INVITED REVIEW

Review: comparison of PET rubidium-82 with conventional SPECT myocardial perfusion imaging

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Summary

Nuclear cardiology has for many years been focused on gamma camera technology. With ever improving cameras and software applications, this modality has developed into an important assessment tool for ischaemic heart disease. However, the development of new perfusion tracers has been scarce. While cardiac positron emission tomography (PET) so far largely has been limited to centres with on-site cyclotron, recent developments with generator produced perfusion tracers such as rubidium-82, as well as an increasing number of PET scanners installed, may enable a larger patient flow that may supersede that of gamma camera myocardial perfusion imaging.

Introduction

Myocardial perfusion imaging (MPI) has been a cornerstone in the assessment of patients with known or suspected coronary artery disease (CAD). Single photon emission computed tomography (SPECT) is a well-established modality for the diagnosis and risk stratification of patients suspected for ischaemic heart disease (Navare et al., 2004). In the mid-1970s, the discovery of thallium-201 (201TI) made it possible to provide information on myocardial perfusion, objectively and non-invasively (Zaret & Cohen, 1977). 201TI, being a relatively good perfusion tracer, is not optimal for clinical cardiac imaging due to high radiation burden and low energy emission with poorer image quality. With the introduction of technetium-99m (99mTc) labelled perfusion tracers (99mTc-sestamibi and 99mTc-tetrofosmine), there were now clear alternatives to 201TI. 99mTc, with a photo peak of 140 keV, has optimal energy for gamma camera detection. The half-life of 6 h enables administration of higher activity and results in better count statistics and picture quality with enhanced signal-to-noise ratio compared with 201TI. The continuous development in cardiac software applications has facilitated the measurements of wall thickening, left ventricle ejection fraction (LVEF) and wall movement of the left ventricle.

With positron emission tomography (PET) scanners being installed in large numbers in North America, Japan and Europe in recent years, primarily driven by the high demand for 18F-fluorodeoxyglucose (18F-FDG) PET imaging in oncology, more and more departments can offer cardiac PET. Thus, with readily available tracers, PET is now regarded a usable alternative to conventional cardiac SPECT with rubidium-82 (82Rb) becoming the most widely used radionuclide for the assessment of myocardial perfusion with PET.

The classical myocardial scintigraphy

In Europe, the 99mTc-based tracers are most commonly used for cardiac SPECT. 99mTc is extracted from blood circulation and accumulated in mitochondria of the myocyte. Image acquisition is obtained by rotating detectors, constituting SPECT. The prognostic and diagnostic values of cardiac SPECT in patients with ischaemic heart disease are well established (Hesse et al., 2008; Marcassa et al., 2008). Recently cardiac SPECT was highlighted in European Society of Cardiology Guidelines on myocardial revascularization with class 1A recommendation for use in patients with intermediate pretest likelihood of obstructive coronary disease (Wijns et al., 2010).

Subjects performing exercise cardiac SPECT with a normal results – with the exception of patients with diabetes or chronic renal failure – have a very good prognosis and a one-year risk for death or non-fatal myocardial infarct of <1%, while patients with an abnormal test results have a corresponding risk of 6% (Shaw & Iskandrian, 2004; Venkataraman et al., 2008). However, patients undergoing a pharmacological stress test are at a higher risk for subsequent cardiac events, regardless of a normal perfusion imaging result, compared...
with subject performing exercise cardiac SPECT (Navare et al., 2004).

The ability of cardiac SPECT to examine ischaemia, viability and left ventricle function makes it a well-validated, valuable and cost-effective clinical tool for the evaluation of ischaemic heart disease (Klocke et al., 2003; Hachamovitch et al., 2004).

However, SPECT displays a number of disadvantages compared with PET. Non-uniform attenuation artefacts and the low heart-to-background ratio of SPECT reduce the specificity to detect coronary artery disease (Tamaki et al., 1988; Rigo et al., 1998; Aarnoudse et al., 2003). However, the use of transmission scan with CT or radioactive sources has improved diagnostic accuracy (Kjaer et al., 2002). Furthermore, cardiac SPECT permits only semi-quantitative measurements of changes in regional perfusion, and in the case of subjects with balanced ischaemia (i.e. three vessel disease, microvascular disease) or submaximal hyperaemia due to intake of methylxanthine containing food or beverages (i.e. coffee) prior to pharmacologic stress with dipyridamole, adenosine or regadenosone, a false-negative result is likely due to homogenous tracer uptake (Ito et al., 2003; Lima et al., 2003; Storto et al., 2009).

**Positron emission tomography**

The radionuclide tracers utilized in PET all decay by emission of positrons. The positron is emitted from the nucleus and rapidly looses kinetic energy before colliding with an electron. Both particles annihilate and emit 2 gamma rays with energies of 511 keV. The two gamma rays travel in opposite directions with a relative angle very close to 180 degrees. Thus, if the ring of detectors surrounding the patient in a PET scanner detects a coincidence pair of 511 keV gamma rays, it is registered as an event. When many such events are detected, the activity distribution of the positron-emitting radionuclide within the volume of interest (e.g. the left ventricle) may be constructed. Cardiac PET provides better spatial resolution and sensitivity compared with cardiac SPECT and has the ability of robust attenuation correction. Reliable attenuation correction methods for PET require determination of an attenuation map, which represents the spatial distribution of linear attenuation coefficients at 511 keV.

After the attenuation map is generated, it can be incorporated into image reconstruction algorithms to correct the emission data for errors contributed by photon attenuation. Attenuation maps are usually generated by transmission scanning using external radionuclide sources or in recent years with the availability of PET/CT scanners based on X-rays.

PET has a higher sensitivity than SPECT. SPECT is limited by collimation, whereas PET is limited by high photon energy. A typical detection efficiency for a collimated SPECT detector is in the order of 0-01%, whereas modern three-dimensional (3D) PET scanners have detection efficiencies around 0.5% or higher (Di Carli, 2007; Rahimim & Zaidi, 2008).

The most common perfusion tracers for clinical cardiac PET are $^{18}$O-labelled ammonia ($^{13}$NH$_3$), $^{82}$Rb and $^{15}$O-labelled water (H$_2$O; Schelbert et al., 1982; Selwyn et al., 1982; Walsh et al., 1988). $^{13}$NH$_3$ and H$_2$O production needs a cyclotron, thereby limiting the availability to larger centres with in-house cyclotrons, and the tracers are primarily used for research due to a laborious workflow.

$^{82}$Rb is a potassium analogue that is generator produced with a physical half-life of 75 s and kinetic properties similar to those of $^{203}$Tl (Di Carli & Lipton 2007). Its parent radionuclide is strontium-82 ($^{82}$Sr), which has a physical half-life of 26 days. Consequently, the $^{82}$Sr/$^{82}$Rb generator only needs to be replaced every 4–6 week. The short physical half-life of $^{82}$Rb and the rapid reconstitution of the generator allow fast sequential perfusion imaging and high patient throughput.

After intravenous injection, $^{82}$Rb rapidly crosses the capillary membrane. Myocardial uptake of $^{82}$Rb requires active transport via the sodium/potassium adenosine triphosphate transporter, which is dependent on coronary blood flow (Selwyn et al., 1982). The single-capillary transit extraction fraction of $^{82}$Rb exceeds 50%. However, as other non-diffusible tracers, its net extraction fraction decreases in a nonlinear fashion with increasing myocardial blood flow (Selwyn et al., 1982; Goldstein et al., 1983; Mullani et al., 1983). However, quantification of myocardial blood flow with $^{82}$Rb was validated against H$_2$O and found to be accurate at high flow rates (Prior et al., 2012).

The maximum kinetic energy of positrons emitted during $^{82}$Rb decay is significantly higher than that of $^{18}$F or $^{18}$O. Consequently, the spatial uncertainty in the location of the decaying nucleus – which depends on the distance travelled by the positrons before their annihilation (positron range) – is greater for $^{82}$Rb (mean positron range 2-6 mm) than for $^{18}$F (0.2 mm) or $^{18}$O (0.7 mm; Di Carli, 2007). Although $^{82}$Rb imaging yields excellent image quality with current PET technology, its longer positron range and its short half-life, which requires significant image smoothing to suppress noise, both mitigate somewhat the improved spatial resolution of PET.

As indicated earlier, cardiac SPECT possesses great qualities in diagnosis of ischaemic heart disease (IHD). Several studies report the sensitivity and specificity of cardiac SPECT for detecting an angiographically significant stenosis of >50% to be 87% [95% confidence interval (CI) 71–97%], and 73% (CI 36–100%), respectively (Klocke et al., 2003). Corresponding sensitivity and specificity for cardiac perfusion PET are reported to be 91% (CI 83–100%) and 89% (CI 73–100%), respectively (Di Carli et al., 2007b).

In a recent systematic review and meta-analysis evaluating the accuracy of $^{82}$Rb PET for the diagnosis of obstructive coronary artery disease in comparison with cardiac SPECT, 15 $^{82}$Rb- PET and eight cardiac SPECT studies were reviewed (Mc Ardle et al., 2012). $^{82}$Rb- PET demonstrated sensitivity and specificity of 90% and 88% for the detection of obstructive coronary disease on invasive coronary angiography (Fig. 1).
$^{82}\text{Rb}$ PET was demonstrated to have superior accuracy in comparison with $^{99}\text{mTc}$-SPECT with both ECG-gating and attenuation correction (Mc Ardle et al., 2012).

PET quantification of myocardial blood flow is well validated using $^{13}$N-ammonia (Kuhle et al., 1992; Muzik et al., 1993; Nitzsche et al., 1996). Quantitative approaches with $^{82}$Rb are more challenging because of its very short physical half-life and, thus, decreased image signal-to-noise ratio, leading to noisy and inconsistent time–activity curves that can affect the accuracy of myocardial perfusion estimates. However, the use of noise-reduction methods improves the accuracy and precision of measurements of myocardial blood flow (Lin et al., 2001a,b). Validation studies of $^{82}$Rb in humans have been performed and have shown high accordance with $^{13}$NH$_3$ perfusion values (El Fakhri et al., 2009), the latter has previously been well validated with microspheres (Schelbert et al., 1979).

Quantifying myocardial blood flow and the coronary flow reserve (CFR) have been determined by dynamic acquisition and tracer kinetic models (Parkash et al., 2004; Di Carli et al., 2007b).

PET has the capability to quantify flow in absolute terms (ml min$^{-1}$ g$^{-1}$) during stress and rest, the ratio of which is also known as the coronary flow reserve (Fig. 2) (CFR; Camici & Crea, 2007; deKemp et al., 2007). Measurement of CFR may have a role in early detection of coronary atherosclerotic

Figure 1 $^{82}$Rb Cardiac PET: pharmacological stress test (adenosine) and rest test of a patient with suspected ischaemic heart disease. Significant decreased activity in stress test in LAD supply area, indicating reversible ischaemia. Patient was referred to invasive cardiac unit, resulting in stenting of a 95% narrowing of LAD. $^{82}$Rb isotope administered during pharmacological stress and rest. Static recordings for 7 min in both phases. Upper row: pharmacological stress cardiac test. Lower row: rest test. Bulls Eye plots in 17 segments for both stress and rest test. LAD: Left anterior descending artery.
disease (microvascular dysfunction) or reveal the presence of diffuse (balanced) obstructive CAD (Parkash et al., 2004; Camici & Crea, 2007). Although this approach has been firmly established in research settings almost three decades ago (Schelbert et al., 1981), a widespread use in the clinical setting has still to be realized. Even so, there is growing interest in its potential added value due to the current limitations of relative MPI in these settings. Recently, one of the first studies to evaluate the prognostic value of PET-derived quantification of CFR using $^{13}$NH$_3$ in patients with suspected ischaemia and one of the first studies to evaluate its added prognostic value compared with relative MPI were published (Herzog et al., 2009). The effect of CFR may be hampered when imaging with $^{82}$Rb because of the nonlinearity between actual myocardial blood flow and $k_1$ (measured flow). Nonetheless, in a recently published paper, impaired CFR was an independent risk in symptomatic patients with a normal PET MPI (Naya et al., 2013). Confirming this in patients with known or suspected CAD, a multicenter observational study showed that the extent and severity of ischaemia and scar on PET MPI provided incremental risk estimates of cardiac death and all-cause death compared with traditional coronary risk factors (Dorbala et al., 2013). Later several studies have shown the value in demonstrating subclinical abnormalities in myocardial blood flow or CFR in multiple patient cohorts including obese patients, diabetics, smokers, patients with hypertension and HIV-infected patients (Kaufmann et al., 2000; Kjaer et al., 2003, 2005; Schindler et al., 2006, 2009; Kristoffersen et al., 2010;
Cardiac radionuclide imaging (SPECT and PET) cannot visualize atherosclerotic changes in the coronary arteries per se (Schuijf et al., 2006; Di Carli et al., 2007a,b). Computed tomography coronary angiography (CTA) appears superior to PET or SPECT in estimating atherosclerosis and stenosis in the coronary vessels. Hence, the latest hybrid PET/CT scanners, similar to SPECT/CT, allow a genuine integration of anatomy and physiology, which may provide improved risk stratification (van Werkhoven et al., 2009). Several studies confirm the expediency of hybrid PET/CT scanners in detecting CAD and viably myocardium in chronic and new-onset heart failure, thus facilitating the determination of heart failure aetiology and guiding a therapeutic strategy (Sheikine & Di Carli, 2008). Coronary artery calcification (CAC) by CT and MPI, either by SPECT or PET, has also demonstrated complementary applications in hybrid scanners. For example, increasing CAC scores add to risk of adverse events in patients with and without ischaemia on PET MPI (Schenker et al., 2008). In selected patients, hybrid imaging may aid in more accurate diagnosis, risk stratification and management in a ‘single point of contact’ setting (Hsiao et al., 2010).

In contrast to cardiac SPECT, image acquisition starts immediately after infusion of 82Rb in cardiac PET. ECG gating under pharmacological stress test can therefore reveal LVEF and wall motion in close relation to peak hyperaemia. ECG-gated studies suggest that subjects without CAD exhibit a rise in LVEF during pharmacological adenosine stress. Subjects with IHD display a rise in LVEF that is inversely correlated with the degree of coronary artery stenosis determined by coronary angiography (Dorbala et al., 2007). In addition, subjects with 3-vessel or left main coronary artery (LM) disease may demonstrate a drop in LVEF under pharmacological stress test, without necessarily displaying perfusion abnormalities. This could prove to be a vital diagnostic and prognostic tool (Dorbala et al., 2007).

More recently, a F-18-labelled perfusion tracer was introduced for MPI with PET (Madar et al., 2006; Huisman et al., 2008). Flurpiridaz, such as FDG, may be distributed to provincial hospitals, in which a cyclotron is not available. Thus, cardiac PET MPI can be performed without a cyclotron and without the costly 86Sr/82Rb-generator, which demands a high patient flow. However, the costs of Flurpiridaz remain unclear. The radiotracer has a high first-pass extraction fraction of 94% and is currently being evaluated in phase three clinical studies. The 110-min half-life of 18F permits its distribution as a single-unit dose on a daily basis. Moreover, the longer half-life of 18F allows the application of the perfusion agent during treadmill exercise, rather than with vasodilator stress alone, as is currently the case with 82Rb PET myocardial perfusion studies. However, compared with 82Rb, it is not possible to perform both rest and stress imaging within 30 min.

### Radiation dosimetry

PET positron emission tracers usually lead to lower radiation exposure than SPECT tracers, mostly driven by shorter half-life of PET tracers. See Table 1. Effective dosages at routine examinations with PET tracers at rest and exercise myocardial perfusion tests are lower than SPECT (Thompson & Cullom, 2006). Due to differences in tracer administration and form, the radiation dose for the staff is approximately six times lower at a combined rest and stress test, compared with a 2-day protocol with 99mTc-labelled tracer (Clarke et al., 1997; Schleipman et al., 2006). PET is therefore superior to SPECT regarding radiation dosage (Senthamizhchelvan et al., 2010).

The typical effective dose to a patient receiving 2 × 1110 MBq 82Rb is 2.8 mSv, and with additional attenuation CT and calcium score CT, the total effective dose is 3.2–5.2 mSv (Senthamizhchelvan et al., 2010). The total dose to staff per patient (from routine stress and rest test) is 0.6 μSv (2 × 1110 MBq 82Rb) versus 3.1 μSv (2 × 700 MBq 99mTc sestamibi). However, staff members may be exposed to higher radiation doses, in both modalities, if a medical emergency requiring staff intervention occurs (Davidson et al., 2011).

| Radio pharmacy | Half-life | Procedure | Effective dose (μSv/MBq) | Dose, MBq | Effective dose, mSv |
|----------------|----------|-----------|--------------------------|-----------|---------------------|
| 99mTc-sestamibi | 6 h      | Rest      | 9-0                      | 700–900   | 6-3-8-1             |
| 99mTc-tetrofosmine | 6 h | Rest      | 7-9                      | 700–900   | 5-5-7-1             |
| 201TI          | 73 h     | Rest/Stress| 7-6                      | 700–900   | 5-3-6-8             |
| 13NH3          | 10 min   | Rest/Stress| 7-0                      | 700–900   | 4-9-6-3             |
| 82Rb           | 75 s     | Rest/Stress| 1-25                     | 1100–1500 | 1-4-1-9             |
| H2 15O        | 112 s    | Rest/Stress| 0-93                     | 700–1500 | 0-7-1-4             |

99mTc, technetium-99m; 201TI, thallium-201; 13NH3, 13N-labelled ammonia; 82Rb, rubidium-82; H2 15O, 15O-labelled water; μSv, microSivert; mSv, millisivert; MBq, megabecquerel.

Rest: cardiac perfusion imaging obtained during rest. Stress: cardiac perfusion imaging obtained during pharmacological and/or exercise stress test.
Economy

PET and SPECT

At Rigshospitalet, Copenhagen University Hospital, we estimate a demand of approximately 15 examinations per week with $^{82}$Rb. The costs generated (generator + infusion system + disposables) are around 400€ per patient, whereas cardiac SPECT is 230€. However, it is expected that logistical efficiency will increase and lower the costs of personnel with a 1-day protocol operating PET as opposed to 2-day protocol narrowing the difference in price between PET and SPECT further. The traditional rest/stress cardiac SPECT can also be performed in a 1-day protocol. However, the protocol is somewhat inefficient, often taking 3–5 h to complete. This limits ability to control costs (Bateman, 2012).

Another important aspect is the reimbursement generated by PET and SPECT, respectively. A study from 2007 examined downstream invasive procedure utilization of diagnostic arteriography, comparing PET to SPECT. They concluded that cardiac PET in patients with intermediate pre-test likelihood of CAD resulted in a 50% reduction in invasive coronary arteriography and coronary artery bypass grafting, a 30% cost savings, and excellent clinical outcome at 1 year compared with SPECT (Merhige et al., 2007).

Conclusion

PET myocardial perfusion imaging with $^{82}$Rb has a number of advantages: improved image quality, higher diagnostic accuracy, less radiation dose to patient and staff as well as rapid examinations time. With the fast propagation of combined PET/CT scanners, we anticipate an increase in PET myocardial perfusion imaging in Europe.

Conflict of interest

The authors have no conflicts of interest.

Authors contribution

All authors contributed to the review and approved the final version of the article.

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