Direct Comparison of \([^{13}\text{N}]\text{Ammonia}\) and \([^{15}\text{O}]\text{Water}\) Estimates of Perfusion With Quantification of Regional Myocardial Blood Flow by Microspheres

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**Background.** Both \([^{13}\text{N}]\text{Ammonia}\) and \([^{15}\text{O}]\text{Water}\) have been used to quantify myocardial blood flow with positron emission tomography using appropriate tracer kinetic models. A direct comparison of the two tracers with radioactive microspheres has not been performed in the same experimental preparation.

**Methods and Results.** The two tracers have been tested for myocardial blood flow quantification in closed-chest dogs with circumflex coronary stenosis or permanent occlusion at rest and during adenosine-induced hyperemia. \([^{13}\text{N}]\text{Ammonia}\)- and \([^{15}\text{O}]\text{Water}\)-derived myocardial blood flow values have been compared with radiolabeled microspheres. Validation studies consisted of simultaneous measurements of blood flow with positron emission tomography and microspheres over a wide range of flow values. Blood pool and regional tissue activity curves were fitted with a three-compartment model for \([^{13}\text{N}]\text{Ammonia}\) with and without arterial metabolite correction and with a single-tissue-compartment model for \([^{15}\text{O}]\text{Water}\). A correction for finite-resolution effect before the fit was also applied. In large regions of interest (5 cm\(^2\)), a good correlation between the microsphere method and \([^{13}\text{N}]\text{Ammonia}\) (with metabolite correction) was obtained \((y = 3 + 0.78x, r = 0.97)\). The correlation with microspheres was slightly better with \([^{15}\text{O}]\text{Water}\) \((y = -3 + 0.89x, r = 0.97)\). Similar correlations were achieved in smaller regions of interest \((1 \text{ cm}^2)\) as well as in akinetic segments and in central infarct regions.

**Conclusions.** Positron emission tomography with appropriate tracer kinetic models using \([^{13}\text{N}]\text{Ammonia}\) and \([^{15}\text{O}]\text{Water}\) provides an accurate quantitative method for measuring regional myocardial blood flow over a wide range of flow values in normally contracting or akinetic canine myocardium in the absence and in the presence of infarction. (Circulation 1993;87:512–525)

**KEY WORDS** • myocardial blood flow • tomography, positron emission

Previous animal and clinical studies with \([^{13}\text{N}]\text{Ammonia}\) and \([^{15}\text{O}]\text{Water}\) and positron emission tomography (PET) have shown the feasibility of qualitative and quantitative estimates of myocardial blood flow.\(^1-14\) These two tracers have some inherent advantages and disadvantages for accurate quantitative measurements of myocardial blood flow, which have been reviewed.\(^15-17\) \([^{15}\text{O}]\text{Water}\) has the advantage of being a diffusible tracer, but its use requires correction for the high \([^{15}\text{O}]\text{Water}\) activity in the blood. \([^{13}\text{N}]\text{Ammonia}\) myocardial retention decreases with high flow rates\(^8\) and is partially affected by the metabolic status of the myocardium.\(^18,19\) Additionally, the arterial input function can be contaminated by labeled metabolites of the tracer.\(^20\) For both tracers, solutions using kinetic analysis have been proposed so as to take into account their known disadvantages.\(^21-25\) Only the approach using \([^{15}\text{O}]\text{Water}\) as a bolus or as an inhalation of \([^{15}\text{O}]\text{CO}_2\) gas and a one-compartment model has been validated with direct assessment of flow-determined microspheres.\(^22,24\)

The present study was designed to compare, in the same closed-chest animals, in vitro microsphere-determined flow with regional myocardial perfusion estimates obtained in vivo with PET and \([^{15}\text{O}]\text{Water}\) or \([^{13}\text{N}]\text{Ammonia}\). The study was performed in conscious dogs under different flow conditions induced by coronary stenosis, permanent occlusion, and adenosine infusion with and without myocardial infarction.

**Methods**

**Experimental Preparation**

Five mongrel dogs (weight, 23–29 kg) were instrumented aseptically through a left lateral thoracotomy...
under pentobarbital anesthesia (group 1). The pericardium was incised and the heart exposed. The proximal left circumflex coronary artery was carefully dissected free 1–2 cm from its origin to accept a cuff occluder and a Doppler ultrasonic flow probe just proximal to the occluder. The artery was then briefly occluded to delineate the ischemic area. A pair of ultrasonic crystals for measurement of wall thickness was implanted across the left ventricular free wall in the center of the area intended to become ischemic. Another pair of crystals for measurement of wall thickness was implanted in a remote normal zone in the left anterior descending coronary artery distribution. A miniature solid-state pressure transducer (Konigsberg Instruments, Pasadena, Calif.) was implanted in the left ventricular cavity through an apical stab incision. Heparin-filled Silastic catheters (Dow Corning Co.) were implanted in the ascending aorta, pulmonary artery, and left atrium. All transducer wires and catheters were tunneled subcutaneously to the dorsal neck surface, exteriorized, and attached to the skin. After surgery, all animals were routinely placed on antibiotic therapy for 10 days. An interval of 2 weeks was allowed for the dogs to recover from this surgical procedure.

Six additional dogs were similarly instrumented but without a Doppler flow probe. A snare occluder was placed around the proximal left circumflex coronary artery, and the artery was acutely ligated. These dogs were studied between 3 and 10 days after permanent coronary ligation (group 2).

**Preparation of Radionuclides**

$^{15}$N was produced by irradiating approximately 2 ml of natural water with 18-MeV protons from the Cyclone 30 (30-MeV proton cyclotron, IBA, Louvain-la-Neuve, Belgium). The irradiation time was 10–20 minutes with a beam current of 15–20 $\mu$A. After bombardment, the irradiated solution was transferred to an automatic processing module, where the $^{15}$N-labeled oxides were reduced to ammonia with 1 g of Devarda alloy mixed in 2.5 g NaOH. The ammonia leaving this hot mixture was trapped by bubbling through a sterile isotonic solution; before injection, this solution was automatically filtered through a 0.22-$\mu$m Millipore filter. The radiochemical purity of $^{15}$N ammonia was determined within 4 minutes by high-performance liquid chromatography (400IC Vydac, strong cation exchange column); the analyses showed a radiochemical purity of >99.5%.

$^{18}$O Water was produced by irradiating natural oxygen with 28-MeV protons from the Cyclone 30. The irradiation time was 10 minutes with a beam current of 20–35 $\mu$A. After bombardment, the irradiated gas was transferred to an automatic processing module, in which it was mixed with hydrogen in an oven containing 2.5 g palladium (Pd) wire at 150°C. The Pd-catalyzed reaction of oxygen with hydrogen produced the $^{18}$O water and natural water vapor that is trapped by bubbling through sterile isotonic water. The nearly quantitative transformation from $^{18}$O$_2$ into $^{18}$O water was done within 3 minutes, filtration through a 0.22-$\mu$m Millipore filter included. Radionuclide purity was controlled by decay curve analysis.
Experimental Protocol and Tomographic Procedure

Myocardial perfusion images were obtained with an ECAT III (model 911/01, CTI Inc., Knoxville, Tenn.) one-ring device, the characteristics of which have been described previously. Measurements were performed with a stationary ring, and images were reconstructed with a Hann filter (cutoff frequency, 0.4) at a nominal in-plane resolution of 9 mm full width at half maximum (FWHM). The collimator aperture was set at 30 mm, resulting in a slice thickness of 15 mm FWHM. The tomograph was cross-calibrated against a well counter using a uniform cylindrical phantom (diameter, 20 cm) filled with a solution of germanium 68.

The animals, who were trained to rest quietly on their right side, were placed on the camera table. Before each tomographic study, the best cross section through the left ventricle at the level of crystal implantation was identified by fluoroscopy, and the chosen reference level was marked on the chest skin with a light pen. To align these marks with the laser reference system of the tomograph, scanning acquisitions were performed with a 30° lateral rotation of the gantry. The dogs were mildly sedated with propranolol (Combene, Bayer). The hemodynamic parameters of arterial pressure, left ventricular pressure, heart rate, wall thickening, and

Doppler flow signal (only in group 1) were monitored and recorded during the experiment. Transmission scans were obtained with an external ring of germanium 68 to confirm proper positioning of the dog. In group 1, myocardial images obtained after intravenous infusion of rubidium 82 were acquired over a period of 2 minutes to verify that a midventricular cross-sectional plane was imaged. In group 1, after all control hemodynamic

**Figure 2.** Plots showing comparison of the input function obtained from direct aorta sampling (synchronized to positron emission tomographic counts per pixel based on phantom studies) with time-activity curves obtained from a region of interest drawn in the left ventricle on $[^{13}]$N ammonia images. The time-activity curves derived from the tomograph are corrected for dead-time, decay, and finite-resolution effects. Two representative studies are illustrated.

**Figure 3.** Plots showing comparison of the input function obtained by external β-probe with time-activity curves obtained from a region of interest drawn in the left ventricle on $[^{15}]$O water images. Two representative studies are illustrated.

**Figure 4.** Plot showing comparison between the integral values of in vivo (left ventricular blood pool [LVBP] curve) and in vitro (external curve) arterial input curves for six $[^{13}]$N ammonia studies (open squares) and five $[^{15}]$O water studies (filled squares).
Thirty serial cross-sectional images were acquired for 180 seconds (15 for 2 seconds and 15 for 10 seconds). A directly measured arterial input function was also obtained with an automatic system that continuously monitored the time–activity curve from the aortic catheter. This positron detection system consisted of a plastic scintillator (NE102; diameter, 45 mm; thickness, 4 mm) coupled to a photomultiplier tube (Philips 56AVP). Output signal was sent through a fast discriminator with a threshold set above the gamma background to a Canberra multichannel analyzer interfaced to the VAX-750 computer. To reduce dispersion, the arterial Teflon catheter was directly connected to an 80-cm extension tubing that was coiled twice and taped to the surface of the plastic scintillator. The other end of the tubing was connected via a three-way tap to a Harvard pump for blood withdrawal at a rate of 6 ml/min. The system was calibrated at the end of each study by counting a sample of whole blood in the well counter. No dead-time correction was needed at the observed counting rates. The dispersion within this external detection system was estimated by measuring the system response to a step input function and was reasonably well described by a monoeponential expression with a time constant of approximately 2 seconds. After the 3-minute tomographic acquisition, radioactive microspheres were injected into the left atrium, and blood was withdrawn from the aortic arch with a Harvard pump at a rate of 7.2 ml/min for a total of 150 seconds. Immediately after the withdrawal of microsphere reference blood samples, 10 mCi of $^{15}$N ammonia was injected intravenously over a 20-second period with an infusion pump. Beginning with tracer injection, 28 serial cross-sectional images were acquired in a decay-compensated mode for 10 minutes (16 for 3 seconds, 10 for 12 seconds, and 2 for 240 seconds). In six studies, an arterial tracer input curve was simultaneously determined manually by frequent arterial blood sampling. Immediately after the tomographic acquisition, another set of radioactive microspheres was injected into the left atrium for the second reference myocardial blood flow determination. At the end of this second reference flow measurement, coronary stenosis was released, and the adenosine infusion was stopped.

Two hours later, the left circumflex coronary artery was again partially occluded in group 1. The severity of the coronary stenosis was carefully adjusted to achieve severe hypokinesia to akinesia in the ischemic region but without complete coronary occlusion. The lack of

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**TABLE 1.** Distribution of Radioactivity of Unmetabolized $^{15}$N Ammonia in Arterial Plasma After Administration of $^{15}$N Ammonia

<table>
<thead>
<tr>
<th>Time (Seconds)</th>
<th>All studies (n=9)</th>
<th>Studies with adenosine infusion (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 Seconds</td>
<td>98±1</td>
<td>98±1</td>
</tr>
<tr>
<td>60 Seconds</td>
<td>91±9</td>
<td>87±11</td>
</tr>
<tr>
<td>90 Seconds</td>
<td>68±16</td>
<td>65±20</td>
</tr>
<tr>
<td>120 Seconds</td>
<td>57±19</td>
<td>54±18</td>
</tr>
<tr>
<td>180 Seconds</td>
<td>38±16</td>
<td>34±15</td>
</tr>
<tr>
<td>240 Seconds</td>
<td>28±16</td>
<td>31±16</td>
</tr>
<tr>
<td>600 Seconds</td>
<td>19±5</td>
<td>21±5</td>
</tr>
</tbody>
</table>

Values are percent of total plasma radioactivity. Numbers in parentheses indicate the range of the data.
complete coronary occlusion was confirmed by the persistence of the Doppler flow signal. New transmission scans were obtained in these experimental conditions. Then, the same sequence of flow data acquisition as the one previously described was performed: $^{15}$O-water injection and tomographic acquisition, microspheres, $^{15}$N-ammonia injection and tomographic acquisition, and another set of microspheres. The four sets of microspheres (15-μm diameter) used for the whole study were labeled with $^{57}$Co, $^{113}$Sn, $^{85}$Sr, and $^{95}$Nb (New England Nuclear, Boston), respectively.

In group 2 with permanent coronary occlusion, the same experimental protocol was followed. Two sets of similar experiments were performed in each dog: 1) at baseline and 2) 2 hours later, during adenosine infusion. $^{15}$O-Water and $^{15}$N-ammonia were injected twice with simultaneous measurements of blood flow by microspheres.

After the last $^{15}$N-ammonia acquisition and the corresponding microsphere measurement, the animals were killed with an overdose of sodium pentobarbital, and the hearts were removed. The ventricles were sectioned parallel to the plane of the implanted crystals. A left ventricular slice 15 mm thick, including the crystals, was cut into 12 myocardial samples. These myocardial samples were divided into three layers (en-
Table 2. Comparison of Blood Flow Estimates by Positron Emitter and Microsphere Techniques in Large Myocardial Regions

<table>
<thead>
<tr>
<th></th>
<th>Least-squares regression equation</th>
<th>Mean difference (systematic error)</th>
<th>SD (random variability)</th>
<th>Coefficient of variation (SD/mean)</th>
<th>t Test</th>
<th>Correlation test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[15O]Water</td>
<td>Method 1</td>
<td>y=13+0.79x</td>
<td>0.89</td>
<td>&lt;0.001</td>
<td>+32</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Method 2</td>
<td>y=-3+0.89x</td>
<td>0.97</td>
<td>&lt;0.001</td>
<td>+26</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>No finite resolution correction and method 2</td>
<td>y=-16+0.86x</td>
<td>0.95</td>
<td>&lt;0.001</td>
<td>+47</td>
<td>46</td>
</tr>
</tbody>
</table>

docardium, midwall, and epicardium), weighed, and counted for radioactivity with the reference blood samples in a multichannel gamma counter at appropriate energy windows. Myocardial blood flow was calculated with the equation: Qm=Cm×(R/Ct), where Qm is myocardial blood flow (milliliter per minute), Cm is tissue counts (counts per minute), R is reference arterial blood flow (milliliter per minute), and Ct is counts in reference blood samples (counts per minute). Flow per gram of myocardium was calculated by dividing blood flow by the sample weight. Transmural flows were obtained by averaging the flows of the three layers corrected by the weight of each sample.

In group 2, the heart slices were placed in a solution of triphenyl tetrachloride (TTC) at 37°C for 30 minutes. Transmural sampling was made in the center of the infarcted (TTC−) tissue. Two of six dogs had too small a subendocardial infarction (less than one third of the left ventricular wall thickness) to be included in the results section of the group 2 dogs with myocardial necrosis. Thus, four dogs with two studies for each dog will be analyzed in the results section. Two dogs had a transmural infarction, and two had a nontransmural infarction but with a TTC− region including more than half of the wall thickness. Myocardial blood flow estimates by microspheres were calculated as described for group 1 dogs.

[13N]Ammonia Blood Sample Analysis

In group 1, heparinized arterial blood samples were removed at 30, 60, 90, 120, 180, 240, and 600 seconds after the beginning of [13N]ammonia injection. The blood samples were centrifuged in an Eppendorf microfuge for 2 minutes, and plasma was removed. Perchloric acid (180 µL, 0.42 M) was added to 400 µL of plasma. The resulting suspension was centrifuged for 30 seconds. Supernatant was neutralized with 200 µL of 0.42 M NaHCO3 and centrifuged for 10 seconds. Supernatant was transferred to the top of a small column (5×70 mm) filled with Dowex AG-50 W-8 (Na+ form) (Bio-Rad Laboratories, Richmond, Calif.) and previously equilibrated with a solution of 30 mM Na2HPO4 (pH 7.5). The column was washed with 1 ml of 30 mM Na2HPO4 (pH 7.5) and dried with air. Eluant and ion exchange resin were counted for radioactivity for each blood sample. The total activity was taken as 100% of radioactivity.

Analysis of Tomographic Data and Calculation of Myocardial Perfusion

After random coincidence subtraction, normalization of sinograms, and correction for attenuation, the reconstructed images (256×256 pixels) were corrected for dead-time (maximum, 20%) and isotope decay. Four large regions of interest representing 5 cm² each and encompassing the whole left ventricular wall were drawn on the last image of the dynamic [13N]ammonia study together with 12 small 1-cm² circular ones (Figure 1). A 2-cm² region of interest was assigned to the left ventricular blood pool to obtain the arterial input function. These 17 regions were then copied on all [13N]ammonia and [15O]water dynamic images to construct the corresponding tissue and blood pool time-activity curves. When a regional defect precluded an adequate drawing of the myocardial regions on the last [13N]ammonia image, early images were used to delineate the myocardium contours between the left ventricular blood pool and the lungs, which were both clearly visualized at that time.

Myocardial perfusion was calculated from tomographic data by fitting the arterial input function and tissue time–activity curves either to a single-tissue-compartment tracer kinetic model for [15O]water studies22 or to a three-compartment model that separates initial tracer extraction from subsequent metabolic conversion to glutamine for [13N]ammonia studies.25 Model parameter estimation was by the nonlinear weighted least-squares fitting routine MINUIT.27 The fits were performed by weighting each data point by the inverse of its variance. Goodness of fit was assessed visually or by χ² statistics or both.28

Two different methods were compared in the calculation of myocardial perfusion by use of [15O]water, both based on the same single-tissue-compartment model.29-31 They differ in the way they take into account the effects of the limited spatial resolution of the tomograph (the so-called partial volume and spillover effects). Their detailed formulations are given in the "Append-
The first method, originally suggested by Iida et al.\textsuperscript{21} and validated by Bergmann et al.\textsuperscript{22} and Araujo et al.\textsuperscript{24} deals with finite-resolution effect by adding two parameters to the original equation. In that case, a value has to be assumed for the tissue/blood partition coefficient, and three parameters are fitted: myocardial blood flow, recovery coefficient of myocardium, and fraction of blood activity contained in tissue (because of spillover and vascular fraction). This method assumes that the arterial input function is not affected by partial volume effect or contaminated by spillover from myocardial activity into the blood pool region of interest. In their validation studies, Bergmann et al.\textsuperscript{22} and Araujo et al.\textsuperscript{24} used the left atrium as arterial input reference level. In the present study, the left ventricle was used because dynamic data were obtained only in a single plane. In the second method used for \textsuperscript{15}O water data analysis, blood pool and myocardial activity curves are corrected for finite-resolution effect by a specially designed Monte Carlo simulation before the fit (see References 32 and 33 and “Appendix”). The partition coefficient is fitted.
TABLE 3. Comparison of Blood Flow Estimates by Positron Emitter and Microsphere Techniques in Small Myocardial Regions

<table>
<thead>
<tr>
<th></th>
<th>Least-squares regression equation</th>
<th>Mean difference (systematic error)</th>
<th>SD (random variability)</th>
<th>t Test</th>
<th>Correlation test</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{15}$NAmmonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual metabolite subtraction</td>
<td>$y=-0.3+0.86x$</td>
<td>0.97</td>
<td>+33</td>
<td>42</td>
<td>&lt;0.001 0.53 &lt;0.001</td>
</tr>
<tr>
<td>$^{18}$OWater</td>
<td>Method 1: $y=9+0.92x$</td>
<td>0.93</td>
<td>+4</td>
<td>52</td>
<td>NS 0.20 NS</td>
</tr>
<tr>
<td></td>
<td>Method 2: $y=-3+0.96x$</td>
<td>0.96</td>
<td>+10</td>
<td>43</td>
<td>NS 0.13 NS</td>
</tr>
</tbody>
</table>

as a parameter together with myocardial blood flow and the vascular fraction.

For $^{15}$NAmmonia studies, myocardial perfusion was estimated from a previously described three-compartment model. In nine of ten studies from group 1, the contribution of $^{15}$NAmmonia to the total radioactive activity has been measured in arterial plasma, and these data have been taken into account in the kinetic model either by correcting the input function for the individually measured metabolites or by using the mean value of the nine studies. In group 2, the input function has been corrected by using the mean value of metabolites obtained in group 1.

Statistical Analysis

The results are expressed as mean±SD. Linear least-squares regression was calculated between the independent microsphere and positron emitter estimations of myocardial blood flow. The mean difference between paired measurements (microsphere minus PET methods) was calculated to evaluate the accuracy or systematic error. The SD of the mean difference was used to evaluate the precision or random variability. The coefficient of variation was defined as the ratio of SD over the mean difference. Two tests were performed on the mean differences: a Student’s $t$ test to assess a nonsystematic error and a Pearson $r$ correlation test to assess a nondependence between the systematic error and the level of the independent microsphere measurement. Differences in correlations as well as in systematic errors between the four regions were tested by ANOVA with $F$ test (BMDP/386 statistical software). A value of $p>0.05$ was considered nonsignificant.

Results

Hemodynamics and Regional Myocardial Blood Flow Measurements

In group 1, during control conditions, heart rate averaged 129±21 beats per minute and mean arterial blood pressure 95±11 mm Hg; end-diastolic and end-systolic wall thicknesses in the circumflex territory were 10±2 and 13±2 mm, respectively, with a systolic wall thickening of 25±6%. After moderate coronary stenosis and adenosine infusion, heart rate decreased to 118±26 beats per minute and mean arterial blood pressure to 78±11 mm Hg; systolic wall thickening in the circumflex territory decreased to 17±7%. After more severe stenosis, heart rate averaged 131±31 beats per minute and mean arterial blood pressure 87±10 mm Hg; end-diastolic and end-systolic wall thicknesses in the circumflex territory were 10±2 and 10±1 mm, respectively, with a mean systolic wall thickening of 4±4%. In the anterior territory, mean systolic thickening was 28±7% with end-diastolic and end-systolic thicknesses of 9±3 and 13±3 mm, respectively. In group 2, during baseline studies, heart rate averaged 132±25 beats per minute and mean arterial pressure 85±15 mm Hg. After adenosine infusion, heart rate increased to 142±18 beats per minute, and mean arterial blood pressure decreased to 72±19 mm Hg. Ultrasonic crystals were used for proper positioning in these dogs but did not give accurate signals for thickness measurements.

TABLE 4. Differences Between Flow Determined by Microspheres and $^{15}$NAmmonia or $^{18}$OWater in Regions of Interest With a Myocardial Wall Thickness <11 mm

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean difference (systematic error)</th>
<th>SD (random variability)</th>
<th>Flow (ml·min⁻¹·100 g⁻¹) by microspheres</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Large regions of interest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{15}$NAmmonia: individual metabolite subtraction</td>
<td>5</td>
<td>+3</td>
<td>+28</td>
<td>85</td>
</tr>
<tr>
<td>$^{18}$OWater</td>
<td>Method 1</td>
<td>5</td>
<td>−2</td>
<td>+20</td>
</tr>
<tr>
<td></td>
<td>Method 2</td>
<td>5</td>
<td>+16</td>
<td>+18</td>
</tr>
<tr>
<td><strong>Small regions of interest</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{15}$NAmmonia: individual metabolite subtraction</td>
<td>8</td>
<td>+10</td>
<td>+22</td>
<td>82</td>
</tr>
<tr>
<td>$^{18}$OWater</td>
<td>Method 1</td>
<td>18</td>
<td>−8</td>
<td>+30</td>
</tr>
<tr>
<td></td>
<td>Method 2</td>
<td>11</td>
<td>+13</td>
<td>+29</td>
</tr>
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</table>
FIGURE 10. Plots showing correlation between myocardial blood flow estimated by positron emission tomography after \(^{13}\)N-ammonia (upper panel) or \(^{15}\)O-water injection (middle and lower panels) and that obtained from microspheres in 22 infarcted regions of group 2 dogs. Open squares (dashed regression line) represent one small region per study drawn at the center of the defect. Filled triangles correspond to the other small regions drawn in the defect. The solid regression line takes all the regions into account. The corresponding regression equations are listed in Table 5.

In the large regions of group 1, myocardial blood flow estimated by microspheres ranged from 37 to 580 ml/min\(^{-1}\)·100 g\(^{-1}\) for the studies concomitant to \(^{15}\)O-water flow determinations and from 58 to 548 ml/min\(^{-1}\)·100 g\(^{-1}\) for the \(^{13}\)N-ammonia studies. In the small regions of the same group, myocardial blood flow ranged from 19 to 653 ml/min\(^{-1}\)·100 g\(^{-1}\) for the \(^{15}\)O-water studies and from 32 to 557 ml/min\(^{-1}\)·100 g\(^{-1}\) for the \(^{13}\)N-ammonia studies. In group 2, only small regions have been analyzed so as to avoid inclusion of heterogeneous tissue. In these regions, transmural myocardial blood flow estimated by microspheres in the TTC- zones ranged from 2 to 113 ml/min\(^{-1}\)·100 g\(^{-1}\).

FIGURE 11. Plots of the difference between microsphere and positron emission tomography estimates of myocardial blood flow versus flow values determined by microspheres for infarcted regions. Open squares represent one small region per study drawn at the center of the defect. Filled triangles correspond to the other small regions drawn in the defect. The solid line shows the mean difference for all the regions, and the dashed lines represent 2 SD from this mean. Three panels are shown: top panel, \(^{13}\)N-ammonia (with mean metabolite correction); middle panel, \(^{15}\)O-water (method 1), and bottom panel, \(^{15}\)O-water (method 2). The statistical significance of these plots is presented in Table 5.
TABLE 5. Comparison of Blood Flow Estimates by Positron Emitter and Microsphere Techniques in Small Infarcted Myocardial Regions

<table>
<thead>
<tr>
<th>Central region</th>
<th>n</th>
<th>Least-squares regression equation</th>
<th>r</th>
<th>Mean difference (systematic error)</th>
<th>SD (random variability)</th>
<th>r Test</th>
<th>Flow (ml · min⁻¹ · 100 g⁻¹) by microspheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>[¹³N]Ammonia: mean metabolite subtraction</td>
<td>7/8</td>
<td>y = 2.5 + 1.47x</td>
<td>0.95</td>
<td>-14</td>
<td>19</td>
<td>NS</td>
<td>27</td>
</tr>
<tr>
<td>[¹⁵O]Water: Method 1</td>
<td>8/8</td>
<td>y = 12.6 + 0.93x</td>
<td>0.92</td>
<td>-10</td>
<td>14</td>
<td>NS</td>
<td>34</td>
</tr>
<tr>
<td>Method 2</td>
<td>6/8</td>
<td>y = 12.1 + 0.93x</td>
<td>0.77</td>
<td>-11</td>
<td>11</td>
<td>NS</td>
<td>15</td>
</tr>
<tr>
<td>All regions</td>
<td>18/22</td>
<td>y = 7.5 + 1.12x</td>
<td>0.93</td>
<td>-12</td>
<td>16</td>
<td>&lt;0.01</td>
<td>34</td>
</tr>
<tr>
<td>[¹³N]Ammonia: mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>metabolite subtraction</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[¹⁵O]Water: Method 1</td>
<td>22/22</td>
<td>y = 41.2 + 0.53x</td>
<td>0.47</td>
<td>-25</td>
<td>37</td>
<td>&lt;0.01</td>
<td>35</td>
</tr>
<tr>
<td>Method 2</td>
<td>18/22</td>
<td>y = 25.0 + 0.66x</td>
<td>0.65</td>
<td>-16</td>
<td>23</td>
<td>&lt;0.01</td>
<td>26</td>
</tr>
</tbody>
</table>

Time–Activity Curve Measurements

Figure 2 shows the good agreement in shape, timing of the initial bolus, and magnitude between the tomographic data obtained from the left ventricular region of interest (after correction for finite-resolution effects) and the in vitro data obtained directly from the aorta for two typical [¹³N]ammonia studies. Count rates in the left ventricular blood pool (given as counts per second in the region) ranged from 60,000 to 140,000 at the time of peak activity. Figure 3 shows the comparison between the left ventricular tomographic curve and the β-probe data from two typical [¹⁵O]water studies. Again the two curves are very similar. Count rates ranged from 85,000 to 220,000 counts per second at the time of peak activity. The good agreement between in vivo and in vitro arterial input curve determinations is shown in Figure 4, which displays the integral values of these curves in a scatterplot for six [¹³N]ammonia studies and five [¹⁵O]water studies. The time-integrated arterial input functions had a correlation coefficient of 0.99 and a slope of 1.02.

Figure 5 illustrates typical examples of time–activity curves for left ventricular blood pool and myocardium derived from serial PET data. At 100 seconds after injection, the [¹³N]ammonia myocardial activity shows high contrast to blood activity, whereas little contrast is observed in [¹⁵O]water tissue activity because of back-diffusion of the tracer from tissue.

Metabolism of [¹³N]Ammonia

Table 1 shows the relative distribution of unmetabolized [¹³N]ammonia in nine studies of group 1 as a fraction of total plasma radioactivity at each time. The [¹³N]ammonia fraction decreases rapidly to 57% of total plasma activity at 120 seconds and to 38% at 180 seconds after injection. The high coronary flow states obtained after adenosine infusion had no influence on the data. The mean values as well as the individual values for each dog were used for the flow calculation by [¹³N]ammonia with the three-compartment model.

Comparison of PET and Microsphere Estimates of Blood Flow in Large Myocardial Regions

Figures 6 and 7 show the flow values in the four large regions of interest (5 cm²) for nine [¹³N]ammonia studies and for the 10 [¹⁵O]water studies in group 1. Only nine of the 10 [¹³N]ammonia studies are reported because [¹³N]ammonia activity was not measured in sequential arterial samples for one study. Figure 6 shows three different methods for estimating flow with [¹³N]ammonia: the three-compartment model without correction for true ammonia activity in plasma, with an individual correction for each study, and with a correction based on the mean values for the nine studies. In Table 2, the least-squares regression equations and the corresponding correlation coefficients are listed for the three methods. In the same table and in Figure 8, the mean differences between microspheres and [¹³N]ammonia values are shown together with their standard deviations. The two best correlations between [¹³N]ammonia and microspheres are achieved when correction for [¹³N]ammonia arterial activity is applied. However, if the method with individual correction is used without correction for finite-resolution effect, the slope decreases to 0.62, and the systematic error increases. Despite the good correlation coefficients and slope values achieved, the mean difference between microsphere and [¹³N]ammonia flow estimates is statistically significant for the described methods. The smallest systematic error and random variability are achieved when a correction for [¹³N]ammonia arterial activity is applied in the model. The significance of the overall systematic error of these two methods (p<0.001) is because of the septal region. In terms of correlations, there is no statistical difference among the four regions.

Figure 7 shows the results of the two methods used for flow calculation with [¹⁵O]water. The corresponding regression equations and correlation coefficients are listed in Table 2. In the same table and in Figure 8, the mean differences between microsphere and [¹⁵O]water studies are shown. The best correlation is achieved when the correction for finite-resolution effect is applied before the fit (method 2). Also, the systematic error and random variability are the smallest with this
method. There is a statistical difference of systematic errors between microspheres and [13N]ammonia with both methods. For method 1, the significance of the overall systematic error is because of the septal region. Moreover, for this method, there is a dependence between the systematic error and the level of microsphere measurement in the septal region (r = 0.68, p = 0.04).

Comparison of PET and Microsphere Estimates of Blood Flow in Small Regions of Interest and in Regions Corresponding to Myocardium Thinner Than 11 mm

The comparison of microsphere with positron estimates of flow was performed in 10 small regions of interest (1 cm²) per study for group 1 (Figure 9). For this purpose, we selected the methods yielding the best results with the large regions, i.e., [13N]ammonia with individual metabolite subtraction and method 2 of [15O]water together with method 1 of [15O]water previously validated with microspheres.22,24 In each study, the two regions of interest adjacent to the ischemic zone (one on each side) were excluded from the analysis to minimize the heterogeneity of flow. Table 3 shows the regression equations for the flow values in regions of interest in which the fits were found valid visually or by χ² statistics or both. The best proportion of valid fits was achieved with method 1 of [15O]water (79%), whereas the proportion was slightly smaller with [13N]ammonia (69%) and with method 2 of [15O]water (64%). In those regions, the correlations between microsphere and positron emitter estimates of blood flow were excellent.

The comparison of microsphere with PET estimates of flow was also made in regions of interest corresponding to akinetic segments during the five studies performed during more severe coronary stenosis in group 1. The myocardial thickness ranged from 8 to 11 mm (10±1 mm) during these studies, with a systolic wall thickening ranging from 0 to 6% (4±4%). The systematic error and the random variability were small and similar among the three methods (Table 4). In the small regions with regional akinesia, the highest proportion of valid fits was achieved with method 1 of [15O]water.

Comparison of PET and Microsphere Estimates of Blood Flow in Small Regions of Interest Corresponding to Necrotic TTC – Regions

Figures 10 and 11, together with Table 5, show the comparison between PET and microsphere estimates of blood flow in 22 small regions of interest (1 cm²) drawn from the corresponding TTC – zones in eight studies of group 2. The counts obtained at the end of the PET acquisition were of the same order of magnitude, at least 10 counts per pixel per second, in the central defect zone for both the water and the ammonia studies. The relation between flow estimates, systematic error, and random variability was good in regions drawn right in the middle of the defect zone. When all the TTC – regions were taken together, the relation between flow estimates was poor for water methods. Again, the best proportion of valid fits was achieved with method 1 of [15O]water.

Discussion

The results of this study indicate that estimates of myocardial blood flow in absolute terms obtained invasively with [13N]ammonia and [15O]water correlate closely over a wide range of flow values with estimates of myocardial blood flow obtained simultaneously by well counting using radiolabeled microspheres. Evidence for this good agreement is found in the comparison of the techniques in an experimental model of low and high flow in noninfarcted myocardial regions of different sizes and with normal or reduced wall thickness, as well as in infarcted regions.

Previously described tracer kinetic models have been used to quantify regional myocardial blood flow with [13N]ammonia25 and [15O]water.21,22,24 Estimation of regional perfusion with [13N]ammonia has been done with a three-compartment model, which accounts for the forward and the backward transfer rates of [13N]ammonia into myocardium and for the metabolic trapping of [13N]ammonia in the form of [13N]glutamine. In the present study, we have also implemented corrections for metabolites contaminating the arterial input function and an independent estimation for finite-resolution effects. A one-compartment model in which tracers in tissue and blood are assumed to be in equilibrium was used for flow estimation with [15O]water. Two different methods were compared with or without application of corrections for finite-resolution effects before the fit.

A prerequisite for the application of all these methods is to obtain an accurate arterial input function derived from dynamic image acquisition with PET. Our study confirms (Figures 2–4) that the invasively derived arterial input function correlated closely with the tomographically derived input function.22,24 Because of the limitations imposed by the use of a single-slice machine, we were not able to measure the arterial time–activity curve from a region of interest in the left atrium. This has been shown to minimize contamination of the arterial time–activity curve from spillover from the myocardium compared with a left ventricular blood pool region.22 Nevertheless, we corrected both the left ventricular blood pool and the tissue time–activity curves for the finite-resolution effects before the fit by the previously described correction procedure.22,23 The best correlation results were obtained both for [13N]ammonia and [15O]water with this correction procedure. Besides the accuracy of the recorded blood pool radioactivity as a measure of the true arterial input function, the activity in the blood should not be contaminated by labeled metabolites of the tracer either. The degree and time course of metabolic contamination of the [13N]ammonia arterial input function have been characterized.20 We have evaluated the effect of the correction for [13N]metabolites in arterial blood on myocardial blood flow estimates by [13N]ammonia. A better correlation was found when this correction factor was applied. This was not suggested by the initial results of Hutchins et al.25 in patients, but the decrease of the [13N]ammonia component appears to be slower in humans than in dogs.26 In our study, there was 91±9% and 57±19%, respectively, of the activity in blood with [13N]ammonia at 1 and 2 minutes in dogs compared with 99±1% and 90±4% in patients (unpublished observations). Thus, the issue of blood metabolite correction seems to be species dependent after [13N]ammonia injection, and in dogs, an adequate correction gives a better correlation between microsphere and positron emitter estimates of blood flow.
Once the arterial input function has been accurately derived through PET, the kinetic models that we applied for both tracers need to be discussed. Myocardial extraction of $^{13}$N-ammonia is nonlinearly and inversely related to flow. By use of a three-compartment tracer kinetic model, $^{13}$N-ammonia extraction can be separated from the metabolic $^{13}$N-ammonia tissue retention, and blood flow measurements can be obtained based on $^{13}$N-ammonia extraction. Also, the operational flow equation incorporates the fraction of blood activity that spills over into tissue. This model has been validated only in a preliminary report against an independent flow method such as the microspheres. In the present study, the best correlation results were achieved when an independent correction for finite-resolution effects was applied before the fit, together with subtraction of arterial metabolites. Without the finite-resolution correction, the correlation with microspheres deteriorated, with a systematic underestimation of flow by $^{13}$N-ammonia as well as a larger random variability. The correlation with microspheres was worse in the septum than in any other myocardial region, presumably because of the activity spillover from the right ventricle. This problem was also observed with the water method. Potential correction for this right ventricle spillover could be included in our Monte Carlo simulation and should be further validated.

$^{18}$O-water is relatively freely permeable across the capillary and cellular membranes. Its first-pass extraction fraction is close to unity and is relatively insensitive to flow changes. Tripp et al. demonstrated very close correlations between measurements of myocardial blood flow with tritiated water and a one-compartment model versus microspheres. Method 1 was based on the conventional theory of the $^{18}$O-water autoradiographic technique as later applied to cardiac positron studies by Bergmann et al. and Lida et al. In method 1, the data measured from the tissue and blood time–activity curves were fitted to an equation with three parameters. Besides myocardial blood flow, the two parameters account for the finite-spatial-resolution effects of the tomograph. Bacharach et al. showed that these estimates compared well with the results of other methods (CO study for the spillover and gated magnetic resonance imaging for the partial volume). This method 1 has been validated against microspheres over a wide range of flow values (29–504 ml·min$^{-1}$·100 g$^{-1}$) with an excellent correlation ($y = 0.0 + 1.096x$; $n = 37$). In the present study, application of this method gave good results also, but the correlation at high flows was not as good as in the study of Bergmann et al. Two features are different between the two protocols. First, we had to use the left ventricular blood pool as the arterial input curve, and second, we used a relatively slow infusion (30 seconds) to reduce the artifacts resulting from the dead-time of the scanner. The rate and duration of infusion selected have been optimized to find a good tradeoff between count statistics and dead-time losses of our scanner.

When we corrected for the finite-resolution effects before fitting with three parameters in the single-tissue-compartment water model (method 2), the best correlation results were obtained even at high flows. It should be noticed that the finite-resolution correction before the fit does not seem to be the only important step for a better correlation. The gain in correlation obtained after correction for finite-resolution effects is in fact smaller than the gain achieved for the $^{13}$N-ammonia model. The main difference between the two approaches is that in method 1, flow is a washout model variable, whereas in method 2 (with or without finite-resolution effect correction), it is an uptake model variable. Although method 2 of $^{18}$O-water gave the best correlation results in the present validation study, it should be noticed that this model configuration with three parameters occasionally produces nonphysiological values for the partition coefficient.

For both $^{13}$N-ammonia and $^{18}$O-water methods, we assessed the effect of the size of the regions of interest on the adequacy of the fitting procedure and on the accuracy of the correlation. In the first analysis, relatively large regions (5 cm$^2$) were adopted to reduce the statistical noise. All the fitting procedures were satisfactory. By use of smaller regions of interest (1 cm$^2$), the best proportion of wall fits (80%) was achieved with method 1 of $^{18}$O-water, whereas it was between 60% and 70% for $^{13}$N-ammonia and method 2 of $^{18}$O-water. Moreover, the correlation with microspheres was better than with large regions with both tracers, presumably because the inclusion of heterogeneous tissue, an admixture of normal and ischemic tissue, was minimized within a small region of interest. Accordingly, as long as the fitting procedure is successful, it would seem preferable to use small regions of interest. The $^{13}$N-ammonia and $^{18}$O-water methods were also satisfactory for blood flow estimates in regions with wall akinesia. The average thickness of the ischemic walls was 10 mm, the thinnest being 8 mm. For thinner myocardial walls, the present correction for finite-resolution effects would not be appropriate, and an independent measurement of the myocardial thickness in conjunction with PET would be necessary.

In the myocardium made necrotic by a permanent coronary occlusion, this study indicates continued good agreement between PET and microsphere estimates of myocardial blood flow. The cell integrity dependence of $^{13}$N-ammonia extraction has been suggested by Rauch et al. in isolated rat heart cells but does not seem to significantly influence in vivo myocardial blood flow estimates by ammonia. For the water studies, the good agreement was observed only if regions were drawn right in the middle of the infarcted zone. The poor prediction of microsphere flow by the water methods outside the central infarct zone can hardly be explained by the spatial resolution of the images or by counting statistics because the two factors affect both ammonia and water studies similarly. An alternative speculation could be that flow measured by water is a flow rate per mass of perfusable tissue excluding scar tissue, whereas the conventional microsphere flow includes nonperfusible space. The larger overestimation observed with method 1 (clearance flow) supports the latter explanation.

Besides myocardial regional thinning and infarction, other pathological conditions in which accurate measurements of myocardial blood flow are important include left ventricular hypertrophy. In that case, the problems of tissue count recovery caused by the limited spatial resolution may be of less importance. An excellent correlation of water PET and microsphere flow estimates was achieved in the study of Araujo et al., in
which the animals had a hypertrophic myocardium with a thickness of about 20 mm. In a clinical study of hypertrophic cardiomyopathy, Camici et al.30 observed underperfusion limited to the subendocardium after dipyridamole with $^{15}$N ammonia in septal regions with a thickness of >30 mm.

We conclude that, with appropriate tracer kinetic models and independent correction for finite-resolution effects, both $^{15}$N ammonia and $^{18}$O water are suited for quantitative measurements of transmural myocardial blood flow. $^{18}$O Water has the desirable features of freely diffusible properties and possibility of quick repetitions between measurements that make this tracer more suitable for perfusion reserve measurements. Alternatively, $^{15}$N ammonia offers the advantage of longer retention and higher count rate statistics at late times, which make it a superior imaging agent.

**Appendix**

The behavior of $^{18}$O water in tissue can be described by the following equation for a single-tissue-compartment model:

$$C_{\text{water}}(t) = f \cdot C_{\text{water}}(t) \cdot \exp(-k \cdot t)$$

where $C_{\text{water}}(t)$ is the tracer concentration in tissue (mCi/100 g), $f$ is the regional blood flow (ml·100 g$^{-1}$·min$^{-1}$), $C_{\text{water}}$ is the arterial blood concentration (mCi/ml), $p$ is the partition coefficient of water (ml/g), $k = f/p$, and $\exp$ stands for convolution.

In practice, because of finite spatial resolution of PET, the tracer concentration measured in a myocardial region of interest differs from the actual tissue concentration. First, the spillover effect leads to a contamination from ventricular blood activity into the myocardial region. This effect is particularly important in water studies because of the high level of activity in the heart chambers. Second, the partial volume effect, together with cardiac and respiratory movements, produces an underestimation of the tissue concentration. A way to correct for these effects is to include them as parameters in the operational equations. Different types of equations representing the same single-tissue-compartment model can be derived to account for these finite-resolution effects.32,4 We tested one of these equations to fit our water data. This method (called method 1 in the text) has been validated by Bergmann et al.22

In their formulation, Equation 1 becomes

$$C_{\text{water}}(t) = F_{\text{mm}} \cdot f \cdot C_{\text{water}}(t) \cdot \exp(-k \cdot t) + TBV \cdot C_{\text{water}}$$

where $F_{\text{mm}}$ is the myocardium recovery (this parameter is called fraction of water-exchanging tissue in References 21, 24, and 44) and TBV is the total fractional blood volume (vascular fraction plus spillover from blood pool into myocardium). In this method, a fixed value must be assumed for the partition coefficient (we used a value of 0.92 ml/g), and the three fitted parameters are $F_{\text{mm}}$, $f$, and TBV.

Another approach consists of correcting the tissue time–activity curves for finite-resolution effect before the fit. For that purpose, we developed a Monte Carlo method that allows the calculation of regional correction factors for spillover and partial volume both for blood and tissue regions of interest and that has been validated versus phantoms and in vitro measurements.23,24 This Monte Carlo simulation assumes a bi-Gaussian spatial resolution that takes into account the deterioration of resolution caused by wall motion. The shapes and sizes of blood pool and myocardium are determined by contours drawn on a selected image in which all the activity is concentrated in the myocardium. Because of the lack of contrast shown by water images, the contours in this study have all been drawn on a $^{15}$N ammonia image. This approach has been tested on our water data (method 2) by correcting both tissue and blood time–activity curves for the finite-resolution effects before fitting the data to the single-tissue-compartment water model. In this method, Equation 1 becomes

$$C_{\text{water}}(t) = (1-BV) \cdot f \cdot C_{\text{water}}(t) \cdot \exp(-k \cdot t) + BV \cdot C_{\text{water}}$$

where $BV$ represents the blood volume contained in the myocardial region. No assumed value is needed for the partition coefficient in this method, and the three fitted parameters are $f$, $p$, and $BV$.

The model used for $^{15}$N ammonia data analysis is the three-compartment model described by Hutchins et al.25 The model equation contains a term that represents the total fractional blood volume (vascular fraction plus spillover from blood pool into myocardium) like the one in method 1 of water data analysis, but it does not correct for partial-volume effect.

Therefore, we compared the results given by the published model with the results obtained when we apply our Monte Carlo correction for finite-resolution effect to both tissue and blood time–activity curves before performing the fit.

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