Copper-62-pyruvaldehyde bis(N^4-methyl-thiosemicarbazone) PET imaging in the detection of coronary artery disease in humans

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Background. **Copper-62 (II)-pyruvaldehyde bis(N^4-methyl-thiosemicarbazone) (PTSM) has been proposed for cardiac imaging with positron emission tomography (PET). This study evaluated the agreement between Cu-62-PTSM and coronary angiography in the detection of occlusive coronary artery disease. The normalcy rate for Cu-62-PTSM PET in a group of healthy volunteers was also assessed.**

Methods and Results. **Forty-five subjects completed the study. Twenty-eight patients underwent stress technetium-99m sestamibi single photon emission computed tomography (SPECT) imaging and cardiac catheterization followed by Cu-62-PTSM rest/dipyridamole stress PET scans, and 17 volunteers underwent Cu-62-PTSM rest/dipyridamole stress PET scans. Cu-62-PTSM myocardial perfusion defects were identified in 100% of patients with 3-vessel disease (n = 8), 100% of patients with 2-vessel disease (n = 9), and 67% of patients with single-vessel disease (n = 6). When considering individual vessels, Cu-62-PTSM perfusion defects were seen in 72% of patients with occlusive disease in the left anterior descending artery territory, 67% in the left circumflex artery territory, and 60% in the right coronary artery territory, respectively. All 17 healthy volunteers had Cu-62-PTSM scans interpreted as normal, for a normalcy rate of 100%.**

Conclusions. **Perfusion abnormalities are demonstrated by means of Cu-62-PTSM PET in 91% of patients with occlusive coronary artery disease seen at the time of cardiac catheterization, and it shows an excellent normalcy rate of 100%. (J Nucl Cardiol 2001;8:67-74.)**

Key Words: Positron emission tomography • copper-62 (II)-pyruvaldehyde bis(N^4-methyl-thiosemicarbazone) • coronary artery disease

The zinc-62/copper-62 generator system has been evaluated as a potential positron emission tomography (PET) radionuclide generator system[1-5] that is capable of providing PET perfusion tracers to stand-alone PET facilities at a reasonable cost. This may be particularly advantageous to satellite PET facilities performing ^{18}F-fluoro-2-deoxyglucose cardiac studies, eliminating the potential shortcomings of the now frequently used hybrid approach, in which perfusion imaging is assessed with single photon emission computed tomography (SPECT) and glucose metabolism with PET. This study evaluated the agreement between Cu-62 pyruvaldehyde bis(N^4-methyl-thiosemicarbazone) (PTSM) PET and coronary angiography in a population of patients with abnormal SPECT technetium-99m sestamibi scans referred for coronary angiography. A group of healthy volunteers with a less than 5% likelihood of coronary artery disease were also studied to determine the normalcy rate for Cu-62-PTSM.

METHODS

Patient Population

The study was approved by the Human Subjects Committee at the University of Wisconsin and Madison Veterans Hospital,

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and written, informed consent was obtained from all patients before the PET study. Twenty-eight patients and 17 healthy volunteers were recruited. The mean pretest likelihood of coronary artery disease in healthy volunteers was based on age, sex, and symptom classification, according to the criteria of Diamond and Forrester et al.[6] Patients recruited for the study were being examined for symptoms of chest pain, dyspnea on exertion, or presurgical evaluation. Most patients were referred for stress Tc-99m sestamibi SPECT imaging and subsequent coronary angiography; however, 5 patients were referred for Tc-99m sestamibi SPECT imaging subsequent to cardiac catheterization. Cu-62-PTSM scans were performed within 28 days of the Tc-99m sestamibi SPECT scans. Patients with unstable angina, recent myocardial infarction (< 3 days), hypotension, significant ventricular arrhythmias, bronchospasm or asthma requiring the use of theophylline, history of cerebrovascular accident, cancer, autonomic insufficiency, uncontrolled hypertension, or other acute illness were excluded. All female subjects had negative results on pregnancy tests before their inclusion in the study.

Zn-62/Cu-62 Generator and Cu-62-PTSM Production

The Zn-62/Cu-62 generator was prepared at Proportional Technologies (Houston, Tex) and shipped to the University of Wisconsin PET Center.[7,8] Quality control was performed in the manner of our earlier study.[9] After overnight shipment, the generator was eluted to obtain doses for clinical study.

Cu-62-PTSM PET Imaging Procedure and Data Processing

PET studies were performed at the University of Wisconsin PET Center with the GE Advance Scanner (General Electric, Waukesha, Wis). For the PET studies, subjects were positioned in the supine position, feet first, in the scanner. After optimization of subject position for visualization of the entire heart, transmission scans were performed for 15 minutes by using 3 rotating germanium-68 pin sources. After the transmission scan, subjects received an intravenous bolus injection of Cu-62-PTSM (20.19 ± 3.06 mCi, mean ± SD) through a peripheral intravenous tube, and PET imaging was performed for 22 minutes. After completion of the resting scans, subjects were removed from the PET scanner. They returned 30 to 40 minutes after the resting scans and were repositioned in the PET scanner. A second transmission image was acquired. For stress scans, patients received 0.56 mg/kg dipyridamole in a 4-minute period, followed by a bolus infusion of Cu-62-PTSM (19.44 ± 3.27 mCi, mean ± SD), 4 minutes after completion of the dipyridamole infusion, and PET images were repeated. Scan data were summed during the final 20 minutes of acquisition, to eliminate blood pool activity, and filtered by using a Butterworth filter with a frequency cutoff of 0.4, order 6.0. Images were then reformatted into standard short-axis, vertical long-axis, and horizontal long-axis planes for interpretation.

SPECT Tc-99m Sestamibi Imaging Procedure and Data Processing

Tc-99m sestamibi SPECT scans were performed on a Trionx Triad 3-headed camera (Twinsburg, Ohio) at the University of Wisconsin Hospital and a General Electric XRT single-head camera (Milwaukee, Wis) at the Veterans Hospital. Data from the Tc-99m sestamibi SPECT scans were displayed in standard short-axis, vertical long-axis, and horizontal long-axis planes. Individual slices were 6 mm thick. When available, stress gated images were analyzed. A Butterworth filter with a frequency cutoff of 0.4, order 5.0 for the stress data and a Hanning Filter with a frequency cutoff of 0.7, order 7.5 for the rest data were used on the Trionx camera. A Butterworth filter with a frequency cutoff of 0.35, order 5.5 for the stress data and a frequency cutoff of 0.32, order 7.5 for the rest data was used on the General Electric camera.

PET and SPECT Image Analysis

Three experienced readers, who had no knowledge of patient or volunteer identity, reviewed the rest and stress PET images, the rest and stress SPECT data, and the gated SPECT images. Because abnormal results on a SPECT scan served as the basis for referral of patients to cardiac catheterization, a direct comparison between the performance of PET and SPECT is not appropriate. A comparison of visual assessment of image quality and defect intensities between PET and SPECT images was performed. Both defect size (0, normal; 1, small; 2, medium; 3, large) and defect intensity (0, normal; 1, mild; 2, moderate; 3, severe) were analyzed for PET and SPECT images. To equalize the readers' prestudy bias between the PET and SPECT studies, normal SPECT studies were randomly inserted into the reading sequence. PET images were interpreted independently and in random order, without knowledge of subject identification. Differences between readers were resolved by means of a consensus opinion. The final report was the consensus of the 3 readers. The heart was subdivided into its 4 major walls: anterior, septum, lateral, and inferior. Each of these 4 quadrants was further subdivided into 3 subsegments: basal, mid, and distal, with the apex considered to be 1 segment, for a total of 13 segments analyzed. A small defect was defined as a defect that involved less than 1 segment of a major wall. A moderate defect involved 2 segments. A large defect involved 3 segments. The walls were defined strictly as the anterior wall from the 10- to 2-o'clock position, the lateral wall from the 2- to 4-o'clock position, the inferior wall from the 4- to 8-o'clock position, and the septum from the 8- to 10-o'clock position. Intensities were defined as: count rates at 100% to 85% of maximum, normal; 85% to 60%, mild decrease; 60% to 40%, moderate decrease; and 40% to 0%, severe decrease in counts. Stress and rest images were analyzed, and a reversible defect was defined as an improvement in defect intensity of at least 20%.

Coronary Angiography

Cineangiograms of the coronary arteries were obtained in multiple projections by using a Philips angiographic system (5-inch intensifier, image resolution of 3.8-line pair/mm). Two

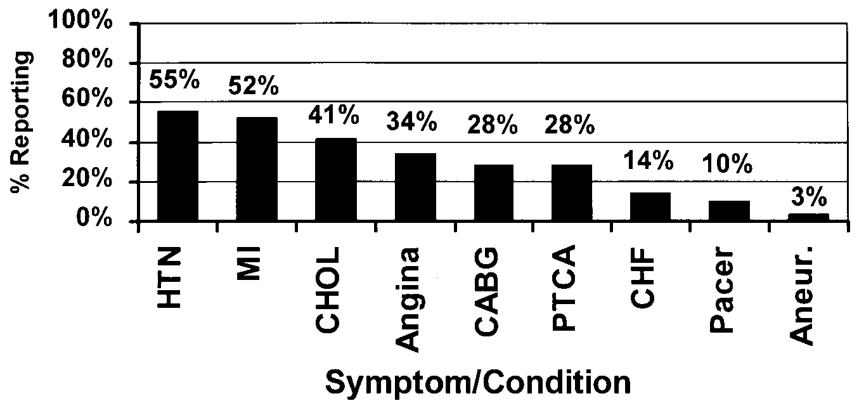


Figure 1. The prevalence of various cardiac-related diseases and symptoms in the patients studied (N = 28).

experienced coronary angiographers who had no knowledge of the Cu-62-PTSM or Tc-99m sestamibi scan results evaluated the angiographic data. The angiographic data were evaluated simultaneously by the 2 reviewers, and a consensus opinion of the coronary stenosis severity was made.

Assignment of Coronary Territories to Myocardial Segments

For PET images, the left anterior descending artery included the anterior wall, septum, and apex. The right coronary artery was assigned the inferior wall. The left circumflex artery was assigned the lateral wall. The inferior wall was reassigned to the left circumflex artery when the latter was dominant.

RESULTS

Patient Characteristics

Twenty-eight patients (24 men, 4 women) and 17 healthy volunteers (7 men, 10 women) were included the study. The mean pretest likelihood of coronary artery disease in our volunteers was 4.3%. Patient age ranged from 41 to 81 years (mean, 62 years), and volunteer age ranged from 21 to 58 years (mean, 31 years). The prevalence of various cardiac-related conditions is shown in Figure 1. Fifteen patients had a history of myocardial infarction. Nine patients had previously undergone coronary bypass grafting surgery, and 9 patients had undergone earlier percutaneous transluminal coronary angioplasty. One male patient did not complete the stress dipyridamole stress Cu-62-PTSM scan and was excluded from analysis. Twenty-two patients underwent treadmill exercise stress Tc-99m sestamibi SPECT scans, 4 patients underwent adenosine stress, and 2 patients underwent dobutamine stress Tc-99m sestamibi SPECT scans. All patients underwent rest-dipyridamole stress Cu-62-PTSM scans.

Table 1. Cu-62-PTSM defects corresponding to number of diseased vessels

	% Cu-62-PTSM defects
3-vessel disease (≥75%)	100% (n = 8)
3-vessel disease (≥50%)	93% (n = 14)
2-vessel disease (≥75%)	100% (n = 9)
2-vessel disease (≥50%)	71% (n = 7)
Single-vessel disease (≥75%)	67% (n = 6)
Single-vessel disease (≥50%)	75% (n = 4)

Detection of Significant Coronary Artery Disease

Of the 28 patients who underwent cardiac catheterization, 23 (82%) had a 75% or greater stenosis, and 25 (89%) had a 50% or greater stenosis in at least 1 vessel. Of the 23 patients with a 75% or greater stenosis, 21 (91%) had 1 or more defects on Cu-62-PTSM, and 21 (91%) had 1 or more defects on Tc-99m sestamibi scans. Of the 25 patients with a 50% or greater stenosis, 21 (84%) had 1 or more defects on Cu-62-PTSM, and 23 (92%) had 1 or more defects on Tc-99m sestamibi scans. Because of the number of diseased coronary vessels, the percentage of patients demonstrating a Cu-62-PTSM perfusion defect in at least 1 segment is shown in Table 1. Agreement between Cu-62-PTSM and coronary angiography for coronary stenosis (≥ 75%) was 91% (21 of 23). Agreement between Cu-62-PTSM and coronary angiography for coronary stenosis (≥ 50%) was 84% (21 of 25). Both defect size (0, normal; 1, small; 2, medium; 3, large) and defect intensity (0, normal; 1, mild; 2, moderate; 3, severe) were greater for Cu-62-PTSM than for Tc-99m sestamibi (1.89 vs 1.76 and 2.05 vs 1.89, respectively). An example of a Cu-62-PTSM PET and Tc-99m

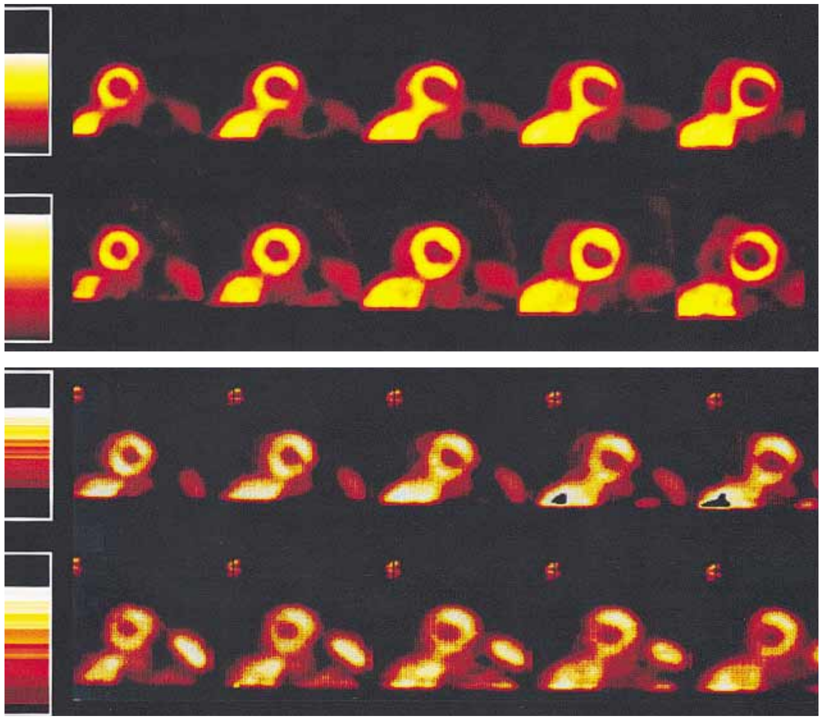


Figure 2. A patient with coronary angiographic evidence of occlusive (75%) stenosis in the proximal left circumflex artery with a reversible perfusion abnormality in the inferolateral on both Cu-62-PTSM PET and Tc-99m sestamibi SPECT is shown. Five short-axis images are shown from apex to base for stress/rest Cu-62-PTSM images *(top)* and stress/rest SPECT Tc-99m sestamibi images *(bottom).*

Table 2. Cu-62-PTSM defects corresponding to individual vessel territories

	% Cu-62-PTSM defects
Left anterior descending artery ≥ 75% (n = 18)	72%
Left anterior descending artery ≥ 50% (n = 22)	67%
Left circumflex artery ≥ 75% (n = 15)	67%
Left circumflex artery ≥ 50% (n = 20)	50%
Right artery ≥ 75% (n = 15)	60%
Right artery ≥ 50% (n = 18)	56%

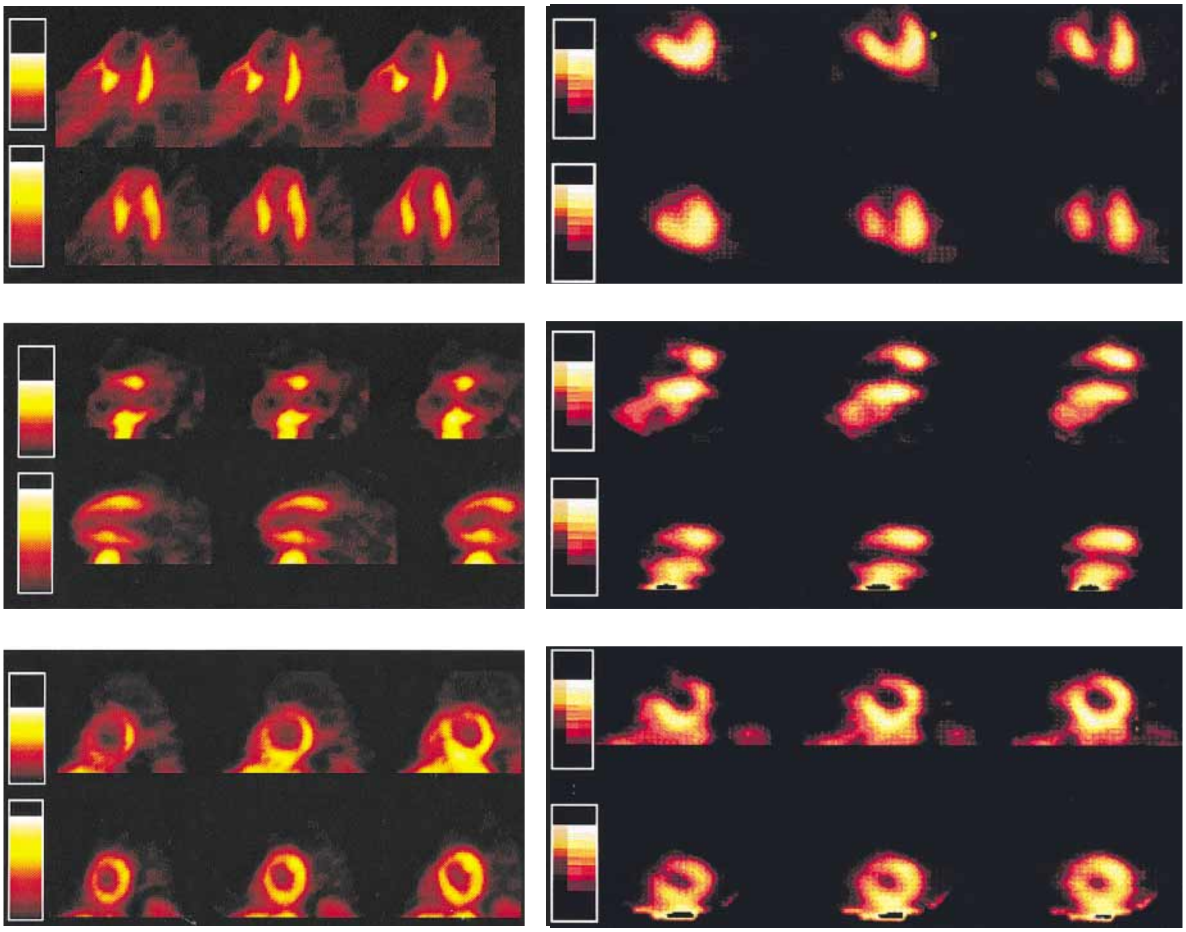
sestamibi SPECT scan from a patient with occlusive single-vessel coronary artery disease (75% stenosis) is shown in Figure 2.

Five patients who had abnormal results on Tc-99m sestamibi scans and who were referred for cardiac catheterization had no coronary artery disease 75% or greater identified with coronary angiography. All 5 of these patients had normal results on the Cu-62-PTSM scans.

Overall image quality as judged by means of defect contrast, background activity, and delineation of myocardial borders appeared to be superior with Cu-62-PTSM, as compared with Tc-99m sestamibi. Readers were asked to visually assess overall image quality (excellent, good, fair, and poor) and to make comments on factors they felt affected image interpretation. Stress images (58.7% vs 13.8%, 34.5% vs 75.8%, 6.8% vs 10.4%, and 0% vs 0%) were scored excellent, good, fair, and poor for Cu-62-PTSM and Tc-99m sestamibi, respectively. Resting images (65.5% vs 13.8%, 34.5% vs 75.9%, 0% vs 10.3%, and 0% vs 0%) were scored excellent, good, fair, and poor for Cu-62-PTSM and Tc-99m sestamibi, respectively. The most common reason for decreased image quality was excessive liver uptake for both Cu-62-PTSM and Tc-99m sestamibi; however, this was more common with Tc-99m sestamibi.

Assessment of Individual Coronary Vessels

A total of 83 vessels were included in Cu-62-PTSM regional analysis. Forty-eight vessels demonstrated a stenosis of 75% or greater, 59 vessels demonstrated a



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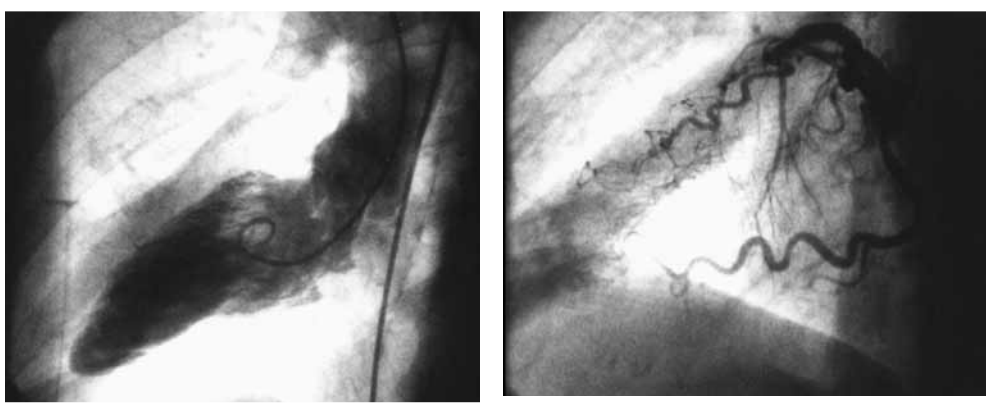

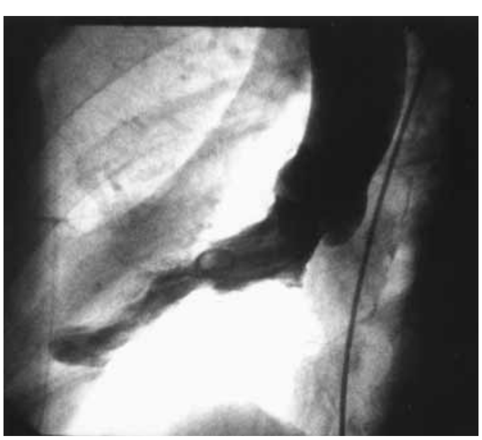

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Figure 3. A, A patient with coronary angiographic evidence of occlusion of the proximal left anterior descending artery with a large defect on PET Cu-62-PTSM and SPECT Tc-99m sestamibi images in the anterior wall, apex, and septum. Three horizontal long-axis, vertical long-axis, and short-axis slices are shown, with stress images displayed above resting images. The Cu-62-PTSM images are displayed on the left, and the Tc-99m sestamibi images are displayed on the right. There is partial reversibility into the anterior wall and septum on Cu-62-PTSM images, which is principally fixed on the Tc-99m sestamibi images. The apical portion of the defect is principally fixed on both Cu-62-PTSM and Tc-99m sestamibi images consistent with an apical myocardial infarction. **B,** Coronary angiogram of the left coronary injection from the lateral view (apex to left of image, base to right of image) demonstrating 100% occlusion of the proximal left anterior descending artery distal to the first septal perforator *(top right)*. End diastolic *(top left)* and end systolic *(bottom left)* frames in the right anterior oblique projection on the corresponding ventriculogram demonstrate a small apical aneurysm.

stenosis of 50% or greater, and 35 vessels did not have significant disease. A Cu-62-PTSM perfusion defect was identified in 67% of territories with 75% or greater disease in an individual vessel and in 58% of territories with 50% or greater disease in an individual vessel. When considering individual vessels, the percentage of segments demonstrating a Cu-62-PTSM defect corresponding to individual coronary territories is shown in Table 2. Reversible perfusion defects were noted in 16 patients (57%), fixed perfusion defects were noted in 14 patients (50%), and no defects were noted in 7 patients (25%). Of the 16 patients with reversible perfusion defects, 9 (56%) were felt to have a combination of ischemia and scar. Of the 5 patients with fixed perfusion defects, 4 had regional akinesis, corresponding to the fixed segment, on a left ventriculogram performed during cardiac catheterization. An example of a patient with a large anterior, apical, and septal defect, which is partially reversible, is shown in Figure 3*A*. One hundred percent occlusion of the left anterior descending artery beyond the first septal perforator with right to left collateral filling of the left anterior descending artery was demonstrated by means of coronary angiograms. An apical aneurysm was demonstrated by means of a left ventriculogram (Figure 3*B*).

Cu-62-PTSM Results in Healthy Volunteers

Seventeen healthy volunteers, with a less than 5% likelihood of coronary artery disease, underwent rest-dipyridamole stress Cu-62-PTSM scans without complications. All scans were interpreted as normal, for a normalcy rate of 100%. Stress and rest image quality were visually scored with (17.6%, 70.6%, 11%, and 0%) stress images, and (47%, 53%, 0%, and 0%) rest images were scored as excellent, good, fair, and poor, respectively.

DISCUSSION

For PET centers that lack the availability of an in-house cyclotron, generator-produced Cu-62-PTSM represents an alternative PET perfusion tracer for the detection of coronary artery disease. The synthesis of Cu-62-PTSM has been simplified with the availability of a compact modular Zn-62/Cu-62 generator system capable of delivering clinically useful doses (35 mCi) every 20 to 30 minutes.[5] Several studies have demonstrated the potential of Cu-62-PTSM as a PET perfusion tracer.[10-16] This study, performed in a heterogeneous group of patients with varying amounts of coronary artery disease and before revascularization typical of a patient population seen in clinical practice, is the first to compare the accuracy of Cu-62-PTSM PET as a means of detecting occlusive coronary artery disease with coronary angiography.

The overall ability of Cu-62-PTSM as a means of demonstrating a defect in patients with angiographically significant coronary artery disease (≥75%) was 91%. This is comparable with clinical studies with Tc-99m sestamibi[17-20] and rubidium 82.[21] The ability to detect individual coronary artery disease for Cu-62-PTSM was also similar to a previous validation study with Tc-99m sestamibi, in which sensitivity rates for the detection of significant left anterior descending, left circumflex, and right coronary artery disease were 69%, 70%, and 77%, respectively.[20] Five patients with abnormal Tc-99m sestamibi scan results in our study were found to have no significant coronary artery disease (≥75%) at the time of cardiac catheterization and had normal results on Cu-62-PTSM scans without perfusion defects. These results demonstrate some of the potential advantages of PET imaging, which may relate to the improved spatial resolution and the ability to obtain attenuation corrected images.

The agent Rb-82 was the first available generator-produced radiopharmaceutical to be used as a means of evaluating coronary artery disease. Clinical studies with Rb-82 have demonstrated high sensitivity and specificity rates for the detection of coronary artery disease (84% to 90%).[22-24] In a large community hospital-based study, the average sensitivity rate was 87%, and the average specificity rate was 88% for the detection of coronary artery disease greater than 67%.[21] The strontium 82/Rb-82 generator is commercially available and typically is purchased by PET centers on a monthly basis. At least 1 center has shown this to be an accurate, cost-effective method for assessing coronary heart disease.[25] The high cost of the generator may be prohibitive at some centers unable to maintain a high clinical volume. Additionally, the supply of Sr-82 is becoming more limited, and this may result in increased costs.

The short half-life of the parent compound Zn-62 ($T_{1/2}$ = 9.3 hrs) is a potential advantage for centers with intermediate or low clinical volumes. Centers can order the generator for days on which perfusion imaging is scheduled, while scheduling other studies on alternate days. The Zn-62/Cu-62 generators used in this study were each produced at a cost of approximately $1000. Thus, if used twice weekly, the cost would be significantly less than that of the Sr-82/Rb-82 generator, which carries an average monthly cost of approximately $25,000.

Human studies have also demonstrated the ability to quantitate blood flow with Cu-62-PTSM, but the results have been disappointing.[12] Competitive binding of Cu-62-PTSM to human serum albumin has been postulated as the most likely reason for the impaired tissue extraction seen in humans at hyperemic flows.[26] Increased uptake of Cu-62-PTSM by the liver may adversely affect image quality, as a result of cross contamination of activity into the inferior wall of the heart.[10] However, this did not affect overall image interpretation in this study or earlier studies. It is less of a problem in PET imaging, because the much higher spatial resolution than that of SPECT affords better spatial separation of heart and liver.[27-29]

Cu-62-PTSM will likely be a clinically useful tracer for the detection of coronary heart disease. The advantages of Cu-62-PTSM include high count rates and myocardial image quality, flexibility of scheduling, lower cost with the Zn-62/Cu-62 generator compared with Rb-82, and favorable half-life and dosimetry of the Cu-62-PTSM complex. Disadvantages of Cu-62-PTSM must be recognized. They include increased liver uptake resulting in spillover into the inferior wall and binding of tracer in the blood pool because of association with serum albumin. Impaired tracer extraction at high flows, making absolute blood flow quantitation difficult, has also been noted. Decreased extraction at high flow rates may be important in the assessment of defect severity, although defect size was greater with Cu-62-PTSM than Tc-99m sestamibi in this study.

Study Limitations

A selection bias was present in this study because of the referral of patients to cardiac catheterization after the Tc-99m-sestamibi SPECT scans. Direct comparisons of the diagnostic accuracy of Cu-62-PTSM and Tc-99m sestamibi in our patients were, therefore, not performed. Our study patients were recruited from a population seen in our laboratory for diagnostic testing with cardiac SPECT and, therefore, represent a typical diverse population referred for cardiac evaluation. A comparison of the Cu-62-PTSM scans with a Tc-99m sestamibi scan in the healthy volunteers would be expected to increase the strength of the normalcy rate for Cu-62-PTSM PET. Volunteers were not age- or weight-controlled in this study, and, on average, they weighed less than patients. This may account for liver spillover having a greater affect on the overall image quality.

Conclusions

We have demonstrated the ability of Cu-62-PTSM PET as a means of detecting occlusive coronary artery disease in a heterogeneous population. In this population, Cu-62-PTSM PET perfusion defects were identified in 91% of patients with occlusive coronary artery disease. Furthermore, the normalcy rate in a group of volunteers with a less than 5% likelihood of coronary artery disease was excellent, at 100%.

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