CURRENT TOPIC

Positron emission tomography in paediatric cardiology

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With the recent development of positron emission tomography (PET), cross sectional functional imaging of the heart has become possible. This demonstrates quantitatively the distribution of radioactive ligands in the myocardium. PET images thus resemble in vivo autoradiographs, providing a potential non-invasive means of quantifying regional myocardial metabolism and perfusion.¹

Types of PET study

There are three types of cardiac PET study: regional blood flow (which can be measured at rest and during pharmacological induced stress), substrate metabolism, and chemical recognition (including receptors and enzymes).² Currently, the main clinical application of PET is in the diagnosis of coronary artery disease, in terms of the differentiation between infarcted and "stunned" myocardial tissue, in which complete recovery of severely ischaemic and non-contracting myocardium is possible after reperfusion.³⁻⁴ Other methods for differentiating recoverable myocardium from non-viable tissue, such as the presence of ECG Q waves, wall motion abnormalities on ultrasound, gated isotope scans, or fixed thallium-201 perfusion defects,⁵ all seriously underestimate viable myocardium even with delayed imaging or reinjection techniques in the last.⁵

A number of tracers have been developed for clinical PET studies. These include oxygen-15, nitrogen-13, carbon-11, fluorine-18, and rubidium-82, all of which may be coupled to a number of physiologically active molecules.³ N-13 ammonia, Rb-82, and O-15 water can be used to assess myocardial blood flow.¹⁻⁶⁻⁷ Carbon-11 labelled fatty acids and F-18 deoxyglucose are commonly used metabolic tracers; C-11 acetate is used to assess oxidative metabolism and oxygen consumption.⁸ Because these tracers have very short half lives and relatively low radiation doses, it is possible to undertake sequential studies of perfusion and metabolism enabling accurate differentiation between stunned and infarcted tissue.³⁻⁹

Metabolic changes in myocardial ischaemia

Depending on plasma substrate levels, hormonal factors, and oxygen supply and demand, the heart can metabolise a variety of substrates, including free fatty acids, glucose, lactate,

pyruvate, ketone bodies, and amino acids. In the normal heart, especially in the fasting state, fatty acid metabolism is the predominant source of myocardial energy production.³⁻⁶⁻¹⁰ The metabolic changes associated with myocardial ischaemia have been well documented using animal experimental models.⁶⁻¹⁰⁻¹¹ Metabolism in ischaemic myocardial tissue is characterised by impaired oxidation of fatty acids, accelerated glycogen breakdown, and increased glycolytic flux. Oxidative fatty acid metabolism is particularly sensitive to tissue hypoxia.¹² These metabolic changes provide the basis for detection of ischaemically compromised myocardium using metabolic imaging with PET. Absent F-18 deoxyglucose (FDG) activity has been proposed as a marker for irreversible myocardial damage while preserved FDG activity, despite regional loss of perfusion, suggests viable myocardial tissue (hibernating myocardium). Paired sequential metabolism and flow studies can, thus, differentiate infarcted from ischaemic but viable myocardial tissue.¹²

Several other approaches to the PET assessment of viability have undergone preliminary testing, including the use of labelled fatty acids (carbon-11-palmitate),¹¹⁻¹² aerobic metabolites (carbon-11 acetate and pyruvate),⁸ and differential washout of rubidium-82.⁷⁻⁸ Carbon-11 acetate is avidly extracted by the myocyte. Within the mitochondria C-11 acetate is converted to acyl CoA, which enters the tricarboxylic acid cycle. This approach offers promise for the absolute quantification of myocardial oxygen consumption.⁶ Radiolabelled amino acids have been introduced for the non-invasive characterisation of myocardial amino acid metabolism; N-13 glutamate has been proposed as a marker for detecting ischaemic myocardial tissue.⁶⁻¹²

PET has the potential to evaluate the relation between hormones and their receptors and may help in the determination of cellular abnormalities associated with the development of cardiomyopathies, arrhythmias, atherosclerosis, and thrombosis.¹³⁻¹⁴ In the future, PET will be useful in the study of end organ pharmacokinetics directly rather than relying on blood levels of cardiac drugs. These new areas should be some of the largest growth areas for PET's clinical applications.¹³⁻¹⁴

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Advantages of PET over other diagnostic procedures

PET has advantages over SPECT (single photon emission computed tomography) with respect to its ability to correct for differences in attenuation, thus permitting true quantification of activity which can be translated into quantification of physiological and metabolic processes. Such quantitation is facilitated further by high temporal resolution, a capability not available with SPECT.¹⁵⁻¹⁷ Thus, PET is the only non-invasive technique allowing absolute quantitation of regional myocardial blood flow.¹⁸⁻²⁰ In addition, the sensitivity and specificity of PET for the diagnosis of coronary artery disease are 95% and 98%, respectively.^{12 18}

Impaired myocardial perfusion, although rare, does occur in children with anomalous coronary artery syndrome and Kawasaki disease.^{21 22} Scintigraphy has been shown to be useful in assessing the adequacy of myocardial perfusion in these children,²³⁻²⁵ but PET is likely to be more informative in terms of differentiating infarcted from stunned myocardial tissue, thus potentially reducing the need for angiography.

In Kawasaki disease, paired PET perfusion studies using O-15-water at rest and with dipyridamole demonstrated reduced myocardial perfusion in children with coronary aneurysms, even though coronary stenosis was not found at angiography.^{26 27} In comparison, studies using thallium scintigraphy showed no evidence of perfusion abnormalities, even when large aneurysms were studied.^{27 28}

Corrective surgery for congenital heart disease can be complicated by coronary thrombosis.^{15 21 22} Coronary occlusion and stenosis can complicate the arterial switch procedure because the coronary arteries are reimplanted into the new aortic root.²³ PET offers a sensitive and quantitative non-invasive technique which carries fewer risks and lower radiation doses than angiography, especially when repeated studies are necessary.²⁷ In congenital heart disease quantitation of left to right shunts using C-15 water inhalation have been shown to be reliable and, in the future, may become the investigation of choice.³

Coronary arteriopathy is a major cause of mortality and morbidity in the late phase after cardiac transplantation. Because the heart is denervated, chest pain does not occur, and so the patient may present with sudden death, myocardial infarction, congestive cardiac failure, or arrhythmias.²⁹ Detection of disease is important because coronary angioplasty, coronary bypass, and retransplantation are therapeutic options for some patients.³⁰ Cardiac PET studies with O-15 water readily detect limited perfusion reserve in cardiac allografts after pharmacologically induced stress with dipyridamole.^{31 32} A reduction in global myocardial blood flow has been shown to correlate directly with late rejection and cytomegalovirus infection. Many authors now recommend sequential PET studies as a more sensitive modality than angiography for monitoring allograft rejection.³⁰ Changes in β adrenergic activity have also been shown in the trans-

planted heart.³¹ In the future PET studies of sympathetic receptor activity may prove valuable.³²

Cardiomyopathies of diverse origin

In the clinical investigation of cardiomyopathies of diverse origin, cardiac PET studies are likely to improve the detection rate and quantitatively assess the effect of therapeutic interventions.¹⁵ In all new cases of dilated or hypertrophic cardiomyopathy PET or scintigraphy should be performed to exclude coronary artery anomalies.^{27 29 30} Markers of sympathetic nervous system activity, including C-11-M-hydroxyephedrine and F-18 fluor-metaraminol, have recently been tested and developed in animals.³¹ They appear to provide accurate delineation of regional sympathetic activity in the heart, which may be of substantial importance in developing a further understanding of the hypertrophic cardiomyopathies,³² and may also enhance our knowledge of the pathophysiology of arrhythmogenesis in cardiomyopathies. Anti-myosin Fab fragments are now commercially available and may ultimately be labelled with positron emitters.⁶ This should help in the assessment of inflammatory myopathies in which myocyte necrosis is evident. In the cardiomyopathy of Duchenne and Becker muscular dystrophy, paired perfusion and metabolism studies have demonstrated regions of hibernating myocardium.^{33 34} Similar perfusion abnormalities have been reported in dystrophic skeletal muscle.³⁵ The underlying pathogenesis remains obscure, but the role of vasoactive cytokines are being considered as a potential cause.³⁶

PET has proved useful in the assessment of metabolic cardiomyopathies. Genetic defects in long chain fatty acid oxidation can lead to cardiomyopathy, skeletal myopathy, and childhood sudden death. The clinical manifestations and their severity vary widely among affected subjects of different age groups. Although measurements of serum and urinary fatty acid intermediary metabolites and enzymatic assays establish the diagnosis of a defect of fatty acid oxidation, they do not predict the clinical manifestations in a particular individual. The rate of clearance of C-11 palmitate—a measure of the rate of oxidation of long chain fatty acids from the myocardium—has been shown in these patients to be markedly prolonged compared with controls. This has been shown to correlate directly with the severity of myocardial involvement.^{37 38}

Conclusion

To date, clinical experience with cardiac PET in paediatrics is limited, but it seems likely that with increasing availability to paediatricians, PET will become the investigation of choice for a variety of disorders, including acquired and congenital heart disease.¹⁷ Furthermore, the development of new radiotracers and radiopharmaceuticals will enhance our understanding of the pathophysiology of cardiomyopathies and the pharmacological effects of new treatments.

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