Copper-62 ATSM as a hypoxic tissue tracer in myocardial ischemia

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Copper-62 labeled diacetyl-bis(N4-methylthiosemicarbazone) (62Cu-ATSM) has been proposed as a generator produced positron-emitting tracer for hypoxic tissue imaging. To clarify the usefulness of 62Cu-ATSM for myocardial ischemia, 62Cu-ATSM PET was performed in 7 patients with coronary artery disease. Increased myocardial uptake of 62Cu-ATSM was observed (myocardium/blood ratio: 3.09) in one patient with unstable angina, who had increased 18F-fluorodeoxyglucose (18F-FDG) uptake under the fasting condition. The other 6 patients, who were clinically stable, did not have increased 62Cu-ATSM uptake, although abnormal 18F-FDG uptake was seen in 4 patients. This preliminary study suggests that 62Cu-ATSM is a promising PET tracer for hypoxic imaging in acute ischemia.

Key words: copper-62 ATSM, hypoxia, coronary artery disease, fluorine-18 FDG, PET

INTRODUCTION

Visualization of hypoxic tissue is important for the evaluation of ischemic change in the brain and heart, and for the characterization of tumors. Nitroimidazole compounds are of great interest because of their selective accumulation in hypoxic tumors as well as ischemic tumors. Various groups have attempted to design nitroimidazole-based drugs labeled with 18F, 131I, or 99mTc for imaging hypoxia but these tracers had low target accumulation due to slow blood clearance and low membrane permeability.

62Cu labeled diacetyl-bis(N4-methylthiosemicarbazone) (62Cu-ATSM) has been proposed as a generator-based positron-emitting tracer for imaging hypoxia. 62Cu-PTSM, developed as a perfusion tracer, is easily reduced by the electron transport system in mitochondria, which can explain its retention. On the other hand, 62Cu-ATSM, an analogue of 62Cu-PTSM, cannot be reduced by normal mitochondria due to its low redox potential. Therefore, 62Cu-ATSM is not retained in the brain and heart, although it has high membrane permeability. The hypoxia-selective retention of 62Cu-ATSM requires an abnormally high NADH concentration caused by oxygen depletion, and also intact mitochondria. It was reported that 62Cu-ATSM has shown sign of high myocardial accumulation in a perfused rat heart model under hypoxic conditions, as well as in an in vivo rat model immediately after LAD occlusion. It was also reported that the blood flow decreased the 62Cu-ATSM accumulation increased; but at flow rates that were approximately 40% of normal, the uptake began to decrease.

To clarify the usefulness of 62Cu-ATSM in myocardial ischemia, 62Cu-ATSM PET was performed in 7 patients with coronary artery disease.

MATERIALS AND METHODS

Copper-62 was obtained with a 62Zn/62Cu generator system from [62Zn]ZnCl2 solution. Cu-ATSM was synthesized according to the method of Gingas et al., and confirmed by elemental analysis and mass spectrometry. 62Cu-ATSM was prepared as follows: Briefly, 4 ml of

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Table 1  Clinical data of 7 patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Clinical diagnosis</th>
<th>Interval* (days)</th>
<th>Stenosis on CAG (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>F</td>
<td>Inferior MI</td>
<td>721</td>
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<tr>
<td>2</td>
<td>80</td>
<td>F</td>
<td>Anterior MI</td>
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<td>99</td>
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<tr>
<td>3</td>
<td>72</td>
<td>M</td>
<td>Anterior MI</td>
<td>1656</td>
<td>99</td>
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<td>M</td>
<td>Anterior MI</td>
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<td>90</td>
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<td>75</td>
<td>M</td>
<td>Lateral MI</td>
<td>48</td>
<td>100</td>
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<tr>
<td>6</td>
<td>64</td>
<td>M</td>
<td>Anterior MI</td>
<td>51</td>
<td>99</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>F</td>
<td>Unstable angina</td>
<td></td>
<td>99</td>
</tr>
</tbody>
</table>

*Interval from the most recent onset of infarction to time of the study.
CAG = coronary angiography; RCA = right coronary artery; LAD = left anterior descending artery; LCX = left circumflex artery; MI = myocardial infarction

Fig. 1  Three transaxial slices illustrate 11 regions of interest definition.

\[ \text{SUV} = \frac{\text{radioactivity concentration (Bq/ml) / (injected dose (Bq)/body weight (g))}}{ } \]

The same ROIs as used in the \( ^{62}\text{Cu}-\text{ATSM} \) PET images of the left ventricle were placed on both the \( ^{13}\text{NH}_3 \) and \( ^{18}\text{F}-\text{FDG} \) images. In the study of myocardial perfusion, the myocardial uptake percent was calculated after normalization to each peak value in the study. The uptake ratio of \( ^{62}\text{Cu}-\text{ATSM} \) was compared with myocardial blood flow (%) and glucose metabolism (SUV) under the fasting condition. The normal range of \( ^{18}\text{F}-\text{FDG} \) uptake was defined as < 3.5 mg/ml (SUV), which was previously reported.\(^{15}\)

RESULTS

Increased \( ^{62}\text{Cu}-\text{ATSM} \) uptake was observed (3.09) in one segment of a patient with unstable angina, who had

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294  Norio Takahashi, Yasuhsa Fujibayashi, Yoshiharu Yonekura, et al  Annals of Nuclear Medicine
Fig. 2 A 65-yr-old woman with unstable angina. She had frequent attacks, which were refractory to medical treatment. The transaxial images of $^{13}$NH$_3$ (A), $^{18}$F-FDG (B), $^{62}$Cu-ATSM (C) are shown. Coronary angiography showed 99% stenosis in circumflex artery. Increased both $^{18}$F-FDG and $^{62}$Cu-ATSM accumulation in areas with moderately reduced myocardial blood flow was observed in the lateral wall.

![Image](image_url)

Fig. 3 The $^{18}$F-FDG uptake (SUV) was plotted against its $^{62}$Cu-ATSM uptake ratio for myocardial segments in each patient with ischemic heart disease. No correlation was observed between $^{62}$Cu-ATSM uptake ratio and $^{18}$F-FDG uptake.

Fig. 4 The relative blood flow was plotted against its $^{62}$Cu-ATSM uptake ratio for myocardial segments in each patient with ischemic heart disease. No correlation was found between $^{62}$Cu-ATSM uptake ratio and relative blood flow.

increased $^{18}$F-FDG uptake under the fasting condition (Fig. 2). The other 6 patients, who were clinically stable, did not have increased $^{62}$Cu-ATSM uptake, although abnormal $^{18}$F-FDG uptake was seen in 18 segments, in 4 of the patients (Fig. 3). Enhanced uptake of $^{62}$Cu-ATSM was not seen in the moderately low flow area (Fig. 4).

DISCUSSION

Although increased glucose metabolism was seen in 5 of 7 patients, only 1 patient with unstable angina had enhanced myocardial uptake of $^{62}$Cu-ATSM. In addition, no increase in $^{62}$Cu-ATSM uptake was observed in the moderately low flow area, which was apparent in the rat acute ischemia model.8,10 As the impairment of contractile function reduces the oxygen demand of hyperperfused myocardium in hibernating myocardium,16 lowered oxygen demand may reduce electron transport in the mitochondria. Accordingly, retention of $^{62}$Cu-ATSM was not increased in the chronically ischemic myocardium. After long duration of ischemia, the myocardium is irreversibly injured, and the leakage of intramitochondrial enzymes occurs, which is necessary for $^{62}$Cu-ATSM retention. Accordingly, $^{62}$Cu-ATSM is considered to be a PET tracer for hypoxic imaging in acute ischemia, highly sensitive to the intactness of mitochondria. $^{18}$F-FDG uptake might indicate abnormality of myocardial metabolism, but not intactness of the energy production system.

Although we have not compared $^{62}$Cu-ATSM and $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO) in this study, $^{62}$Cu-ATSM has two advantages. First, $^{62}$Cu can be obtained by a generator system from $^{62}$Zn, which has a 9 hr half-life and could be delivered for long distances. The second advantage is that the faster myocardial uptake of $^{62}$Cu-
ATSM than \(^{18}\text{F}-\text{FMISO}\) allows more rapid imaging of ischemic but viable myocardium. In \(^{18}\text{F}-\text{FMISO}\) PET, the difference between normal and hypoxic tissues does not become clear until 2 hours post injection due to slow blood clearance.\(^{17}\) \(^{62}\text{Cu}-\text{ATSM}\) PET imaging can be done within 20 min after injection due to its high membrane permeability.\(^{18}\) Therefore, the more efficient washout kinetics of \(^{62}\text{Cu}-\text{ATSM}\) in acute ischemia in comparison with \(^{18}\text{F}-\text{FMISO}\) offers the possibility of a faster and more efficient means of evaluating of myocardial hypoxia by PET imaging.

There are some limitations to this study. The number of patients was small and the results are preliminary but enhanced uptake of \(^{62}\text{Cu}-\text{ATSM}\) was observed in a patient with unstable angina, and imaging was completed only 20 minutes after the injection. Although experimental studies have already supported the possibility of identifying myocardial hypoxia with the other agents for imaging hypoxia, \(^{18}\text{F}-\text{FMISO}\) and \(^{99m}\text{Tc}-2\text{-nitroimidazole}\) BMS181321,\(^{17,18}\) neither of them has been used successfully in visualizing hypoxic myocardium in human subjects.

In conclusion, this preliminary study suggests that \(^{62}\text{Cu}-\text{ATSM}\) is a promising PET tracer for hypoxic imaging in acute ischemia not in chronic ischemia. Further clinical trials will needed to determine the usefulness of \(^{62}\text{Cu}-\text{ATSM}\) for myocardial ischemia.

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REFERENCES