ORIGINAL ARTICLE

Feasibility of exercise treadmill ^{13}N-ammonia positron emission tomography myocardial perfusion imaging using an off-site cyclotron

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Background. Myocardial perfusion imaging with treadmill exercise nitrogen-13 (^{13}N)-ammonia positron emission tomography (PET) presents a logistical challenge. We investigated the feasibility of exercise treadmill (GXT) ^{13}N-ammonia PET MPI using an off-site cyclotron for production of ^{13}N-ammonia.

Methods. Thirty-three patients underwent GXT ^{13}N-ammonia PET MPI over 23 months. ^{13}N-ammonia doses were prepared at an off-site cyclotron. Patients underwent ^{13}N-ammonia resting and ^{13}N-ammonia GXT emission and transmission scans at our facility. Image quality, perfusion data, and clinical variables were evaluated.

Results. We analyzed 33 patients (7/26 female/male). Mean age was 63 ± 12 years and mean BMI was 33.7 ± 6.9. GXT PET was feasible in all patients. Image quality was good in 29 patients, adequate in 3, and severely compromised in 1 patient. Summed stress score was 4.5 ± 5.7. Resting and GXT left ventricular ejection fractions were 63.7 ± 10.9% and 66.3 ± 13.1%. TID ratio was 1.0 ± 0.1.

Conclusions. Treadmill exercise ^{13}N-ammonia PET is feasible in a large medical center without access to an on-site cyclotron. This technique requires close coordination with an off-site cyclotron but expands the role of PET to patients for whom exercise is more appropriate than pharmacologic stress imaging. (J Nucl Cardiol 2022;29:938–45.)

Key Words: ^{13}N-ammonia · PET · cyclotron · exercise

Abbreviations		PET	Positron emission tomography
ALARA	As low as reasonably achievable	SPECT	Single-photon emission computed tomography
CABG	Coronary artery bypass graft		
CAD	Coronary artery disease	GXT	Exercise treadmill test
EOS	End of synthesis		
FFR	Fractional flow reserve		
MPI	Myocardial perfusion imaging		

INTRODUCTION

Positron emission tomography (PET) myocardial perfusion imaging (MPI) has become widely available and has demonstrated significant value in assessing known or suspected coronary artery disease (CAD) and determining prognosis related to cardiac events, including death and myocardial infarction.[1,2] Previous meta-analyses have demonstrated the high sensitivity and diagnostic accuracy of PET MPI for the detection of significant angiographic coronary artery stenosis and have also demonstrated that stress PET was superior to that of both SPECT and stress echocardiography.[3,4] Due to the widespread availability of Rubidium-82 on-site generator production and short physical half-life of ^{82}Rb, PET MPI is typically performed using the vasodilator agents, regadenoson, dipyridamole, and adenosine with the patient in the scanner and connected to the ^{82}Rb generator. ^{13}N-ammonia, with its longer physical half-life, is compatible with conventional exercise protocols as the patient does not have to be physically in the scanner during injection. PET studies from institutions with an on-site cyclotron have demonstrated the feasibility of exercise PET using ^{13}N-ammonia and have shown that a treadmill ^{13}N-ammonia PET produced larger perfusion defects than vasodilator PET.[5,6] Routine attenuation correction, high spatial and contrast resolution, as well as high temporal resolution are several technical advantages of stress PET that account for its improved image and diagnostic quality compared to SPECT. Therefore, in patients who can exercise, ^{13}N-ammonia PET may be superior to both vasodilator PET and exercise SPECT.

Despite the promising data on exercise ^{13}N-ammonia PET MPI, the limited availability of on-site cyclotrons restricts widespread adoption of the technique. To date, there is no study that has shown the feasibility of performing exercise MPI using ^{13}N-ammonia produced at an off-site cyclotron. In this study, we address that feasibility.

METHODS

Study Population

Between February 2018 and October 2019, 4624 patients presented to our laboratory for myocardial perfusion imaging. Of those, 3126 were referred for SPECT. Of those, 2029 were pharmacologic stress and 1097 were performed following treadmill exercise. One thousand four hundred ninety-eight patients were referred for PET, 75 of whom received ^{13}N-ammonia while 1423 received ^{82}Rb. Of the 75 ^{13}N-ammonia studies, 33 were performed during treadmill exercise and 42 received regadenoson. Selection for treadmill stress was determined by the ordering provider. If the patient met insurance coverage criteria for PET, treadmill ^{13}N-ammonia was selected as the protocol of choice.

Off-Site Cyclotron Production of ^{13}N-Ammonia

All resting and treadmill exercise stress doses of ^{13}N-ammonia were prepared at an off-site cyclotron run by Wisconsin Medical Cyclotron (West Allis, WI) approximately 7 miles (Figure 1) from our institution. Due to the 10-minute physical half-life of ^{13}N-ammonia, there are several considerations that are necessary to ensure that the drug arrives at our facility on-time for resting and stress imaging at the appropriate doses. Orders for ^{13}N-ammonia are typically transmitted to the off-site cyclotron facility no less than 24 hours before calibration time and are placed into a production planning tool which back-calculates the timing of critical manufacturing events from the estimated time of injection. The planning tool provides a schedule for the start and end of cyclotron target irradiation, the time of end of synthesis (EOS), latest time of departure from the cyclotron facility, and arrival time at the imaging center's hot lab. Three personnel are required to manufacture, dispense, and deliver unit doses of ^{13}N-ammonia. A production technician will typically prepare the manufacturing systems, materials, and batch documentation about 30 minutes before start of cyclotron irradiation. Following irradiation and purification, 6.0 mL of ^{13}N-ammonia in a sterile vial is available for dispensing. Quality control is routinely performed by the staff of the cyclotron facility. A pharmacist dispenses a unit dose (up to 30 mCi at time of calibration) into a syringe and a pharmacy technician performs packaging and delivery functions, both of which require approximately 10 minutes, while the production technician readies for a subsequent sub-batch of ^{13}N-ammonia. The delivery driver must consider local traffic and plan for an approximately 20-minute car trip, depending on the time of day and weather conditions. Once the driver is en route, staging begins at our institution with the patient on the treadmill ready to begin exercise at the pre-determined time allotting for an average of 6-10 minutes of graded exercise. The Wisconsin Medical
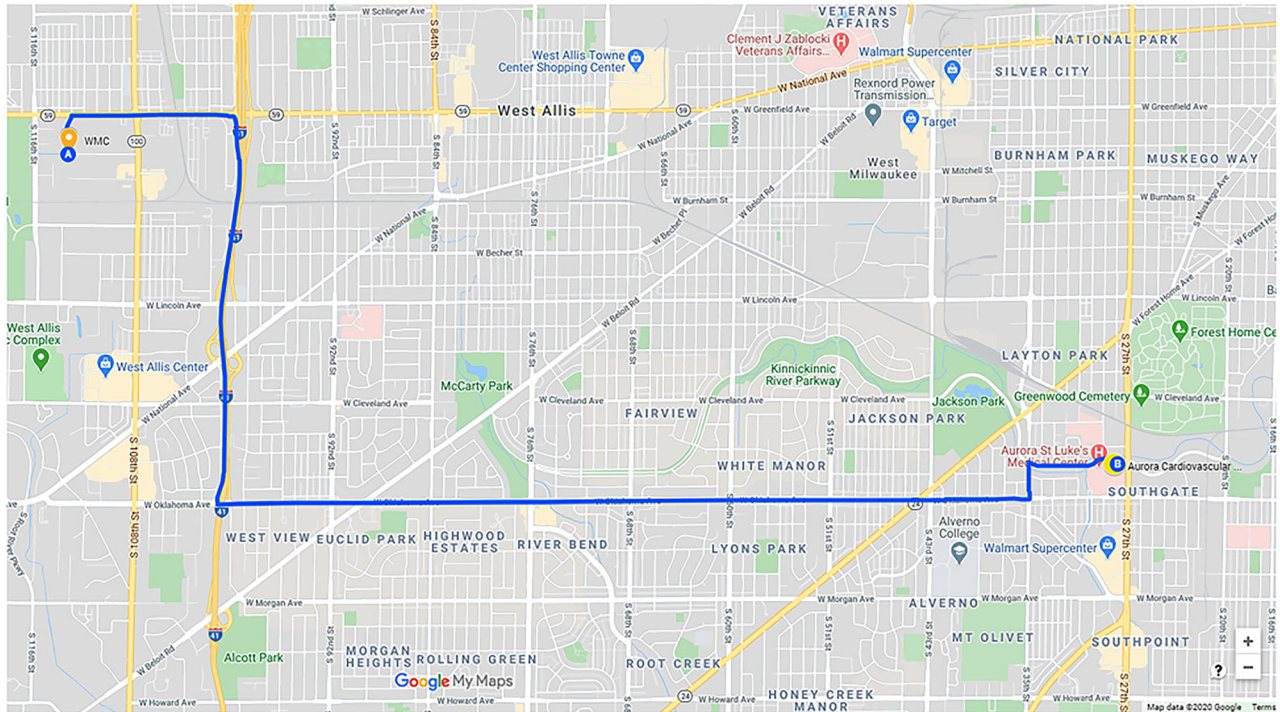
Figure 1. The Wisconsin Medical Cyclotron (left) delivery person travels approximately 7 miles from the off-site cyclotron facility to our medical center (right).
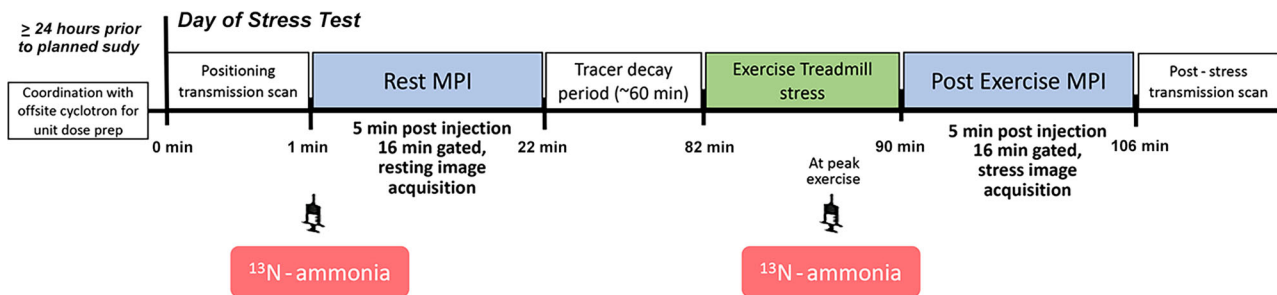

Figure 2. Typical protocol for rest/exercise PET myocardial perfusion imaging using an off-site cyclotron for production of ^{13}N-ammonia.

Cyclotron (WMC) can repeat the entire process for up to 8 doses each, 60 minutes apart.

Exercise ^{13}N-ammonia Acquisition Protocol

All studies were performed on a dedicated cardiac PET scanner (MiE, Elk Grove Village, IL) using a rest-stress protocol (Figure 2). The patient is initially placed in the scanner and a positioning scout transmission image is acquired for 60 seconds using germanium-68 rod sources. A laser-guided mark is made on the patient's chest to document positioning in the scanner. Immediately following the positioning scan, the patient receives a 10 megabecquerel per kilogram (MBq·kg) dose of ^{13}N-ammonia up to a maximum dose of 30 mCi. After a five-minute delay post-injection, a 16-minute gated emission scan is acquired which is immediately followed by a 75Kct transmission scan. A 60-minute decay period follows the initial acquisition. Following the decay period, and in coordination with the WMC delivery driver, the patient begins graded, symptom-limited treadmill exercise according to a standard Bruce protocol on a treadmill located in a room adjacent to, and approximately 25 feet from, the scanner. At peak exercise, the patient is injected with a 10 MBq·kg (up to a maximum dose of 30 mCi) of ^{13}N-ammonia. Exercise

is continued for approximately one additional minute to maximize tracer uptake. The patient is then transferred to the scanner for positioning. There is an approximate 5-minute delay between the peak exercise injection and the stress acquisition to allow for correct positioning and recovery of the patient to reduce motion artifact secondary to breathing. Subsequently, emission and transmission images are acquired as described above.

Image Processing and Interpretation

List mode emission data were reconstructed into 16-frame gated data sets using 4DM post-processing software (INVIA Medical Solutions, Ann Arbor, MI). Regional myocardial perfusion was assessed by automated quantitative and semi-quantitative visual analysis using the 17-segment AHA model. Standard summed stress, rest, and difference scores were calculated by the software, modified by the interpreting physician as necessary, and recorded. Left ventricular ejection fractions at rest and with stress were calculated by the software. When necessary, operator adjustment of the mitral valve plane was performed. Additionally, the transient ischemic dilatation ratio was recorded. Overall image quality was rated as good, adequate (containing some flaw but interpretable), or inadequate where interpretation was severely compromised.

Statistical Analysis

Continuous variables are presented as the mean ± SD and categorical data as the number of patients with a variable and corresponding percentages of the study population or sub-population.

RESULTS

Baseline Characteristics

Thirty-three patients underwent treadmill exercise (GXT) ^{13}N-ammonia PET MPI from February 2018 to October 2019. Mean age was 63.4 ± 12.3 years and 79% were male. The mean BMI was 33.7 ± 6.9 kg·m^2. Based on the history obtained by the cardiologist that ordered the study, 88% (29/33) patients were reported to have some degree of CAD based on either prior cardiac catheterization, CT-coronary angiography, or CT coronary artery calcium scoring. Of those 29 patients, 17 were known to have had prior intervention with PCI or coronary artery bypass graft (CABG) (51% of the total study population). Hypertension was diagnosed in 26/33 (79%) patients and diabetes mellitus was present in 9/33 (27%) patients. Twelve patients (36%) were either

current or former smokers and 16 patients had a documented family history of heart disease (48%).

Treadmill Exercise

All 33 patients were able to perform graded treadmill exercise according to a standard Bruce protocol. Mean resting heart rate was 73.3 ± 14.1 and resting blood pressure was 132 ± 18.6/74 ± 7.8. Twenty-nine patients (87.8%) were able to achieve at least 85% of their age-predicted maximum heart rate prior to injection of ^{13}N-ammonia. The mean heart rate at peak exertion was 143.2 ± 17.9, and the mean blood pressure at peak exertion was 180 ± 19.9/75 ± 6.8. The average exercise time was 7.6 ± 1.8 minutes.

Dosimetry, Image Quality, Myocardial Perfusion, and LV Function

The ^{13}N-ammonia produced off-site was available in 100% of planned cases. The mean resting dose was 29.2 ± 5.7 mCi, and the mean stress dose was 30.8 ± 7.3 mCi.

Figure 3 shows examples of normal and abnormal rest/exercise studies with ^{13}N-ammonia. Figure 4 compares a patient's prior sestamibi SPECT with the current ^{13}N-ammonia images.

Image quality was rated as good in 29 patients, adequate in 3, and inadequate in 1 patient. The inadequate study was due to patchy myocardial uptake that was a function of suboptimal counts and motion. Figure 5 shows examples of differences in exercise ^{13}N-ammonia image quality.

The mean summed stress score was 4.5 ± 5.7, summed rest score was 2.7 ± 5.0, and summed difference score was 2.1 ± 3.6. The TID ratio was 1.0 ± 0.1.

Resting and post-exercise left ventricular ejection fractions were 64.1 ± 11.1% and 66.6 ± 13.3%.

DISCUSSION

Our study demonstrates the feasibility of performing exercise PET myocardial perfusion imaging with ^{13}N-ammonia produced at an off-site cyclotron. All ^{13}N-ammonia doses were received on schedule. All patients performed symptom-limited treadmill exercise with 88% of patients attaining or exceeding 85% of the age-predicted maximum heart rate. Exercise imaging was completed in all patients. Other centers have previously demonstrated the feasibility of performing treadmill ^{13}N-ammonia PET but have had access to on-site cyclotron production of unit-dose ^{13}N-ammonia.[5,6] These results challenge the commonly held notion that all PET MPI must be performed with vasodilator stress
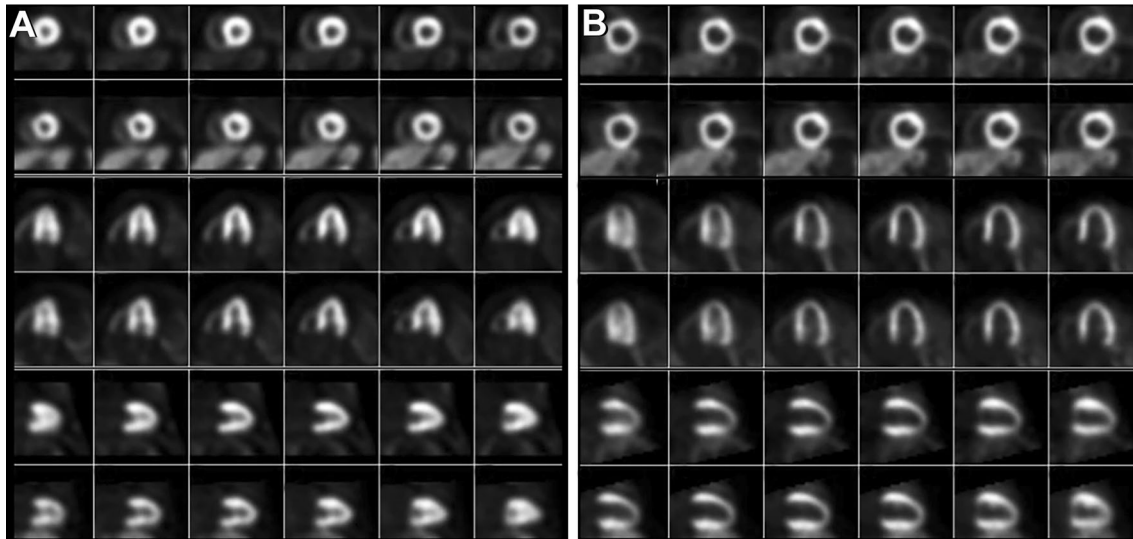
Figure 3. Representative ^{13}N-ammonia myocardial perfusion images from exercise (top rows) and rest (bottom rows). Panel **A** shows normal exercise and rest myocardial perfusion. Panel **B** demonstrates a small, fixed inferoapical perfusion abnormality consistent with small inferoapical infarct.
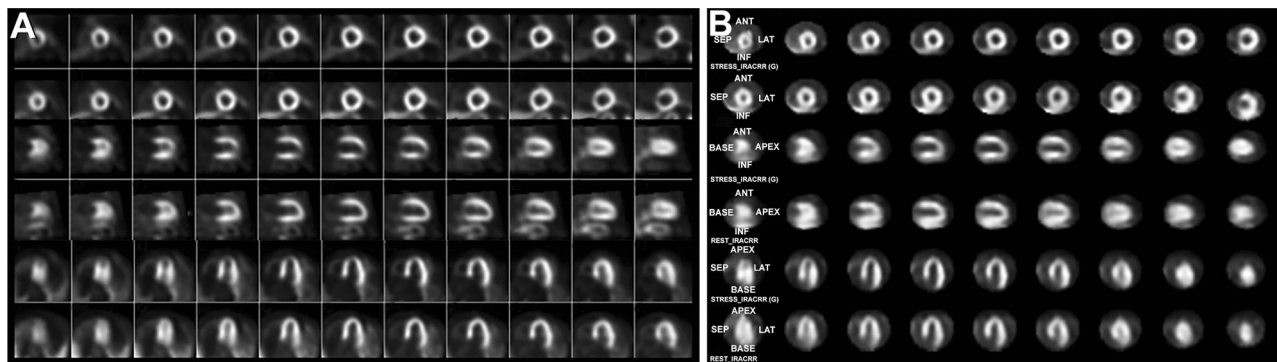

Figure 4. (Panel **A**) ^{13}N-ammonia PET MPI demonstrates reversible apical defect; (Panel **B**) demonstrates treadmill SPECT from the same patient 4 years earlier.

imaging, relegating all exercise MPI to SPECT imaging. In addition, there is now a small cyclotron available for production of unit-dose ^{13}N-ammonia that can be housed in a nuclear cardiology laboratory or in a department of nuclear medicine. To date, one center has reported the ability to deliver high quality ^{13}N-ammonia PET MPI with the Ionetix ION-12SC (San Francisco, CA).[7]

Image quality was considered good in all but three patients. In two patients, there was excessive subdiaphragmatic activity, but images were still considered interpretable. By comparison, we found a 10% rate of excessive subdiaphragmatic activity in 42 patients who underwent vasodilator ^{13}N-ammonia PET MPI during the same time period. Liver and/or gut activity may be encountered with ^{13}N-ammonia imaging—its appearance is unpredictable.[8] Lung uptake is usually minimal but may be increased in smokers, those with chronic pulmonary disease and in patients with depressed left ventricular function.[9] One patient in our cohort had poor image quality considered to be related to lung uptake, motion, and suboptimal counts, the latter unrelated to the ^{13}N-ammonia dose.

Exercise vs. Vasodilator MPI

Current ASNC guidelines for myocardial perfusion imaging recognized exercise as the preferred stressor for those capable of exercising.[10,11] The addition of exercise and ECG variables contribute to the diagnostic and
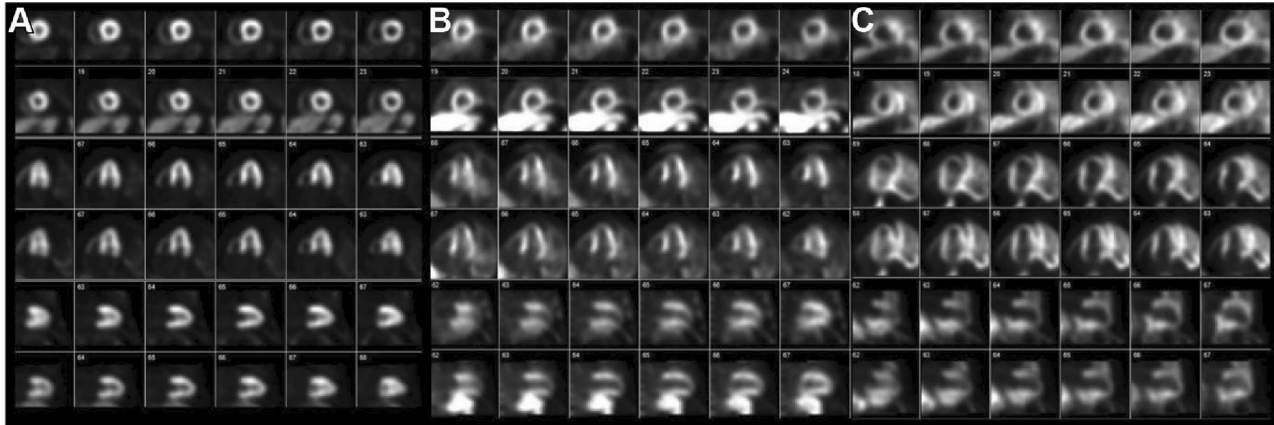
Figure 5. Examples of Image Quality: Panel **A** shows an example of a Good quality image. Panel **B** shows an example of an Adequate quality image. Panel **C** demonstrates an Inadequate image.

prognostic content of the examination. Quantitative scoring such as the Duke treadmill score is a powerful predictor of subsequent outcome that is lost with vasodilator imaging. Additionally, Chow et al. demonstrated larger perfusion defects on exercise PET studies compared with vasodilator-induced defects in the same patients.[6,12] PET MPI is also considered better than SPECT MPI in obese patients and Aggarwal et al. have demonstrated the feasibility and accuracy of exercise treadmill ^{13}N-ammonia PET MPI in obese patients.[5,13,14]

Since patients are on the treadmill and not in the scanner at the time of the injection of ^{13}N-ammonia, it is not possible to measure myocardial blood flow during exercise PET. Myocardial blood flows have been shown to be of diagnostic and prognostic value in the assessment of suspected coronary artery disease. Measurement of myocardial blood flows and flow reserves may help in detection of endothelial dysfunction, microvascular disease, and multivessel CAD and have been shown to be prognostically important in patients with and without CAD.[15–18] To our knowledge, there is no literature directly comparing the relative diagnostic and prognostic powers of exercise PET results to pharmacological PET with myocardial blood flow results. In our institution, the choice of exercise or pharmacologic stress is determined by the ordering cardiologist based on patient-specific factors. In certain patients, the choice would be obvious, such as those with chest pain and normal coronary arteries or those with MINOCA in which myocardial blood flows and flow reserves would be the primary focus of the examination. Further studies are needed to determine other scenarios in which it is more appropriate to sacrifice the prognostic information contained in an exercise study in order to obtain non-invasive assessments of myocardial blood flow or vice versa.

Radiation Exposure

Current practice guidelines continue to reinforce choosing the most appropriate test for a patient while being mindful of the radiation exposure and adhering to the principle of as low as reasonably achievable (ALARA).[19,20] Due to their relatively short, physical half-lives, PET tracers may offer lower patient radiation doses than SPECT tracers. Our technique could expand the role of ^{13}N-ammonia in many centers by overcoming the limitation of on-site cyclotron production. Treadmill ^{13}N-ammonia PET can result in a lower effective dose than comparable Tc-99 m exercise protocols while maintaining the high diagnostic sensitivity of PET myocardial perfusion imaging.[19,21] Radiation dose can potentially be further lowered using a stress-first protocol. Two low-risk patients in our cohort were studied according to a treadmill stress-first protocol. After review of their normal stress images, they did not undergo reinjection for resting images yielding an average dose of 16.5 mCi ^{13}N-ammonia (approximately 1.6 mSv est. effective dose). According to estimates of effective doses of standard myocardial perfusion imaging protocols,[19,20] this technique should result in similar or greater reductions in effective dose compared to low-dose, stress-only protocols using technetium 99 m SPECT and are comparable to the effective doses achieved in ''ultra-low dose'' protocols using Tc-99 m and CZT SPECT.[20]

Cost and Implementation

One of the limitations of the routine use of PET for MPI is its cost. PET imaging with [82]Rb is associated with high cost due to its requirement of an on-site generator and regular, high volume use to make the generator cost-effective.[22] Acquiring unit-dose ^{13}N-ammonia for treadmill stress MPI may be more cost-effective but further studies and expansion of this dataset will be needed to determine scalability and economy of this technique. Future expansion of decentralized production of PET tracers with the use of small, in-laboratory cyclotrons[7] may make tracers like ^{13}N-ammonia more widely available for remote centers. Until that time, however, our technique offers a more immediate solution. Use of a remote cyclotron offers the ability for multiple hospitals in a metropolitan area to share a single cyclotron facility across a larger geographic area thus lowering the financial burden on a single institution. There are already ongoing clinical operations using remote cyclotrons for pharmacologic ^{13}N-ammonia PET, and there are 101 commercial cyclotrons distributed around the US that could potentially be recruited for this purpose.[23]

Limitations of the Study

This is a single-center observational feasibility study with a relatively low number of patients. The study was not designed to test the relative diagnostic accuracy or extent/severity of perfusion defects with exercise compared to pharmacological PET MPI. The nature of the study precludes the ability to assess the cost-benefit ratio of obtaining unit-dose ^{13}N-ammonia vs. generator-produced Rubidium-82. The protocol described herein may not be applicable to centers where there is no medical cyclotron within an appropriate driving distance.

NEW KNOWLEDGE GAIN

Treadmill exercise ^{13}N-ammonia PET is feasible in a large regional medical center with access to a nearby off-site cyclotron. In this limited study, image quality was consistently good and, in our opinion, superior to that seen in our large experience with [82]Rb imaging. As exercise is the preferred method of stress testing in many clinical situations, the use of ^{13}N-ammonia expands the potential for PET imaging to serve that population. It remains to be demonstrated that the approach can be cost-effective.

Disclosures

The authors declare that they have no conflict of interest to disclose.

References

1. Bateman TM, Heller GV, McGhie AI, Friedman JD, Case JA, Bryngelson JR et al (2006) Diagnostic accuracy of rest/stress ECG-gated Rb-82 myocardial perfusion PET: Comparison with ECG-gated Tc-99m sestamibi SPECT. J Nucl Cardiol 13:24-33

2. Yoshinaga K, Chow BJ, Williams K, Chen L, deKemp RA, Garrard L et al (2006) What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? J Am Coll Cardiol 48:1029-39

3. Mc Ardle BA, Dowsley TF, deKemp RA, Wells GA, Beanlands RS (2012) Does rubidium-82 PET have superior accuracy to SPECT perfusion imaging for the diagnosis of obstructive coronary disease?: A systematic review and meta-analysis. J Am Coll Cardiol 60:1828-37

4. Parker MW, Iskandar A, Limone B, Perugini A, Kim H, Jones C et al (2012) Diagnostic accuracy of cardiac positron emission tomography versus single photon emission computed tomography for coronary artery disease: A bivariate meta-analysis. Circ Cardiovasc Imaging 5:700-7

5. Aggarwal NR, Drozdova A, Askew JW 3rd, Kemp BJ, Chareonthaitawee P (2015) Feasibility and diagnostic accuracy of exercise treadmill nitrogen-13 ammonia PET myocardial perfusion imaging of obese patients. J Nucl Cardiol 22:1273-80

6. Chow BJ, Beanlands RS, Lee A, DaSilva JN, deKemp RA, Alkahtani A et al (2006) Treadmill exercise produces larger perfusion defects than dipyridamole stress N-13 ammonia positron emission tomography. J Am Coll Cardiol 47:411-16

7. Pieper J, Patel VN, Escolero S, Nelson JR, Poitrasson-Rivière A, Shreves CK et al (2019) Initial clinical experience of N13-ammonia myocardial perfusion PET/CT using a compact superconducting production system. J Nucl Cardiol. https://doi.org/10.1007/s12350-019-01886-7

8. Di Carli MF, Dorbala S, Meserve J, El Fakhri G, Sitek A, Moore SC (2007) Clinical myocardial perfusion PET/CT. J Nucl Med 48:783-3

9. Nakazato R, Berman DS, Alexanderson E, Slomka P (2013) Myocardial perfusion imaging with PET. Imaging Med 5:35-46

10. Henzlova MJ, Duvall WL, Einstein AJ, Travin MI, Verberne HJ (2016) ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. J Nucl Cardiol 23:606-39

11. Dilsizian V, Bacharach SL, Beanlands RS, Bergmann SR, Delbeke D, Dorbala S et al (2016) ASNC imaging guidelines/SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. J Nucl Cardiol 23:1187-26

12. Chow BJ, Ananthasubramaniam K, de Kemp RA, Dalipaj MM, Beanlands RS, Ruddy TD (2005) Comparison of treadmill exercise versus dipyridamole stress with myocardial perfusion imaging using rubidium-82 positron emission tomography. J Am Coll Cardiol 45:1227-34

13. Harnett DT, Hazra S, Maze R, Mc Ardle BA, Alenazy A, Simard T et al (2019) Clinical performance of Rb-82 myocardial perfusion PET and Tc-99m-based SPECT in patients with extreme obesity. J Nucl Cardiol 26:275-3

14. Taqueti VR (2019) Myocardial perfusion imaging in extreme obesity: Leveraging modern technologies to meet a modern challenge. J Nucl Cardiol 26:284-7

15. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G et al (2011) Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. Circulation 124:2215-24

16. Ziadi MC, Dekemp RA, Williams K, Guo A, Renaud JM, Chow BJ et al (2012) Does quantification of myocardial flow reserve using rubidium-82 positron emission tomography facilitate detection of multivessel coronary artery disease? J Nucl Cardiol 19:670-80

17. Fukushima K, Javadi MS, Higuchi T, Lautamaki R, Merrill J, Nekolla SG et al (2011) Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical 82Rb PET perfusion imaging. J Nucl Med 52:726-2

18. Herzog BA, Husmann L, Valenta I, Gaemperli O, Siegrist PT, Tay FM et al (2009) Long-term prognostic value of 13N-ammonia myocardial perfusion positron emission tomography added value of coronary flow reserve. J Am Coll Cardiol 54:150-6

19. Cerqueira MD, Allman KC, Ficaro EP, Hansen CL, Nichols KJ, Thompson RC et al (2010) Recommendations for reducing radiation exposure in myocardial perfusion imaging. J Nucl Cardiol 17:709-18

20. Case J, deKemp R, Slomka P, Smith M, Heller G, Cerqueira M (2017) Status of cardiovascular PET radiation exposure and strategies for reduction: An information statement from the cardiovascular PET task force. J Nucl Cardiol 24:1427-39

21. Stabin MG (2008) Radiopharmaceuticals for nuclear cardiology: Radiation dosimetry, uncertainties, and risk. J Nucl Med 49:1555-63

22. Maddahi J (2012) Properties of an ideal PET perfusion tracer: New PET tracer cases and data. J Nucl Cardiol 19(Suppl 1):S30-7

23. Ikotun O, Clarke B, Sunderland J (2012) A snapshot of United States PET cyclotron and radiopharmaceutical production operations and locations. J Nucl Med 53:1085