Noninvasive Evaluation of Regional Myocardial Perfusion in 112 Patients using a Mobile Scintillation Camera and Intravenous Nitrogen-13 Labeled Ammonia

WALLEN R. WALSH, M.B., F.R.A.C.P., PAUL V. HARPER, M.D. LEON RESNEKOV, M.D., F.R.C.P., AND HEIKO FILL, M.D.

SUMMARY The short half-life positron emitter $^{13}$N, as labeled ammonia ("$^{13}$NH$_3$",), was evaluated as a myocardial imaging agent. Regional myocardial uptake of $^{13}$NH$_3$ correlated with the distribution of labeled microspheres in experimental myocardial infarction. Using intravenous $^{13}$NH$_3$, myocardial scintigraphy was performed in 85 cardiac patients and 27 normal subjects. Ninety-five scintograms were suitable for analysis. Eighteen of 24 normal subjects had homogenous myocardial images; six had inhomogeneous images attributable to early technical problems. Perfusion defects were observed in the scintigrams of 82% (57/69) of patients with coronary artery disease, being most common in patients with myocardial infarction (27/28). Six sequential studies showed changes in perfusion consistent with the clinical course of each patient. Scintographic abnormalities were also observed in 4/6 patients with valvular heart disease. $^{13}$NH$_3$ myocardial scintigraphy is a valid and sensitive method of assessing regional myocardial perfusion and is especially useful for sequential imaging at short intervals.

THE INTRODUCTION OF RADIOPHARMACEUTICALS which localize in the myocardium at levels dependent upon regional blood flow has made possible the noninvasive assessment of regional myocardial perfusion using a scintillation camera. Experience with this new technique was initially limited by production difficulties and unsatisfactory imaging characteristics of the available radioisotopes. In 1971 Hunter and Monahan observed myocardial uptake of $^{15}$N-labeled ammonia during animal metabolic studies and suggested that it might be a useful agent for imaging the myocardium. Subsequently, myocardial uptake of $^{15}$NH$_4^+$ was demonstrated in man. Because of the advantages of using a short half-life isotope we evaluated $^{15}$N-labeled ammonia as a myocardial imaging agent for the assessment of regional myocardial perfusion. The relationship between myocardial uptake of $^{15}$NH$_4^+$ and regional perfusion was determined in animal studies, following which a clinical imaging study using this agent was carried out in 112 patients to determine the myocardial scintigraphic patterns in the normal subject and in patients with cardiovascular disease.

References


17. Parsonnet V: Magnet pacemaker reversion. JAMA 224: 1428, 1973
Materials and Methods

\(^{13}\text{NH}_4^+\) Production

Nitrogen-13 labeled ammonia was produced in a small on-site cyclotron, initially by deuteron bombardment of methane, as described by Tilbury et al.\(^{18}\) This product was used in the early scintigraphic studies, although its radiochemical purity was only approximately 80%. Since image quality tended to be inconsistent and occasional very poor quality images with low contrast were obtained, a new method of production was developed and introduced in April, 1973. \(^{14}\)N, in the form of nitrate, was produced by proton bombardment of water and reduced by titanous hydroxide to ammonia, which was recovered by distillation from the base within a few minutes. The ammonia so produced had radiochemical purity greater than 99% and contained less than 15–20 \(\mu\)g of carrier ammonia per production run.\(^{19}\)

Instrumentation

Imaging was carried out using a Searle Radiographics Pho/Gamma HP scintillation camera. In 1971 mobility of the imaging equipment was obtained by mounting the camera on a mobile platform and attaching it by a swivel to a small electric tractor. The camera was interfaced to a portable Ohio-Nuclear 150 Digital Data System in May 1973, permitting the data to be acquired, stored, and processed in digital form.

A standard 550 parallel hole, high energy lead collimator was used in the early studies, but proved unsatisfactory because septal thickness greater than system resolution resulted in the collimator hole pattern being conspicuously superimposed on the image. A specially designed tungsten collimator, with the same hole size but narrower septa, was therefore constructed and used in all imaging studies performed after May 1972. The increased number of holes improved the collimator efficiency and reduced the hole pattern in the image, improving image quality.\(^{14}\)

A 20% pulse height analyzer window centered around the 511 keV gamma energy peak from the positron annihilation of \(^{13}\)N was used for imaging.

Animal Studies

The porcine animal model was used because of the similarity of its coronary anatomy to that of man.\(^{18}\) The distal left anterior descending coronary artery was ligated in the first animal to create a transmural anteroseptal infarct, and the first diagonal branch of this artery was ligated in the second animal to produce a transmural anterolateral infarct. One hour later both \(^{13}\text{NH}_4^+\) (36.5 mC, 36.5 mC) and \(^{99m}\text{Tc}\) labeled microspheres (3.5 mC, 3.3 mC), 15–30 \(\mu\) in diameter, were administered directly into the left atrium using separate syringes. The animals were sacrificed 10 min later and a transverse slice taken through the center of the infarct together with the neighboring tissue, normal on gross examination. Twenty to twenty-five full thickness adjacent tissue samples, each of approximately 500 mg, were individually weighed, counted for \(^{13}\)N activity excluding \(^{99m}\text{Tc}\) activity, and after decay of \(^{13}\)N were counted for \(^{99m}\text{Tc}\) activity. The tissue sample counts for both nuclides were compared to injection standards and the percentage of the injected dose of each agent per gram of tissue was calculated.

Patient Population

Myocardial scintigraphy using intravenous \(^{13}\text{NH}_4^+\) was performed in 85 cardiac patients and 27 normal subjects between October 1971 and January 1975. The scintigrams of 14 cardiac patients and three normal subjects were unsuitable for interpretation because of poor myocardial localization of \(^{13}\text{NH}_4^+\) or unsatisfactory image quality. Sixteen of these 17 studies were performed before the improvements in collimator design and \(^{13}\text{NH}_4^+\) production were instituted. Therefore, the study population for analysis comprised 24 normal subjects (mean age of 39, range 21–59 years) who served as controls, and 71 cardiac patients who were divided into four clinical groups on the basis of historical, electrocardiographic and laboratory data.

Group I: Acute Myocardial Infarction

Twenty-eight patients (mean age 54, range 40–74 years) had been admitted to the Coronary Care Unit with acute myocardial infarction (MI). Criteria for diagnosis were a typical clinical history for infarction, evolutionary ST-segment changes, and a transient rise in the serum levels of the enzymes CPK and SGOT. The development of new pathological Q waves indicated transmural infarction. Thirteen patients had anterior transmural MI; seven, inferior transmural MI; three, anterior nontransmural MI; three, inferior nontransmural MI; and two had both anterior and inferior transmural MI. Six of the 28 patients (21%) had historical and/or ECG evidence of previous MI. The time interval between admission and study varied from 5 hours to 3 weeks with a mean of 6 days. Fourteen patients were imaged within 72 hours of admission. Five patients were imaged two to four times during the acute phase of their illness.

Group II: Suspected Myocardial Infarction

This group comprised 17 patients (mean age 61, range 46–83 years) admitted for infarction, in whom subsequent investigation failed to show electrocardiographic or enzymatic evidence of infarction. Nine patients had a history or ECG evidence of old MI. The time interval between admission and imaging varied from 1–21 days with a mean of 9 days. Five patients were studied within 72 hours of admission. The final diagnoses of the 17 patients were unstable angina (six), dysrhythmia (three) congestive heart failure (seven), noncardiac pain (one). One patient with unstable angina was imaged four times during the first eleven days following admission.

Group III: Stable Angina

Twenty patients (mean age 57, range 46–72 years) with chronic stable angina were studied at rest. Sixteen (80%) had history or ECG evidence of previous MI.

Group IV: Valvular Heart Disease

Six patients (mean age 49, range 24–66 years) had valvular heart disease, of whom three were studied following prosthetic valve replacement. The etiology of the valvular
heart disease was rheumatic in five and secondary to acute endocarditis in one. No patient had evidence of coexisting coronary artery disease.

Imaging Procedure

Informed consent was obtained in all cases. All patients in groups I, II, and IV were studied at the bedside using the mobile gamma camera system. The normal subjects and group III patients were studied in the Nuclear Medicine Department using the same imaging equipment. In the AP position, 20–25 mCi of carrier-free $^{13}$NH$_4^+$ was administered intravenously into a peripheral vein and the initial passage of the bolus through the heart observed on the digital video display to insure correct patient positioning. Collection of images containing one million counts was commenced immediately and continued until the count rate became too low, usually 30–40 min. Only myocardial images obtained after pulmonary uptake had substantially cleared, permitting clear delineation of the lateral border of the heart, were used for interpretation. Usually two to four one million count images were available. Six subjects had acceptable images recorded in three views (AP, LAO, RAO), 32 in two views (AP and LAO or RAO), and 57 in one view only (AP). Analogue images were recorded on Polaroid film and digitized scintillation data stored on magnetic tape in 10-second frames. No complications resulting from the administration of intravenous $^{13}$NH$_4^+$ were observed.

Scintigraphic Analysis

The normal scintigraphic anatomy was determined in an open-chested porcine model. Intravenous $^{13}$NH$_4^+$ was administered and the myocardial image with the mobile gamma camera system. A technetium-99m point source was placed at specific locations on the heart, and the $^{99m}$Tc images so obtained were superimposed on the $^{13}$NH$_4^+$ image to provide an anatomically correct interpretation of the $^{13}$NH$_4^+$ myocardial image.

On the basis of this animal data, each myocardial scintigram was divided into four segments for interpretation: lateral, apical, inferior, septal (fig. 1). The uptake of $^{13}$NH$_4^+$ in each segment was visually graded as: a) normal — substantial and homogeneous; b) abnormal — localized uptake defect. Each defect was further subdivided into large (> 50% segmental area) or small (< 50% segmental area). No attempt was made to grade intensity of uptake. The scintigrams were interpreted by two different observers (W.W., H.F.), one of whom was unaware of the clinical diagnosis.

There was a 98% agreement between the biased and unbiased reader in the detection of uptake defects. There was a 72% agreement on the anatomic location of the defects. The disagreement resulted almost exclusively from differences in judging the location of the apex. The first scintigraphic study performed was used for clinical correlation in patients who had more than one study. Only segmental readings where both observers agreed were used for the clinical correlation analysis. Comparison of the myocardial images in the sequential studies was made in the same view at a similar time interval.

Results

Animal Experiments

The regional myocardial uptake of $^{13}$N-labeled ammonia was compared with the distribution of microspheres labeled with $^{99m}$Tc in two animals in whom myocardial infarction, in different locations, had been experimentally created. The results of the first experiment are illustrated in figure 2. In each experiment a strong correlation was demonstrated between the tissue uptake (as measured by the percentage of injected dose per gram of tissue) of $^{13}$NH$_4^+$ and $^{99m}$Tc. The correlation coefficients were 0.94 and 0.91 respectively. Levels of activity were very low in the infarcted region, high in the grossly normal tissue, and intermediate in the transitional ischemic zone (fig. 2). Thus, since the tissue distribution of labeled microspheres has been shown to be an index of perfusion,10,11 the regional myocardial uptake of $^{13}$NH$_4^+$ in normal, ischemic, and infarcted myocardium is an appropriate reflection of perfusion level.

Clinical Scintigraphic Analysis

Pulmonary and Hepatic Uptake

Immediately after administration of $^{13}$NH$_4^+$ substantial but transient pulmonary uptake, obscuring the lateral border of the heart, occurred in all 95 patients. Pulmonary activity cleared sufficiently to delineate the myocardial image in 3 to 36 min, depending upon the smoking habits of the patient. Clearance was most rapid in nonsmokers (mean 5.3 min) and slowest in smokers (mean 13.6 min). Eleven patients had unusually prolonged pulmonary activity (mean clearance time 22 min) permitting only a single acceptable myocardial image to be obtained.

All cases demonstrated significant hepatic uptake of $^{13}$NH$_4^+$. In 12 studies (13%) the uptake by the left lobe of the liver prevented clear separation of the liver border from the inferior wall of the myocardium. Liver interference was maximal in the AP position and in later images. No patient study had to be totally rejected because of interference by either pulmonary or hepatic uptake.

Normal Controls

The normal myocardial scintigraphic pattern was studied in 24 healthy subjects. Eighteen demonstrated homogeneous myocardial images of characteristic "doughnut" configuration with a small area of reduced uptake located between the septal and lateral segments, corresponding to the region of the aortic and mitral valves (fig. 3). A slight reduction in apical uptake observed in four patients was attributed to a motion artifact.
Inhomogeneous uptake patterns were observed in the scintigrams of six healthy volunteers. In all cases technical factors were believed to have been responsible. Five were early studies of inferior quality, performed with the high energy lead collimator using the original relatively impure ammonia preparation. The remaining study was the only case not imaged under basal conditions. Two of these subjects, including the latter case, had normal scintigrams when restudied after the improvements in ammonia production and collimator design had been instituted.

Clinical Correlation

The myocardial scintigraphic findings were correlated with the clinical diagnosis in each of the 71 cardiac patients. The results are summarized in table 1.

Group 1: Acute Myocardial Infarction

Twenty-seven of the 28 patients with acute myocardial infarction had abnormal scintigrams. The scintigraphic findings and the electrocardiographic site of infarction in the 28 patients studied are listed in table 2. Illustrative myocardial images observed in acute myocardial infarction are shown in figure 4.

The most common perfusion abnormality pattern seen in the 16 patients with anterior infarction was a combination of large septal and apical perfusion defects separated by the clear ventricular cavity (six patients) (fig. 4B). Additional inferior perfusion defects were present in eight patients who had no ECG changes suggestive of inferior wall damage. Lateral wall perfusion defects were seen in three patients only, in part due to the anterolateral wall being obscured by

Figure 3. Normal myocardial scintigram in a healthy volunteer. Abbreviations: S = septum, L = lateral, A = apex, I = inferior, PL = posterolateral, V = valve region.
the left ventricular cavity in the AP and LAO projections. The single normal scintigram was in a patient imaged in one view only, very early in the series.

Three of the ten patients with acute inferior infarction had large inferior perfusion defects alone; four had large apical defects alone; two, a combination of large apical and inferior defects (fig. 4C); and one had large defects in the septal, inferior and apical segments. The location of large perfusion defects provided a better means of discriminating anatomically between patients with anterior MI and patients with inferior MI. In most cases small perfusion defects represented extensions of a large defect into the adjacent myocardial segment.

Two patients with acute transmural anterior and inferior myocardial infarction had widespread perfusion abnormalities (E.D., H.G., table 2). All six cases with nontransmural infarction had abnormal myocardial scintigrams with perfusion defects indistinguishable from those seen in patients with transmural myocardial infarction.

In the scintigraphic studies of four patients with acute MI the segmental myocardial uptake defects, which were seen initially, disappeared in a mean time of 23 min after the administration of ammonia. In late images these segments had a normal perfusion pattern. This phenomenon was observed in the septal segment in three cases and in the inferoseptal region in one case (fig. 5).

**Group II: Suspected Myocardial Infarction**

A summary of the clinical and scintigraphic findings of the 17 patients in this group is given in table 3. All but one patient had underlying coronary artery disease. Twelve patients showed perfusion defects on their scintigrams. In three patients with unstable angina and one with a dysrhythmia the most prominent perfusion defect corresponded to the electrocardiographic site of an old myocardial infarction. Four of the five patients with normal myocardial

### Table 1. Regional Myocardial Perfusion in 71 Cardiac Patients

<table>
<thead>
<tr>
<th>No.</th>
<th>Previous MI</th>
<th>Abnormal scintigram</th>
<th>Segmental perfusion defects*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lateral</td>
</tr>
<tr>
<td>Ac ANT MI</td>
<td>16</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Ac INF MI</td>
<td>10</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Ac ANT-INF MI</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Suspected MI</td>
<td>17</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Stable angina</td>
<td>20</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>6</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

*Numbers outside parentheses are the number of large defects only; numbers within parentheses are the total number of both small and large defects.

Abbreviations: ANT = anterior; INF = inferior; MI = myocardial infarction.

### Table 2. Regional Myocardial Perfusion in Patients with Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Name</th>
<th>Acute infarct</th>
<th>Previous infarction</th>
<th>Interval after admission (days)</th>
<th>Segmental perfusion defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.V.</td>
<td>ANT*</td>
<td>8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>W.Mc.</td>
<td>ANT</td>
<td>2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>I.M.</td>
<td>ANT</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>A.T.</td>
<td>ANT</td>
<td>0.3</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>E.S.</td>
<td>ANT</td>
<td>0.2</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>E.P.</td>
<td>ANT</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C.W.</td>
<td>ANT</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H.W.</td>
<td>ANT</td>
<td>3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P.F.</td>
<td>ANT</td>
<td>9</td>
<td>NORMAL</td>
<td></td>
</tr>
<tr>
<td>O.Mc.</td>
<td>ANT</td>
<td>5</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>W.B.</td>
<td>ANT</td>
<td>7</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>E.K.</td>
<td>ANT</td>
<td>6</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>J.C.</td>
<td>ANT</td>
<td>9</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>A.L.</td>
<td>ANT (NT)</td>
<td>6</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>S.M.</td>
<td>ANT (NT)</td>
<td>6</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M.S.</td>
<td>ANT (NT)</td>
<td>YES†</td>
<td>21</td>
<td>+</td>
</tr>
<tr>
<td>G.M.</td>
<td>INF</td>
<td>2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>S.D.</td>
<td>INF</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>R.S.</td>
<td>INF</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>J.M.</td>
<td>INF</td>
<td>2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>L.Mc.</td>
<td>INF</td>
<td>0.8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>R.R.</td>
<td>INF</td>
<td>2</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M.G.</td>
<td>INF</td>
<td>12</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>E.R.</td>
<td>INF (NT)</td>
<td>19</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>O.J.</td>
<td>INF (N)</td>
<td>1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>R.A.</td>
<td>INF (NT)</td>
<td>3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>E.D.</td>
<td>ANT + INF</td>
<td>6</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H.G.</td>
<td>ANT + INF</td>
<td>YES†</td>
<td>7</td>
<td>+</td>
</tr>
</tbody>
</table>

*Transmural unless otherwise specified.
†Site unknown.
Abbreviations: ANT = anterior; INF = inferior; NT = nontransmural. ++ = large defect; + = small defect.
scintigrams, including three patients who had evidence of previous myocardial infarction, were imaged in more than one projection.

**Group III: Stable Angina**

Five of the 20 patients with stable angina, including four with old myocardial infarction, had normal myocardial scintigrams. In ten of the 15 patients with abnormal scintigrams the location of the perfusion defect observed corresponded to the ECG site of an old infarction. The remaining five patients with abnormal scintigrams at rest had normal electrocardiograms. An early septal defect which disappeared after approximately 19 min of imaging was seen in one patient with a history of an old anterior MI.

**Group IV: Valvular Heart Disease**

Two of the six patients with valvular heart disease had normal scintigrams. Three patients who were studied two weeks, three weeks, and three months respectively following prosthetic valve replacement had large apical or inferior defects (fig. 4D). All three cases were vented through the apex of the left ventricle during surgery. One patient developed postoperative left bundle branch block and two had active infective endocarditis at the time of imaging. Right ventricular uptake of $^{13}$NH$_4^+$ was also observed in the scintigrams of these three patients, all of whom had previously documented pulmonary hypertension and most probably secondary right ventricular hypertrophy. The remaining abnormal scintigram was in a patient with acute endocarditis and cardiac failure.

**Sequential Studies**

Five patients with acute myocardial infarction and one patient with unstable angina were imaged sequentially following admission to the Coronary Care Unit. The size and location of the perfusion defects were observed serially and correlated with the clinical progress of patients (table 4).

In three patients with initial large defects involving the lower septum, inferior wall and apex, there was a progressive reduction in the size of the defect over three days leaving only a residual apical perfusion abnormality (fig. 6). All three patients became asymptomatic within 24 hours and had uncomplicated courses thereafter. The fourth patient, who had an acute inferior myocardial infarction, showed persistence of a large apical defect and extension of an in-

---

**TABLE 3. Suspected Myocardial Infarction—Clinical and Scintigraphic Findings**

<table>
<thead>
<tr>
<th>Final diagnosis</th>
<th>No.</th>
<th>Abnormal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>6</td>
<td>3 (3)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>3</td>
<td>3 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>7</td>
<td>6 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Noncardiac pain</td>
<td>1</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate the number of patients with history of previous myocardial infarction.

---

**FIGURE 4. Myocardial scintigraphic patterns observed in (A) anterior infarction — dominant septal perfusion defect; (B) anterior infarction — dominant septal and apical perfusion defects; (C) inferior infarction; (D) valvular heart disease, three months after prosthetic aortic and mitral valve replacement. Note large apico-infero perfusion defect and right ventricular uptake of $^{13}$NH$_4^+$ in plate D.**

---

**FIGURE 5. Myocardial scintigram of a patient with inferior infarction showing disappearance of the initial infero-apical defect during the course of the imaging study. (Intervals given in minutes.)**
When imaged five days later. The sixth patient changed of assessing regional myocardial can prove attention. The development of the first week. His was complicated by early ventricular dysrhythmias and during of the resolution showed 21 mechanical, 20' myocardium failure tricular patient, who had sustained an extensive anterior myocardial infarction (peak CPK 1800), had sustained disease has and required hemodynamic management during the first week. His initial extensive perfusion defects were unchanged when imaged five days later. The sixth patient showed resolution of his original lateral defect, persistence of the apical abnormality, and development of a new septal defect during a period of five days. This last patient’s course was complicated by early ventricular dysrhythmias and recurrent chest pain.

**Discussion**

Preservation of myocardial function in patients with coronary artery disease has recently been receiving increasing attention. The development of pharmacological, 18, 19 mechanical, 20, 21 and surgical techniques 22 which may improve perfusion to ischemic regions and salvage jeopardized myocardium can be useful if a reliable noninvasive method of assessing regional myocardial perfusion is available. Myocardial imaging with an agent such as 13N-labeled ammonia, whose uptake and distribution reflects tissue blood flow, would appear to be a useful approach to this clinical problem.

The need for an on-site cyclotron to produce quantities of 15NH₃ limits its use, but as the medical uses of accelerator produced nuclides become more apparent, more cyclotrons may be established at hospitals. 14

15NH₃, *Distribution and Uptake*

Harper and coworkers have previously shown the blood disappearance of injected 15NH₃ to be very rapid, with 90% of myocardial uptake occurring during the first pass, and only 15% of the injected activity remaining in the blood pool after one minute. 13 This enables the myocardial image to be visualized early without interference from the blood pool background. Organ distribution studies have demonstrated that the liver is the principal site of uptake of 15NH₃, containing approximately 15% of the injected dose in animals, but in man substantial uptake also occurs in the brain, the heart, the lungs, the kidney, and the bladder. 19, 25 Uptake by

**TABLE 4. Regional Myocardial Perfusion in Patients with Sequential Imaging Studies**

<table>
<thead>
<tr>
<th>Name</th>
<th>Diagnosis</th>
<th>Time from admission (days)</th>
<th>Views</th>
<th>Lateral</th>
<th>Apex</th>
<th>Inferior</th>
<th>Septum</th>
<th>Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.P.</td>
<td>Unstable Angina</td>
<td>1</td>
<td>2</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>No complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
<td>++</td>
<td></td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>2</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>2</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.Mc.</td>
<td>Ac Inferior MI</td>
<td>&lt;1</td>
<td>1</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td></td>
<td>No complications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>1</td>
<td>++</td>
<td></td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G.M.</td>
<td>Ac Inferior MI</td>
<td>9</td>
<td>1</td>
<td>++</td>
<td></td>
<td>++</td>
<td>++</td>
<td>No complications</td>
</tr>
<tr>
<td>C.W.</td>
<td>Ac Anterior MI</td>
<td>1</td>
<td>2</td>
<td>++</td>
<td></td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>2</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>2</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.S.</td>
<td>Ac Anterior MI</td>
<td>&lt;1</td>
<td>1</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>1</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A.T.</td>
<td>Ac Anterior MI</td>
<td>1</td>
<td>2</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td>Dysrhythmia, pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>2</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>2</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ac = acute.
++ = large defect.
+ = small defect.

apoventricular defect on restudy. This patient was in mild left ventricular failure and required digitalis and diuretics. The fifth patient, who had sustained an extensive anterior myocardial infarction (peak CPK 1800), was in congestive heart failure and required close hemodynamic management during the first week. His initial extensive perfusion defects were unchanged when imaged five days later. The sixth patient showed resolution of his original lateral defect, persistence of the apical abnormality, and development of a new septal defect during a period of five days. This last patient’s course was complicated by early ventricular dysrhythmias and recurrent chest pain.

**FIGURE 6. Sequential AP myocardial scintigrams in a patient (C.W.) with acute anterior myocardial infarction demonstrating progressive improvement in regional myocardial perfusion during a 48-hour period.**
the liver is slower than myocardial uptake, reaching a peak of activity approximately 10 min after injection and remaining fairly constant for the duration of the procedure. Pulmonary uptake is usually early and transient except in the patients who are chronic smokers in whom delayed washout of $^{15}$NH$_3$ is observed. The explanation for this delay in smokers remains obscure.

Approximately 2-4% of the injected dose is taken up by the myocardium, and in man this fraction remains almost constant for up to 30 min. The mechanism of uptake of ammonia by the myocardial cell has not yet been elucidated, but its blood disappearance kinetics suggest that it probably differs from that of potassium and its analogues. $^{15}$NH$_3$ is freely permeable to all cell membranes but at physiological pH is predominantly in the ionized form NH$_4^+$, which is a relatively impermeable cation. Studies in other tissues have demonstrated that NH$_4^+$ may enter the cell by substituting for potassium and utilizing the Na$^+$/K$^+$-ATPase dependent membrane system. Once within the cell, ammonia is metabolized via the glutamine synthetase pathway to glutamine, which enters the body amino acid pool. This metabolic pathway has been demonstrated to be present in the myocardium in animal studies.

Clinical Correlations

The regional distribution of microspheres in an organ has been used extensively as an index of tissue perfusion. The application of this technique to the study of regional myocardial perfusion was first described by Domenech et al. and subsequently developed by other workers. The experimental demonstration that the myocardial uptake of $^{15}$NH$_3$ parallels the distribution of microspheres in acute myocardial infarction suggests that the observed uptake defects represent areas of diminished or absent perfusion. These conclusions are further supported by the observations made in the clinical scintigraphic study. Normal subjects had homogeneous images indicating uniform perfusion, while patients with varying manifestations of coronary artery disease showed localized uptake defects consistent with the abnormal regional perfusion known to be present.

The highest incidence of myocardial perfusion abnormalities occurred in patients with acute myocardial infarction, including both transmural and nontransmural infarction. Patients with anterior MI usually had large perfusion defects involving the septal and/or apical segments, while those with inferior MI had large perfusion defects involving the infero-apical region. Although the electrocardiographic site of infarction commonly corresponded to the location of a large perfusion defect, frequently the defects were more extensive and involved more distant segments of the myocardium than suggested by the ECG abnormalities alone. As a result, there was an overlap in the segmental distribution of myocardial perfusion defects between the patients who had an anterior MI and those who had an inferior MI. The region of overlap most frequently was the apex.

Since $^{15}$NH$_3$ myocardial scintigraphy provides a qualitative assessment of the regional perfusion, perfusion abnormalities which were indistinguishable from those seen in acute myocardial infarction, were present in patients with other clinical manifestations of coronary artery disease.

Thus, there was a high incidence of perfusion defects in the myocardial scintigrams of patients with unstable angina, exacerbations of cardiac failure, dysrhythmias or stable angina, both with and without old MI. In patients who have a history of previous myocardial infarction, the defects most probably represent avascular scar tissue. In those patients without evidence of recent or old infarction the perfusion defects indicate either a myocardial infarct, not detected by routine clinical and laboratory investigations, or a region of severe ischemia. In the presence of an old infarction a normal perfusion pattern suggests the development of an adequate collateral circulation resulting in an improvement in regional perfusion to the damaged area. The filling in of segmental perfusion defects seen during continued imaging in some patients with acute myocardial infarction or angina probably indicates that slower regional accumulation of ammonia activity may occur in severely underperfused segments. Although the reason for this phenomenon occurring in the patients with acute MI has not been established, it is possible that the initial perfusion defect represents largely ischemic rather than necrotic myocardium. This could eventually allow sufficient tissue uptake of $^{15}$NH$_3$ to result in a homogeneous image.

The evaluation of the abnormalities in regional perfusion seen in the patients with valvular heart disease is complicated by the possible effects of cardiac surgery and infective endocarditis on regional myocardial perfusion. Although none of the patients with endocarditis had clinical evidence of myocardial infarction, silent coronary embolism may have been responsible for the perfusion defects. In addition, perioperative infarction could be invoked as an explanation for the abnormalities seen in the postoperative patients.

The sequential studies performed on patients during the acute phase of myocardial infarction or unstable angina suggest a possible clinical application of the scintigraphic technique. $^{15}$N-labeled ammonia is very suitable for frequent imaging studies on the same patient, first, because it has the shortest half-life of any of the myocardial imaging agents in clinical use, and second, as a result of this property, it gives only a very modest radiation dose to the patient. (Harper et al. have previously calculated the whole body radiation dose to be 5 mRads/mC, and the liver dose to be 25 mRads/mC.) Although the number of patients serially imaged was small, there was a remarkable correlation between changes in regional myocardial perfusion and the clinical status of each patient. The three patients with an uncomplicated course were the only cases to show a progressive reduction in the size of the original perfusion defect. This was interpreted as reflecting an improvement in the perfusion of the peripheral ischemic tissue surrounding the infarcted myocardium. Further experience in sequential myocardial imaging may permit the early effects of specific therapeutic interventions upon the regional perfusion to this jeopardized peripheral zone to be determined. Serial changes in the regional perfusion pattern may also be helpful in assessing the prognosis of patients with acute myocardial infarction and unstable angina.

The clinical application of myocardial imaging has been limited until recently by the logistic difficulties involved in performing imaging procedures on cardiac patients who were being managed in intensive care units. Patients had to
be moved, together with monitoring and resuscitative equipment, to the Nuclear Medicine Department for imaging. The present study has demonstrated the feasibility of using a mobile gamma camera and data acquisition system in the Coronary Care Unit to provide bedside imaging to patients who require close cardiac monitoring. The recent availability of small, commercially built mobile cameras will greatly facilitate bedside imaging studies and allow a more widespread application of this useful technique.

Limitations

Specific

There are important technical limitations which interfere with the wider use of intravenous $^{13}$NH$_4^+$ for myocardial imaging. It is necessary for there to be an on-site cyclotron facility, preferably with proton beam capability to insure an ammonia preparation of high grade purity. Inconsistent image quality and the occasional apparent inhomogeneous uptake in normal volunteers did not occur when the ammonia of high grade purity was used. Nitrogen-13 is not an ideal nuclide for imaging with a gamma camera because its relatively high photon energies result in difficulties with high energy lead collimation. A tungsten collimator with narrower septa than the high energy lead collimator has to be used to eliminate most collimator artifacts in the image.

In addition, the slow clearance of $^{13}$NH$_4^+$ from the lungs of patients who are smokers can cause difficulties. In most cases the lungs clear rapidly enough to allow satisfactory myocardial images to be produced in more than one plane. However, in a minority of smokers slow clearance from the lungs of $^{13}$NH$_4^+$ may permit only one acceptable image to be obtained. In these cases interpretation of the scintigrams requires more caution since only a single projection is available and there is a possibility that an initial perfusion defect may have filled in prior to pulmonary clearance. Nevertheless, careful attention to details of the procedure does permit adequate studies to be obtained in the majority of smokers.

General

The three-dimensional shape and the motion of the heart limit the diagnostic sensitivity and specificity of two-dimensional, single projection $^{13}$NH$_4^+$ image. Overlapping regions of the heart are not separated, and activity in the more distant regions of the heart is not readily detected. These geometric problems can be partly overcome by imaging the heart in multiple projections, but this increases the duration of the procedure, which in the case of ammonia, is limited by the short half-life of the $^{13}$N. The current development of tomographic myocardial scintigraphy offers the best prospect of resolving these geometric limitations. These techniques utilize the coincidence detection of a positron emitter such as ammonia by a positron camera system to produce a number of tomographic images through the heart in one plane.

The long axis of the ventricle changes considerably during the cardiac cycle, and frequent changes in shape taking place may introduce errors in image analysis. Motion effects can be reduced by using an external ECG triggered gating device to collect counts only during specific brief periods of the cardiac cycle, most commonly end-systole and end-diastole. This again considerably lengthens the imaging procedure.

The three dimensional shape and the motion of the heart are important reasons for the difficulty experienced in the precise localization of myocardial perfusion defects and for the overlap in the scintigraphic perfusion patterns in patients who had electrocardiographically different sites of myocardial infarction. These limitations, together with the fact that both ischemic and infarcted regions are detected by agents such as $^{13}$NH$_4^+$, result in standard myocardial perfusion imaging being currently less useful for infarct sizing.

Dual isotope imaging, with an infarct labeling agent such as $^{99m}$Tc-pyrophosphate and a perfusion agent like $^{13}$NH$_4^+$, is presently being explored to differentiate the ischemic and the infarcted myocardium and increase the reliability of the scintigraphic technique for infarct sizing.

Conclusion

The present study has shown that high quality, high count density scintigrams can be obtained using intravenous $^{13}$NH$_4^+$ and a mobile scintillation camera. This method can be used reliably and safely for the detection of myocardial perfusion defects in patients with cardiac disease, and is especially useful when serial myocardial imaging at short intervals is desired. However, the motion and three-dimensional geometry of the heart limit the accuracy of conventional imaging techniques in anatomically defining perfusion defects.

References


Angiocardioigraphy with Iridium-191m
An Ultrashort-lived Radionuclide (T½ 4.9 sec)
S. Treves, M.D., S. Kulprathipanja, Ph.D., and D. J. Hnatowich, Ph.D.

SUMMARY Iridium-191m is a potential tracer for angiocardography and may be of particular value in the evaluation of heart disease in children. It possesses a short half-life (4.9 sec), suitable photon energy (129 keV) and may be obtained as a generator product by decay of its long lived (15.3 day) parent 191Os. An 191Os → 191Ir generator capable of providing 15 mCi of 191Ir in 1.5 ml of eluant is described. The separation of 191Ir from 191Os is achieved by absorbing 191OsCl4 on an anion exchange resin. The generator employs an additional resin column which is exchanged to prevent 191Os breakthrough to become excessive. By this procedure, the breakthrough may be kept below 0.001% over a period of at least one month and after multiple elutions.

RADIONUCLIDE ANGIOCARDIOGRAPHY is an established method for evaluation of the circulation within the heart, great vessels, and the lungs.1-4 Its use in clinical practice is increasing since a large number of hemodynamic parameters can be evaluated nonintraoperatorily following a single intravenous injection of radionuclide. One major use of this technique is in the evaluation of children with congenital heart disease. The information obtained with radioangiography is of importance in the diagnosis and management of these patients and, at times, can take the place of a cardiac catheterization. At present, radionuclide angiography is performed with technetium-99m and gamma camera-computer systems.

Within the constraints imposed by modern imaging devices (i.e., limited spatial resolution), a major limitation of the method is the inability to obtain multiple projections within a short period of time because of high background from the initial radionuclide injection. As a consequence, currently employed radionuclides (notably technetium-99m) preclude more detailed anatomical evaluation of the cardiovascular system and study of the effects of exercise or pharmaceutical agents on the hemodynamics. In addition, since the duration of radionuclide angiography is only 20 seconds and the half-life of technetium is six hours, the

---

From the Departments of Radiology at Harvard Medical School and Children's Hospital Medical Center, Boston, Massachusetts, and Department of Nuclear Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts. Supported by National Institutes of Health Grant HL 17625. Address for reprints: Dr. S. Treves, Division of Nuclear Medicine, The Children's Hospital Medical Center, 300 Longwood Avenue, Boston, Massachusetts 02115. Received January 19, 1976; revision accepted March 12, 1976.
Noninvasive evaluation of regional myocardial perfusion in 112 patients using a mobile scintillation camera and intravenous nitrogen-13 labeled ammonia.
W F Walsh, P V Harper, L Resnekov and H Fill

Circulation. 1976;54:266-275
doi: 10.1161/01.CIR.54.2.266

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/54/2/266