Current and Future Clinical Applications of Cardiac Positron Emission Tomography

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Nuclear imaging, predominantly with single-photon emission tomography, has established and demonstrated value for the assessment of cardiovascular disease (CVD). Formerly, the clinical application of positron emission tomography (PET) was precluded by methodological complexity, high operating costs and lack of widespread availability. However, as PET and radiotracer development technologies have improved and continue to do so, PET is expected to become a mainstay diagnostic cardiovascular imaging modality. Not only is PET imaging of great importance for routine clinical decision-making and diagnosing CVD, it is also gaining prominence in fundamental and translational research models. The scope of this review is to summarize the state-of-the-art advances in PET imaging methodology, clinical utility and potential future application. (Circ J 2013; 77: 836–848)

Key Words: Inflammation imaging; Myocardial perfusion imaging; Myocardial viability imaging; Noninvasive imaging; Positron emission tomography

First demonstrated more than 30 years ago for the evaluation of myocardial perfusion, the clinical value of cardiac positron emission tomography (PET) imaging has continued to evolve. Because PET uses radiotracers that mimic the actions of molecules naturally occurring within the body, it provides a window into the complex mechanisms acting within the heart at the molecular level. Therefore, PET can be used to identify metabolic, neurologic, or vasoactive processes that underlie the pathophysiology of multiple cardiomyopathies and atherosclerosis. As radiotracer development technologies further advance, novel and specific radiotracers for the evaluation of cardiovascular disease (CVD) are expected to emerge and contribute towards further propelling the clinical application of cardiac PET.

In this state-of-the-art review, we will discuss the rationale of cardiac PET and present an overview of the radiotracers currently being utilized in clinical practice. We will also focus on current and future developments within this field of cardiovascular imaging.

Rationale of PET

PET enables imaging and evaluation of the cardiovascular system at multiple levels, including perfusion, metabolism, sympathetic innervation and inflammation. This is all feasible because the radiotracers used for PET comprise molecules labeled with positron-emitting radionuclides and these radiolabeled molecules are analogous to molecules naturally occurring within the body. Thus, it is feasible to specifically interrogate a process of interest and non-invasively image it.

In contrast to single-photon emission tomography (SPECT) cameras, positron decay can be localized without the need for collimation. Therefore, PET cameras are more sensitive than SPECT cameras. The spatial resolution of current PET cameras is within the range of 4–7 mm. In addition, PET systems incorporate algorithms that correct for photon attenuation and scatter. Attenuation correction can be accurately and reliably achieved with PET either using radioactive sources on older scanners or CT on more recent “hybrid” scanners.

Typically, both static perfusion images averaged over the entire acquisition, as well as ECG-gated images, are acquired for the evaluation of left ventricular (LV) function and wall motion. With more recent PET systems, list mode data acquisition is used whereby all detected coincidences are recorded and ECG-gated and static images are obtained simultaneously. Furthermore, current cameras use 3-D technology whereby the septa can be retracted, or are absent altogether, and novel software is used for improved scatter correction. These advances, in turn, increase count sensitivity and contribute towards improved image quality. “Time of flight” technology enables more accurate localization of the initial annihilation.
reaction along the line of coincidence detection, thereby improving spatial resolution. These approaches offer several important advantages and many are now available on the most recently developed PET systems. However, the effect on overall diagnostic accuracy has not yet been as well determined.

**Myocardial Perfusion Imaging**

**Myocardial PET Perfusion Tracers: \(^{13}\text{NH}_3\), \(^{82}\text{Rb}, \(^{15}\text{O-water}\)**

Radiotracers used for myocardial perfusion imaging (MPI) for PET include rubidium-82 (\(^{82}\text{Rb}\)), nitrogen-13 ammonia (\(^{13}\text{NH}_3\)) and oxygen-15 water (\(^{15}\text{O-water}\)) (Table). Within North America, the most commonly used perfusion imaging tracers in the clinical setting are \(^{82}\text{Rb}\) and \(^{13}\text{NH}_3\), both of which have received U.S. Food and Drug Administration approval. \(^{15}\text{O-water}\) is an alternative perfusion tracer that diffuses freely between the blood pool and myocardium, making it the ideal radiotracer for quantitative flow measurement. However, it has an extremely short half-life and poor image contrast between blood pool and myocardium, resulting in difficulty with obtaining clear static perfusion images. \(^{15}\text{O-water}\) is primarily used for research purposes in North America, with some clinical application in Europe.

Increasingly, \(^{82}\text{Rb}\) is being used in the clinical setting. It is produced using a strontium-82/\(^{82}\text{Rb}\) generator system and thus does not need a cyclotron for its production. The use of \(^{82}\text{Rb}\) is most cost-effective and justified in high volume centers where 30–40 patients can be imaged on a weekly basis. \(^{82}\text{Rb}\) has a half-life of 76s, resulting in very low radiation dosimetry (effective dose of approximately 2mSv for a rest/stress protocol with CT attenuation correction), but also has the disadvantage of rendering exercise stress testing impractical. Furthermore, in comparison with other PET radiotracers, \(^{82}\text{Rb}\) has the lowest first-pass extraction (Table). This may contribute towards reduced uptake at high flow rates, which can limit sensitivity for detecting mild flow-limiting stenosis, although its accuracy is still superior to SPECT and its prognostic value has been well shown. Finally, \(^{82}\text{Rb}\) also has low spatial resolution relative to other radiotracers and the highest positron range.

\(^{13}\text{NH}_3\) production requires an onsite cyclotron but provides high-contrast resolution images because of the combination of a high first-pass myocardial extraction fraction of 80% (>90% initial extraction) and relatively long half-life of 10 min. Both of these properties enable utilization of \(^{13}\text{NH}_3\) for exercise stress testing. \(^{13}\text{NH}_3\) also offers good accuracy for measuring absolute myocardial blood flow (MBF), but is less practical than \(^{82}\text{Rb}\) because it requires a cyclotron.

\(^{15}\text{O-water}\) is a novel radiotracer that is currently undergoing evaluation in a Phase 3 trial. Given that it is an \(^{15}\text{F}\)-labeled compound, a cyclotron is required for production. \(^{15}\text{F-flurpiridaz}\) has a longer half-life of 110 min, which affords the option of centralized production and distribution to individual centers within close proximity. Moreover, \(^{15}\text{F-flurpiridaz}\) is also suitable for exercise stress testing; has superior spatial resolution because of its very short positron range, as well as high first-pass extraction even at increased flow rates, rendering it ideal for flow quantification.

In Japan, as of April 2012, \(^{13}\text{NH}_3\) has received approval from the Japanese Ministry of Health, Labor and Welfare for including \(^{13}\text{NH}_3\) within health insurance coverage plans for the assessment of CAD. However, it is recommended that the use of \(^{13}\text{NH}_3\) should be limited to cases in which standard SPECT imaging is not sufficient to detect CAD. \(^{82}\text{Rb}\) has not yet received approval.

**Diagnostic Accuracy of PET-MPI for the Detection of CAD**

With SPECT, stress and rest MPI are commonly performed to evaluate for the presence of either myocardial ischemia (reversible defects) and/or infarction (fixed defects). Compared with SPECT imaging, PET-MPI provides great-

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**Table. Characteristics of Cardiac Positron Emission Tomography Perfusion Radiotracers**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>(^{82}\text{Rb})</th>
<th>(^{13}\text{NH}_3)</th>
<th>(^{15}\text{O-water})</th>
<th>(^{15}\text{F-flurpiridaz})*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>1.27 min</td>
<td>9.97 min</td>
<td>2.04 min</td>
<td>110 min</td>
</tr>
<tr>
<td>Initial Extraction (flow)</td>
<td>40–70% (stress-rest)</td>
<td>94–98% (stress-rest)</td>
<td>95–100% (stress-rest)</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Retention fraction (uptake)</td>
<td>30–55% (stress-rest)</td>
<td>60–90% (stress-rest)</td>
<td>Not retained in tissues</td>
<td>60–90% (stress-rest)</td>
</tr>
<tr>
<td>Production method</td>
<td>(^{82}\text{Sr/Rb}) generator</td>
<td>Cyclotron</td>
<td>Cyclotron</td>
<td>Cyclotron</td>
</tr>
<tr>
<td>Advantages</td>
<td>Commercially available generator product</td>
<td>High contrast resolution</td>
<td>Ideal for flow quantification</td>
<td>High contrast resolution</td>
</tr>
<tr>
<td></td>
<td>Capability to assess quantitative flow</td>
<td>Capability to assess quantitative flow</td>
<td>(Freely diffusible)</td>
<td>Potential Capability to assess quantitative flow</td>
</tr>
<tr>
<td></td>
<td>Short half-life for rapid testing</td>
<td>Potential for use with exercise</td>
<td>Short half-life for rapid testing</td>
<td>Potential for use with exercise</td>
</tr>
<tr>
<td></td>
<td>Low radiation</td>
<td>Low radiation</td>
<td>Low contrast resolution</td>
<td>Can be distributed from central production</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Long positron range – lower resolution</td>
<td>Needs on-site cyclotron</td>
<td>Needs on-site cyclotron</td>
<td>Not yet commercially available</td>
</tr>
<tr>
<td></td>
<td>Lower retention at higher flow rates</td>
<td>Moderate retention at higher flow rates</td>
<td>Short half-life – cannot do exercise</td>
<td>Moderate retention at higher flow rates</td>
</tr>
<tr>
<td></td>
<td>Short half-life – cannot do exercise</td>
<td>Heterogeneity; retention in the lateral wall – 10% less</td>
<td>Low contrast resolution</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Tissue equilibrium with blood pool)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{82}\text{Rb}, \text{rubidium-82}; \(^{13}\text{NH}_3\), nitorgen-13 ammonia; \(^{15}\text{O-water}, \text{oxygen-15 water}; \(^{15}\text{F-flurpiridaz}, \text{fluorine-18-flurpiridaz}.\)

*Based on data from the references 32, 37 & 38.
Figure 1. Proposed algorithm for the appropriate use of rubidium (Rb)-82 PET perfusion imaging from the Cardiac Care Network of Ontario (CCNO). (With permission of CCNO. Adapted in part from recommendations by American Society of Nuclear Cardiology: Cerqueira M et al, J Nucl Cardiol 2010.) BMI, body mass index; CAD, coronary artery disease; CT, computed tomography; PET, positron emission tomography; SPECT, single-photon emission tomography.

Figure 2. Summary receiver-operating characteristic curves comparing the diagnostic accuracy of Rb-82 PET and Tc-99m SPECT with ECG-gating and attenuation correction. Area under the curve (AUC) was compared for Rb-82 PET (A) and Tc-99m SPECT (B), with Rb-82 PET showing superior accuracy (P<0.001). ECG, electrocardiography; PET, positron emission tomography; Q, Cochran Q statistic; Rb, rubidium; SPECT, single-photon emission computed tomography; Tc, technetium. (With permission from the Journal of the American College of Cardiology.)
Figure 3. Role of SPECT and PET imaging in 2 patients presenting with atypical chest pain. (A) In a 79-year-old male patient presenting with atypical chest pain, Tc-99m-tetrofosmin demonstrates moderate to severe defects at stress and rest in the RCA territory and apex indicating non-transmural scar without ischemia (red arrows). (B) Rb-82 PET on the same patient demonstrates defects at stress with resolution at rest indicating ischemia in the RCA±LCX (red arrows). Coronary angiography demonstrated a total occlusion in the mid RCA, 90% stenosis in the LCX, luminal irregularities in the left main and 40% stenosis in the LAD. This case indicates that PET offers superior sensitivity for the detection of significant CAD in comparison with SPECT. (C) Tc-99m-tetrofosmin SPECT images from a 58-year-old female patient presenting with atypical chest pain demonstrating a mild reversible defect in the mid to distal anterior wall and apex suggestive of ischemia in the LAD territory. (D) Shows images from a subsequent 82Rb-PET scan that demonstrates normal perfusion. The patient therefore did not require invasive coronary angiography. RCA, right coronary artery; LCX, left circumflex artery; LAD, left anterior descending.
er spatial resolution and contrast resolution (target to background ratio), resulting in improved resolution of regional differences and variability of radiotracer uptake. Moreover, PET offers greater sensitivity for the detection of flow-limiting coronary lesions than either 201Tl or 99mTc-labeled SPECT imaging.\(^5\)\(^\rightarrow\)\(^4\)\(^4\) The greater specificity observed in PET is a result of more robust attenuation correction that enables accurate differentiation between true perfusion defects and attenuation artifacts, particularly in more susceptible patients (ie, obese, females).\(^5\)\(^6\) A proposed algorithm for the appropriate use of \(^82\)Rb PET-MPI is presented in Figure 1.

Two recent meta-analyses have examined the accuracy of MPI with PET or SPECT. In their meta-analysis, Mc Ardle et al focused their comparison on \(^82\)Rb-PET and contemporary \(^99m\)Tc-SPECT with ECG-gating and attenuation correction.\(^4\)\(^4\) The weighted-mean sensitivity and specificity for \(^82\)Rb-PET were 90% and 88%, respectively, compared with 85% for both sensitivity and specificity with \(^99m\)Tc-SPECT. When low likelihood patients were removed, the difference in specificity increased (87% to 91%). The area under the curve (AUC) between \(^82\)Rb-PET and \(^99m\)Tc-SPECT was 0.95 and 0.90, respectively (P<0.0001) (Figure 2). In the second analysis by Parker et al, 108 SPECT studies, 4 PET studies, and 5 studies of both PET and SPECT were included.\(^4\)\(^4\) \(^82\)Rb was the most frequently used tracer for PET imaging (6 of 9 studies), while the other studies utilized \(^13\)NH\(_3\), \(^15\)O-water, or \(^18\)F-fluorodeoxyglucose (FDG). The authors reported greater pooled mean sensitivity for PET in comparison with SPECT (92.6% vs. 88.3%, P=0.035), although specificity was higher but not statistically significantly different between PET and SPECT (81.3% vs. 75.8%, P=0.39). These studies indicate that PET offers superior diagnostic accuracy for the detection of significant CAD in comparison with SPECT. Case examples are presented in Figure 3.

Despite the accuracy of PET perfusion imaging for the diagnosis of flow-limiting CAD, similar to SPECT imaging, its sensitivity in the setting of multivessel disease remains limited, because of the relative nature of standard MPI whereby perfusion is “normalized” to myocardium with the highest uptake. In patients with triple-vessel disease, this “normal” segment may in itself have diminished perfusion, and hence may not be detected.\(^4\)\(^6\)\(^\rightarrow\)\(^4\)\(^8\) However, other features such as stress-induced transient ischemic dilation of the LV\(^4\)\(^9\) or a decrease in LV ejection fraction (LVEF) of greater than 5%\(^6\)\(^\rightarrow\)\(^9\) if present, point towards increased risk of adverse outcomes.

**Clinical Utility of Quantification of MBF With PET**

PET is the noninvasive modality of choice for accurately quantifying MBF. With PET-MPI, dynamic imaging can be performed to quantify MBF in absolute terms (ml·min\(^{-1}\)·g\(^{-1}\)) following stress and at rest, the ratio of which is termed myocardial flow reserve (MFR). MFR is a valuable parameter because it overcomes the limitation of relative perfusion imaging in patients with multivessel disease.\(^4\)\(^6\)\(^8\)

Flow quantification also has value in determining the functional significance of single- vessel stenosis. Results from both the FAME-1\(^1\)\(^5\) and FAME-2\(^2\)\(^5\) studies, in which fractional flow reserve (FFR) was assessed during angiography, have emphasized the importance of functional evaluation to guide revascularization. Further studies have demonstrated a relationship between regional MFR and invasive FFR.\(^3\)\(^8\) However, FFR measures the pressure difference across a single stenosis whereas MFR is a measure of blood flow both across a lesion, as well as the entire epicardial vessel and the microcirculation; thus both measures cannot be directly compared (Figure 4A).\(^5\)

A proposed schema cannot be directly compared (Figure 4B).

Furthermore, MFR can also be used to detect subclinical atherosclerosis or microvascular dysfunction that cannot be evaluated with standard MPI in patients who are unlikely to demonstrate sufficient heterogeneity of flow to result in a perfusion defect. Subclinical abnormalities in MBF or MFR indicative of coronary artery endothelial or microvascular dysfunction, felt to be a precursor of overt CAD, during various forms of vasomotor stress have been demonstrated in multiple patient cohorts including obese patients,\(^4\) diabetics,\(^5\)\(^3\) smokers,\(^6\) and patients with hypertension,\(^7\)\(^\rightarrow\)\(^8\) with limited evidence showing improvement in vasomotor function with treatment. Whether or not reversal of these mild flow abnormalities has an effect on future risk is not certain. Future studies are needed.

**Prognostic Value of PET: MPI, MFR**

As with SPECT, a normal PET-MPI is indicative of good prognosis with hard cardiac event rates varying from 0.09% to 0.9%, depending on the population and cut-off implemented.\(^7\)\(^8\) On the other hand, adverse event rates increase in relation to the extent of defects on PET-MPI. Recently published results from a multicenter registry including 7,001 patients demonstrated that the risk-adjusted hazard of cardiac death increased with each 10% myocardial abnormality with mildly, moderately, or severely abnormal stress PET (hazard ratio [HR]: 2.3, 95% confidence interval [CI]: 1.4–3.8, P=0.001; HR: 4.2, 95% CI: 2.3–7.5, P<0.001, and HR: 4.9, 95% CI: 2.5–9.6, P<0.0001, respectively)\(^9\) (normal MPI: referent) (Figure 5).

Furthermore, several studies have demonstrated the incremental prognostic value of flow quantification in patients with known or suspected CAD. Tio et al found that MFR was a better predictor of cardiac death than resting LVEF (HR: 4.11 vs. 2.6 per SD decrease in MFR or LVEF, respectively).\(^9\) Herzog et al showed that patients with normal relative perfusion and preserved MFR (>2) had a warranty period of 3 years with \(^13\)NH\(_3\)-PET.\(^10\) Ziadi et al demonstrated that flow quantification using \(^82\)Rb predicted major adverse cardiac events independent of the summed stress score and other parameters.\(^8\) Murthy et al evaluated over 3,000 patients and demonstrated that the degree of flow reserve reduction measured using \(^82\)Rb-PET predicted adverse outcomes including death.\(^1\) Those studies suggest that routine assessment of \(^82\)Rb-PET quantified MFR could improve risk stratification. Finally, Mc Ardle et al have proposed an algorithm for incorporating MFR into PET interpretation\(^2\)\(^8\) (Figure 6).

**Evaluation of Myocardial Viability Using FDG-PET**

**Myocardial Metabolism**

During normal conditions, 50–70% of total myocardial energy requirement is obtained from the oxidation of fatty acids with the remainder obtained primarily from carbohydrates such as glucose and lactate.\(^6\) However, the proportional contribution varies with changes in the substrate, hormonal and myocardial flow environment. During the postprandial state, glucose stimulates an elevation in plasma insulin levels that increases the translocation of glucose transporters to the cell membrane of myocytes, leading to increased glucose uptake. Beta-oxidation of fatty acids is highly oxygen dependant, so in the setting of myocardial ischemia, glucose becomes the primary substrate for both increased anaerobic glycolysis and persistent but reduced oxidative metabolism.\(^1\) In states of chronic or...
repetitive myocardial ischemia, there is an overall metabolic downregulation secondary to upregulation of anti-apoptosis and cytoprotective gene transcription, termed “hibernation”\textsuperscript{64,65} where glucose is the preferred energy substrate.

**Myocardial Viability**

Viable but dysfunctional myocardium can be classified as stunned, hibernating, or remodeled. Stunning is a state of transient dysfunction caused by an abrupt interruption with subsequent restoration of coronary blood flow (ie, post-ischemic dysfunction). The duration of stunning is directly proportional to the duration of the preceding ischemia. Hibernation ensues following chronic or repetitive ischemia, resulting in downregulation to persistent, but potentially reversible, dysfunction with revascularization.\textsuperscript{66} Remodeling can occur, resulting in dysfunctional myocardium adjacent to the infarct or hibernation core that may or may not improve with revascularization, depending on improvement in other regions of the ventricle.

FDG is a glucose analog that is taken up by the myocardium via the glucose transporter before being phosphorylated, and then becoming trapped within the cell, as it cannot undergo further metabolism. Hence, FDG is utilized to identify “glucose avid” hibernating myocardium, usually in conjunction with a perfusion tracer. In this sense, hibernating myocardium is characterized as having reduced perfusion with preserved FDG uptake (Figure 7). Observational evidence suggests that FDG-PET has the greatest sensitivity for predicting global LV functional recovery following revascularization, when com-

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**Figure 4.** (A) Conceptual plot of coronary flow reserve (CFR) and fractional flow reserve (FFR). Six patterns of interaction or regions can be identified by the combined assessment of CFR and FFR. The region termed “above average reference CFR” comprises patients whose CFR without focal disease is greater than the mean CFR in young healthy volunteers. The gray region termed “only small vessel disease” consists of patients with reduced CFR but with a FFR near 1. The red quadrant labeled as “adequate and concordant” refers to patients with FFR >0.8 and CFR >2. The blue quadrant (reduced and concordant) contains patients with FFR <0.8 and CFR <2. The orange or “discordant FOCAL > diffuse” quadrant consists of patients with a dominant focal stenosis and FFR <0.8 but relatively preserved CFR >2. The yellow quadrant labeled “discordant DIFFUSE > focal” contains patients with dominant diffuse disease that reduces CFR <2 with FFR >0.8. Patients with myocardial or coronary steal fall below the dashed line at CFR=1. (With permission from the Journal of the American College of Cardiology\textsuperscript{53}) (B) Clinical classification of stress myocardial blood flow and stress/rest flow reserve. (Adapted from Johnson et al with permission.\textsuperscript{53}) Ischemia is identified by the combined effects of impaired flow reserve <1.5, and stress flow <1.1 ml · min\textsuperscript{-1} · g\textsuperscript{-1}. A normal resting flow value of 0.75 ml · min\textsuperscript{-1} · g\textsuperscript{-1} shown on the diagonal line, defines the relation between normal flow reserve (eg, 4.0) and normal stress flow (eg, 3.0 ml · min\textsuperscript{-1} · g\textsuperscript{-1}).
Figure 5. Unadjusted hazard of events by percent myocardium abnormal on vasodilator stress rubidium-82 PET. Cardiac death (6,037 patients, 169 cardiac deaths) was lowest in patients with normal PET-MPI and increased gradually in patients with minimal, mild, moderate, and severe abnormalities. CI, confidence interval; HR, hazard ratio; PET, positron emission tomography; MPI, myocardial perfusion imaging. (With permission from the Journal of the American College of Cardiology)³⁹

Figure 6. Proposed algorithm for incorporation of myocardial flow reserve (MFR) into PET interpretation based on current practice at University of Ottawa Heart Institute. Note that hazard ratios (HRs) from Ziadi et al were for MFR > vs. <2.0. Greater event rates occurred in patients with MFR <1.5 in this⁸ and other studies,⁹⁰⁹¹ but the study from Murthy et al⁹¹ showed HR 3.4 for cardiac death in the intermediate group compared with those with MFR ≥2. ICA, invasive coronary angiography; PET, positron emission tomography. (Reproduced with permission of Future Cardiology)²⁸
They found that the change in LVEF after revascularization was significantly greater in patients with less scar tissue (change of 9.0%, 3.7%, and 1.3% for small, moderate, or large scars, respectively).

Although there is a wealth of observational data supporting viability imaging, the results from the 2 large prospective studies (PARR-2 trial and STICH viability substudy) have not yielded clear conclusive positive findings. Only one of these trials, PARR-2, implemented FDG-PET for the selection of patients with LV dysfunction for revascularization or medical therapy to assess whether this strategy would produce an outcome benefit. Although the intention-to-treat analysis did not show a significant reduction of events in PET-assisted patients, a post-hoc analysis demonstrated direct benefit in patients where PET recommendations were followed.

In the STICH viability substudy, there was no relationship...
between myocardial viability and outcome benefit from revascularization. However, there are several key limitations that should be taken into consideration. The patients were not randomized to viability imaging and the modalities used for the assessment were DSE and thallium-201 SPECT, both of which have limited sensitivity for the detection of hibernation. Furthermore, the patient population included was younger and had a lower prevalence of triple-vessel disease, prior coronary artery bypass grafting and comorbidities such as renal dysfunction. As a whole, viability imaging may provide additional information for decision making in complex patients where the risk and potential benefit of revascularization are greatest. Ongoing randomized prospective studies, such as IMAGE-HF, may provide further additional insight in this regard.

**FDG-PET for Imaging Inflammation**

As described, FDG is a glucose analog that accumulates in metabolically active cells. This is the rational for its use in detecting malignancy and evaluating myocardial viability, but can also be further extended for the identification of areas with increased glucose utilization secondary to inflammatory processes.

Theron et al initially reported that FDG-PET could detect large-vessel inflammation in patients with Takayasu arteritis. However, recent technological advancements such as hybrid CT/PET imaging have facilitated the assessment radiotracer uptake in smaller vessels such as the carotid or coronary arteries. Atherosclerosis is the pathophysiological process underlying CVD, such as acute coronary syndrome and stroke. The concept that atherosclerosis is a chronic inflammatory process is increasingly recognized. Lesions responsible for acute events may not necessarily be critically obstructive, and non-invasive markers of “vulnerable plaque” (a plaque that is at high risk of disruption leading to thrombosis) are being sought. FDG-PET may serve as 1 such marker and Rudd et al have previously demonstrated that FDG-PET can detect inflamed carotid lesions. Furthermore, inflammation within the carotid and thoracic vasculature may respond to statin treatment, given that a reduction in FDG uptake has been noted following such therapy. Thus far, visualization of FDG uptake within coronary arteries has been limited by the low spatial resolution and avid FDG uptake by the myocardium. However, myocardial FDG uptake may be suppressed with a high-fat, low-carbohydrate diet prior to imaging.

CS is characterized by chronic inflammation and is associated with significant morbidity and mortality. Diagnosing CS is challenging, but in recent years there has been a surge of interest in using advanced imaging such as CMR and FDG-PET.
PET for diagnosing and monitoring disease progression. In terms of FDG-PET, myocardial FDG uptake within healthy myocardium has to be suppressed to enable identification of focally active inflammatory lesions, which may be achievable with fasting and low-carbohydrate/high-fat diet regimens prior to imaging\(^8\) (Figure 8). Intravenous administration of low-dose heparin prior to scanning also increases fatty acid uptake, which may result in improved image quality.\(^{94}\) FDG-PET has been shown to have greater sensitivity than other radionuclide imaging modalities such as \(^{201}\)Tl, \(^{99m}\)Tc, and \(^{68}\)Ga scintigraphy.\(^{22,85,86}\) On the other hand, CMR may also be useful for diagnosing and monitoring CS.\(^{87}\) In general, both FDG-PET and CMR are considered sensitive and specific, although there are limited data available of direct comparisons of FDG-PET and CMR. In 21 patients, Ohira et al\(^8\) performed both FDG-PET and CMR imaging. They found that both modalities provided good sensitivity for diagnosing CS, but the specificity of FDG-PET for CS was lower. Potentially, the relatively lower specificity of FDG-PET may be related to nonspecific myocardial uptake of FDG in the normal heart or early-stage or isolated sarcoid lesions in the heart of patients who do not meet the diagnostic criteria of CS. FDG-PET can also be used to direct biopsy,\(^8\) monitor disease activity and response to immunosuppressive therapies.\(^{99,90,91}\) Despite this, the prognostic value of FDG-PET in CS has not yet been evaluated. Larger prospective studies are required.

**Future Directions**

Advances in the production of novel radiotracers are expected to expand the role and application of PET imaging. One such tracer is \(^{18}\)F-fluorpiridaz, a novel PET perfusion tracer that is currently in Phase 3 trials, as mentioned earlier. The role of neurohormonal regulation in heart failure (HF) and arrhythmia development is well established. In the recently completed PAREPET trial, C-11-HED was used to determine if it is predicts cardiac events in patients with HF.\(^92\)

Positive results could see increased application of these methods to facilitate decisions for implantable cardioverter device insertion in patients with borderline indications.

The renin-angiotensin-aldosterone system (RAAS) is also of interest, because of its well-recognized action as a blood pressure regulator and key in HF pathophysiology. It is also a proinflammatory mediator that may be a key player in the pathogenesis of CVD. RAAS activation contributes to pathological processes such as interstitial fibrosis, myocardial hypertrophy and apoptosis.\(^95\) Radiolabeled ligands of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor (AT1R) have been developed.\(^96\) Fukushima et al reported that dynamic PET/CT using the novel AT1R ligand, \(^{11}\)C-KR31173, can detect myocardial radiotracer retention in animal and human models.\(^97\) In the animal model of myocardial infarction, AT1R upregulation was noted in the infarct area relative to remote myocardium.\(^97\) Thus, PET imaging may have the potential to provide insight into RAAS activation and its role in cardiac disease and adverse myocardial remodeling. This approach may be able to direct therapies in hypertension, HF and kidney disease.

In terms of atherosclerosis, tracers that more specifically reflect macrophage activity have been evaluated in preliminary studies.\(^97–99\) New tracers applied in humans, specific to different stages of the plaque inflammation process, include radiolabeled \(^{11}\)C-pk11195, a selective ligand of the macrophage translocator protein (18 kDa TSPO);\(^97–99\) annexin 5, a marker of macrophage apoptosis;\(^97–99\), and active calcification using \(^{18}\)F-sodium fluoride (NaF).\(^78,100\) However, the potential clinical role of atherosclerotic plaque inflammation imaging is still uncertain.

Increasingly, modern PET scanners are dual systems with CT components that allow for hybrid imaging. Recent advances have also led to the development of prototype hybrid PET/MRI systems. This system possesses significant potential to evaluate myocardial structure, function and perform tissue characterization, while reducing radiation exposure. Between 2009 and 2010, the Chalk River reactor was closed resulting in a shortage of \(^{99m}\)Tc. In the near future, Chalk River is scheduled for permanent closure, which is concerning given that this facility produces a significant proportion of the world’s supply of \(^{99m}\)Tc. There is renewed interest in finding and developing strategies for alternative perfusion imaging. The low radiation dosimetry profile of PET, in addition to its superior diagnostic accuracy and prognostic information from flow quantification, make it an attractive alternative and we may see more widespread implementation in the near future.

**Conclusions**

Although previously limited by cost and availability, PET imaging has an important role to play both in clinical practice and as a research tool for evaluating and understanding CVD. Recent large prospective studies support its clinical use in perfusion and viability imaging. Emerging evidence supports its application in inflammatory conditions such as aortitis and CS. New tracers for the vasculature and the myocardium present considerable promise for new applications of PET, but will require translational research and validation studies. With increasing data on accuracy and prognosis, combined with anticipated \(^{99m}\)Tc-99m shortages, cardiac PET is poised to emerge as an even more important tool than ever before to assist clinical decision-making.

**Disclosures**

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