PET Imaging with ^{62}Cu-ETS in a Human Clinical Trial at the University of Wisconsin - Madison

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***Abstract*–Copper(II) *bis*(thiosemicarbazone) compounds show promise for clinical use in the measurement of tissue blood flow with positron emission tomography (PET). ^{62}Cu-PTSM has been extensively evaluated as a myocardial and general purpose flow agent. Although an effective agent, it exhibits albumin binding in human plasma which limits its performance in high blood flow imaging. A new agent, ^{62}Cu-ETS, exhibits no such species differentiation of albumin binding. In this study, ten healthy human volunteers were subjected to ^{62}Cu-ETS PET imaging to obtain percent injected dose values for major organs, including the blood, brain, kidneys, liver, lungs, and myocardium, by measuring count densities within defined regions of interest (ROI's) around the general anatomical structure and dividing by the injected dose, correcting for losses at the injection site. These results were then compared to an analogous ^{62}Cu-PTSM PET imaging study completed previously utilizing the same imaging methods. For effective comparison, data for the ^{62}Cu-PTSM study was reanalyzed using the same ROI procedure as was performed on the ^{62}Cu-ETS study. ^{62}Cu-ETS shows similar myocardial uptake compared to ^{62}Cu-PTSM, but kidney uptake is two fold higher than resting myocardium compared with only 1.3 fold for ^{62}Cu-PTSM. Hence ^{62}Cu-ETS shows high promise for the important application of hyperemic myocardial flow measurement as well as renal imaging. An additional advantage of ^{62}Cu-ETS is that liver uptake which can interfere with myocardial imaging is reduced by about 2 fold relative to that of ^{62}Cu-PTSM.**

I. Introduction

RADIONUCLIDE methods for imaging regional tissue perfusion are well established in the clinical evaluation of myocardial, cerebral, and tumor perfusion. Positron emission tomography (PET) offers clear advantages for actual *quantitative* measurement of regional perfusion, most notably, absolute correction of images for the effects of photon attenuation by the body. Despite the advantages, its widespread clinical application has been limited by the economic burden associated with purchase, operation, and maintenance of the in-house biomedical cyclotron required to produce short-lived radionuclides required for perfusion measurements. Proportional Technologies, Inc. (PTI) has developed a convenient ^{62}Zn/^{62}Cu generator system for production of ^{62}Cu-labeled *bis*(thiosemicarbazone) compounds, such as ^{62}Cu-PTSM, ^{62}Cu-ETS, and ^{62}Cu-ATSM. A highly simplified and miniaturized generator has been developed which produces sterile, pyrogen free $^{62}Cu^{2+}$, and together with lyophilized ligand kits (e.g. H_2PTSM, H_2ETS, and H_2ATSM), the respective ^{62}Cu-labeled radiopharmaceuticals can be instantly synthesized. This modular generator and ligand kits can be delivered at a low cost to users throughout the continental US via overnight delivery from PTI's production facilities in Houston.

Copper(II) *bis*(thiosemicarbazone) compounds show promise for clinical use in the measurement of tissue blood flow and hypoxia with PET. The lead compound, Cu-PTSM, exhibits great promise as a multi-organ tracer for flow quantification; however, studies have shown that interaction with human serum albumin (HSA) limits this radiopharmaceutical in *quantification* of myocardial (or renal) perfusion at high flow rates by limiting the tracer's ability to passively diffuse into tissue at high rates of flow [1]. The "second generation" ^{62}Cu-ETS radiopharmaceutical exhibits properties similar to ^{62}Cu-PTSM *in vivo*, while avoiding limitations imposed by human albumin binding. Previous limited human studies have demonstrated the potential of ^{62}Cu-ETS PET as a quantitative regional perfusion agent with exceptional high flow uptake characteristics.

Research efforts in validation of Cu-ETS as a PET tracer of regional perfusion are continued in the current biodistribution study of ^{62}Cu-ETS utilizing whole-body PET imaging in ten healthy human volunteers, conducted at the University of Wisconsin at Madison. Biokenetic behavior in human subjects is reported and compared to previous results using similar technique for ^{62}Cu-PTSM.

II. Methods

PET imaging was performed on a GE Advance Whole-body Tomographic Scanner (General Electric, Inc., Waukesha, WI). The volunteers were positioned feet first in the scanner and arms down at their sides, and a whole-body transmission scan was performed prior to the intravenous injection of 10-25 mCi of ^{62}Cu-ETS. Imaging was performed starting from the top of the head and ending at mid thigh level. Three minute PET static acquisitions were done at six positions, and a total of three whole-body PET scans were performed at 20 minute intervals.

Image analysis consisted of reconstruction of the ^{62}Cu-ETS raw image data in the transaxial format with attenuation correction, which was then reformatted into coronal slices

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used for region of interest (ROI) analysis. The reconstructed coronal images were converted to a 10 point color scale and displayed so that the major organs of interest could be easily visualized. The maximum uptake in the organ of interest was defined as 100% uptake and borders were then defined by general organ anatomy and limited by uptake that was at 20% of the 100% maximum value. Count densities were determined as the total activity for that organ. These count densities were then divided by the injected dose corrected for losses at the injection site to give percent uptake. This method eliminates the use of standard organ weights and gives a self-calibrating, absolute percentage of injected dose.

The ^{62}Cu-PTSM data was taken from an analogous PET imaging study formerly completed utilizing the same methods described for the ^{62}Cu-ETS study [2], [3]. At that time, biodistribution analysis was completed using a simplified method of drawing a representative region within the organ of

Fig. 1 ^{62}Cu-ETS coronal whole body PET images (9 mm slice) transecting the heart in normal volunteers.

Fig. 2 ^{62}Cu-PTSM coronal whole body PET images (9 mm slice) transecting the heart in normal volunteers.

interest and extrapolated using standard organ weights. For the purposes of comparison, this data has been reanalyzed defining regions in the same manner as was done for the ^{62}Cu-ETS study.

III. Results

^{62}Cu-ETS and ^{62}Cu-PTSM coronal whole body images for a total of 19 subjects, showing 9 mm coronal slices optimally transecting the heart and kidneys, are shown in Fig. 1-4.

Percent injected dose values and ratios for ^{62}Cu-ETS and ^{62}Cu-PTSM for major organs are listed in Table I. As expected from *in vitro* work, ^{62}Cu-ETS shows about a two fold greater blood uptake and more than a two fold greater kidney and lung uptake. Lung uptake of ^{62}Cu-ETS shows a striking gradient increasing by more than two fold moving from anterior to posterior lung. Liver uptake is reduced about two fold while resting heart uptake is somewhat greater than ^{62}Cu-PTSM. Uptake of ^{62}Cu-ETS in the brain is significantly lower

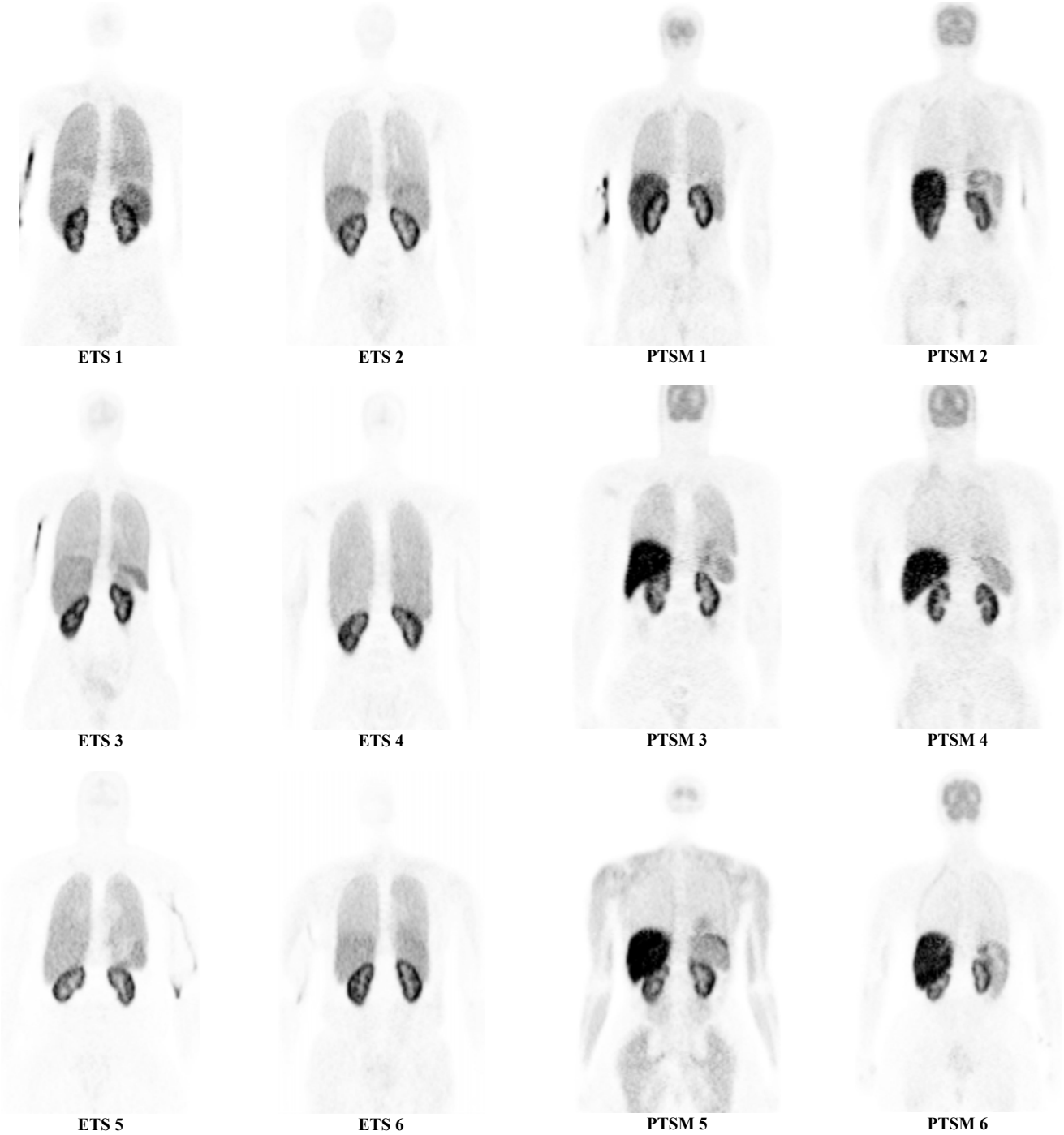

Fig. 3 ^{62}Cu-ETS coronal whole body PET images (9 mm slice) transecting the kidneys in normal volunteers.

Fig. 4 ^{62}Cu-PTSM coronal whole body PET images (9 mm slice) transecting the kidneys in normal volunteers.

(less than two fold) than that of ^{62}Cu-PTSM.

TABLE I
PERCENT INJECTED DOSE IN ORGANS OF INTEREST

Organ	^{62}Cu-ETS	^{62}Cu-PTSM	Ratio, ETS/PTSM
Blood	15.24	7.89	1.9
Brain	1.45	3.67	0.4
Kidneys	6.19	2.81	2.2
Liver	10.29	18.10	0.6
Lungs	12.35	3.74	3.3
LV Myocardium	1.37	1.20	1.2

As another measure of response to high flow, Table II compares the percent injected dose per cc of the left ventricular myocardium and the kidney respectively for the two agents. ^{62}Cu-ETS showed a full two fold kidney/myocardium uptake ratio while the kidney/myocardium ratio was only 1.3 for ^{62}Cu-PTSM. To the degree that kidney flow can be considered a surrogate for stressed myocardial flow, this analysis provides further evidence of the great promise of ^{62}Cu-ETS for hyperemic myocardial imaging.

TABLE II
PERCENT INJECTED DOSE PER CC OF TISSUE AND KIDNEY/MYOCARDIUM RATIOS

Organ	^{62}Cu-ETS	^{62}Cu-PTSM
LV Myocardium	0.0055	0.0043
Kidney	0.0112	0.0056
Kidney/LV Myocardium Ratio	2.0	1.3

Surrounding organ uptake, specifically lung and liver uptake, can interfere with myocardial imaging. In order to judge such interference it is appropriate to compare surrounding organ uptake per cc of tissue to heart uptake per cc. Table III compares the percent injected dose per cc of the left ventricular myocardium, lung, and liver for the two agents. In these measurements uptake over the entire organ was averaged in all cases. ^{62}Cu-ETS showed liver uptake to be 1.15 times greater and lung uptake to be 0.73 times less than myocardium uptake, while ^{62}Cu-PTSM showed liver uptake to be almost two fold greater and lung uptake to be 0.33 times less than myocardium uptake. Compared to ^{62}Cu-PTSM, the ^{62}Cu-ETS agent showed a much improved myocardium/liver ratio. Although lung uptake increased more than 2 fold with ^{62}Cu-ETS, it should be noted that average lung uptake was still significantly less than the myocardium. It also should be noted that lung uptake is not uniform showing a well known anterior to posterior gradient diminishing for anterior lung, the portion adjacent to the myocardium.

TABLE III
PERCENT INJECTED DOSE PER CC OF TISSUE AND MYOCARDIUM/LIVER/LUNG RATIOS

Organ	^{62}Cu-ETS	^{62}Cu-PTSM
LV Myocardium	0.0055	0.0043
Liver	0.0063	0.0081
Lung	0.0040	0.0014
LV Myocardium/Liver/Lung Ratio	1 / 1.15 / 0.73	1 / 1.88 / 0.33

IV. CONCLUSION

In summary, PET imaging was performed with ^{62}Cu-ETS in 10 healthy human subjects. This clinical study further validates ^{62}Cu-ETS as a PET tracer of regional perfusion. Compared to ^{62}Cu-PTSM, ^{62}Cu-ETS shows a much improved response to increased flow levels suggesting that ^{62}Cu-ETS will perform much better in the measurement of hyperemic myocardial flow in response to pharmacological or exercise stress. Also this new agent has much lower liver uptake in comparison to ^{62}Cu-PTSM giving it another advantage for myocardial imaging. Finally, ^{62}Cu-ETS is clearly promising for renal blood flow measurement applications.

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