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***Pet Assessment of Cardiac Function: Current & Prospective  
Radiopharmaceuticals, and Clinical Applications***

Continuing Education for Nuclear Pharmacists and Nuclear Medicine Professionals

By

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# **PET ASSESSMENT OF CARDIAC FUNCTION: CURRENT & PROSPECTIVE RADIOPHARMACEUTICALS, AND CLINICAL APPLICATIONS**

## **STATEMENT OF LEARNING OBJECTIVES:**

1. Utilization of FDG as a tool for evaluation of cardiac function
2. Implications of FDG usage in particular patient populations
3. Understanding particular applications of other currently available PET agents.
4. Identification of new PET radiopharmaceuticals with potential utility in cardiac assessment.

## COURSE OUTLINE

<b>RADIOTRACERS .....</b>	<b>6</b>
<b>INDICATIONS.....</b>	<b>7</b>
LIMITATIONS OF CARDIAC PET .....	8
NOVEL TRACERS .....	9
FUTURE .....	9
<b>ASSESSMENT QUESTIONS .....</b>	<b>10</b>

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## **RADIOTRACERS**

Rubidium-82 is used for myocardial perfusion studies, where its short half-life (76 sec) allows for rapid rest/stress paired studies to be performed. This tracer can be produced from a column generator, with no need consequently for an in-house cyclotron. The image quality of  $^{82}\text{Rb}$  is sub-optimal due to its relatively long positron range. The short half-life of  $^{82}\text{Rb}$  necessitates PET instruments of high-efficiency so that statistically adequate images may be acquired. The short half-life has the advantage of interventional studies being carried out relatively rapidly, but again, the intervention needs to be pharmacologic – physiologic stress cannot be carried out as radioactive decay during the interval between injection and acquisition precludes adequate images.

Oxygen-15 labeled water ( $\text{H}_2^{15}\text{O}$ ) is perhaps the ideal physiologic tracer to estimate perfusion since water mirrors perfusion – the short half-life necessitates an in-house cyclotron, and the photon flux of  $^{15}\text{O}$  is also sub-optimal, with image quality being very poor. Its physiologic advantages are considerably compromised by its imaging characteristics, and the tracer is rarely used in myocardial imaging.

While the short half-life of  $^{13}\text{N}$  also necessitates production of  $^{13}\text{NH}_3$  in an in-house cyclotron, its excellent imaging characteristics have made it perhaps the most optimal tracer for the accurate measurement of myocardial blood flow. Moreover, the half-life, while short, is adequate for imaging after physiologic stress, further improving the utility of the agent. This tracer moves from the vascular space to tissue by both active transport (sodium-potassium pump) as well as by passive diffusion. Once inside cells, this tracer is primarily metabolized by the glutamic acid-glutamine pathway. The tissue retention fraction of  $^{13}\text{NH}_3$  from blood is rapid, resulting in high-contrast images.

Fluorine-18 labeled fluorodeoxyglucose (FDG) is the most widely used PET tracer today. FDG is transported by a number of glucose transporters into the cell, where it is phosphorylated by

hexokinase, all in a manner analogous to the cellular uptake of glucose. However, unlike glucose-6-phosphate, FDG-6-phosphate is not further metabolized and therefore accumulation of FDG is used as a surrogate marker for glucose utilization. While the myocardium does not constitutively utilize carbohydrates for energy (preferring fatty acids), in the satiated state FDG uptake in the viable myocardium is considerable and thus myocardial metabolism and hence viability may be assessed by FDG PET.  $^{13}\text{NH}_3$  studies are often combined with  $^{18}\text{FDG}$  to compare myocardial blood flow with glucose metabolism in an effort to detect "mismatch", an index of viable tissue.

In summary, therefore:

- Rb-82 is the most widely available radiotracer for perfusion assessment since there is no need for an in-house cyclotron and the ready availability of a generator for its production. Its short half-life limits intervention to pharmacologic agents.
- O-15 water requires an on-site cyclotron and yields images of sub-optimal quality, though it is the most representative for myocardial perfusion.
- N-13 labeled ammonia yields can be readily produced in in-house cyclotrons, yield images of excellent quality, and can be used with physiologic stress.
- FDG is an excellent indicator of myocardial viability, in the satiated state.

## **INDICATIONS**

Most Nuclear Cardiology studies involve myocardial perfusion and reserve, and are carried out with some form of intervention. While the intervention is usually physiologic, there are instances when pharmacologic intervention is necessary/preferred – these include agents that increase cardiac heart rate and output (in a manner analogous to physiologic exercise, dobutamine being the archetype), or coronary vasodilators (e.g. adenosine) that induce coronary “steal”, increasing relative flow to normally perfused areas and thus increasing the differential between normal and ischemic regions.

Most Nuclear Cardiology studies are SPECT studies, which have high sensitivity and specificity for double-vessel as well as single-vessel disease. SPECT cardiology typically is not very accurate in the detection of triple-vessel disease. The relatively low specificity of cardiac SPECT in triple vessel disease has been improved by the addition of attenuation correction methods, which minimize artifacts caused by breast attenuation as well as permit better estimation of diaphragmatic uptake. The continuing development of SPECT/CT cameras which allow for improved attenuation correction will no doubt increase the specificity of single photon imaging for Nuclear Cardiology.

Practically, PET currently has an extremely important advantage – the ability to get better contrast images in large patients – increasingly frequent in the USA. PET has at least 2 other distinct advantages over SPECT: a significantly better contrast (or signal:noise ratio) and the potential for quantification. These make PET particularly useful in those cases where complex clinical questions need to be answered in a non-invasive manner.

The short  $T_{1/2}$  of Rb-82 as mentioned above precludes its use with physiologic stress. Exercise has the advantage that electrocardiographic monitoring is also sensitive especially in non-obese males. While this may be mitigated in Rb-82 PET imaging by carrying out pharmacologic intervention using dobutamine, this is usually not practically feasible; the pharmacologic intervention of choice for Rb-82 cardiac PET has therefore been adenosine or dipyridamole. The short  $T_{1/2}$  of Rb-82 also necessitates administration of large amounts of radioactivity to obtain sufficient image statistics, which in turn demands PET instruments capable of handling high count rates.

N-13 ammonia obviates most of the above problems of Rb-82 – it has a short  $T_{1/2}$  that permits physiologic intervention studies yet does not make demands on PET instrumentation. However, an in-house cyclotron is necessary. While production can be carried out on most medical cyclotrons (including lower energy prototypes currently being tested), two cyclotron runs are necessary – one at baseline and one after intervention – for every patient, which poses demands on cyclotron staff.

FDG PET is probably the most accurate method for assessment of myocardial viability and is currently used in instances when stunned or hibernating myocardium is suspected. Since the fasting myocardium constitutively utilizes fatty acids for energy, it is important to ensure that the patient has been adequately fed prior to FDG imaging.

### **Limitations of cardiac PET**

The success of cardiac SPECT is probably the single most important reason for the limited utilization of cardiac PET. Another important reason is the inability of most PET units to carry out quantitative estimates of myocardial perfusion or viability. Quantification would increase the accuracy of triple-vessel disease detection and considerably enhance the utility of cardiac PET. Availability of radiotracer and of adequate instrumentation are other issues that are probably consequences of an uneven supply and demand cycle.

## **Novel tracers**

Positron-labeled fatty acids have the potential to be extremely useful in the evaluation of myocardial energy utilization – as noted above, the fasting heart constitutively utilizes fatty acids. Sympathetic enervation may also be assessed by measurement of norepinephrine transport – the availability of I-124 and the increasing feasibility of high specific activity I-124 mIBG production have renewed interest in this imaging modality.

While cardiac PET imaging has focused on the heart, the increasing awareness of the importance of atherosclerotic plaque in the evolution of myocardial and other vascular events has stimulated the development of various “plaque imaging” agents.

## **Future**

Cardiac PET is under-utilized, largely owing to the success of cardiac SPECT. Limitations concerning both radiotracers as well as PET equipment have further precluded rapid development of this modality. It is likely that cardiac PET will gain utility as PET itself becomes more ubiquitous, and as the identification of those patients unlikely to benefit from SPECT, and most likely to benefit from PET, will be part of the paradigm of the evaluation of patients with cardiac and vascular disorders. SPECT is here to stay, and developments in cardiac CT (CTA) will also limit enthusiasm for cardiac PET development. The inherent sensitivity of PET will however sustain interest in the development of this extremely important tool for cardiovascular molecular imaging.

## ASSESSMENT QUESTIONS

1. Rubidium-82 is used in myocardial perfusion studies for rapid rest/stress paired studies. An advantage of using Rb-82 is:
  - a. a half-life useful for exercise stress tests.
  - b. production onsite from a column generator.
  - c. small amounts of radioactivity are required for imaging.
  - d. it is highly cost effective radiopharmaceutical.
  
2. Oxygen-15 labeled water is rarely used for myocardial imaging since:
  - a. the half-life is too long for PET imaging.
  - b. the photon-flux is sub-optimal with poor image quality.
  - c. it is produced from a column generator.
  - d. it is very difficult to produce in usable amounts.
  
3. Nitrogen-13 labeled ammonia provides an accurate measurement of myocardial blood flow. High contrast images result from:
  - a. rapid tissue retention fraction from the blood.
  - b. rapid phosphorylation of the radiopharmaceutical.
  - c. rapid active transport of a phosphate analog.
  - d. high affinity of ammonia for myocardium.
  
4. The majority of nuclear cardiology studies are SPECT studies because they:
  - a. are much more profitable than other modalities
  - b. have high sensitivity and specificity for double-vessel disease.
  - c. get better contrast images in large patients.
  - d. are more suitable for pharmacological stress.
  
5. FDG PET is probably the most accurate method for assessment of myocardial viability. An important explanation for the limited utilization of cardiac PET for this purpose is:
  - a. an inability to carry out quantitative estimates of perfusion or viability.
  - b. the poor evaluation of myocardial energy utilization in obese patients..
  - c. the interference of atherosclerotic plaque in imaging double vessel disease.
  - d. the complicated chemical reactions in radiopharmaceutical preparation.