of submission. Dr. Otto Muzik was supported by the Austrian Erwin Schroedinger Foundation project number: J0473-MED.

## REFERENCES


1. Schelbert HR, Wisenberg G, Phelps ME, et al. Non-invasive assessment of coronary stenosis by myocardial imaging during pharmacologic coronary vasodilation. VI. Detecton of coronary artery disease in man with intravenous N-13 ammonia and positron computed tomography. *Am J Cardiol* 1982;49:1197.
2. Yonekura Y, Tamaki N, Senda M. Detection of coronary artery disease with ammonia and high-resolution positron-emission computed tomography. *Am Heart J* 1987;113:645–654.
3. Demer LL, Gould KL, Goldstein RA, et al. Assessment of coronary artery disease severity by positron emission tomography. Comparison with quantitative arteriography in 193 patients. *Circulation* 1989;79:825.
4. Go RT, Marwick TH, McIntyre WJ. Initial results of comparative Rb-82 and Tl-201 myocardial perfusion imaging in diagnosis of CAD [Abstract]. *J Nucl Med* 1989;30:759.
5. Stewart RE, Schwaiger M, Molina E, et al. Comparison of rubidium-82 positron emission tomography and thallium-201 SPECT imaging for detection of coronary artery disease. *Am J Cardiol* 1991;67:1303–1310.
6. Hutchins GD, Schwaiger M, Rosenspire KC, Krivokapich J, Schelbert H, Kuhl DE. Non-invasive quantification of regional myocardial blood flow in the human heart using N-13 ammonia and dynamic PET imaging. *J Am Coll Cardiol* 1990;15:1032–1042.
7. Krivokapich J, Smith GT, Huang SC, et al. N-13 ammonia myocardial imaging at rest and with exercise in normal volunteers. Quantification of absolute myocardial perfusion with dynamic positron emission tomography. *Circulation* 1989;80:1328–1337.
8. Muzik O, Beanlands R, Hutchins G, et al. Experimental validation of a tracer kinetic model for N-13 ammonia in comparison to O-15 water for quantification of myocardial blood flow [Abstract]. *J Nucl Med* 1991;32:926.
9. Bergmann SR, Herrero P, Markham J, Weinheimer CJ, Walsh MN. Noninvasive quantification of myocardial blood flow in human subjects with oxygen-15-labeled water and positron emission tomography. *J Am Coll Cardiol* 1989;14:639–652.
10. Araujo L, Lammertsma AA, Rhodes CG, et al. Non-invasive quantification of regional myocardial blood flow in oxygen-15-labeled carbon dioxide inhalation and positron emission tomography. *Circulation* 1991;83:875–885
11. Shelton ME, Green MA, Mathias CJ, Welch MJ, Bergmann SR. Kinetics of copper-PTSM in isolated hearts: a novel tracer for measuring blood flow with positron emission tomography. *J Nucl Med* 1989;30:1843–1847.
12. Shelton ME, Green MA, Mathias CJ, Welch MJ, Bergmann SR. Assessment of regional myocardial and renal blood flow with copper-PTSM and positron emission tomography. *Circulation* 1990;82:990–997.
13. Robinson GD, Zielinski FW, Lee AW. The zinc-62/copper-62 generator: a convenient source of copper-62 radiopharmaceuticals. *Int J Appl Radiat Isotopes* 1980;31:111–116.
14. Yagi M, Kondo K. A Cu-62 generator. *Int J Appl Radiat Isotopes* 1979;30:569–570.
15. Green MA, Mathias CJ, Welch MJ, et al. Copper-62-labeled pyruvaldehyde bis(N-4-methylthiosemicarbazone) copper(II): Synthesis and evaluation as a positron emission tomography tracer for cerebral and myocardial perfusion. *J Nucl Med* 1990;31:1989–1996.
16. Green MA, Klippenstein DL, Tennison JR. Copper(II)bis (thiosemicarbazone) complexes as potential tracers for evaluation of cerebral and myocardial blood flow with PET. *J Nucl Med* 1988;29:1549–1557.
17. Kotzerke J, Hicks R, Wolfe E, et al. Three-dimensional assessment of myocardial oxidative metabolism: a new approach for regional determination of PET-derived carbon-11-acetate kinetics. *J Nucl Med* 1990;31:1876–1893.
18. Mathias CJ, Welch MJ, Raichle ME, et al. Evaluation of a potential generator-produced PET tracer for cerebral perfusion imaging: single-pass extraction measurements and imaging with radiolabeled Cu-PTSM. *J Nucl Med* 1990;31:351–359.
19. Green MA. A potential copper radiopharmaceutical for imaging the heart and brain: copper-labeled pyruvaldehyde bis(N4-methylthiosemicarbazone). *Nucl Med Biol* 1987;15:59–61.
20. Petering DH. The reaction of 3-methoxy-2-oxobutyraldehyde bis (thiosemicarbazonato)copper(II) with thiols. *Bioinorg Chem* 1972;1:273–288.
21. Winkelmann DA, Bermke Y, Petering DH. Comparative properties of the antineoplastic agent 3-ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone)-copper(II) and related chelates. *Bioinorg Chem* 1974;3:261–277.
22. Minkel DT, Saryan LA, Petering DH. Structure-function correlations in the reaction of bis(thiosemicarbazone)copper(II) complexes with Ehrlich ascites tumor cells. *Cancer Res* 1978;38:124–129.
23. Wilson RF, Marcus ML, White CW. Effects of coronary bypass surgery and angioplasty on coronary blood flow and flow reserve. *Prog Cardiov Dis* 1988;31:95–114.
24. White CW, Wilson RF, Marcus ML. Methods of measuring myocardial blood flow in humans. *Prog Cardiovasc Dis* 1988;31:79–94.
25. Verani MS, Mahmarian JJ, Hixsom JB, Boyce TM, Staudacher RA. Diagnosis of coronary artery disease by controlled coronary vasodilation with adenosine and thallium-201 scintigraphy in patients unable to exercise. *Circulation* 1990;82:80–87.
26. Schelbert HR, Phelps ME, Huang S-C, et al. N-13 ammonia as an indicator of myocardial blood flow. *Circulation* 1981;63:1259–1271.
27. Bergmann SR, Hack S, Tewson T, Welch MJ, Sobel BE. The dependence of accumulation of $^{13}NH_3$ by myocardium on metabolic factors and its implications for quantitative assessment of perfusion. *Circulation* 1980;61:34–43.
28. Beanlands R, Muzik O, Lee K, et al. Evaluation of copper-62-PTSM as a myocardial flow tracer [Abstract]. *J Nucl Med* 1991;32:1028.
29. Krivokapich J, Huang S-C, Phelps ME, MacDonald NS, Shine KI. Dependence of $^{13}NH_3$ by myocardial extraction and retention on flow and metabolism. *Am J Physiol:Heart Circ Physiol* 1982;242:H536–H542.
30. Shah A, Schelbert HR, Schwaiger M, et al. Measurement of regional myocardial blood flow with N-13 ammonia and positron-emission tomography in intact dogs. *J Am Coll Cardiol* 1985;5:92–100.
31. Wilson RA, Shea M, Landsheere CD, et al. Rubidium-82 myocardial uptake and extraction after transient ischemia: PET characteristics. *J Comp Assist Tomogr* 1987;11:60–66.
32. Selwyn AP, Allan RM, L'Abbate A, et al. Relation between regional myocardial uptake of rubidium-82 and perfusion: absolute reduction of cationic uptake in ischemia. *Am J Cardiol* 1982;50:112–121.
33. Goldstein RA, Mullani NA, Marani SK, Fisher DJ, Gould KL, O'Brien HA. Myocardial perfusion with rubidium-82. II. Effects of metabolic and pharmacologic interventions. *J Nucl Med* 1983;24:907–915.
34. Marshall RC, Leidholdt EM, Zhang D-Y, Barnett CA. Technetium-99m hexakis 2-methoxy-2-isobutyl isonitrile and thallium-201 extraction, washout and retention at varying coronary flow rates in rabbit heart. *Circulation* 1990;82:990–1007.
35. Weich HF, Strauss HW, Pitt B. The extraction of thallium-201 by the myocardium. *Circulation* 1977;56:188–191.
36. Grunwald AM, Watson DD, Holzgreefe HH, Irving JF, Beller GA. Myocardial thallium kinetics in normal and ischemic myocardium. *Circulation* 1981;64:610–618.
37. Leppo JA, Meerdink DJ. Comparative myocardial extraction of two technetium-labelled BATO derivatives (SQ30217, SQ32014) and thallium. *J Nucl Med* 1990;31:67–74.
38. Herrero P, Markham J, Weinheimer CJ, Green MA, Welch MJ, Bergmann SR. Quantification of myocardial perfusion with Cu-62-PTSM and positron emission tomography [Abstract]. *J Nucl Med* 1991;32:937.
39. Stone CK, Martin CC, Mueller B, Pyzalski RA, Perlman SB, Nickles RJ. Comparison of myocardial uptake of copper pyruvaldehyde thiosemicarbazone with N-13 ammonia in humans by PET [Abstract]. *J Nucl Med* 1991;32:999.