Copper-62-Labeled Pyruvaldehyde *Bis*(N^4-methylthiosemicarbazonato)copper(II): Synthesis and Evaluation as a Positron Emission Tomography Tracer for Cerebral and Myocardial Perfusion

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Generator produced positron-emitting radionuclides could potentially expand the application of positron emission tomography (PET) to centers that do not have access to a local cyclotron. The zinc-62/copper-62 radionuclide generator system could serve as a source of positron-emitting copper-62 (^{62}Cu) ($t_{½}$ = 9.74 min) for physiologic imaging. Accordingly, we have prepared zinc-62/copper-62 generators capable of high output (>300 mCi) and used the no-carrier-added eluate in a rapid high yield synthesis of [^{62}Cu]Cu(PTSM) that provides the radiopharmaceutical in a form suitable for intravenous injection (where Cu(PTSM) = pyruvaldehyde *bis*(N^4-methylthiosemicarbazonato) copper(II)). We then demonstrated in pilot studies that [^{62}Cu]Cu(PTSM) provides high quality brain and heart images with PET, accurately delineating cerebral and myocardial perfusion in both experimental animals and in humans (corroborating results of previous experimental studies utilizing longer-lived copper isotopes). The results of this work demonstrate that ^{62}Cu can be conveniently obtained from high-level generators and, when used to label Cu(PTSM), provides a generator-produced radiopharmaceutical capable of providing estimates of cerebral and myocardial perfusion independent of cyclotron-produced radionuclides.

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Positron emission tomography (PET) is a powerful medical imaging technique that can quantitatively map the spatial distribution of positron-emitting nuclides inside the living body (*1–3*). Some of the most useful PET measurements are obtained with tracers that distribute into tissue in proportion to regional rates of blood flow. Currently, PET imaging studies of regional perfusion in the brain and heart have applications both in biomedical research (*2–7*) and in clinical practice (*8, 9*). PET imaging studies of cerebral sensory, motor, and cognitive operations have provided previously unavailable information about cerebral function in normal and abnormal subjects (*10–15*). PET also is useful in functional brain mapping prior to neurosurgery (*16*) and, in the future, may provide prognostic information about functional capacity and functional recovery following brain injury (*17–19*). In many of these neurologic mapping studies, PET cerebral blood flow (CBF) measurements serve as a sensitive, simple, and versatile probe of brain function by providing information similar to that available with metabolic tracers (*20–22*). In studies of the heart with PET, assessment of myocardial perfusion and perfusion reserve after exercise or pharmacologic coronary vasodilatation has been useful both diagnostically and for research evaluation of patients with coronary artery disease, as well as for the objective assessment of mechanical and pharmacologic interventions designed to improve nutritive perfusion (*23–27*).

The widespread application of these PET techniques has been limited by the need for a hospital to operate an "in-house" cyclotron for production of the short-

lived positron-emitting nuclides (oxygen-15, nitrogen-13, carbon-11, fluorine-18) most widely used for radiotracer labeling (*1–3,28,29*). Positron-emitting radiopharmaceuticals labeled with a nuclide that can be obtained from a parent/daughter generator system would make PET imaging available to a much broader range of investigators by reducing or eliminating the need for a local cyclotron facility. Copper-62 ($t_{½}$ = 9.74 min) is attractive in this regard, forming as the decay product of a longer-lived parent (zinc-62, $t_{½}$ = 9.26 h) that is readily produced with a medium-energy cyclotron (*30–35*). The 9.74-min half-life of the ^{62}Cu daughter is well suited to the time frame of perfusion imaging studies with PET. In addition, the ^{62}Cu half-life is attractive because it is short enough to allow repeat imaging at reasonably brief time intervals, yet long enough to potentially allow the chemical synthesis of a variety of ^{62}Cu radiopharmaceuticals. Our previous studies with pyruvaldehyde *bis*(N^4-methylthiosemicarbazonato)copper(II), Cu(PTSM), labeled with longer-lived ^{67}Cu and ^{64}Cu have shown this compound to be a promising radiopharmaceutical for evaluation of cerebral, myocardial, and renal perfusion. Tracer Cu(PTSM) is relatively highly extracted into both cerebral and myocardial tissues under diverse physiologic conditions, whereupon the copper label is efficiently trapped and retained (*36–42*). The prolonged tissue retention of the copper label is consistent with the known susceptibility of Cu(PTSM) to reductive decomposition by reaction with ubiquitous intracellular sulfhydryl groups, a process that liberates the label as ionic copper which is subsequently bound by intracellular macromolecules (*43–47*).

We report here the preparation of high level (>300 mCi) ^{62}Zn/^{62}Cu generator systems; the synthesis of [^{62}Cu]-Cu(PTSM); and a comparison of [^{62}Cu]-Cu(PTSM) PET images of the brain and heart with the images obtained using a validated, cyclotron-produced, perfusion tracer (oxygen-15-water) (*48–50*).

EXPERIMENTAL METHODS

General. The H_2(PTSM) ligand was prepared as described in the literature (*51*). Dowex −1 × 8 (200–400 mesh) anion exchange resin (p.a. grade) was purchased from Fluka Chemical Company (Ronkonkoma, NY). Ultrapure hydrochloric acid and ultrapure sodium acetate were obtained from Aesar Johnson-Matthey (Seabrook, NH). Water used in the [^{62}Cu]-Cu(PTSM) synthesis and in the preparation of reagents was purified to a resistivity of 10-17 MΩ/cm (MilliQ® Pyrogen-Free Water System, Millipore Corporation, Milford, MA). Thin-layer radiochromatograms were analyzed with a Berthold Tracemaster 20 linear thin-layer chromatography analyzer. Radiopharmaceutical doses were measured in a Capintec CRC 7 radionuclide dose calibrator. MIRD (Medical Internal Radiation Dose) dosimetry calculations were based on published biodistribution data for [^{67}Cu]-Cu(PTSM) (*37*). Trace metals analyses using inductively coupled plasma spectroscopy (ICP) were obtained from a commercial laboratory (Skinner & Sherman Laboratories, Waltham, MA).

Zinc-62 Preparation. Zinc-62 was prepared by the ^{63}Cu(p,2n)^{62}Zn reaction using either the MC-40 model cyclotron (Soanditronix Ltd.) or CS-30 model cyclotron (The Cyclotron Corporation) in the Maryland Heights Cyclotron Facility of Mallinckrodt Medical, Inc. Typically, a 99.99% pure copper target, custom manufactured to receive the internal cyclotron beam at a grazing angle in order to sustain a beam power density of ca 300 Watts/cm^2, was irradiated with protons at an average energy of 27.5 MeV. The plate thickness was sufficient to degrade the proton energy below the 13.5 MeV threshold for the ^{62}Cu(p,Zn)^{62}Zn reaction. The target copper plate was water cooled internally. The target was irradiated for 1–1.5 hr and processing begun 6-8 hr after the end of bombardment (EOB) to allow for the almost total decay of ^{63}Zn. The average production yield was ca 4.5 mCi/μA-hr at EOB, agreeing well with the theoretical value calculated from published cross-sectional data (*35*).

The irradiated target processing was completely done inside a hot cell equipped with master-slave type manipulators. The target copper plate was twice etched for 5 min with 10 ml hot 4N HNO_3. The nitric solution was then carefully evaporated to dryness, the residue rinsed with 2 ml water for injection (USP), and again evaporated to dryness. The residue was then dissolved in 20 ml concentrated HCl and carefully evaporated to dryness. The residue was dissolved in 10 ml 2N HCl and loaded onto an anion exchange column (AG 1 × 8, 100-200 mesh). The column was eluted with 50 ml 2N HCl to remove the copper and other metallic impurities, while the ^{62}Zn and a small amount of ^{65}Zn are retained. The column was then eluted with 50 ml water-for-injection to collect the zinc radionuclides. This solution was evaporated to dryness and the ^{62}Zn reconstituted in 5.5 ml 2N HCl and dispensed.

Zinc-62/Copper-62 Generator Construction. The ^{62}Zn/^{62}Cu generator system was generally prepared by loading the ^{62}Zn/2N HCl solution (270 - 456 mCi; 1 mCi = 3.7 × 10^7 Bq) onto a 0.7 cm inside diameter × 4 cm Dowex 1 × 8 (200-400 mesh) column previously equilibrated and subsequently eluted with ultrapure 2N HCl. The top (inlet) of the column was connected to a 2N HCl solvent reservoir and the ^{62}Cu eluted by application of negative pressure to the bottom (outlet) of the column using a disposable plastic syringe (1-12 ml). The generator column was enclosed in a cylindrical lead shield with 2.6 cm walls and lid, and this assembly was stored behind 10-cm lead walls to reduce personnel radiation exposure.

[^{62}Cu]-Cu(PTSM) Synthesis. The procedure employed for the synthesis of [^{62}Cu]-Cu(PTSM) is based on the method previously described for [^{67}Cu]-Cu(PTSM) (*37*). Typically, 2 ml of the ^{62}Cu/2N HCl generator eluant was buffered by addition of 2.67 ml 3N ultrapure sodium acetate. The H_2(PTSM) ligand (1.5 μg) was added to the ^{62}Cu-acetate solution in 0.100 ml ethanol using an aliquot of a ligand stock solution containing 1.5 mg H_2(PTSM) in 100 ml absolute ethanol. After mixing, the solution was allowed to stand at room temperature for 2-3 min. The [^{62}Cu]-Cu(PTSM) reaction mixture was then passed through a C_{18}-SepPak Light® solid-phase extraction cartridge (Millipore Corporation, Milford, MA) that had been prewetted by flushing with 5 ml ethanol and 3 ml water (per manufacturer instructions). The cartridge was washed with 4 ml H_2O and the [^{62}Cu]-Cu(PTSM)

product then recovered by eluting the C_{18}-SepPak with ethanol in 0.1-ml fractions. The ethanol fractions containing appreciable ^{62}Cu activity were combined, diluted with saline to a 5% ethanol concentration, and filtered through a sterile 0.2-μm polytetrafluoroethylene membrane filter unit (Milliport Millex-FG) into a sterile container. The [^{62}Cu]-Cu(PTSM) product was generally recovered in the second and third 0.1-ml ethanol fractions eluted from the C_{18}-SepPak. The radiochemical purity of the [^{62}Cu]-Cu(PTSM) was determined by thin-layer chromatography on silica gel plates eluted with ethyl acetate, as described previously (*36,37*). The radionuclide purity of the product was determined by gamma counting and gamma spectroscopy after allowing the ^{62}Cu to decay to background levels. This synthetic procedure can be completed within 4.5-6.0 min following generator elution with a 50% end-of-synthesis yield of [^{62}Cu]-Cu(PTSM) (yield without decay correction, based on ^{62}Cu available at end of elution).

PET Experiments

Monkey Studies. All studies were performed in a single male nemistrina using a protocol approved by the Animal Studies Committee of Washington University School of Medicine. Positron emission tomography was performed with the PETT VI in the high resolution mode (*52,53*). Data were collected simultaneously for seven slices with center-to-center separations of 14.4 mm. Transverse reconstructed resolution was ~12 mm in the center of the field of view. The animal was trained with operant conditioning, using positive reinforcement only, to climb without assistance into a modified primate chair. A 20-gauge i.v. catheter was inserted into a leg vein to permit i.v. administration of radiopharmaceuticals or drugs. The head was securely positioned in a headholder attached to the modified primate chair (*54*). The entire chair, with the animal in place, then was advanced into PETT VI.

Regional perfusion was measured after bolus i.v. injections of [^{62}Cu]-Cu(PTSM) and 5-min PET scans. An initial resting-state scan was performed after injection of a low dose (2.7–4.2 mCi) with the animal lying quiet and still. After 20 min, 15–17 mCi of [^{62}Cu]-Cu(PTSM) were injected and a second scan was obtained while a vibrator (130 Hz, 2-mm amplitude, Daito Model 91, Higashi, Osaka, Japan) was held to the right forepaw. After these emission scans, ketamine (7–10 mg/kg i.v.) was administered. A transmission scan was then collected using a ring source of $^{68}Ge/^{68}Ga$ that permitted individually measured attenuation correction.

Regional response in vibrotactile stimulation was determined using subtraction image analysis (*10*). Resting-state control scans were subtracted pixel-by-pixel from scans during vibration after global normalization. We defined a region of interest (ROI) about 9 mm × 9 mm (3 × 3 pixels) over the area of maximum response in a previously performed vibration minus resting-state pair obtained using ^{15}O-water as the blood-flow tracer (*54*). The anatomical location of this ROI was identified by comparison with a stereotactic atlas of the monkey brain using proportional measurements in three orthogonal axes (*55*).

Human Studies. Brain imaging with [^{62}Cu]-Cu(PTSM) was performed on one of the investigators (M.J.W.), who was positioned in a Super Pet IIB time-of-flight 7-slice tomograph, a PET camera with a 50-cm diameter field. The subject's head was restrained utilizing a polyfoam mask. A transmission scan was done using an external $^{68}Ge/^{68}Ga$ source to allow individual attenuation correction. Then ^{15}O-water (60 mCi) was injected as an i.v. bolus and a single 40-sec cerebral blood flow image collected. Twenty minutes later 12 mCi of [^{62}Cu]-Cu(PTSM) were injected intravenously. Copper-62 imaging was then conducted over a 20-min time period with list mode data collection.

The myocardial uptake of [^{62}Cu]-Cu(PTSM) was also evaluated in one of the investigators (M.A.G.). For this study, the subject was positioned in Super PET I, a whole-body time-of-flight PET camera, which permits the simultaneous acquisition of seven transverse tomographic slices. After obtaining an attenuation scan using an external ring of $^{68}Ge/^{68}Ga$, 0.3 mCi/kg of ^{15}O-labeled water were administered as a rapid i.v. bolus and data were acquired for 120 sec. After permitting sufficient time for decay of the radioactivity, the subject inhaled 40 mCi of ^{15}O-carbon monoxide and a 5-min emission scan was obtained to permit delineation of the blood pool. Subsequently, after the return of radioactivity to background levels, 16.9 mCi of [^{62}Cu-Cu(PTSM) were injected as a rapid i.v. bolus and emission data were collected over 15 min. Images of ^{62}Cu data were reconstructed from data obtained in consecutive 5-min intervals beginning immediately after administration of tracer. The distribution of ^{15}O-labeled water and [^{62}Cu]-Cu(PTSM) were reconstructed by confidence weighting, and (where indicated) corrected for radioactivity residing in the vascular space using a correction technique previously described (*24–27*).

RESULTS AND DISCUSSION

The generator system that we have employed for separation of ^{62}Cu from its ^{62}Zn parent is based on the low-level generators described by Robinson et al. (*32, 33*). The generator consists of a short Dowex 1 × 8 column eluted with 2N HCl (Fig. 1). Under these conditions, the Dowex 1 × 8 anion exchange resin avidly retains zinc(II), while copper(II) and other divalent first-row transition metal ions are much less tightly bound (*56*). Quite adequate performance was obtained using a 0.7-cm inside diameter column, 4 cm in length;

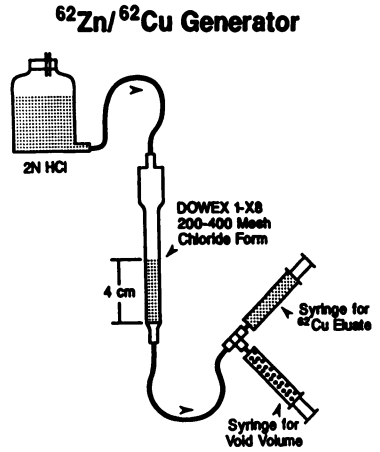

FIGURE 1
Schematic diagram of $^{62}Zn/^{62}Cu$ generator system.

elution yields were typically >90% of available ^{62}Cu activity and the elution profile is such that >80% of available ^{62}Cu is obtained in a 2-3-ml volume (following elution of the system void volume). (Note that we normally allowed 30-60 sec to conduct a 5-ml elution of the generator. Under these conditions, precise calculation of elution yield is somewhat difficult, due to significant ^{62}Cu decay and significant ^{62}Cu regrowth on the column, even during the time of elution).

Scaling the generator up to the 300-500 mCi level (at time of loading) resulted in no adverse effects on generator performance relative to the 10-15-mCi generators described by Robinson (*32*). No signs of radiolytic damage to the column bed or glass housing were detected, other than some slight discoloration (yellowing) in the top 1 cm of the column bed and housing where the ^{62}Zn is confined. Zinc-62 breakthrough was 1.5 (± 1.0) × 10^{-3}% of eluted ^{62}Cu activity (n = 6 for 4 generators). Parent breakthrough at this level is judged insignificant, as it will cause a negligible contribution to the total radiation exposure of a patient who is administered a ^{62}Cu radiopharmaceutical within 5-20 min following generator elution (*57*). The leaching of ^{62}Zn from the column is relatively constant; if a 10-ml elution is collected in 1-ml fractions, essentially equal levels of ^{62}Zn are found in each sample.

The synthesis of [^{62}Cu]-Cu(PTSM) is straightforward (Fig. 2), proceeding with high radiochemical yield and purity on a time frame compatible with the 9.74 min half-life of the label. The procedure, based on that described for [^{67}Cu]-Cu(PTSM) (*37*), involved buffering the acidic generator eluate with two equivalents of sodium acetate, followed by addition of ca 1.5 μg H_2(PTSM) dissolved in 0.100 μl ethanol and then mixing for 2-3 min. Since the product is thereby obtained in a concentrated salt solution, it was purified by adsorption from this aqueous solution onto a C_{18}-SepPak solid phase extraction cartridge, from which the [^{62}Cu]-Cu(PTSM) can be recovered in 0.1-0.2 ml ethanol.

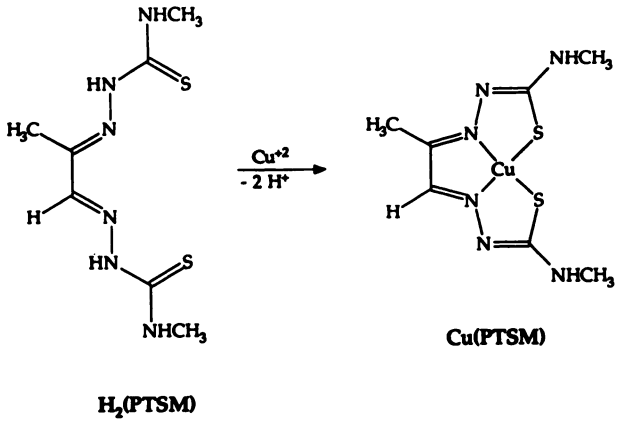

FIGURE 2
Synthesis and structural formula of Cu(PTSM).

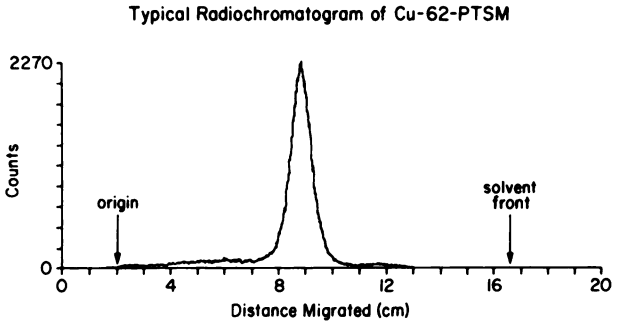

FIGURE 3
Radiochromatogram demonstrating radiochemical purity of the [^{62}Cu]-Cu(PTSM) product. (Silica gel thin-layer chromatography plate eluted with ethyl acetate).

This ethanol solution was then diluted with saline to a 5% alcohol concentration and filtered through a 0.2-μm sterile membrane to provide a product suitable for intravenous injection. End-of-synthesis radiochemical yields (based on ^{62}Cu activity available at end of elution without decay correction) were reproducibly around 50% with a synthesis time of 4.5–6 min. The radiochemical purity of the product, as assessed by thin-layer chromatography, generally exceeded 98% (Fig. 3).

The salt concentration of the initial [^{62}Cu]-Cu(PTSM) preparative solution could be reduced by eluting the generator with a more dilute HCl solution. The use of 2N HCl has been chosen, however, since it gives optimal separation of the copper(II) and zinc(II) ions on Dowex-1 (*56*). Since the final [^{62}Cu]-Cu(PTSM) product must be provided in a reasonably small volume of isotonic solution suitable for i.v. injection (<10 ml), this use of 2N HCl as the generator eluent ultimately necessitates the C_{18}-SepPak purification procedure used to isolate the product from the hypertonic reaction mixture. However, it should be recognized that this C_{18}-SepPak procedure has the added advantage of removing any remaining ionic copper from the product. In addition, the levels of ^{62}Zn breakthrough in the final [^{62}Cu]-Cu(PTSM) product are very substantially reduced by this SepPak purification. In three preparations where ^{62}Zn levels were determined in both the generator eluate and the final radiopharmaceuticals product, it was found that >99.97% of ^{62}Zn present in the initial ^{62}Cu solution was removed from the [^{62}Cu]-Cu(PTSM) product by the SepPak procedure described.

The specific activity of carrier-free ^{62}Cu is 1.89 × 10^{10} Ci/mole. As the actual specific activity of the ^{62}Cu radiopharmaceuticals that can be prepared will be limited by trace levels of copper in the synthetic reagents, prepurified Dowex-1 and ultrapure solvents were used in all operations. Although zinc concentrations in some of the reagents could exceed the concentration of copper(II), this poses no problem in Cu(PTSM) synthesis, since the affinity of the PTSM ligand for Cu(II) is 10^{10} greater than its affinity for Zn(II) (*44,58*). Copper levels

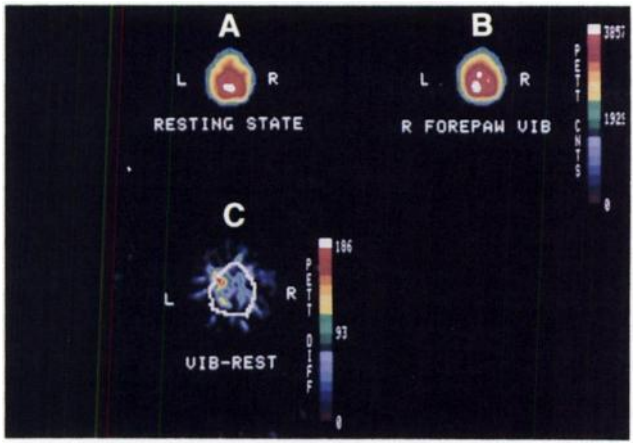

FIGURE 4
Horizontal PET images made after injection of (A) 4.2 mCi or (B) 17 mCi of [^{62}Cu]-Cu(PTSM) in a monkey. The length of each scan was 5 min. The animal was awake during the resting state scan (A) and a vibrator was passively held against the right forepaw during the second scan (B). Pixel-by-pixel subtraction of these two images after global normalization to a mean value of 1,000 PETT counts yields the subtraction image (C). The peak value on the subtraction-image scale indicates an 18.6% increase above the global mean value. The images are oriented anterior up with the animal's right to the right of the image.

in the final [^{62}Cu]-Cu(PTSM) product (0.2 ml ethanol eluate from the C_{18}-SepPak diluted to 10 ml with deionized water) are less than the 10 μg/l detection limit of ICP for copper. Thus, the amount of copper present in a final [^{62}Cu]-Cu(PTSM) preparation is dwarfed by the normal 1.4-2.1 mg/kg copper content of the human body (*59*).

The potential of Cu(PTSM) as a radiopharmaceutical for studying regional blood flow in multiple organs, most notably the brain and heart, has been previously demonstrated with longer-lived copper isotopes (^{64}Cu and ^{67}Cu) (*36–42*). The Cu(PTSM) complex has been shown to be relatively highly extracted by these organs, whereupon the copper label appears to be trapped intracellularly. The trapping of the copper label in tissue can proceed with reasonably high efficiency, since the highly stable Cu^{II}(PTSM) complex is quite susceptible to reductive decomposition by reaction with abundant cellular sulfhydryl groups (*43–47*). This reductive decomposition process liberates ionic copper, which is subsequently bound by intracellular macromolecules (*43–47*). The high tissue extraction of Cu(PTSM) insures a good correlation between tissue uptake and regional perfusion, while efficient trapping of the radiolabel in tissue allows imaging over an extended time frame, limited only by the physical half-life of the label. The 9.7-min half-life of ^{62}Cu appears to offer a good compromise between the need to image for several minutes to achieve good counting statistics (and allow use of slower, less sensitive PET cameras) and the need for rapid decay to allow sequential imaging studies at reasonable time intervals.

TABLE 1
Dosimetry Estimates for [^{62}Cu]-Cu(PTSM)

Organ	Absorbed dose (rads/mCi)
Kidneys	0.27
Liver	0.17
Lungs	0.054
Bone marrow (red)	0.0053
Whole body	0.013

Detection of regional changes in cerebral blood flow with ^{15}O-water and 40-sec PET scans provides an excellent method for mapping brain function (*11–5,60–62*). Copper-62-Cu(PTSM), with its longer half-life and apparent intracellular trapping, may permit longer acquisition times for such studies. To test this, we measured vibration-induced perfusion changes with [^{62}Cu]-Cu(PTSM) in the sensorimotor cortex of an awake monkey. The subtraction image (stimulation scan minus resting-state scan) shows a local increase in perfusion in sensorimotor cortex (Fig. 4). The measured regional perfusion increase was about 16% above the global mean value. This is comparable to values found using ^{15}O-water and a 40-sec scan (*54*). There did not appear to be a decrease in the regional response during the 5-min scan, as assessed by 1-min frames. Therefore, [^{62}Cu]-Cu(PTSM) can be used to identify stimulation-induced changes in brain perfusion and has the advantage of permitting longer times of data acquisition. However, there is the accompanying disadvantage that fewer ^{62}Cu than ^{15}O scans can be collected in a single subject in the same study session, due to the longer physical half-life of the generator-produced copper radionuclide.

Human radiation dosimetry estimates for [^{62}Cu]-Cu(PTSM) were made using previously published biodistribution data for [^{67}Cu]-Cu(PTSM) in the cynomolgus monkey (*37*). The radiation dose estimates presented in Table 1 were calculated by the MIRD system (*63–65*), assuming for each organ that the physical and biologic half-lives of the tracer are identical (i.e., no tracer clearance occurs) and that ^{62}Zn breakthrough does not contribute significantly to the total absorbed dose (*57*). The kidneys are expected to be the critical organ limiting the total dose of [^{62}Cu]-Cu(PTSM) that can be administered to human subjects with reasonable safety.

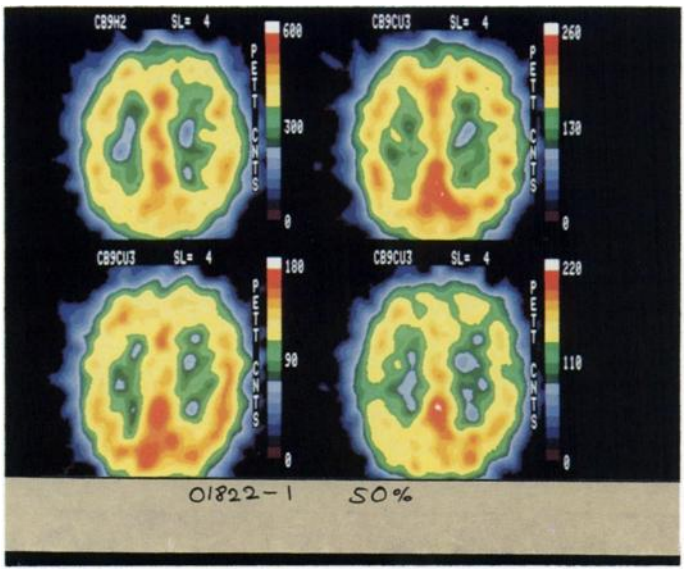

FIGURE 5
PET images of one transaxial slice of the human brain obtained with [^{62}Cu]-Cu(PTSM) and ^{15}O-water. The subject is facing the top of the image with his right to the right side of the image. Copper-62 images were reconstructed from data collected over three time periods postinjection: 0-5 min (upper right), 5-10 min (lower left), and 10-20 min (lower right). The cerebral perfusion image obtained with ^{15}O-water is shown upper left.

The results of a human brain-imaging PET study with [^{62}Cu]-Cu(PTSM) are illustrated in Figure 5. As observed in previous studies with non-human primates (*41*), Cu(PTSM) provides images of the human brain that compare favorably to the ^{15}O-water perfusion image (*49,50*). Reconstruction of ^{62}Cu images from data acquired over various time periods postinjection demonstrates that there is no clearance or redistribution of the tracer during this 20-min imaging period, consistent with our earlier animal results (*37,41*). Thus, [^{62}Cu]-Cu(PTSM) appears promising as a tracer for cerebral blood flow that could be used by PET-imaging facilities lacking an in-house cyclotron.

Relatively high quality images were also obtained of human myocardium after i.v. administration of [^{62}Cu]-Cu(PTSM) to a normal human subject (Fig. 6). The distribution of radioactivity after administration of ^{62}Cu correlated closely to the distribution of ^{15}O-labeled water (Fig. 6), which we have previously shown to accurately reflect regional myocardial perfusion (*23–27*). The results of this preliminary human study of the heart suggest that [^{62}Cu]-Cu(PTSM) will be a valuable tracer for delineation of myocardial perfusion. We previously demonstrated that single-pass extraction fraction of Cu(PTSM) by the heart was high, and that once extracted, Cu activity was retained (*40*). In dog studies with [^{67}Cu]-Cu(PTSM), we demonstrated that the distribution of tracer correlated closely with flow estimated by concomitantly administered radiolabeled microspheres (*42*). Nonetheless, further studies will be necessary to delineate the kinetics of this tracer over a wide range of flow and physiologic conditions. Myocardial images obtained after [^{62}Cu]-Cu(PTSM) injection were superior to those obtained in our laboratory after administration of rubidium-82-chloride, because the ultra-short physical half-life of rubidium-82 (76 sec) results in poor counting statistics. Accordingly, [^{62}Cu]-Cu(PTSM) should be particularly useful in centers with PET, but without a cyclotron. In addition, the availability of a generator-produced flow tracer should enable the study of patients with acute cardiac disorders, such as acute ischemia, on a 24 hr per day basis and allow

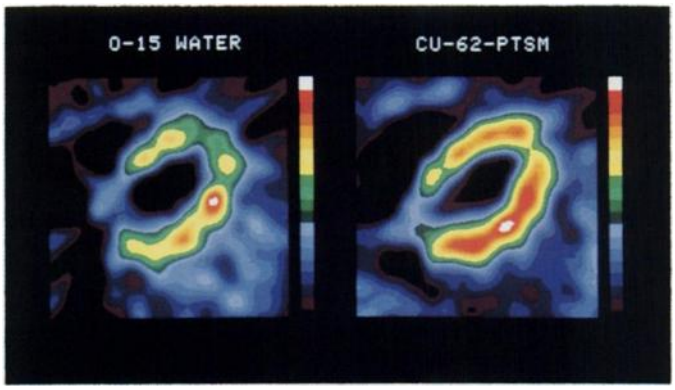

FIGURE 6
Reconstructions of one midventricular transverse slice of the human heart obtained from a normal subject after administration of intravenous ^{15}O-water (left) and after administration of [^{62}Cu]-Cu(PTSM). Both reconstructions have been corrected for radioactivity emanating from the blood pool. The distribution of [^{62}Cu]-Cu(PTSM) is homogeneous and correlates well with the distribution of labeled water. In these images, anterior myocardium is to the upper right, septum is to the upper left, and the left ventricular free wall to the lower right. The discontinuity at the lower left represents the mitral valve plane.

assessment of the adequacy of reperfusion after interventions such as thrombolytic therapy or balloon angioplasty.

CONCLUSIONS

The results of this study demonstrate the acceptable performance of a $^{62}Zn/^{62}Cu$ radionuclide generator system at high activity levels. Copper-62-labeled Cu(PTSM) can be conveniently prepared within 10 min with a radiochemical purity which exceeds 98%. Preliminary studies in monkey as well as in human subjects demonstrate the ability of [^{62}Cu]-Cu(PTSM) to provide high quality images of the brain and heart and to accurately map cerebral and myocardial perfusion, corroborating previous experimental studies with longer-lived copper radionuclides. Accordingly, [^{62}Cu]-Cu (PTSM) should be a useful generator-produced radiopharmaceutical permitting assessment of cerebral and myocardial perfusion with PET in centers that do not have access to cyclotron-produced radionuclides.

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