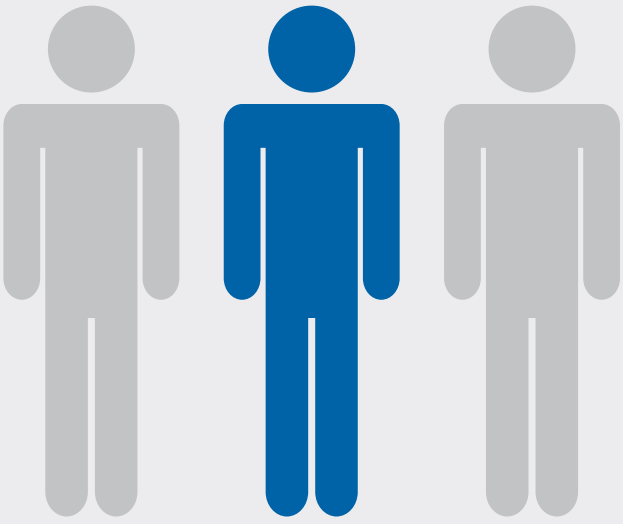
State-of-the-art PET/CT Imaging for the diagnosis and monitoring **of coronary artery disease**

Cardiovascular disease remains the world's top cause of death, representing 31 percent of all deaths globally[1], or 17.9 million deaths, and 37 percent of all premature deaths under the age of 70[1]. In the US, cardiovascular diseases claim more lives annually than all types of cancer and chronic lower respiratory diseases combined[2].



More than one out of three premature deaths under the age of 70 are **caused by cardiovascular disease globally.**

Figure 1: *Impact of cardiovascular disease on premature death.*

With PET imaging we can perform fast rest and stress studies in less than 30 minutes with a low radiation dose to both the patient and the staff.

Prof. Kirsten Bouchelouche, MD
Chief Physician, DMSc,
Assistant Professor in the Department of Nuclear Medicine & PET Centre at Aarhus.

Medical imaging plays an important role in the diagnosis of cardiovascular disease. While CT, MR and SPECT have all been utilized in the diagnostic work-up of cardiac patients, PET/CT is rapidly gaining in use for the detection and management of cardiac diseases worldwide. Cardiac PET/CT exams have significantly increased in volume over the last decade, from just under 40,000 exams per year in the US in 2012 to nearly 200,000 exams per year in the US in 2016[3]. And, it shows no sign of slowing. The Advisory Board (Washington, DC) predicts outpatient Myocardial PET imaging services will continue to grow at a rapid pace of nearly 65% over the next five years[4].

"We have seen a tremendous growth in PET myocardial perfusion scans," says Ronny R. Buechel, MD, nuclear medicine physician and cardiologist leading the Cardiac Imaging Division at the Department of Nuclear Medicine, University Hospital Zurich. The hospital is one of the largest and most important teaching hospitals in Europe and performs approximately 700 ^{13}N-ammonia PET Myocardial Perfusion Imaging (MPI) and exams, 300 cardiac 18F-FDG PET and PET/MR exams each year.

And, at the largest hospital in Northern Europe, Aarhus University Hospital in Denmark, the Department of Nuclear Medicine & PET Centre has performed more than 1,500 cardiac PET studies each year to evaluate myocardium perfusion. With cyclotrons and a generator, the hospital uses both ^{82}Rb and ^{15}O-H_2O tracers. Since 2012, when the department first began using ^{82}Rb PET, more than 7,000 patient exams have been performed. Over 300 ^{15}O-H_2O PET research-based exams have been performed since 2011. The facility expects to transition from ^{82}Rb to ^{15}O-H_2O PET* in a large clinical scale at the end of 2019.

PET protocols and tracers

"With PET imaging we can perform fast rest and stress studies in less than 30 minutes with a low radiation dose to both the patient and the staff. We also have a high diagnostic accuracy and prediction of future cardiac events with PET," says Kirsten Bouchelouche, Chief Physician, DMSc, MD, Assistant Professor in the Department of Nuclear Medicine & PET Centre at Aarhus.

The PACIFIC study (The Prospective Comparison of Cardiac PET/CT, SPECT/CT Perfusion Imaging and CT Coronary Angiography With Invasive Coronary Angiography) was a prospective controlled clinical single-center study of 208 patients that sought to establish the diagnostic accuracy of CCTA, SPECT and PET for detecting hemodynamically significant stenosis in at least one coronary artery and the relative diagnostic accuracy in detecting hemodynamically significant CAD. It revealed PET to exhibit the highest accuracy for diagnosis of myocardial ischemia[5].

Three tracers are commonly used in cardiac PET myocardial perfusion imaging (MPI) exams: nitrogen-13-ammonia (^{13}N ammonia), Rubidium-82 (^{82}Rb) and Oxygen-15 Water (^{15}O-H_2O) (see Figure 4).

Rubidium

With a half-life of 76 seconds, ^{82}Rb is produced in a generator beside the scanner at Aarhus so that it can be injected into the patient while starting the PET scan.

Di Carli et al summarized published results of ^{82}Rb PET in regard to diagnostic accuracy and reported their findings in 2007. A review of nine studies found that ^{82}Rb PET had an average sensitivity of 90 percent, average specificity of 89 percent and average accuracy of 90 percent[6]. Results from a multi-center study evaluating ^{82}Rb PET demonstrated that in patients with known or suspected CAD, the extent and severity of perfusion defects detected on ^{82}Rb PET provide insight into a patient's prognosis[7]. Sub-analyses in bypass and obese patients reported similar results[7].

Professor Bouchelouche and colleagues have also examined whether the standard dose of 1110 MBq ^{82}Rb PET could be reduced without impacting diagnostic accuracy. They found that a dose of 740 MBq ^{82}Rb PET had no impact on the quality of the study or the results[8]. This remained true even when they looked at absolute flow values; there was no difference in the diagnosis/evaluation of perfusion defects.

In the ^{82}Rb PET protocol used in Aarhus, a low-dose CT scan is first acquired for attenuation correction. The tracer (740 MBq) is injected and dynamic images at rest are captured in approximately five minutes. Next, adenosine is administered for stress and the PET scanner captures a second five-minute study. The result is a 30-minute complete rest/stress PET myocardial perfusion study with a patient dose of approximately 2 mSv (see Figure 2).

While there are multiple advantages to using ^{82}Rb PET—fast MPI study, good diagnostic accuracy and nearly quantitative Myocardial Blood Flow (MBF)—the disadvantage is the cost of the generator. This means that Aarhus must scan between 30-35 patients each week to justify the cost of the generator. Without sufficient volume, ^{82}Rb PET would be too expensive, Professor Bouchelouche explains.

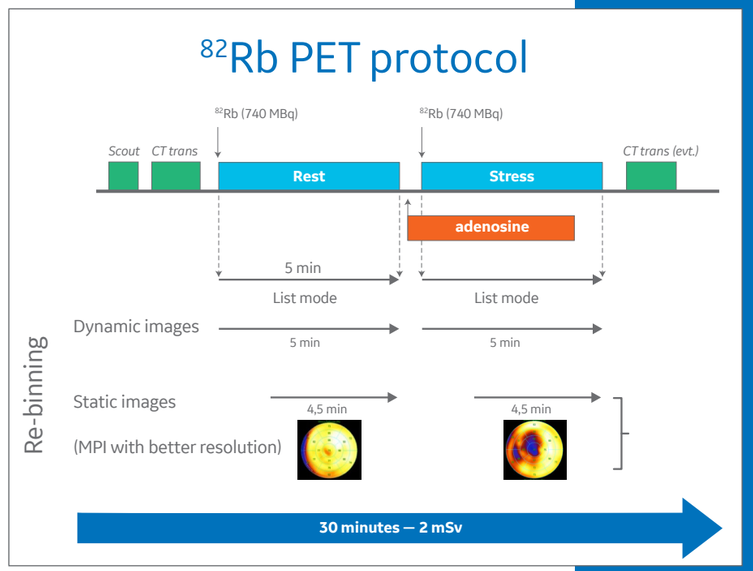


Figure 2: *Rubidium imaging protocol used at Aarhus University Hospital, Denmark.*

If you have a cyclotron available, then Rubidium tracers are expensive because of the additional need for a generator. Hence, for us ammonia is a better choice economically.

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Nuclear Medicine physician and cardiologist leading the Cardiac Imaging Division at the Department of Nuclear Medicine, University Hospital Zurich.

Ammonia

"If you have a cyclotron available, then Rubidium tracers are expensive because of the additional need for a generator. Hence, for us ammonia is a better choice economically. Also, ammonia offers better resolution and a shorter positron range," Dr. Buechel explains. *"So, even if I had both tracers available, I would choose ammonia."* Ammonia can be produced with a cyclotron that can be used to produce other radiotracers, such as ^{18}F-FDG.

Another advantage of ^{13}N ammonia PET, explains Dr. Buechel, is the lower patient radiation dose, which is advantageous for young patients. The ability to obtain quantitative absolute myocardial blood flow is also important for excluding microcirculatory dysfunction for example in diabetic patients.

Although ^{13}N ammonia has a longer half-life at 10 minutes than either ^{82}Rb or ^{15}O-H_2O, it still requires injection shortly after production. University Hospital Zurich has addressed this through scheduling and coordination with the production of FDG.

All cardiac ammonia exams are scheduled in the early morning or late afternoon—before and after the department uses the FDG that was produced overnight. One batch of ammonia is produced for two patients in the morning, and then several batches of ammonia are produced in the late afternoon after the daily FDG production is exhausted to accommodate another four to six cardiac patients.

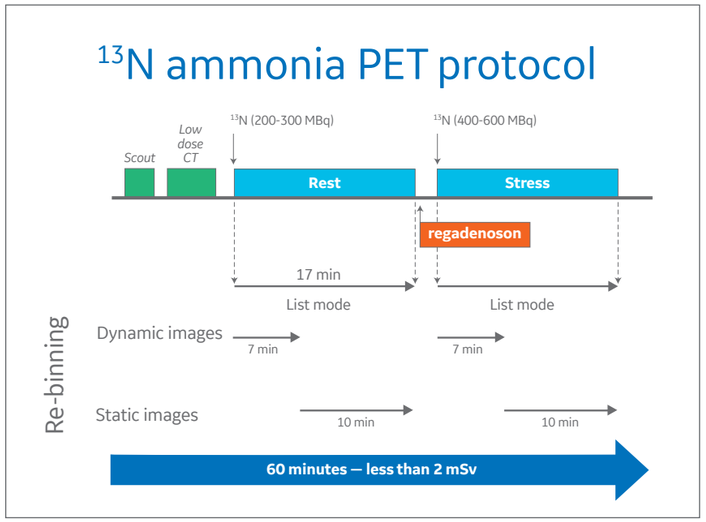

Figure 3: *Ammonia imaging protocol used at University Hospital Zurich, Switzerland.*

^{15}O-H_2O tracer

While ^{82}Rb and ^{13}N ammonia are most commonly used for cardiac PET imaging, ^{15}O-H_2O is the most accurate according to Professor Bouchelouche.

Driessen et al compared the characteristics of different PET tracers for myocardial perfusion imaging with PET[9] (see Figure 4). They found that ^{15}O-H_2O PET provided the highest accuracy for the diagnosis of myocardial ischemia (see Figure 5). Based on these results, the Department of Nuclear Medicine & PET Centre at Aarhus will shift from ^{82}Rb PET to ^{15}O-H_2O PET.

Specifically, Professor Bouchelouche adds, *"^{15}O-H_2O has excellent quantitation properties and is the 'gold standard' for measuring tissue perfusion, including myocardial perfusion."*

	$H_2{}^{15}O$	$^{13}NH_3$	^{82}Rb
Half-life	123 s	9.97 min	76 s
Production	Cyclotron	Cyclotron	Generator
Kinetics	Freely diffusible, metabolically inert	Metabolically trapped in myocardium	Metabolically trapped in myocardium
Mean positron range in tissue	1.1 mm	0.4 mm	2.8 mm
Data acquisition	Dynamic	Dynamic, static	Dynamic, static
Scan duration	6 min	20 min	6 min
Gating/LV function	–	+	+
Radiation dose	~0.4 mSv	~1 mSv	~3 mSv
Quantification	Excellent	Good	Moderate
Image quality	Good (parametric images)	Very good	Good

Figure 4: *Characteristics of PET tracers for myocardium perfusion imaging[9].*

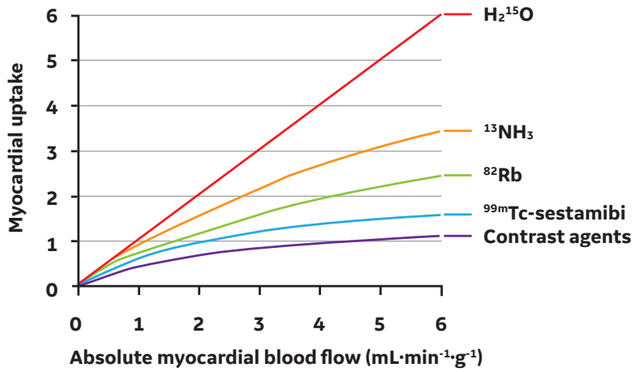

Figure 5: *Kinetics of myocardial perfusion tracers and contrast agent. Graphical presentation of the relationship between absolute myocardial blood flow and tracer uptake for currently available PET radiotracers. Also included are the kinetics of the commonly used SPECT radiotracer (^{99m}Tc-Sestamibi) as well as contrast agents for CT and CMR perfusion (i.e. iodine and gadolinium based contrast agent).*

We can create and align parametric images just like with Rubidium and SPECT.

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"^{15}O-water diffuses freely in and out of the cells," explains Professor Bouchelouche. *"While Rubidium PET provides suboptimal myocardial blood flow quantification, when there is a change in myocardial perfusion, we can see the similar change on the ^{15}O-water PET scan."*

The protocol for ^{15}O-H_2O PET is quite similar to ^{82}Rb PET (see Figure 6). It requires the use of a cyclotron. According to Professor Bouchelouche, it can be performed within 30 minutes like ^{82}Rb PET, however, it also delivers all the dynamic data needed with a lower dose to the patient and the staff at 400 MBq.

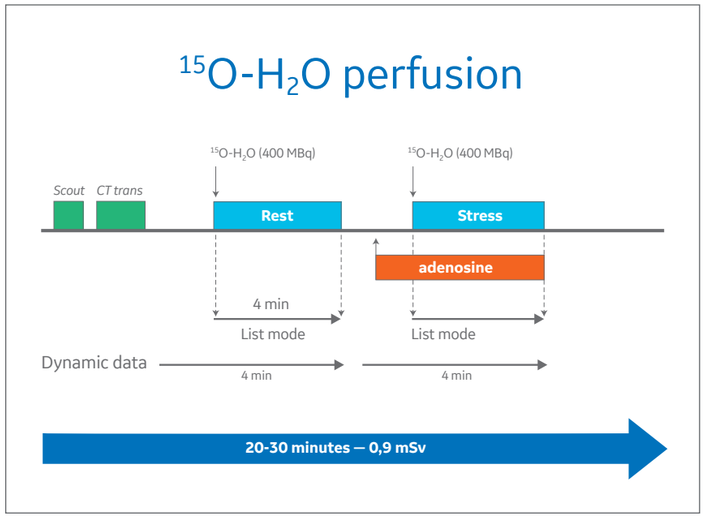

Figure 6: *^{15}O-water imaging protocol used at Aarhus University Hospital, Denmark.*

Recent advancements in software for ^{15}O-H_2O PET have made it easier for interpretation and reporting. An article by Harms et al comparing different commercially available software demonstrated excellent agreement and intra-observer reproducibility[10].

"We can create and align parametric images just like with Rubidium and SPECT," Professor Bouchelouche explains. *"We have all the absolute flow values at rest and stress, and the flow reserve, and everything is fully automated. It has been shown in a research study that ^{15}O-water PET delivers excellent results with very good reproducibility and very small interobserver and intraobserver variability[11]."*

The use of serial ^{15}O-H_2O PET has also been shown to be useful for evaluating treatment response in a study that compared PET to fractional flow reserve (FFR) measurements[12]. Left ventricular volumes and ejection fraction from ^{15}O-H_2O PET were found to have good correlation to cardiac MRI[13].

However, the very short half-life of ^{15}O-H_2O can be a barrier as it requires injection to be performed right after production of the radiotracer with a cyclotron located next door.

The availability and costs of cardiac tracers is a barrier to the adoption of cardiac PET. Institutions with in-house tracer production can expand their production to ammonia or water by adding the appropriate target. They can add cardiac tracer production runs after the completion of the FDG run as performed in Zurich with its PETtrace™ cyclotron that produces both FDG and Ammonia.

It is also possible to dedicate a small footprint cyclotron such as the MINItrace™ to the production of cardiac tracers. In both cases, the short lifetime of the isotopes, especially ^{15}O-water, requires the cyclotron to be located close to the scan room.

FDG viability

"We use ^{18}F-FDG for viability studies in combination with ^{82}Rb PET," says Professor Bouchelouche. *"In the future, we'll use ^{15}O-water for these studies instead of ^{82}Rb. FDG PET is used for discriminating between hibernating myocardium and scar tissue."*

Regional wall-motion	Rest perfusion	FDG-uptake	Diagnosis
Reduced	Reduced	Normal or increased	Hibernating myocardium
Reduced	Severe reduced	Reduced	Scar

Figure 7: *FDG cardiac PET imaging to discriminate between hibernating myocardium and scar tissue.*

While Acipimox plus oral glucose is the most common method used for FDG viability studies, Professor Bouchelouche and colleagues at Aarhus have found the optimal method is to use a hyperinsulinaemic-euglycaemic clamp. The patient is clamped and injected with a 20% glucose (variable infusion) 200 mg/ml and tested for blood sugar levels to keep it stable between 4 and 5 mmol/L. After one hour, FDG is injected. One hour later, the later the patient is placed in the PET/CT scanner without insulin infusion to avoid hypoglycemia in the scanner.

"I strongly recommend performing a stress test in a viability study because otherwise you may miss patients with reversible ischemia," Professor Bouchelouche explains. *"Reversible ischemia is not always in the same area with decreased rest perfusion so please perform more stress imaging in viability studies."*

I want the exam to be repeatable and give the same result with different readers. One way to achieve this is with quantitative data.

Dr. Ronny R. Buechel, MD,
Nuclear Medicine physician and cardiologist leading the Cardiac Imaging Division at the Department of Nuclear Medicine, University Hospital Zurich.

Quantitation

One of the most important benefits of PET MPI is the ability to obtain quantitation of the myocardial blood flow and flow reserve. Data from the PET scan can be used to estimate the K1 and obtain the absolute flow values in ml/min/g tissue.

"Most nuclear cardiac physicians will tell you that quantitation of the blood flow is key," says Dr. Buechel. *"Compared to traditional static imaging relying solely on relative perfusion differences within the myocardium, quantitation has a substantial impact on diagnostic accuracy."*

Without dynamic, quantitative PET data, it is possible to miss diffused impairment in the blood flow if a region is assumed to be normally perfused but is not, Dr. Buechel explains. *"If I perform a quantitative analysis and measure the absolute values, I'm not depending on a qualitative normal or abnormal diagnosis. I have the number, and from this I know if it is normal or not."*

In fact, Dr. Buechel adds that the sensitivity and specificity of PET MPI is higher with quantitation compared to both SPECT and MRI[5]. Yet, it is the reproducibility across readers that he believes is even more important.

"I want the exam to be repeatable and give the same result with different readers. One way to achieve this is with quantitative data," Dr. Buechel explains. *"If we have the numbers, then there is less room for interpretation in the analysis."*

With PET perfusion quantification, Professor Bouchelouche can obtain the absolute flow values at rest and stress, and the flow reserve. The absolute flow values that can be derived include the global values, regional values and segmental values.

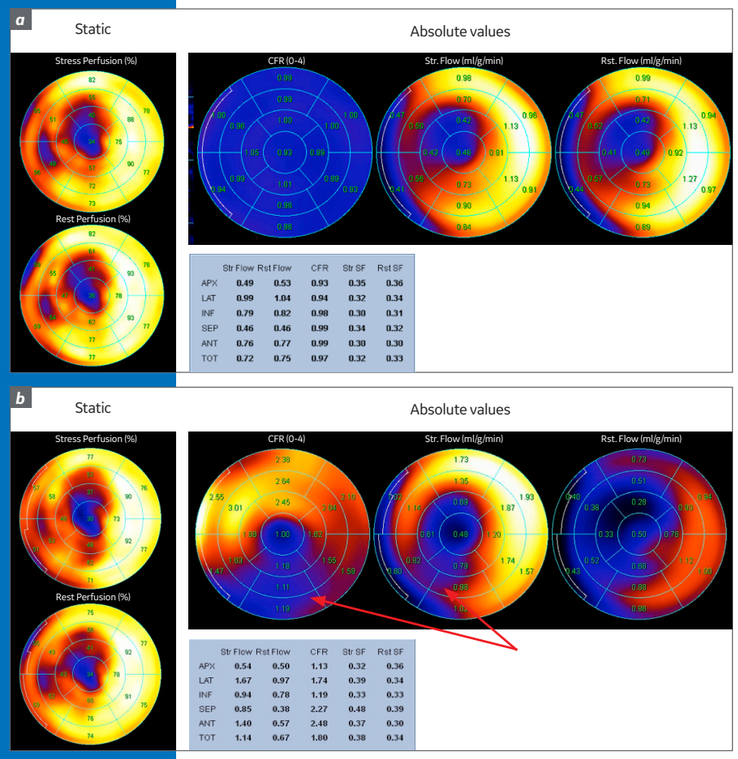

Figure 8: *Rubidium PET/CT data of a 69-year-old man who experienced a STEMI in 2012 treated with PCI of LAD and Cx and referred to PET/CT years later due to chest pain. In (a) static images only show scar tissue. Absolute flow values are unchanged between rest and stress due to either a severe balanced 3-vessel disease or to caffeine intake. Patient was then rescanned with strict instructions to abstain from any caffeine for 2 days prior to the test. Data in (b) demonstrate partial reversible defect (arrows). The patient was then referred to the CathLab for PCI.*

"Quantitation is very important, especially when you have a patient with three-vessel or small-vessel disease. You want to detect early impairment of myocardial perfusion and this is possible with PET quantitation," Professor Bouchelouche explains.

However, she cautions that when using ^{82}Rb, the clinician must be careful to not look at one single segment for the absolute flow values. Other factors, such as caffeine intake prior to the PET study, can impact the results as illustrated in Figure 8.

"If the patient has coffee prior to adenosine stress, it can mask reversible ischemia because it blocks the adenosine receptors," Professor Bouchelouche explains. However, reversible ischemia can be detected when using absolute quantification with cardiac PET.

Digital PET

As previously noted, the high image quality of the Discovery™ MI 4-ring and 5-ring digital PET/CT system enables both Dr. Buechel and Professor Bouchelouche to lower the amount of radiotracer used, and thus lower patient and operator dose as compared to Discovery 710 or equivalent. There is also an economic benefit to lowering patient dose: a facility can scan more patients with the same radiotracer production.

With the installation of two Discovery™ MI digital PET systems in 2016 that deliver higher image quality compared to the prior generation system, Dr. Buechel and his colleagues realized an opportunity to further lower patient dose. In 2017, the BMI-adjusted protocol was lowered to a range of 200-600 MBq of ^{13}N ammonia for both rest and stress, for an average patient dose of 1 mSv. According to Dr. Buechel, patient dose has been reduced by 50 percent compared to the protocol used with the prior system (see Figure 9).

Similarly, *"after installing the digital PET, we can obtain such excellent images that it is possible to further reduce the ^{82}Rb dose to 592 MBq, or 16 mCi, without any issues,"* explains Professor Bouchelouche.

While the lower dose is an important advantage, there are other benefits derived by using digital PET.

"The high image quality in digital PET is a tremendous step forward. In our experience, it helps when imaging patients with a high BMI of up to 50 or 60 kg/m^2," says Dr. Buechel.

In most cases, patients with this high of a BMI are being evaluated to exclude relevant ischemia. Using a traditional dose of the radiotracer, Dr. Buechel can achieve the quality results needed for a confident diagnosis.

Additionally, University Hospital Zurich recently upgraded its Discovery™ MI from 4-ring to 5-ring, providing an even higher sensitivity.

Using Q.Clear, GE's pioneering PET image reconstruction technology, provides up to two-times the improvement in SNR over OSEM, which may potentially be helpful when looking at scar tissue and ischemia.

Once you use digital PET/CT, it will be difficult to go back to analog. Actually, it's impossible in my opinion.

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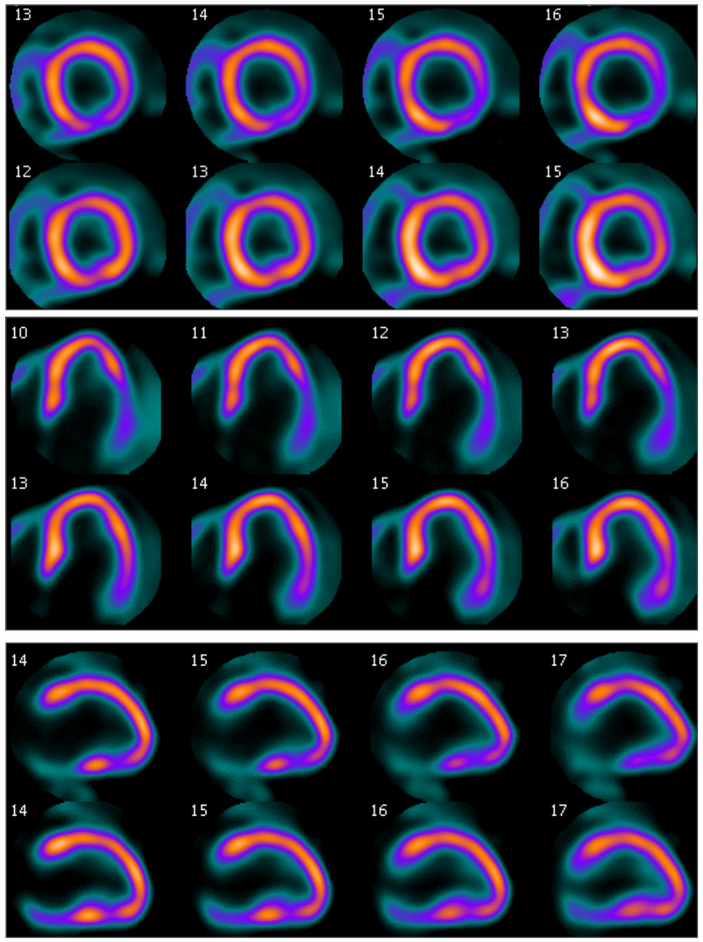

Figure 9: *Example of ^{13}N ammonia study acquired on Discovery MI after injection of 200MBq for rest study and 400MBq for stress study. Images present excellent resolution and contrast.*

Professor Bouchelouche also anticipates investigating the impact of Q.Clear on image quality, lesion detection and dose reduction compared to standard reconstruction methods. Currently, she reports that for a fixed administered ^{82}Rb dose of 30 mCi, the appropriate range of beta factors is 25-100 when using Q.Clear with ^{82}Rb PET.

A study by O'Doherty J et al found that Q. Clear reconstruction in [13N]-NH3 (^{13}N ammonia) cardiac PET data does not affect significantly the quantification of the rest MBF over all cardiac territories. Further, the use of Q.Clear reconstruction with a beta value above 300 produced images with less image noise compared to OSEM reconstruction[14**].

"It is amazing the excellent images we get from the digital PET," says Professor Bouchelouche. *"Once you use digital PET/CT, it will be difficult to go back to analog. Actually, it's impossible in my opinion."*

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* PET Radiopharmaceutical may not be approved by ministers of health in all regions

** Each article's results and conclusions only apply to that specific case, they are not able to generalized to any degree.

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