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REVIEW ARTICLE – DEBATE ARTICLE : WHICH PET FLOW TRACER IS THE BEST FOR MBF QUANTIFICATION?

PET/CT with ^{13}N-ammonia: Characteristics and Utility in Coronary Artery Disease

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Abstract

Currently, ^{13}N-ammonia and Rubidium-82 (^{82}Rb) are the only FDA-approved myocardial perfusion positron emission tomography (PET) tracers for myocardial perfusion imaging in the evaluation of suspected or known coronary artery disease (CAD), quantification of left ventricular volumes and systolic function and quantification of global and regional myocardial blood flow (MBF) and myocardial flow reserve (MFR). Nevertheless, there are physical, chemical and molecular differences between them. The ideal perfusion tracer would include 100% extraction from blood to tissue, and 100% retention, resulting in a linear relationship between MBF and the measured tracer activity over a wide range. However, both ^{13}N-ammonia and ^{82}Rb have limited characteristics. In this review, we aim to analyze ^{13}N-ammonia in detail, and its differences with other radiotracers for the assessment of myocardial perfusion.

Keywords: ^{13}N-ammonia, Coronary artery disease, Global myocardial blood flow, Myocardial flow reserve, Positron emission tomography

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^{13}N-ammonia is a ^{13}N-labeled compound that has been developed as a positron emission tomography (PET) tracer for the non-invasive assessment of myocardial perfusion (1). ^{13}N-ammonia was approved by the United States Food and Drug Administration (FDA) in 2000 for cardiac PET imaging and in over this almost 20 years of clinical utility, it has proven to be very useful in the assessment of coronary artery disease (CAD) giving important prognostic information in patients with clinical and subclinical forms of cardiomyopathy.

In Mexico is regulated by the Federal Commission for Protection against Sanitary Risks (Comisión Federal para la Protección contra Riesgos Sanitario–COFEPRIS-) and we have been used ^{13}N-ammonia since 2002 with the opening of the first PET-Cyclotron Unit on Latinamerica localed on the Faculty of Medicine at the National University of Mexico (UNAM). The first case of myocardial perfusion imaging with ^{13}N-ammonia was reported on 2002 and a first cut of our experience with 1004 patients was reported in 2014 (2, 3).

^{13}N-ammonia has considerable advantages over other cardiac radiotracers (4). From the list mode acquisition of ^{13}N-ammonia PET study we can typically integrate the analysis of static, gated and dynamic datasets facilitating the inclusion of all quantification results in one clinical review. Firstly, static images are used to define the extent and severity of regional hypoperfusion comparing rest and stress images. Secondly, gated PET images allow automated quantification of left ventricular volumes and left ventricular ejection fraction (LVEF), left ventricular end-diastolic volume, left ventricular end-systolic volume and other functional parameters, such as diastolic function and contraction synchrony. Thirdly, dynamic reconstruction of the data allows us the extraction of the time activity curves from the blood pool and myocardium, to calculate the absolute regional MBF in ml/g/min at rest and during vasomotor stress, and consequently quantitation of

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myocardial flow reserve (MFR). Currently, the perfusion PET scan is considered the gold standard for measuring MFR (5).

Production of ^{13}N-ammonia

The first compound of ammonia labeled with ^{13}N was first produced by Joliot and Curie. Ammonia is normally produced in the body from the deamination of amino acids and the deamidation of amides. As a nonionic form is freely permeable to all cell membranes (6). Is taken up by the myocardium by passive free diffusion across cell membranes as ammonia (NH3) where it equilibrates with its charged form ammonium (NH4) and gets trapped inside the cell by conversion through glutamine synthase to ^{13}N-glutamine (7, 8). The ^{13}N-ammonia is a positron emitter radiotracer with a physical half-life ($t_{½}$) of 10 min. This is precisely one of its competitive advantages over other radiotracers: Rubidium-82 (^{82}Rb) with $t_{½}$ of 75sec and ^{15}O Water with $t_{½}$ of 2 min) (6–8). Those radiotracers have as disadvantage the need of an onsite generator or an onsite cyclotron for their production, respectively, which translates in higher costs and mayor logistical difficulties. ^{13}N-ammonia being the one with the longest physical half-life allows us to be able to acquire studies in places where a cyclotron is located at relatively short distances from the cyclotron, as it has been demonstrated to be feasible in our experience (we have acquired more than 500 studies in a PET center that is located about 5km from the regional cyclotron).

Pharmacokinetic parameters of ^{13}N-ammonia

After intravenous injection, ^{13}N-ammonia rapidly clears from the circulation. It is taken up mainly by the myocardium, brain, liver, kidneys, and skeletal muscle (6, 9). In the myocardium ^{13}N-ammonia is removed from the blood and metabolically trapped within the tissues (7, 10).

^{15}O-water washes out so rapidly that there is effectively no tracer retention in cardiac tissue above the blood background level (9, 10). This linear relationship between the distribution of ^{13}N-ammonia and the regional blood perfusion makes feasible the use of this radiotracer for the visualization of myocardial perfusion and the quantification of myocardial blood flows. The combination of the high first-pass myocardial extraction fraction, trapping in the myocardial cells as ^{13}N-glutamine and the relatively long physical half-life may account for the high contrast resolution. These properties confer statistically high count to the myocardium, producing an image of the highest quality and allowing visual and semiquantitative evaluation of myocardial perfusion abnormalities on rest and stress (10).

Because of the improving spatial resolution, the distance from positron emission to positron annihilation (positron range) is one factor of increasing importance on PET studies. Positron range impairs resolution in PET imaging, especially for high-energy emitters (9, 11). ^{13}N-ammonia is the radiotracer with the lowest positron range (barely 2.53 mm) over other perfusion radiotracers (^{82}Rb with 8.1 mm and ^{15}O with 4.14 mm) (8, 10). The positron range of ^{13}N-ammonia results in an excellent high image resolution tracer, Table 1.

Imaging protocol

Patient preparation for pharmacologic stress with PET is the same as for ^{99m}Tc single photon emission computed tomography (SPECT). Patients must fast for a minimum 4 h, avoid smoking for at least 4 h, and avoid caffeine or theophylline intake for at least 12 h before vasodilator stress (adenosine, dipyridamole, and regadenoson has been evaluated using ^{13}N-ammonia) (12, 13). For ^{13}N-ammonia, acquisition time takes about 10–20 minutes approximately per phase, with a 4–5 half-lives delay between the rest study and stress testing, that is typically required to allow for isotope decay (12, 14).

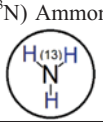
The activity injected depends on the equipment for scanning (2D=370MBq, 3D=555mBq). Contemporary, PET scanners operate in 3D acquisition mode, therefore ^{13}N-ammonia standard protocol involves an injection of 370 MBq at rest followed by a 10 min image acquisition protocol. After decay time, pharmacological stress is performed and a second 370 MBq injection of ^{13}N-ammonia is injected and images are acquired (12, 14).

List mode acquisition is recommended because it allows flexibility in the timing and reconstruction of images (dynamic for MBF, static for MPI and electrocardiography-gated images for left ventricular ejection fraction). It is important to flush the tracer injection line with a volume of saline high enough to clear the tracer activity out of the cephalic, axillary, and subclavian veins to avoid scatter from focal activity near the edge of the field of view leading to artifacts, especially on 3D scans (12, 13).

^{13}N-ammonia is a valuable agent for measuring either absolute or relative myocardial blood flow. For measurements of absolute flow, dynamic acquisition from time of injection is required. Uptake is relatively rapid (typically often nearly complete in 90 seconds) (12, 15). The static image should not include the initial rapidly changing uptake portion of the study. A minimum of 90 seconds should typically elapse between the end of infusion and the beginning of the static scan. In fact, the arterial blood concentration of ammonia is often still quite significant even at 90 seconds after a rapid bolus injection. Nonetheless, many published data are based on only a 90-second delay before starting of imaging (12–15).

Several factors affect the accuracy of this test, in particular, uncorrected nonuniform attenuation and photon scatter from extra-cardiac sources, particularly the liver. Attenuation artifacts are frequently observed due to the diaphragm as well

Table 1 ^{13}N-ammonia basic characteristics and advantages

Chemical name and structure	(^{13}N) Ammonia 	Agent Category:	Compound
Abbreviated name:	[^{13}N] NH_3	Target:	Glutamine synthetase
Synonym:	Ammonia N-13	Target Category:	Soluble, microspherelike, metabolic trapping in cells by enzymatic conversion to [^{13}N] glutamic acid
Supplied:	Cyclotron	Method of detection:	Positron Emission Tomography (PET)
Maximum energy (MeV)	1.20	Positron range	2.53 mm
Half-life	9.96 min	Function	Myocardial Perfusion
First-pass extraction	80% (linear with increasing blood flow)	Stress	Pharmacological
Data acquisition	From list mode: dynamic, static, gated	MBF Quantification	Yes
Scan Duration	20 min	Interval between doses	30 min
Dose–2D	15–25 mCi	Image quality	Excellent
Dose–3D	15 mCi		

as in obese patients and female patients (14).

When dedicated PET scans were used, prior to the injection of ^{13}N-ammonia, a transmission scan using a ^{68}Ge source was performed for 10 minutes to ensure correct positioning of the patient within the field of view and to yield the attenuation map that was used to correct for attenuation. But, nowadays all PET scans for cardiac imaging are hybrid PET/CT systems and have an inherent attenuation correction CT scan. The Hounsfield units (HU) generated by the CT scanner can usually be accurately converted into PET attenuation values (16).

First, a scout CT acquisition (120 kVp, 10 mA) must be performed to ensure proper patient positioning, then a CT transmission scan was acquired (140 kVp, 20 mA) for subsequent attenuation correction. A second CT transmission scan (140 kVp, 20 mA) is acquired for attenuation correction of the stress images (15). CT-based attenuation correction typically adds less than 10 seconds to the cardiac scan time. But the high speed of CT scans, however, freezes the heart and lungs at one phase of the respiratory cycle, causing potential misalignment between the CT-based transmission and emission scans (16).

Misalignment of the attenuation CT and PET emission images, potentially exacerbated by patient and respiratory motion during hyperemic stress, may introduce moderate to severe artifacts and can result in significant changes in MBF quantification (13).

Software realignment must be performed to minimize any remaining misalignment. Other techniques (e. g., slow CT, respiratory gating, and 4D-CT) are under development for compensating for respiratory motion, but are still in the research (16).

Clinical role of ^{13}N-ammonia PET/CT

Perfusion and flow quantification before diagnostic accuracy for identifying obstructive CAD

The clinical utility of ^{13}N-ammonia and ^{82}Rb PET for identifying obstructive CAD is well established (15–21). Currently, PET is considered the quantitative reference standard myocardial perfusion (17). The average sensitivity and specificity of myocardial perfusion with PET for detecting more than 50% luminal narrowing on coronary angiography are reported to be 91% and 89%, respectively (12). However, most of those studies used ^{82}Rb (9–15), and there is very little information on the diagnostic accuracy of PET with ^{13}N-ammonia as myocardial perfusion radiotracer (12). Schelbert et al. (1982) reported a sensitivity of 97% and specificity of 100% (22). Fathala et al. (2019) reported a sensitivity of 90%, specificity of 90%, positive predictive value of 96%, negative predictive value of 76%, and diagnostic accuracy of 80% (18). Furthermore, we have reported a sensitivity of 92%, specificity of 35%, positive predictive value of 37% and negative predictive value of 91% based on a study with 1004 Latin American patients (3) (Figures 1 and 2).

Perfusion and flow quantification

^{13}N-ammonia has been validated and extensively used for quantitation of MBF and MFR.

The reported weighted mean of MBF values at rest and stress were 0. 71 mL/minute/g (range 0. 61–1. 1) and 2. 58 mL/g/minute (range 1.86–4.33), respectively and the mean of MFR was 3. 54 (range 3. 16–4. 8) (12). Meanwhile, several investigations have aimed to identify the optimal threshold values of hyperemic MBFs or MFR to identify epicardial obstructive lesions. Using ^{13}N-ammonia, the diagnostic value for detecting ≥70% epicardial lesions was the highest, when a hyperemic MBF threshold value was of <1.85 ml/g/min used

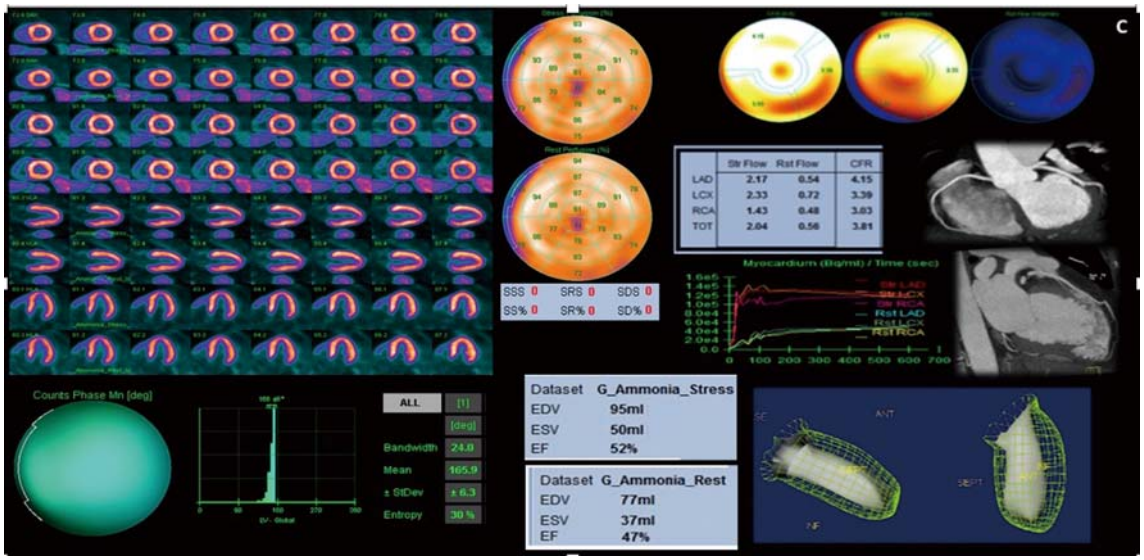


Figure 1 ^{13}N-ammonia PET/CT. Normal myocardial perfusion study. Splash and polar maps with normal uptake. SDS=0. Normal synchrony. Adequate systolic functions with normal movement of all walls and segments. Normal flow quantitation: Rest MBF, 0.56; stress MBF, 2.04; MFR, 3.81. CCTA without obstructive lesions.

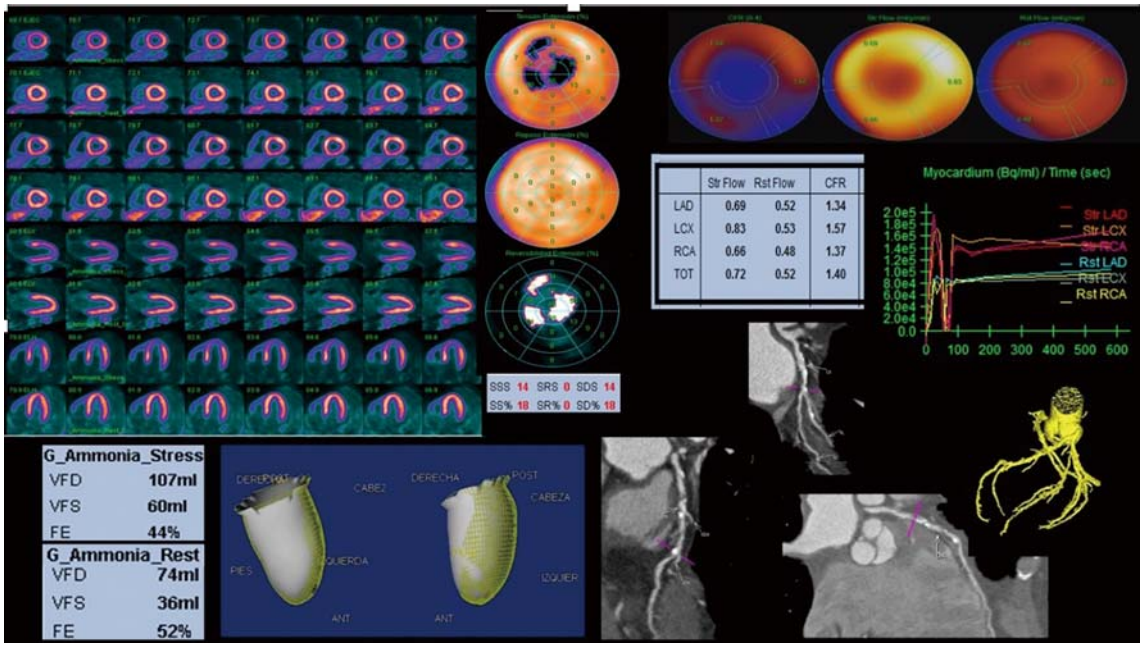


Figure 2 ^{13}N-ammonia PET/CT. Abnormal myocardial perfusion study. Splash and polar shows moderate ischemia on the anterior wall, anterolateral segments and apex with SDS of 18%. Mild systolic dysfunction with an ejection fraction of 52% on rest, that decrease up to 44% on stress. Global hypokinesia. Abnormal flow quantitation: Rest MBF, 0.52; stress MBF 0.72; MFR, 1.40. CCTA with multiple calcified plaques conditioning significant obstruction on the left coronary artery (left anterior descending artery and the circumflex branch) and on the right coronary artery. Multivessel disease was confirmed.

(17). Also, an abnormal global MFR <2.0 was found to be independently associated with a higher annual event rate for major adverse cardiac events and cardiac death over 3 years compared with normal MFR (20). More recently, Fiechter et al. defined an abnormal MFR of ^{13}N-ammonia as less than 2.0 mg/dl/min and employing this predefined threshold of MFR with a sensitivity, specificity, and diagnostic accuracy of 96%, 80%, and 92% respectively for detecting ≥50% epicardial obstructive lesion (21).

The ability of myocardial perfusion tracers to concurrently assess regional MBFs and MFR may allow to characterize the clinical manifestation identifying all epicardial lesions in patients with multivessel CAD. Herzog et al. demonstrated that when ^{13}N-ammonia PET flow studies identified a stress-induced regional myocardial perfusion defect as indicative of an obstructive CAD lesion, an abnormally reduced MFR

provided incremental information to the conventional stress ^{13}N-ammonia perfusion PET study for predicting an adverse outcome. When the findings of stress ^{13}N-ammonia perfusion PET and MFR studies were normal, it meant a "warranty" period of event-free survival of approximately 3 years as compared with those with an abnormally reduced MFR (23).

In a recent evaluation of a large cohort of symptomatic patients undergoing invasive diagnostic coronary angiography, nearly 60% did not have obstructive CAD. A substantial proportion of patients with nonobstructive coronary atherosclerosis may have underlying microvascular dysfunction (MVD) as the functional substrate of their angina symptoms.

Flow tracers such as ^{13}N-ammonia, ^{82}Rubidium, ^{18}F-Flurpiridaz, and ^{15}O-water can identify MVD noninvasively by assessing reductions in hyperemic MBF in absolute terms (milliliters per minute per gram) and/or MFR (24–26).

In a recent study by Reanud et al., 14 subjects with <5% risk of CAD underwent rest and stress ^{82}Rb and ^{13}N-ammonia PET imaging and found that when using the retention model may have higher sensitivity for detection and localization of abnormal flow and MFR using ^{82}Rb and ^{13}N-ammonia, whereas the ^{13}N-ammonia two-compartment model has higher precision for absolute flow quantification. (27).

Despite that widespread imaging techniques for the functional evaluation of CAD are SPECT and stress echocardiography, mycardial perfusion PET scan has some unique features compared with SPECT such as the ability of quantify MBF in absolute units and to calculate MFR, a routine attenuation correction with CT, low radiation dose and the short time of the study completion. Besides all available PET tracers track flows better at high MBF values when compared with the commonly used SPECT tracers (28).

Other clinical applications

Furthermore, ^{13}N-ammonia has also shown to have and role on the identification of subclinical manifestations in patients with DM2, high blood pressure and dyslipidemia (23).

The addition of Coronary computed tomography angiography (CCTA) can be quite helpful to differentiate patients with extensive obstructive CAD from those with predominantly microvascular dysfunction giving information to improve the specificity of PET, especially in the setting of abnormal MBF values (12).

CCTA and coronary artery calcium scoring

Quantifying calcium score allows an assessment of the extent of atherosclerotic plaque burden and an insight into the patient's risk and prognosis (6).

Calcium score and CT angiography can be performed immediately after ^{13}N-ammonia PET scan, but also, coronary calcium score CT can be used for attenuation correction of cardiac rest/stress with the advantage of dose reduction (29).

Future perspective

Despite the increasing widespread use of ^{13}N-ammonia PET/CT for the assessment of myocardial perfusion, future research is still needed in order to fully understand the clinical impact of the tracer in assessment of ischemic heart disease. Furthermore, studies are needed in order to improve quality image and to standardize protocols.

Conclusion

^{13}N-Ammonia is used as myocardial perfusion and flow imaging tracer, with physical, chemical and molecular characteristics resulting in improving spatial resolution imaging and reproducible quantification of MBF and MFR that affords high sensitivity and overall accuracy for the detection of CAD and the prediction of outcomes. Therefore, the clinical value of ^{13}N-Ammonia PET is expected to improve patient outcomes and optimize therapeutic decisions.

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No conflict of interest relevant to this article was reported.

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