Initial clinical experience of N13-ammonia myocardial perfusion PET/CT using a compact superconducting production system

Justin Pieper, MD,[a] Vaiibhav N. Patel, MD,[b] Sylvia Escolero, BS,[c] Jacob R. Nelson, BS,[c] Alexis Poitrasson-Rivière, PhD,[f] Christopher K. Shreves, BS,[d] Nick Freiburger, BS, MPH,[d] David Hubers, RPh, BCNP,[e] Jill Rothley, BS, CNMT,[e] James R. Corbett, MD,[b,e] Joseph Oliverio, BS, MBA,[d] Edward P. Ficaro, PhD,[f] Richard L. Weinberg, MD, PhD,[b] and Venkatesh L. Murthy, MD, PhD[b,e]

[a] Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[b] Division of Cardiovascular Medicine, Department of Medicine, University of Michigan, Ann Arbor
[c] University of Michigan Medical School, Ann Arbor, MI
[d] Ionetix Corporation, San Francisco, CA
[e] Division of Nuclear Medicine, Department of Radiology, University of Michigan, Ann Arbor, MI
[f] INVIA, Ann Arbor, MI

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Background. **Although N13-ammonia has favorable properties among FDA approved radiotracers, complexity of implementation has limited its use. We describe the initial patient experience of N13-ammonia PET imaging using a compact N13-ammonia production system.**

Methods. **N13 was produced using the ION-12SC, a 12MeV, 10uA superconducting minimally shielded cyclotron, and reduced to N13-ammonia in an automated multi-use purification unit. Patients were power injected with 9.3 ± 1.1 mCi (344.1 ± 40.7 MBq) of N13-ammonia for rest imaging, and 18.8 ± 0.9 mCi (695.6 ± 33.3 MBq) of N13-ammonia was injected at peak hyperemia for stress testing. Images were interpreted for relative perfusion, left ventricular volumes/function, blood flow quantification, and scored for image quality.**

Results. **In total 97 patients underwent 98 N13-ammonia PET scans (32 rest only/65 rest-stress/1 stress only). Image quality was 91.8% good or excellent. None were poor/non-diagnostic. Study durations were acceptable. Tracer related radiation dosimetry to patients was 0.7 ± 0.1 mSv (rest only), and 2.1 ± 0.1 mSv (rest-stress).**

Conclusion. **Clinical N13-ammonia production by the Ionetix ION-12SC delivers high quality myocardial PET perfusion images in a rapid protocol. (J Nucl Cardiol 2021;28:295–9.)**

Key Words: PET • tracer development • instrumentation • perfusion imaging agents

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Justin Pieper and Vaiibhav N. Patel contributed equally to this work and are co-first authors.

Richard L. Weinberg and Venkatesh L. Murthy contributed equally to this work and are co-senior authors.

Reprint requests: Justin Pieper, MD, Department of Internal Medicine, University of Michigan, 1500 E Medical Center Drive, Ann Arbor, MI 48109, USA; *jpieper@med.umich.edu*

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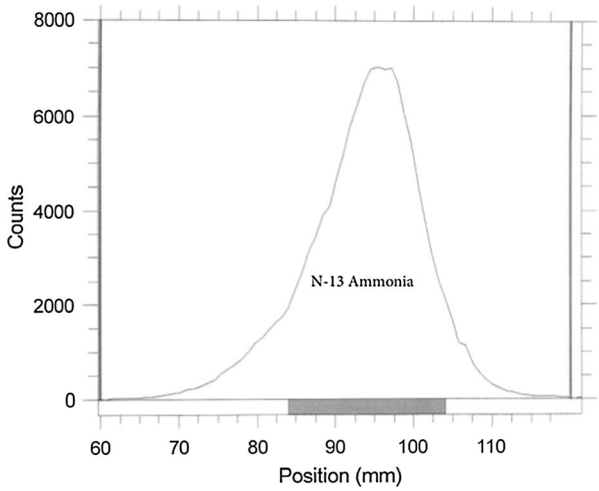

Figure 1. An example of thin layer chromatography from a batch of N13-ammonia produced Feb 8, 2019. Radiochemical purity was > 99% in all samples.

See related editorial, pp. 300–302

INTRODUCTION

Although several studies have demonstrated that positron emission tomography (PET) myocardial perfusion imaging (MPI) is the gold standard for diagnosis of coronary artery disease (CAD), utilization remains low.[1–3] Challenges preventing more widespread adoption of PET MPI include limited production of strontium-82 (Sr-82), limited Sr-82/rubidium-82 (Rb-82) generator manufacturing capacity, and Sr-82 break through events leading to significant unintentional patient radiation exposures. Nitrogen-13 (N13)-ammonia has been shown to be valuable in prognosis and diagnosis of CAD.[4,5] While it has several favorable properties compared to Rb-82, including (1) improved spatial and defect contrast resolution,[6] (2) decreased patient doses,[7] and (3) ability to perform exercise MPI,[8] it has been difficult to use clinically due to the need for an onsite cyclotron. Because Rb-82 is a generator product, implementation has been substantially simpler than for N13–ammonia. Furthermore, the ultra-short half-life of Rb-82 (76 seconds) enables rapid rest-stress protocols which can be completed in as little as 30 minutes of scanner time per patient whereas standard N13-ammonia protocols require an hour or longer to allow for isotope decay.[3]

Advances in superconducting cyclotron design and automated multi-use purification unit have enabled development of a highly automated minimally shielded mini-cyclotron system. We report the initial clinical experience with such a system.

Table 1. Describing baseline characteristics of our 97-patient cohort

Baseline characteristics	N = 97 (%)
Age	63.1 ± 13 year
Sex (F)	42 (43.3)
BMI	32.4 ± 9.38 kg/m^2
Hypertension	71 (73.2)
Hyperlipidemia	54 (55.7)
Type 2 diabetes	42 (43.3)
Coronary artery disease	38 (39.2)
Heart failure	40 (41.2)
Tobacco use	53 (54.6)
Stroke	15 (15.5)
ICD	17 (17.5)
Ventricular tachycardia/fibrillation	9 (9.3)
Atrial fibrillation/flutter	20 (20.6)
Peripheral arterial disease	11 (11.3)
Aspirin	55 (56.7)
Statin	50 (51.5)
Beta Blocker	49 (50.5)
ACE/ARB	57 (58.8)
Mineralocorticoid antagonist	17 (17.5)
$P2Y_{12}$ inhibitor	18 (18.6)
Nitrates	6 (6.2)
Calcium chanel blocker	23 (23.7)
Anticoagulation	24 (23.7)
Mean rest dose	9.1 ± 1.1 mCi
Mean stress dose	18.8 ± 0.9 mCi

ICD, Implantable cardioverter/defibrillator; *ACEi/ARB*, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker

MATERIALS AND METHODS

Due to disruption in the Sr-82/Rb-82 generator supply chain, over approximately one month (January 14th to February 14th, 2019), 97 patients referred for clinical PET MPI underwent imaging using N13-ammonia as the sole radiotracer.

N13-ammonia was manufactured by technicians trained by the cyclotron manufacturer to safely and effectively operate the production system. The system consists of the ION-12SC (Ionetix, Inc, San Francisco, CA), which produced in-target Ammonia N 13, and an automated multi-use purification system, which purified and formulated the final drug product. The first dose (quality control sub-batch) was inspected daily for appearance (visual inspection), pH, radiochemical purity/identity through thin layer chromatography (Figure 1), radioactive concentration, bacterial endotoxin, filter integrity test (bubble point), and sterility. The patient sub-batches were

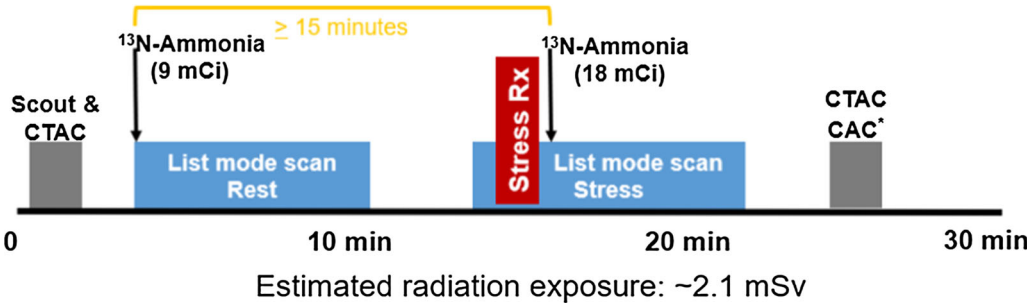

Figure 2. Graphic representation of protocol described in ''Methods.'' *CTAC*, CT-based attenuation correction; *CAC*, coronary artery calcium scan (*where clinically indicated). The estimated radiation exposure is reported for rest/stress scan.

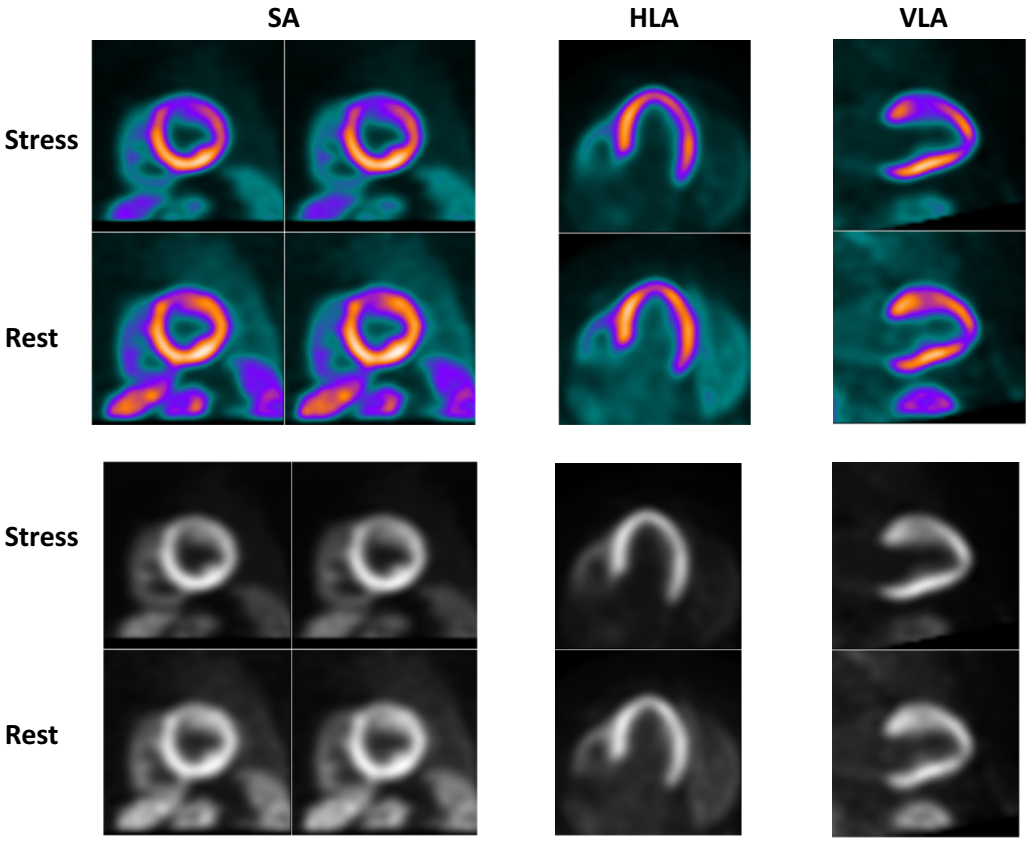

Figure 3. N13-ammonia PET/CT myocardial perfusion scan of a 59-year-old female with an anterior and anteroseptal, partially reversible, as well as completely reversible lateral and anterolateral defects. *SA*, short axis; *HLA*, horizontal long axis; *VLA*, vertical long axis.

evaluated for appearance (visual inspection), radioactive concentration and a filter integrity test (bubble point).

For imaging, patients were power injected with 9.3 ± 1.1 mCi (344.1 ± 40.7 MBq) N13-ammonia (Medrad® Spectris Solaris® EP Injection System modified to with tungsten shield, 20 mL at 1 mL/s followed by a 10 mL normal saline flush). List mode imaging was performed for 10 minutes beginning at tracer injection. For stress testing, after a minimum of five minutes post rest imaging (15 minutes post tracer injection), 0.4 mg of regadenoson was injected intravenously. At peak hyperemia, 18.8 ± 0.9 mCi (695.6 ± 33.3 MBq) N13-ammonia was injected (20 mL at 1 mL/s followed by a 10 mL normal saline flush). List mode imaging was performed for 9 minutes, beginning one minute prior to tracer injection (Figure 2).

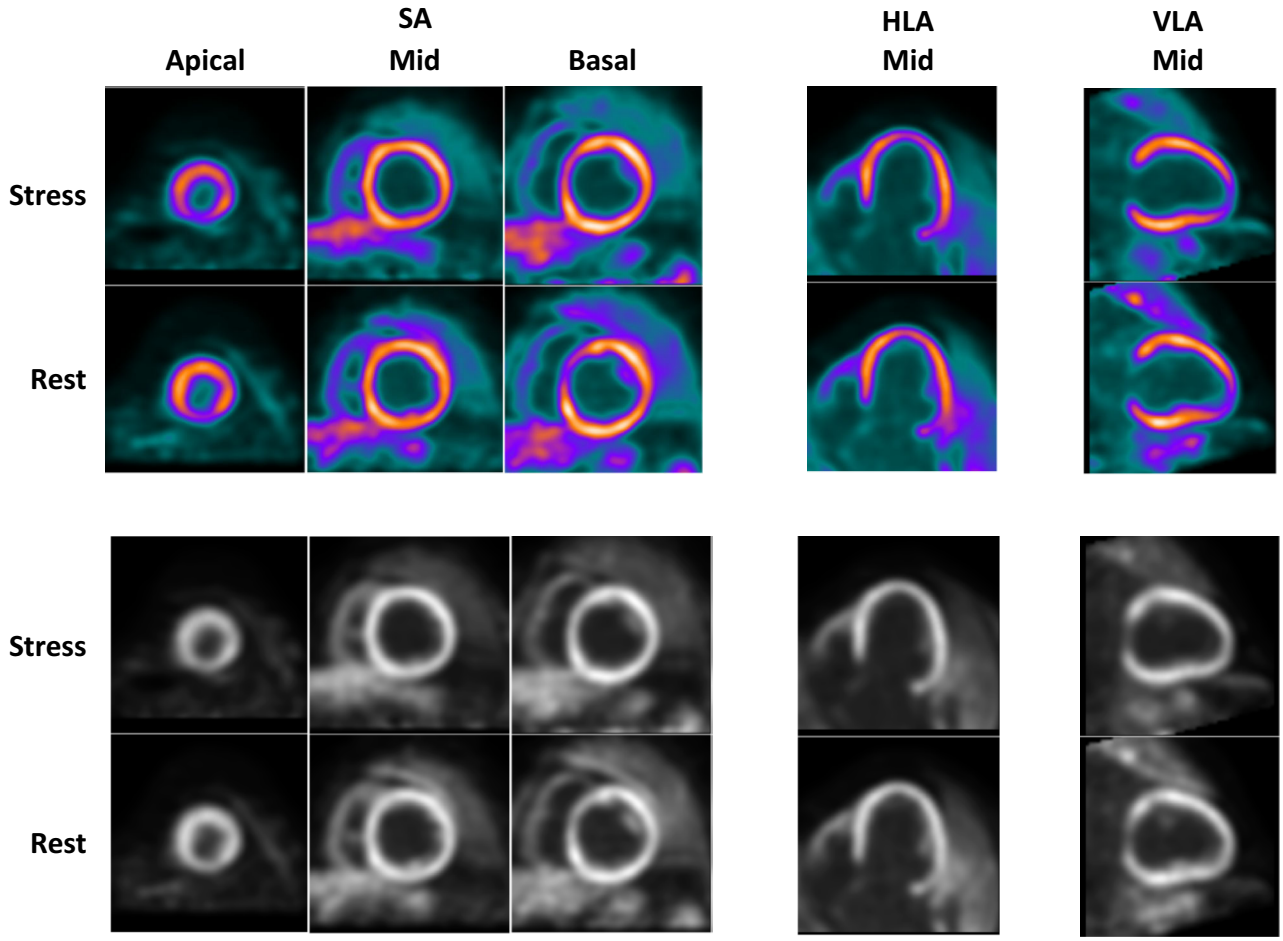

Figure 4. N13-ammonia PET/CT myocardial perfusion scan of a 76-year-old male with dilated, non-ischemic cardiomyopathy and severe left ventricular hypokinesis. The right ventricular wall and moderator band can be appreciated especially in the short axis (SA). *HLA*, horizontal long axis; *VLA*, vertical long axis.

Static, ECG-gated, and dynamic images were unlisted. Images were interpreted clinically for relative perfusion, left ventricular volumes/function, blood flow quantification, and scored for image quality using 4DM (INVIA Medical Imaging Solutions, Ann Arbor, MI). The studies were interpreted by three board certified nuclear cardiologists and were scored as poor, fair, good, or excellent based on overall image quality including noise, contrast, patient motion and quality of tracer bolus administration. Patients were monitored for a minimum of 20 minutes for adverse reactions.

RESULTS

N13-ammonia was produced in approximately 4-mL with > 95% yield (decay corrected). Quality control procedures aligned with the N13-ammonia USP monograph, and no quality control failures occurred during the operational period. Radiochemical purity analysis of all manufactured batches was found to be greater than 99% with potential anionic impurity levels being below the analytical limit of detection. An example can be seen in Figure 1. The ION12-SC was collocated within a shielded vault with a GE PETtrace cyclotron (GE Healthcare); therefore, radiation from the ION-12SC could not be independently measured. Daily microbiologic testing for sterility was negative. Beam current was 10μA for each run, and average activity per run was 52.4 ± 2.3mCi.

In total 97 patients underwent 98 N13-ammonia PET scans (32 rest only/65 rest-stress/1 stress only). The majority of patients were men (56.7%). Further baseline characteristics can be seen in Table 1. Eighteen patients had prior PET/CT MPI performed. Image quality was 91.8% good or excellent, 6.1% good, and 2.0% fair. None were poor/non-diagnostic. Study durations were acceptable: 16.5 (IQR 15.8-18.0) minutes for rest only, 48.1 (IQR 47.0-60.9) minutes for rest-stress, and 29

minutes for stress only. Time between rest and stress scans was 22.3 ± 10.3 minutes. Tracer related radiation dosimetry to patients was 0.7 ± 0.1 mSv (rest only), and 2.1 ± 0.1 mSv (rest-stress).[9] Subjects per day averaged 4.1 ± 1.0. There were no major complications. There were no adverse reactions observed during rest infusions. All symptoms during stress infusion were similar in quality, frequency, and severity to those described for the stress agent (regadenoson).

Example images are presented in Figures 3, 4. Figure 3 highlights the advantages of using N13-ammonia in assessing perfusion defects. In this image, there is excellent visualization of a partially reversible anterior and anteroseptal defect, as well as completely reversible lateral and anterolateral defects. Figure 4 showcases the ability of N13-ammonia to visualize cardiac sub-structures such as the moderator band with excellent definition.

DISCUSSION

We found that N13-ammonia produced by the Ionetix ION-12SC delivered high quality myocardial PET perfusion images in a safe and reliable manner with a rapid protocol. To our knowledge, this is the first study assessing the clinical performance of an automated N13–ammonia production system. Consequently, we are hopeful that this option may improve availability of cardiac PET MPI.

Importantly, this system does have several tradeoffs relative to Rb-82. Because of differences in half-life of the tracers, at present Rb-82 rest/stress scans are still slightly shorter in duration than N13-ammonia studies. This could potentially be improved as time between rest and stress scans was greater than intended in some cases (22.3 ± 10.3 minutes). Furthermore, given excellent count rates during stress imaging, shorter stress acquisitions may be feasible. At present the minimum duration of a N13-ammonia protocol is 23 minutes plus time for patient preparation and recovery from stress as compared to 17 minutes for Rb-82 protocols. Although daily volumes were limited during this initial experience, there are no intrinsic limitations preventing extended scanning at the current levels of hourly throughput which would enable 8-10 scans per business day. Further, we believe there is substantial opportunity for further process optimization enabling further improved patient throughput.

CONCLUSION

N13-ammonia can be safely and efficiently produced for clinical PET MPI using an automated mini-cyclotron system.

Disclosures

Justin Pieper, Vaiibhav N. Patel, Sylvia Escolero, Jacob R. Nelson, David Hubers, Jill Rothley, and Richard L. Weinberg have no disclosures or conflicts of interest related to this publication. Edward P. Ficaro and James R. Corbett have financial interest in INVIA Medical Imaging Solutions, which licenses the commercial software used for imaging processing. Alexis Poitrasson-Rivière is employed by INVIA. INVIA Medical Imaging Solutions did not provide direct support to this study. Joseph Oliverio, Christopher K. Shreves, and Nick Freiburger own stock options and are employed by Ionetix Corporation. Venkatesh L. Murthy has received consulting fees and stock options from Ionetix, Inc., owns stock in General Electric and Cardinal Health, has a research Grant from Siemens Medical Imaging, and has provided expert witness testimony on behalf of Jubilant Draximage. Venkatesh L. Murthy is supported by 1R01HL136685 from the National, Heart, Lung, Blood Institute and 1R01AG059729 from the National Institute on Aging.

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