Clinical Perspectives

Does positron emission tomography contribute to the management of clinical cardiac problems?

Introduction

The great potential of positron emission tomography to elucidate tissue function is reflected in the increasing number of centres being established that offer this technique. Not only does the system offer greater accuracy in the measurement of regional radioactivity concentration than other available techniques, but it also enables the use of true biological tracers. Positron emission tomography is still seen as an expensive tool, principally because of the need for a cyclotron to produce the short-lived isotopes. However, in recent years, much attention has been directed to the development of compact, self-shielding cyclotrons which do not need a team of engineers for their maintenance. In addition, automated kits for the production of commonly used tracers are now available, and in some cases, central cyclotron facilities are being installed to distribute tracers (principally \(^{18}\)F-labelled compounds) to nearby centres. Parallel innovations in tomographic scanner design continue to blossom, providing more efficient photon detection and improved image resolution. New detector and electronic designs are bringing with them greater reliability.

Does positron emission tomography have a clinical role?

There has been much discussion about the dual roles of 'research' and 'clinical' positron emission tomography. A number of centres, particularly in the United States, have installed positron emission tomography systems purely for clinical diagnosis, mainly in the determination of myocardial viability, but also for applications in oncology and neurology. Diagnostic testing of this kind is clearly derived from original work carried out at research establishments. The terms 'research' and 'clinical' should, therefore, be regarded as complementary. A straightforward answer to the question which forms the title of this paper is difficult. It is generally accepted that positron emission tomography is useful to identify viable myocardium which can be revascularized in patients with coronary artery disease and chronic left ventricular dysfunction. In many of these patients, however, comparable information can be achieved by means of less expensive tools, such as echocardiography or conventional nuclear techniques. The problem is to identify those patients in whom positron emission tomography can offer superior information. Positron emission tomography is also emerging as a potentially useful tool to assess non-invasively the function of the coronary circulation, either to evaluate the functional significance of a coronary stenosis or to probe the coronary microcirculation.

Positron emission tomography for the assessment of myocardial viability

With the advent of coronary revascularization and thrombolysis, it has become apparent that restoration of blood flow to asynergic myocardial segments may result in improved regional and global ventricular function. This is particularly important as left ventricular function is the most significant factor in assessing prognosis in patients with coronary artery disease. In addition, the greatest clinical benefit from revascularization is seen in those patients with the most severe forms of left ventricular dysfunction. Therefore, the clinically important task is to be able to detect, pre-operatively, those dysfunctional segments which contain viable myocardium and thus to select those patients who may benefit from revascularization.

Initial studies indicated that myocardial ischaemia and infarction could be distinguished by analysis of tomographic images of the perfusion tracer \(^{15}\)N labelled ammonia (\(^{15}\)NH\(_3\)) and the glucose analogue \(^{18}\)F-2-fluoro-2-deoxy-D-glucose (FDG), acquired after an oral glucose load. Regions which showed a concordant reduction in both myocardial blood flow and FDG uptake ('flow–metabolism match') were hypothesized to be infarcted and irreversibly injured, whereas regions in which FDG uptake was relatively preserved or increased, despite having a perfusion defect ('flow–metabolism mismatch'), were considered ischaemic and viable. This hypothesis was tested by Tillisch et al. who performed pre-operative positron emission tomography scans in 17 patients undergoing coronary artery bypass grafting. Regional wall motion increased after surgery in 35/41 segments displaying 'flow–metabolism mismatch' and remained depressed in 24/26 segments demonstrating 'flow–metabolism match'. This method has identified the presence of viable myocardium in regions that were considered necrotic, and thus non-viable, on the basis of conventional investigations.
tracer uptake throughout the heart and enables positron emission tomography imaging. More recent studies have shown that a significant proportion of myocardial regions which have reduced end-diastolic wall thickness and no systolic wall thickening, as defined by spin-echo gated magnetic resonance imaging, have residual FDG uptake on positron emission tomography imaging. A study performed in 82 patients with advanced coronary disease and severe left ventricular dysfunction suggests that the 'flow-metabolism mismatch' pattern identifies a subgroup of patients who are at an increased risk of sudden death and adverse cardiac events (i.e. myocardial infarction, cardiac arrest, late revascularization) and who may thus benefit most from revascularization.

The acceptance of positron emission tomography for demonstrating myocardial viability is based upon a relatively small number of semi-quantitative studies and the current standard protocols, though indicative of the presence of metabolically active tissue components, may not accurately define the amount of viable tissue within the asynergic region.

**FDG uptake during hyperinsulinaemic euglycaemic clamp**

With recent suggestions that semi-quantitative and quantitative analyses of FDG uptake may enhance detection of viable myocardium using positron emission tomography, there is an urgent need rigorously to fix the study conditions. In addition, many patients with coronary artery disease are insulin resistant (i.e. the amount of endogenous insulin released after feeding will not induce maximal stimulation due to partial resistance to the action of the hormone). This results, in many cases, in poor FDG image quality after an oral glucose load. To circumvent the problem of insulin resistance, an alternative protocol has recently been applied to positron emission tomography viability studies. This is now accepted by most European centres participating in the multicentre study (European Community Concerted Action on Positron Emission Tomography Investigation of Cellular Regeneration and Degeneration). The protocol is based on the use of the hyperinsulinaemic euglycaemic clamp, essentially the simultaneous infusion of insulin and glucose acting on the tissue as a metabolic stressor and stimulating maximal FDG uptake. The use of the euglycaemic hyperinsulinaemic glucose clamp provides excellent image quality, demonstrates uniform tracer uptake throughout the heart and enables positron emission tomographic studies to be performed under standardized metabolic conditions. This permits a comparison of the absolute values of the metabolic rate of glucose (μmol. g⁻¹. min⁻¹) amongst different subjects. This approach is particularly useful in studying the many coronary artery disease patients who have some degree of insulin resistance, as well as enabling more meaningful comparisons of data from different patient populations and study centres.

By using the euglycaemic hyperinsulinaemic glucose clamp in conjunction with myocardial regional wall motion information from various sources (e.g. echocardiography or conventional radionuclide ventriculography) the need for a simultaneous flow tracer is obviated. The images obtained with FDG by the clamp technique are also of sufficient quality for it to be possible to reduce the period of image acquisition to approximately 30 min, giving a total scan time of about 1 h. Another significant benefit of this method is its particular sensitivity in patients with coronary artery disease and poor left ventricular function. (Fig. 1).

**Positron emission tomography measurement of myocardial blood flow**

Coronary sinus thermodilution and more recently intracoronary Doppler catheterization, provide widely available techniques for the measurement of coronary blood flow in man. However, the methods are invasive and limited in that they measure flow (or flow velocity) through an epicardial coronary artery, rather than flow through a defined mass of myocardium (tissue perfusion). Although methods based on the clearance of non-radioactive (nitrous oxide, hydrogen, helium and argon) and radioactive (xenon-133) gases from the myocardium have been developed for measuring myocardial perfusion, in practice they have been abandoned due to inherent complexities and limitations.

Planar gamma scintigraphy or single photon emission computed tomography (SPECT) with different single photon emitters, e.g. thallium-201, allow the detection of directional changes in regional myocardial blood flow (i.e. relative regional increase or decrease). However, because of the physical constraints of these techniques, quantification of myocardial blood flow in absolute units is not possible. The physical properties of positron emission coupled to coincidence detection and accurate attenuation correction can overcome the limitations of single photon imaging. Further advances in positron emission tomography technology have led to rapid dynamic imaging becoming feasible and, following the development of appropriate tracer kinetic models, quantification of myocardial blood flow has been achieved.

In the measurement of myocardial blood flow using positron emission tomography, several tracers have been used, including oxygen-15 labelled water ($^{15}$O), nitrogen-13 labelled ammonia.
PET-FDG Assessment Of Myocardial Viability

Non viable

Myocardial viability in two patients with coronary artery disease and severe chronic left ventricular dysfunction assessed by positron emission tomography with $^{18}$F-labelled fluordeoxyglucose (FDG) during hyperinsulinaemic euglycaemic clamp. The upper scan shows good global ventricular uptake of FDG (>0.25 µmol. min $^{-1}$. g $^{-1}$), suggesting that most of the myocardium is viable. In the lower scan, the uptake of FDG is significantly reduced throughout the heart (<0.25 µmol. min $^{-1}$. g $^{-1}$), suggesting that most of the myocardium is non-viable. The cut-off point of 0.25 µmol. min $^{-1}$. g $^{-1}$ corresponds to the mean myocardial FDG uptake minus one standard deviation, measured during the clamp in a group of 33 patients with coronary artery disease and chronic left ventricular dysfunction, who subsequently underwent coronary revascularization.

Non-viable assessment of the coronary vasodilator reserve

Myocardial blood flow can increase above resting levels during reactive hyperaemia (i.e. the increase in blood flow which follows transient coronary occlusion), exercise and pacing or following the injection of vasoactive agents such as adenosine or dipyridamole. If the stimulus is able to produce maximal or near-maximal coronary vasodilatation, then the ratio of hyperaemic flow to resting flow is an expression of the coronary vasodilator reserve or, in other words, of the reactivity of the coronary circulation. It is important to note, though, that this definition of coronary vasodilator reserve (a) depends upon knowledge about the coronary perfusion pressure and (b) assumes that the drug used achieves maximal vasodilatation. Under normal circumstances, the small coronary arterioles below 450 µm in diameter are the principal determinants of coronary vascular resistance, whereas the larger arteries offer very little resistance to flow. In the absence of significant coronary artery disease, the assessment of the coronary vasodilator reserve provides a means to test the function of the coronary microcirculation.
Table 1  Positron emission tomography measurements of myocardial blood flow in normal subjects

<table>
<thead>
<tr>
<th>Study authors</th>
<th>Tracer</th>
<th>Agent</th>
<th>No. of subjects</th>
<th>Age (years)</th>
<th>MBF_{bas}</th>
<th>MBF_{hyp}</th>
<th>hyp/bas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergmann[31]</td>
<td>H$_2^{15}$O</td>
<td>Dip</td>
<td>11</td>
<td>25</td>
<td>0.9 ± 0.2</td>
<td>3.6 ± 1.2</td>
<td>4.1 ± 1.2</td>
</tr>
<tr>
<td>Gelman[32]</td>
<td>H$_2^{15}$O</td>
<td>Dip</td>
<td>16</td>
<td>25 ± 4</td>
<td>1.2 ± 0.3</td>
<td>4.6 ± 1.6</td>
<td>3.8 ± 1.1</td>
</tr>
<tr>
<td>Camici[47]</td>
<td>$^{13}$NH$_3$</td>
<td>Dip</td>
<td>12</td>
<td>51 ± 8</td>
<td>1.0 ± 0.2</td>
<td>2.7 ± 0.9</td>
<td>2.9 ± 1.0</td>
</tr>
<tr>
<td>Sambuceti[66]</td>
<td>$^{13}$NH$_3$</td>
<td>Dip</td>
<td>14</td>
<td>49 ± 7</td>
<td>1.1 ± 0.3</td>
<td>3.7 ± 0.8</td>
<td>3.6 ± 0.9</td>
</tr>
<tr>
<td>Chan[67]</td>
<td>$^{13}$NH$_3$</td>
<td>Ado</td>
<td>20</td>
<td>35 ± 16</td>
<td>1.1 ± 0.2</td>
<td>4.4 ± 0.9</td>
<td>4.4 ± 1.5</td>
</tr>
<tr>
<td>Chan[67]</td>
<td>$^{13}$NH$_3$</td>
<td>Dip</td>
<td>20</td>
<td>35 ± 16</td>
<td>1.1 ± 0.2</td>
<td>4.3 ± 1.3</td>
<td>4.3 ± 1.9</td>
</tr>
<tr>
<td>Araujo[28]</td>
<td>C$_2$O$_2$</td>
<td>Dip</td>
<td>11</td>
<td>26 to 42</td>
<td>0.8 ± 0.1</td>
<td>3.5 ± 1.1</td>
<td>4.2 ± 1.2</td>
</tr>
<tr>
<td>Merlet[68]</td>
<td>H$_2^{15}$O</td>
<td>Ado</td>
<td>6</td>
<td>51 ± 5</td>
<td>0.9 ± 0.1</td>
<td>3.5 ± 0.8</td>
<td>4.0 ± 0.7</td>
</tr>
<tr>
<td>Muzik[69]</td>
<td>$^{13}$NH$_3$</td>
<td>Ado</td>
<td>6</td>
<td>26 ± 3</td>
<td>0.8 ± 0.2</td>
<td>3.6 ± 1.0</td>
<td>---</td>
</tr>
<tr>
<td>Uret[69]</td>
<td>H$_2^{15}$O</td>
<td>Dip/Ado</td>
<td>43</td>
<td>47 ± 20</td>
<td>1.0 ± 0.2</td>
<td>3.2 ± 1.3</td>
<td>3.4 ± 1.3</td>
</tr>
<tr>
<td>Radwaas[50]</td>
<td>C$_2$O$_2$</td>
<td>Dip</td>
<td>8</td>
<td>27 ± 5</td>
<td>0.8 ± 0.2</td>
<td>3.1 ± 0.8</td>
<td>3.8 ± 0.8</td>
</tr>
<tr>
<td>Czernin[70]</td>
<td>$^{13}$NH$_3$</td>
<td>Dip</td>
<td>18</td>
<td>31 ± 9</td>
<td>0.8 ± 0.2</td>
<td>3.0 ± 0.8</td>
<td>4.1 ± 0.9</td>
</tr>
<tr>
<td>Czernin[70]</td>
<td>$^{13}$NH$_3$</td>
<td>Dip</td>
<td>22</td>
<td>64 ± 9</td>
<td>0.9 ± 0.3</td>
<td>2.7 ± 0.6</td>
<td>3.0 ± 0.7</td>
</tr>
</tbody>
</table>

Ado = adenosine; Dip = dipyridamole; MBF_{bas} = baseline myocardial blood flow (ml. min$^{-1}$. g$^{-1}$ of tissue); MBF_{hyp} = hyperemic myocardial blood flow (ml. min$^{-1}$. g$^{-1}$); MBF_{hyp/bas} = coronary flow reserve. Data are mean ± SD

Positron emission tomography makes it possible to measure non-invasively absolute myocardial blood flow (i.e. in ml. min$^{-1}$. g$^{-1}$ of tissue). The short physical half-life of both H$_2^{15}$O and $^{13}$NH$_3$ allows the measurement of myocardial blood flow at rest and then repetition of the measurement after presentation of a pharmacological challenge to the coronary microcirculation. Coronary vasodilator reserve is of value in the assessment of the functional significance of coronary stenoses in patients with coronary artery disease[45,46]. In addition, positron emission tomography may be of particular assistance in those clinical conditions in which coronary vasodilator reserve is globally (rather than regionally) blunted because of a generalized coronary microvascular dysfunction, e.g. in hypertrophic cardiomyopathy[47].

**Evaluation of the functional significance of a coronary arterial stenosis**

The relationship between coronary arterial stenosis severity, measured by quantitative coronary angiography, and myocardial blood flow assessed by positron emission tomography with H$_2^{15}$O and $^{13}$NH$_3$ has been the subject of two recent studies[45,46]. In contrast with a canine model[48,49], the human studies showed that resting myocardial blood flow was preserved despite there being a stenosis of up to 95% of vessel diameter in the epicardial artery supplying the relevant myocardial territory. In agreement with the animal studies, however, the hyperaemic response to dipyridamole and adenosine began to be attenuated when the coronary stenosis was greater than 40% of vessel diameter and was abolished when the stenosis was greater than 80%[45,46,50]. There was a highly significant inverse relationship between stenosis severity and coronary vasodilator reserve, although the scatter of the data was wide. This variability was considerably reduced when minimal coronary resistance (i.e. the pressure/flow ratio during hyperaemia) was plotted against stenosis severity. This finding emphasizes the importance of normalizing for interindividual differences in coronary perfusion pressure[45,46] (Fig. 2).

**Myocardial blood flow in physiological and pathological left ventricular hypertrophy**

Physiological left ventricular hypertrophy, which may occur as a response to athletic training, can be difficult to distinguish from hypertrophic cardiomyopathy on either clinical, electrocardiographic or echocardiographic grounds. Such a distinction is of importance, because sudden cardiac death during an episode of physical exertion may be the first presentation of hypertrophic cardiomyopathy, the latter also being the leading cause of sudden cardiac death in young people[51]. Indeed, there are several reports of sudden death in athletes confirmed to be due to hypertrophic cardiomyopathy at autopsy[52-54]. In the light of previous demonstrations of a blunting of coronary vasodilator reserve in hypertrophic cardiomyopathy, we have recently performed a comparative study of patients with hypertrophic cardiomyopathy and elite athletes with left ventricular hypertrophy using positron emission tomography with H$_2^{15}$O[55]. Baseline myocardial blood flow was comparable in both groups, but hyperaemic flow following dipyridamole differed significantly between the athletes and patients (2.7 ± 1.2 ml. min$^{-1}$. g$^{-1}$ vs 1.5 ± 0.5 ml. min$^{-1}$. g$^{-1}$, P < 0.05). The coronary vasodilator reserve was also more blunted in the patients with hypertrophic cardiomyopathy than in the athletes (2.0 ± 0.7 vs 3.6 ± 1.0 respectively, P < 0.001). Amongst the echocardiographic data, a significant difference was
found between the athletes and patients with respect to the E/A ratio (1.8 ± 1.0 and 3.3 ± 1.0 respectively, P<0.05). However, it was of interest to note that all the patients with an E/A ratio overlapping with values in the athletes’ group had a blunted vasodilator reserve. Therefore, although positron emission tomography is an expensive and not easily available technique, since the number of potential subjects in whom the differential diagnosis between ‘athlete’s heart’ and hypertrophic cardiomyopathy can be particularly difficult is going to be relatively small, we believe that it is reasonable to propose using this technique as an adjunctive investigation to make this distinction since it might help identify subjects at risk of sudden death.

Hypertrophic cardiomyopathy (primary left ventricular hypertrophy)

Chest pain of anginal quality is common in patients with hypertrophic cardiomyopathy despite there being no evidence of epicardial coronary artery disease in the majority of cases. A range of investigations, including atrial pacing with measurement of lactate production[56], thallium-201 scintigraphy (demonstrating perfusion defects)[57] and necropsy (demonstrating regions of previous myocardial infarction)[58], all suggest a role for myocardial ischaemia in the pathogenesis of the chest pain in this disease. Coronary vasodilator reserve measured by positron emission tomography with $^{13}$NH$_3$ has been shown to be blunted in both the hypertrophied and non-hypertrophied walls of the left ventricle, suggesting a primary abnormality of the coronary microcirculation[47]. Likewise, severe impairment of coronary vasodilator reserve, measured by positron emission tomography with $^{13}$NH$_3$, has recently been found during submaximal supine exercise both in hypertrophied and non-hypertrophied myocardium in a small series of symptomatic patients with hypertrophic cardiomyopathy[59]. Impairment of coronary vasodilator reserve may also be present in asymptomatic subjects with a family history positive for hypertrophic cardiomyopathy[60].

Hypoperfusion of the subendocardium documented following intravenous dipyridamole, with a reduced ratio of subendocardial to subepicardial flow, has also been demonstrated in these patients using positron emission tomography[61] and treatment with calcium channel blockers has been found to produce a more homogeneous transmural flow distribution without an increase in total transmural flow[62]. Overall, these studies seem to suggest that coronary microvascular dysfunction is very common in patients with hypertrophic cardiomyopathy and may contribute to the

Figure 2 No significant correlation was found between corrected basal flow and percent diameter stenosis (open circles). Hyperaemic blood flow (solid circles) falls significantly with increasing percent diameter stenosis (top panel). Corrected coronary vasodilator reserve also falls with increasing percent diameter stenosis (top panel). Minimal total coronary resistance increases significantly with the severity of the stenosis (lower panel). Normal control values of corrected basal and hyperaemic blood flow, coronary vasodilator reserve and minimal total coronary resistance are shown at zero percent diameter stenosis for comparison on the left of each panel.
Secondary left ventricular hypertrophy

It has been recognised for years that patients with pathological left ventricular hypertrophy secondary to pressure or volume overload may experience chest pain in spite of a normal coronary arteriogram. This symptom has been attributed to myocardial ischaemia because of microvascular dysfunction, since a reduction in coronary vasodilator reserve has been demonstrated in both conditions. However, until recently, there had been no direct quantitative comparison of coronary vasodilator reserve between patients with primary or secondary left ventricular hypertrophy. We have recently completed such a study, with separate subgroups of normal controls to allow for the natural difference in age between patients with hypertrophic cardiomyopathy and those with secondary hypertrophy as well as recognising the natural decline in coronary vasodilator reserve with age. Resting myocardial blood flow was higher in the secondary hypertrophy patients, as was hyperaemic blood flow; the resulting coronary vasodilator reserve values were impaired in both patient groups. Coronary vasodilator reserve was 2.05 ± 0.61 for hypertrophic cardiomyopathy patients vs 3.81 ± 0.98 for their matched controls; P = 0.0001. For the secondary hypertrophy patients, coronary vasodilator reserve was 2.06 ± 0.62 vs 2.95 ± 1.25 for their control group, P < 0.02. However, the values for minimal coronary resistance (defined as the post-dipyridamole mean arterial pressure/myocardial blood flow) was comparable: 55 ± 14 arbitrary units for the hypertrophic cardiomyopathy patients and 47 ± 17 arbitrary units for the secondary hypertrophy patients. It was concluded that the comparable values of minimal coronary resistance suggested equivalent degrees of structural remodelling of the coronary microcirculation in primary and secondary left ventricular hypertrophy (Fig. 3).

Conclusion

Positron emission tomography remains the ‘gold standard’ for the assessment of myocardial viability, but work in the field is far from static and positron emission tomography investigators far from complacent. The techniques are being further refined and the data being applied with an even finer focus. The availability of non-invasive, absolute measurements of myocardial blood flow with positron emission tomography is now contributing to the evaluation of the effects of epicardial coronary stenoses upon regional microvascular function as well as aiding in the discrimination of benign and pathological myocardial hypertrophy.

P. G. CAMICI
S. D. ROSEN
MRC Clinical Sciences Centre
Hammersmith Hospital
London, U.K.
References


