Noninvasive Evaluation of Sympathetic Nervous System in Human Heart by Positron Emission Tomography

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The noninvasive functional characterization of the cardiac sympathetic nervous system by imaging techniques may provide important pathophysiological information in various cardiac disease states. Hydroxyephedrine labeled with carbon 11 has been developed as a new catecholamine analogue to be used in the in vivo evaluation of presynaptic adrenergic nerve terminals by positron emission tomography (PET). To determine the feasibility of this imaging approach in the human heart, six normal volunteers and five patients with recent cardiac transplants underwent dynamic PET imaging after intravenous injection of 20 mCi [11C]hydroxyephedrine. Blood and myocardial tracer kinetics were assessed using a regions-of-interest approach. In normal volunteers, blood [11C] activity cleared rapidly, whereas myocardium retained [11C] activity with a long tissue half-life. Relative tracer retention in the myocardium averaged 79±31% of peak activity at 60 minutes after tracer injection. The heart-to-blood [11C] activity ratio exceeded 6:1 as soon as 30 minutes after tracer injection, yielding excellent image quality. Little regional variation of tracer retention was observed, indicating homogeneous sympathetic innervation throughout the left ventricle. In the transplant recipients, myocardial [11C]hydroxyephedrine retention at 60 minutes was significantly less (−82%) than that of normal volunteers, indicating only little non-neuronal binding of the tracer in the denervated human heart. Thus, [11C]hydroxyephedrine, in combination with dynamic PET imaging, allows the noninvasive delineation of myocardial adrenergic nerve terminals. Tracer kinetic modeling may permit quantitative assessment of myocardial catecholamine uptake, which will in turn provide insights into the effects of various disease processes on the neuronal integrity of the heart. (Circulation 1990;82:457–464)

The role of the sympathetic nervous system in the pathophysiology of congestive heart failure and dysrhythmia is being increasingly recognized.1–4 Clinical and animal studies have linked the heterogeneity of sympathetic innervation after myocardial ischemia to the increased incidence of sudden death in patients with coronary artery disease.1,2,5,6 In patients with congestive heart failure, there is evidence that pharmacological β-receptor blockade improves cardiac function, presumably by protecting the heart from overexposure to catecholamines.3,4

The evaluation of the sympathetic nervous system of the heart has been limited in the past to either postmortem examination or invasive procedures to determine the arteriovenous differences of plasma catecholamine concentrations.7 More recently, the imaging of sympathetic nerve terminals has become possible with the introduction of radiolabeled catecholamine analogues.8 Neuronal uptake of radioiodinated metaiodobenzylguanidine (MIBG), as assessed by planar or single photon emission computed tomography (SPECT) imaging, provides a noninvasive method for assessment of regional neuron density and has been used in clinical and experimental studies for the evaluation of sympathetic nerve integrity in various cardiac diseases.9–11
Positron emission tomography (PET) is an improved imaging technology that permits the regional quantification of tracer concentration in tissue. In addition, labeling of compounds with short-lived radionuclides such as carbon-11 or fluorine-18 allows the administration of relatively large tracer doses, yielding superior image quality. Hydroxyephedrine has been developed in our laboratory as a new norepinephrine analogue. Animal experiments indicate that there is a highly specific uptake and retention of this tracer in sympathetic nerve terminals, with little non-neuronal binding. Tracer retention after intravenous injection of hydroxyephedrine correlates closely with regional tissue norepinephrine concentration in a canine model of regional denervation. Based on these encouraging results, the radiosynthesis of hydroxyephedrine has been refined for clinical applications.

The purpose of this study was to assess the feasibility of this new tracer approach for the noninvasive evaluation of the sympathetic nervous system of the human heart. The blood and myocardial kinetics of hydroxyephedrine were determined by dynamic PET imaging in normal volunteers and in patients with recent cardiac transplants who served as a clinical model of global cardiac denervation.

Methods

Subjects

Six healthy volunteers with a mean age of 23±7 years were studied. The presence of cardiac disease was excluded by history, physical examination, and resting electrocardiogram. None of the subjects were taking any cardiac or noncardiac medication at the time of the study.

In addition to these normal volunteers, five patients with recent (5.5±3.0 months) cardiac transplants were selected from a pool of heart transplant recipients at the University of Michigan Medical Center. The clinical status of these individuals was stable with no evidence of transplant rejection. All transplant patients received immunosuppressive therapy consisting of cyclosporine, immunure, and steroids. None of the patients was taking any medication known to interfere with norepinephrine uptake by sympathetic nerve terminals. All of the individuals participating in this study signed an informed consent form approved by the institutional committee for clinical research before consideration for evaluation by PET.

Radiochemistry of Hydroxyephedrine

Hydroxyephedrine was synthesized by direct N-methylation of metaraminol with [11C]methyl iodide in DMF-DMSO and purified by preparative reverse-phase high-performance liquid chromatography (HPLC) in an isotonic buffered aqueous system with direct formulation after filter sterilization. The chemical structure of hydroxyephedrine is shown in Figure 1. The total time for synthesis was 45 minutes. Hydroxyephedrine was produced with a 40–50% radiochemical yield with a specific activity of more than 1,000 Ci/mmol at the end of synthesis (>4,500 Ci/mmol at end of bombardment). Typical radiochemical and chemical purities of the final tracer were 95% and 98%, respectively.

Data Acquisition

The subjects were positioned in a whole body scanner (model CTI 931, Siemens CPS, Knoxville, Ind.). This instrument allows simultaneous acquisition of 15 cross-sectional images (eight direct planes, seven cross planes) with a spatial resolution of 6–8 mm. Transmission scans were acquired for 15 minutes using a retractable germanium-68 ring source. The transmission scans were used for positioning the patient as well as for subsequent attenuation correction of the emission scans.

The imaging protocol consisted of a myocardial blood flow study followed by dynamic PET imaging after hydroxyephedrine administration. Sixty milli-curies of rubidium-82 (82Rb) or 20 mCi [13N]ammonia were used for the determination of regional blood flow distribution. Imaging acquisition was started 60 seconds after the infusion of 82Rb or 3 minutes after the bolus injection of [13N]ammonia. Imaging data were acquired for 10 minutes. Fifteen minutes after the end of 82Rb infusion or 50 minutes after the end of [13N]ammonia administration, 20 mCi [11C]hydroxyephedrine was injected as a slow bolus over 30 seconds. Dynamic PET imaging was initiated simultaneously with hydroxyephedrine injection. The imaging protocol was six 30-second, two 60-second, two 150-second, two 300-second, two 600-second, and one 1,200-second images, for a total data acquisition time of 60 minutes. Heart rate and blood pressure were recorded before hydroxyephedrine injection and again every 2 minutes for 10 minutes after tracer injection. The electrocardiogram was continuously monitored throughout the study.

Data Processing and Data Analysis

The data were reconstructed into transverse cross-sectional images using filtered back-projection and a Hanning filter with a cutoff frequency of 0.35 per pixel. True cross-sectional images perpendicular to the long axis of the heart were generated with a SUN workstation and customized software (Analyze, Mayo Clinic, Rochester, Minn.).

The relative myocardial distribution of [13N]ammonia or 82Rb was evaluated visually to determine the homogeneity of blood flow. In addition, circumferential profile analysis was used to compare regional tracer uptake in our subjects with that of a normal data base.

![Figure 1. Chemical structure of [11C]hydroxyephedrine.](image-url)
Regional $^{11}$C-hydroxyephedrine kinetics were determined by placing regions-of-interest over the myocardium and ventricular blood pool. In the transplant patients, the myocardial regions were defined based on blood flow images because of the poor $^{11}$C-hydroxyephedrine uptake in these patients. The selected regions-of-interest were subsequently copied to all image planes, and time-activity curves of blood pool and myocardium were generated. The $^{11}$C activity was normalized to peak blood and myocardial activity and expressed as the percentage of peak blood activity.

In addition, the ventricular $^{11}$C activity derived from the last image was normalized to the integral of the blood activity to determine the $^{11}$C retention fraction. The regional tracer retention within the left ventricle was plotted on a polar map, which displays circumferential activity profiles from the base to the apex of the left ventricle. Regional activity was normalized to peak ventricular activity and expressed as the percentage of the peak ventricular activity in normal volunteers.

Statistics

All values are given as mean±SD. Statistical comparisons were performed using Student’s t test and linear regression analysis. A p value of less than 0.05 was considered statistically significant.

Results

All patients tolerated the intravenous bolus injection of $^{11}$C-hydroxyephedrine without side effects. The hemodynamic data before and after tracer injection are reported in Table 1. There was no significant change in heart rate or blood pressure after the injection of $^{11}$C-hydroxyephedrine in the normal volunteers or patients with cardiac transplant.

Regional myocardial blood flow was homogeneous in all individuals studied. There was no evidence of regional perfusion abnormalities.

Table 1. Heart Rate and Blood Pressure Response to $^{11}$C-hydroxyephedrine

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 min</th>
<th>4 min</th>
<th>6 min</th>
<th>10 min</th>
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<td><strong>Normal volunteers</strong></td>
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<tr>
<td>HR (beats/min)</td>
<td>57±8</td>
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<td>57±6</td>
<td>58±6</td>
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<td>SBP (mm Hg)</td>
<td>118±11</td>
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<td>118±11</td>
<td>117±12</td>
<td>117±12</td>
<td>126±8</td>
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<td>DBP (mm Hg)</td>
<td>77±9</td>
<td>72±10</td>
<td>72±11</td>
<td>72±11</td>
<td>72±12</td>
<td>78±11</td>
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<td><strong>Cardiac transplant patients</strong></td>
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<tr>
<td>HR (beats/min)</td>
<td>90±9</td>
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<td>SBP (mm Hg)</td>
<td>134±14</td>
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<td>140±20</td>
<td>141±19</td>
<td>148±22</td>
<td>144±18</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
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<td>100±11</td>
<td>99±11</td>
<td>100±11</td>
<td>102±12</td>
<td>98±8</td>
</tr>
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HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are given as mean±SD.

The regional time-activity curves obtained from the same cardiac transplant patient from regions-of-interest placed over the myocardium and blood pool are shown in Figure 5. The blood $^{11}$C activity decreased rapidly, in a manner similar to that in the normal population. However, $^{11}$C retention in the myocardium was markedly reduced compared with that in normal volunteers. The tracer retention by the myocardia of all transplant patients was significantly lower from 6 to 60 minutes after tracer injection compared with the control population (Table 2). There was no significant difference in the blood $^{11}$C clearance patterns of the transplant patients compared with the control population.

Figure 6 shows the myocardial retention by normal volunteers and patients with cardiac transplants of $^{11}$C activity at 60 minutes, normalized to the integral uptake of $^{11}$C-hydroxyephedrine. There is homogenous distribution of $^{11}$C activity throughout the myocardium, paralleling the blood flow homogeneity determined by $^{82}$Rb distribution. The heart-to-blood and heart-to-lung activity ratios at 30 minutes after tracer injection were 5.0 and 4.2, respectively, in this normal volunteer. Regional tracer distribution was quantified using circumferential profile techniques and shown in relation to maximal myocardial activity using the polar map approach (Figure 2, bottom panel). This simplified three-dimensional representation of regional tracer retention indicated a homogenous distribution of $^{11}$C within the normal left ventricle, again paralleling the blood flow pattern shown on the left side of Figure 2b.

Figure 3 shows time-activity curves obtained from a region-of-interest placed over the left ventricular cavity and myocardium in the same normal volunteer. $^{11}$C in the blood cleared rapidly. Myocardial activity initially decreased to about 75% of that at peak uptake, but remained essentially constant for the remainder of the data acquisition.

Figure 4 shows cross-sectional short-axis images of the left ventricle of a patient with a recent cardiac transplant after the injection of $^{82}$Rb and $^{11}$C-hydroxyephedrine. The $^{82}$Rb images indicated a homogeneous blood flow distribution. In contrast, regional $^{11}$C-hydroxyephedrine retention at 30 minutes after tracer injection was markedly reduced compared with that of $^{82}$Rb.
of the arterial input function. The tissue retention percentage of the tracer was 1.6±1.0% in patients with cardiac transplant, compared to 7.0±1.0% in normal volunteers (p<0.001). Myocardial 11C activity in all volunteers averaged 78% of initial peak myocardial activity at 10 minutes, 80% at 30 minutes, and 79% at 60 minutes after tracer injection. Relative tissue and blood activity at 1, 2, 4, 6, 10, 30, and 60 minutes after tracer administration (normalized to peak blood activity) is reported in Table 2. In all subjects, there was only 8% of peak blood activity remaining at 10 minutes after injection. Heart-to-blood activity ratios exceeded 2 as soon as 4 minutes after the tracer injection and increased to 6.9 by 60 minutes in the normal volunteers (Table 2).

Regional Variation of 11C Hydroxyephedrine Retention
To determine the regional retention of 11C hydroxyephedrine throughout the normal left ventricle, the relative 11C activity at 60 minutes after tracer injection was averaged in all six normal volunteers, expressed as a percentage of peak myocardial activity, and displayed as an average polar map (Figure 7). There was no significant regional change of tracer retention in the circumferential or longitudinal direction in the normal volunteers.

Discussion
These data indicate the feasibility of noninvasively evaluating the sympathetic nervous system of the human heart with the new radiopharmaceutical 11C hydroxyephedrine. There was no significant change in heart rate or blood pressure in either study population, indicating the absence of a significant pharmacological effect of 11C hydroxyephedrine after intravenous injection. The resulting PET images were of excellent quality, with clear delineation of myocardial activity as soon as 10 minutes after tracer injection. The myocardial retention of 11C hydroxyephedrine was markedly reduced (by 82%) in patients with cardiac transplants compared with that in normal volunteers, indicating the specificity of this tracer for the sympathetic nervous system and its low non-neuronal binding in the denervated human heart.

Tracer Characteristics
11C Hydroxyephedrine is a norepinephrine analogue with the same uptake and storage mechanisms as the naturally-occurring neurotransmitter.14 Animal experiments performed in our laboratory have demonstrated that myocardial 11C retention can be markedly reduced by pharmacological inhibition of uptake-1 by desipramine as well as by inhibition of vesicular storage by reserpine. However, unlike norepinephrine, 11C hydroxyephedrine is not metabolized by monoamine oxidase in the cytosol of sympathetic nerve terminals.15 Thus, the retained 11C activity reflects uptake and storage of 11C hydroxyephedrine in the large neuronal norepinephrine pool. Chemical analysis of 11C activity by HPLC in the guinea pig showed less than 5% metabolites in the myocardium at 30 minutes after injection.16 The tissue half-life of 11C activity was long, consistent with the slow turnover (several hours) of neuronal norepinephrine.18 The short physical half-life of 11C (20 minutes) prohibits the accurate determination of 11C hydroxyephedrine release from the nerve terminals and hence does not allow the measurement of norepinephrine tissue release based on 11C hydroxyephedrine tissue kinetics. Therefore, the physiological information obtainable with 11C hydroxyephedrine pertains primarily to the catecholamine uptake and storage capacity of adrenergic nerve terminals. Tissue retention of 11C hydroxyephedrine correlated closely with the tissue norepinephrine concentrations determined postmortem in a canine model of regional cardiac denervation.13 The relative decrease of 11C hydroxyephedrine retention was paralleled by the same degree of norepinephrine depletion, indicating that little non-neuronal binding of this tracer occurred in canine myocardium.

The reported data in the patients with cardiac transplants are similar to these animal data. The retention of 11C hydroxyephedrine of these subjects was 82% less than that of the normal volunteers. Because the PET images were corrected for photon attenuation, the regional 11C activity directly reflects tissue 11C hydroxyephedrine concentration, allowing
quantitative assessment of tracer concentration. The arterial input function derived from regions-of-interest over the left ventricle has been shown to correlate closely with the results of direct arterial blood sampling.\(^9\) Thus, the retained myocardial \(^{11}\text{C}\) activity can be normalized to the arterial input, yielding a quantitative parameter of neuronal \(^{11}\text{C}\)hydroxyephedrine retention (Figure 6). The calculated myocardial retention fraction of 7% of the arterial input agrees closely with the retention fraction normalized to the injected dose in animal experiments.\(^13\) Current research in our laboratory is focusing on the development and validation of a tracer kinetic model for \(^{11}\text{C}\)hydroxyephedrine. Preliminary results in the open-chest model after intracoronary tracer administration indicate the feasibility of this approach. The calculated tissue retention of \(^{11}\text{C}\)hydroxyephedrine correlated closely \((r=0.87)\) with tissue norepinephrine concentration.\(^15\) The tracer kinetic model describes the tissue kinetics of \(^{11}\text{C}\)hydroxyephedrine in three compartments. The vascular space and extravascular and neuronal tracer pools are linked by individual rate constants. Accurate quantification of these rate constants requires definition of the tracer input function. Metabolic studies in humans have shown that \(^{11}\text{C}\)hydroxyephedrine is metabolized and \(^{11}\text{C}\)-labeled metabolites of \(^{11}\text{C}\)hydroxyephedrine rapidly appear in blood.\(^20\) Although more than 85% of the blood \(^{11}\text{C}\) activity represented \(^{11}\text{C}\)hydroxyephedrine 5 minutes after intravenous injection, only 52% of the \(^{11}\text{C}\) activity was identified as being due to \(^{11}\text{C}\)hydroxyephedrine at 20 minutes.\(^20\) A simple assay technique is being developed in our laboratory that will allow rapid measurement of blood metabolites and subsequent correction of the \(^{11}\text{C}\) input function required for tracer kinetic modeling.

**Figure 4.** Cross-sectional PET images in a patient with recent cardiac transplantation. Rubidium-82 (Rb-82) images above show homogeneous blood flow. Myocardial retention of \(^{11}\text{C}\)hydroxyephedrine (C-11 HED) 30 minutes after tracer injection is markedly reduced compared with that of \(^{82}\text{Rb}\).

**Comparison with Metaiodobenzylguanidine**

MIBG has been used in numerous studies to delineate the sympathetic nervous system of the heart.\(^8\)\-\(^11\) However, the limited quality of images provided by conventional scintigraphic techniques provides only qualitative information. In addition, the lipophilicity of MIBG, specifically the metaiodophenyl moiety, results in its enhanced nonspecific binding to myocyte membranes compared with the more polar phenolamine \(^{13}\text{C}\)hydroxyephedrine. Direct comparison of both tracers in the rat model revealed only a 44% reduction of MIBG retention compared with a reduction of 92% of \(^{13}\text{C}\)hydroxyephedrine following pharmacological inhibition of uptake-1 by desmethylimi-
ramine. Additional studies in rats sympathectomized by administration of the neurotoxin 6-hydroxy-
dopamine indicated that [11C]hydroxyephedrine is
approximately 20% more selective for the myocar-
dial adrenergic neurons than is radioiodinated
MIBG (Wieland et al, unpublished observation).
Thus, the improved imaging technology of PET,
together with the more specific physiological infor-
mation provided by [11C]hydroxyephedrine, promises
an improved evaluation of the sympathetic nervous
system by this new approach.

Clinical Implications

The evaluation of the sympathetic nervous system
in the human heart has been limited in the past to
invasive methods. Measurement of arteriovenous
differences in plasma norepinephrine concentrations
allows only the indirect assessment of sympathetic
nerve activity. More than 70% of norepinephrine
released by the sympathetic nerve terminals under-
goes reuptake. This internal reutilization of norepi-
 nephrine cannot be estimated by the measurement
of norepinephrine spillover into the venous effluent.
Therefore, arteriovenous sampling techniques do not
permit differentiation between increased norepi-
 nephrine release and decreased reuptake of the
neurotransmitter. A recent approach using radiolab-
elabeled norepinephrine and analysis of radiolabeled
metabolites in the venous effluent has improved the
specificity of the invasive methods in the determina-
tion of sympathetic nerve activity. This technique,
however, is limited to the catheterization laboratory
and allows only the global evaluation of the cardiac
sympathetic nervous system. Therefore, the noninva-
sive imaging approach using radiolabeled catechol-
amines appears to be applicable to the clinical eval-
uation of patients with various heart diseases.

Several experimental studies have indicated the
importance of the uptake-1 and subsequent vesicular
storage for the removal of norepinephrine from
myocardial tissue. This sequestration process is
responsible for the regulation of the extravascular
norepinephrine concentration in the myocardium.
Thus, [11C]hydroxyephedrine may prove to be a valu-
able tool in the assessment of the capacity of the
sympathetic nervous system to remove norepinephrine
from myocardial tissue, and may provide a noninvasive
means of correlating regional neuronal function with
electrophysiological data. Finally, this new tracer
approach may allow the study of the pharmacological

| TABLE 2. Relative Retention of Carbon-11 Activity in Heart and Blood |
|-----------------|---|---|---|---|---|---|
|                 | 1 min | 2 min | 4 min | 6 min | 10 min | 30 min | 60 min |
| Normal volunteers |       |       |       |       |       |       |       |
| Heart (% peak activity) | 43±18 | 33±16 | 34±15 | 35±15 | 35±15 | 35±14 | 35±13 |
| Blood (% peak activity)   | 100   | 30±18 | 12±15 | 8±5   | 6±3   | 5±3   | 5±2   |
| Heart:blood               | 0.43±0.1 | 1.1±0.1 | 2.9±0.8 | 4.4±0.9 | 5.8±1.2 | 7.1±2.0 | 6.9±1.6 |
| Cardiac transplant patients |       |       |       |       |       |       |       |
| Heart (% peak activity) | 52±17 | 26±8 | 22±6* | 18±6* | 14±4* | 12±3* | 9±3* |
| Blood (% peak activity)   | 100   | 32±17 | 14±2 | 9±1   | 8±2   | 6±1   | 6±1   |
| Heart:blood               | 0.5±0.13 | 0.8±0.18 | 1.6±0.50 | 2.0±0.50 | 1.78±0.59 | 2.0±0.68 | 1.5±0.54 |

All tissue and blood data normalized to peak blood activity.
*p<0.01 compared with data in normal volunteers.
Values are given as mean±SD.

 Swaliger et al  Evaluation of Sympathetic Nervous System by PET

FIGURE 6. Bar graph of carbon-11 (C-11) retention frac-
tions (RFs) as determined by the normalization of myocardial
11C activity (Carterial) to the integral of the arterial blood activity
(Cblood) 60 minutes after tracer injection. RF=Carterial/Cblood×100.

FIGURE 7. Average polar map of relative regional distribu-
tion of blood flow and [11C]hydroxyephedrine retention at 60
minutes in six normal volunteers. Average regional activity was
normalized to peak myocardial activity and expressed as a
percentage of peak myocardial activity. ANT, anterior; SEP, sepal;
LAT, lateral; INF, inferior.
effects of many cardiovascular drugs on the uptake of norepinephrine by the sympathetic nervous system. However, further careful validation of the efficacy of [11C]hydroxyephedrine in animal studies is necessary to the development of quantitative techniques for future applications in the clinical environment.

Conclusions

[11C]Hydroxyephedrine, used in combination with PET, is a new noninvasive approach to the study of the sympathetic nervous system in the human heart. The normal heart is characterized by homogeneous retention of [11C]hydroxyephedrine. The retention of the tracer was markedly lower in patients with recent cardiac transplants than in normal volunteers, indicating the specificity of this tracer and the potential of assessing presynaptic catecholamine uptake by PET imaging. This approach is a promising new dimension of PET imaging and may be useful in the evaluation of the sympathetic nervous system in various disease states such as myocardial infarction, congestive cardiomyopathy, and dysrhythmia.

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References


KEY WORDS • [11C]hydroxyephedrine • positron emission tomography • nervous system, sympathetic
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