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Review Article

Application of animal and human PET in cardiac research

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Abstract: Purpose of Review: After a warm-up period of imaging research, several modalities of positron emission tomography (PET) are under development for evaluating ischemic heart disease. Recent Findings: Several types of well-documented stem/progenitor PET imaging have been utilized for changes in myocardial blood flow and carbohydrate metabolism. Some recent experimental and human studies reported that these data may have beneficial effects on cardiac research. Summary: Although the role of PET in the pathology of ischemic heart disease has not been sufficiently elucidated, many studies attempting imaging research of myocardial metabolism and neural regulation have been reported. Further studies are needed to better evaluate the potential of PET in evaluating ischemic heart disease.

Keywords: Positron emission tomography, cardiac research, ischemic heart disease

Introduction

Cardiac ischemia is the serious event in heart surgery. A great need exists for improved formulations and mechanisms to prevent and protect the myocardial tissues from reperfusion damage caused by myocardial ischemia. Current efforts to prevent reperfusion damage to the myocardial tissues, which in many cases leads to myocardial infarction and circulatory arrest [1-3]. The neural regulation is involved in an imbalance in metabolic supply and demand within the ischemic myocardial tissues [4-8], which is a natural prevention from ischemia and reperfusion-associated tissue inflammation and organ dysfunction. Modern imaging, such as positron emission tomography (PET), has revolutionized our view of ischemic heart disease [9-13], allowing the opportunity to investigate the metabolic regulation mechanisms of heart by measuring the changes in myocardial blood flow or carbohydrate metabolism, and to offer potential information to further improve prognostic outcome of ischemic heart disease [14-17].

Positron-emitting tracers

Today, the field of PET medicine is undergoing great development [18]. Traditionally, there have been several options for positron-emitting tracers, i.e., ^{15}O-water, ^{13}N-ammonia and ^{82}Rubidium. However, some new sources of positron-emitting tracers were successively accumulated, such as ^{18}F-labeled myocardial flow radiotracer flurpiridaz [14], and the potential for PET in conjunction with several radiotracers seems to be expanding very rapidly. Rapid development of labeling biologic chemistry gives great potential for the development of new PET tracer candidates [15]. It is known that nanoparticle imaging rely on MRI detection of the iron oxide cores [19, 20], and a study of Ueno [21] showed that dextran nanoparticles the PET isotope copper-64 detected heart transplant rejection and predicted organ survival by reporting on myeloid cells.

The applications of an ^{18}F-labeled perfusion agent [^{18}F fluorodeoxyglucose (^{18}F-FDG) and ^{18}F-sodium fluoride (^{18}F-NaF)] for PET have

Table 1. Radiotracer characteristics and application of PET in cardiac Research

Researcher	Species	Radionuclide	Application
Daly [24]	C57BL/6 mice	[^{13}N]NH_3 and [^{18}F]FDG	Monitoring the development of cardiac allograft rejection
Hoff [16]	Rat	^{13}NH3 and [^{18}F]FDG	A potential diagnostic role of PET
Ueno [21]	Female 57BL/6 mice	Isotope copper-64	Predicting organ survival by reporting on myeloid cells
Srivatsava [17]	Patients	[^{18}F]FDG	The assessment of myocardial viability in patients with left ventricular dysfunction
Meeder [13]	Patients	[^{13}N]NH_3	Exploring the pathophysiology of smoking-related coronary events
Gerber [25]	Patients	[^{18}F]FDG	Predicting recovery of global cardiac function
Siebelink [26]	Patients	[^{13}N]NH_3 and [^{18}F]FDG	The assessment of revascularization with suspicion of jeopardized myocardium
De Jong [27]	Patients	[(11)C]CGP 12177	Measurement of myocardial beta-adrenoceptor density
De Boer [28]	Patients	Tc-MIBI and [^{18}F]FDG	The assessment of myocardial viability

revealed details on the pathophysiology of cardiovascular diseases [22]. Some radiotracers have unique effects, such as F-labeled fluorodeoxyglucose ([F]FDG) reflects glucose flux and N-labeled ammonia ([N]NH3) stand for a biomarker of blood flow [23].

The relevant characteristics of radiotracer, animal models compared with human disease are listed in **Table 1** and discussed below.

PET imaging to monitor the allograft rejection

Owing to have the potential to be a specific, sensitive and quantitative diagnostic test, PET imaging in conjunction with radiotracers such as F-labeled fluorodeoxyglucose ([F]FDG) reflecting glucose flux and N-labeled ammonia ([N]NH3) reflecting blood flow, is increasingly used in clinical routine for transplant rejection detection [29, 30], yielding high diagnostic information, while providing valuable outcome in human transplant recipients [31]. Hoff [16] evaluated for the ability of positron-emitting tracers [^{13}NH3 and ^{18}F 2-fluoro 2-deoxyglucose (^{18}F-FDG)] to detect acute allograft rejection after heterotopic cardiac transplantation in the rat with sham-operated controls, nonrejecting isografts, and rejecting allografts, and found that uptake of ^{18}F-FDG and ^{13}NH3 in native hearts of animals from all experimental groups is not significantly different from that in sham-operated controls, suggesting that glucose may be a preferred metabolic substrate during rejection, which supports a humoral mechanism for substrate preference during transplant rejection and a potential diagnostic role for PET.

Daly [24] evaluated N-labeled ammonia ([N]NH3) reflecting myocardial perfusion and ^{18}F-labeled fluorodeoxyglucose ([^{18}F]FDG) small animal PET imaging in a well-established murine cardiac rejection model, and found that there was a significant increase in [F]FDG uptake in allografts from 14 d to 21 d, and [F]FDG uptake correlated with an increase in rejection grade within allografts between 14 d and 28 d after transplantation; whereas the uptake of [N]NH3 was significantly lower relative to the native heart in allografts with chronic vasculopathy compared to isograft controls on 28 d, suggesting that PET imaging with [F]FDG can be used after transplantation to monitor the evolution of rejection, and decreased uptake of [N]NH3 in rejecting allografts may be reflective of decreased myocardial blood flow. These data suggest that combined [F]FDG and [N]NH3 PET imaging could contribute to unravel pathophysiological mechanisms underlying allograft rejection as a noninvasive, quantitative technique, and has potential application for serial monitoring of allograft rejection in human transplant recipients.

PET imaging to monitor the cerebral glucose metabolic change after cardiac ischemia/reperfusion

There is a growing concern about heart-brain neural crosstalk. Understanding neural mechanisms could lead to a better comprehension of cerebral circuit structure and function after cardiac ischemia/reperfusion injury. We used PET imaging to monitor the cerebral glucose metabolic changes after cardiac ischemia/reperfusion (**Figure 1**). Surgical procedures of myocardial ischemia-reperfusion injury models were performed following previously described methods [32-35]. After reperfusion, approximate 500 ± 50 μCi 18-fluoro-6-deoxy-glucose (^{18}F-FDG) was injected via the tail vein. After 1 h of ^{18}F-FDG uptake, rats were anesthetized with 2% isoflurane. Images were obtained with the

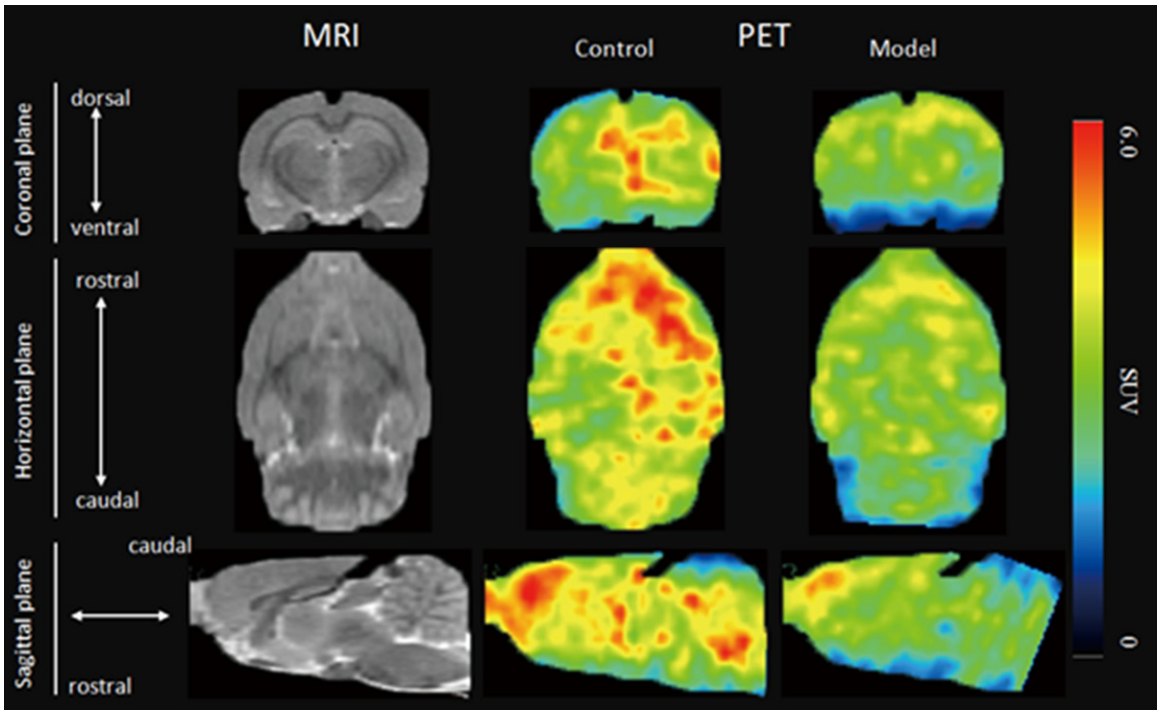

Figure 1. Alternations of glucose metabolism by small animal PET scanning. Representative images of ^{18}F-FDG accumulation in the rats' brains of two groups (Control group and Model group). The images were displayed in three planes: coronal, horizontal, and sagittal planes.

whole body scanning pattern (5 min per scanning bed) by the Trans-PET BioCaliburn 700 system (Raycan Technology Co., Ltd, Suzhou, China). The PET images were reconstructed using the three-dimensional (3D) OSEM method with a voxel size of 0.5 × 0.5 × 0.5 mm^3. A volume-of-interest (VOI) analysis was conducted using the AMIDE software package (The Free Software Foundation Inc., Boston, Massachusetts, USA).

PET imaging in the assessment of sympathetic re-innervation after heart transplantation

Some reports show that structural sympathetic re-innervation of the transplanted heart can develop after cardiac transplantation [36-39], but the evidence can be difficult to diagnose. Schwaiblmair [40] investigated the influence of sympathetic re-innervation on cardiopulmonary exercise testing after orthotopic heart transplantation in 35 patients underwent PET, and found that sympathetic re-innervation enabled an increased peak oxygen uptake, suggesting that partial sympathetic reinnervation after cardiac transplantation is of functional significance. Schwaiger [41] studied possible re-innervation of the human transplant after cardiac transplant by PET imaging approach in combination with catecholamine analogue [11C] hydroxyephedrine ([11C]HED), and found that there is the presence of sympathetic neuronal tissue in the terminals of transplanted human heart, which may reflect local sympathetic re-innervation. Bengel [42] described individual growth of sympathetic terminals late after cardiac transplantation by a longitudinal quantitative assessment, and found that sympathetic re-innervation was happened in the basal anterior region, apex, septal, and lateral wall, whereas inferior wall remained denervated; the largest reinnervated area surveyed in an individuum was 66% of the left ventricle, suggesting that re-innervation remained regionally heterogeneous.

PET imaging to predict recovery of global cardiac function

The past decade has seen strong progress in understanding PET imaging accuracy for predicting recovery of cardiac function after revascularization [43-45]. Gerber [25] assessed the accuracy of PET to predict recovery of global

cardiac function after revascularization in 157 male patients with coronary artery disease, and found that the highest sensitivity (79%) and specificity (55%) predicted postoperative ejection fraction improvement by using ^{18}F-FDG PET, suggesting that FDG positron emission tomography can predict improvement of cardiac function coronary patients with impaired ejection fraction. Srivatsava [17] prospectively studied 120 patients with left ventricular (LV) dysfunction who underwent 99mTechnetium-Sestamibi myocardial perfusion SPECT-CT and 18FFDG cardiac PET-CT, and indicated that the change in LV impaired ejection after surgical management was statistically significant compared to medical management, and the assessment of myocardial viability was performed in patients who present after 12 h of acute myocardial infarction or with LV dysfunction due to ischemic heart disease to decide upon appropriate surgical management, suggest that there is an important role of PET-CT in assessment of myocardial viability in patients with LV dysfunction.

PET imaging to evaluate the cardiovascular effects of drugs and stimulation

Within the last decade, PET imaging has translated from a mere research tool to the cardiovascular efficacy of drugs by myocardial perfusion imaging and flow quantification. Molecular imaging tools including PET are increasingly applied in the drug development process [46].

Ueno [21] imaged the effects of angiotensin-converting enzyme inhibitor (5 mg/kg enalapril) in mice with heart allografts, and found that enalapril significantly decreased macrophages-avid nanoparticle signal by using sensitive positron emission tomography-computed tomography (PET-CT) imaging, and reduced a number of myeloid cells in the graft, blood, and lymph nodes by histology and flow cytometry, suggesting that angiotensin-converting enzyme inhibitor significantly prolong allograft survival.

Spinal cord stimulation causes significant symptomatic improvement in many patients with refractory angina pectoris [37, 47-49], and the mechanism underling this beneficial response is not fully known [50-53]. Hautvast [54] assessed the effect of spinal cord stimulation on myocardial blood flow by positron emission tomography in patients with refractory angina pectoris, and found that after 6 weeks of stimulation, both frequency of daily anginal attacks and nitrogen consumption decreased, and the coefficient of variation of flow, representing flow heterogeneity, decreased after treatment, both at rest and after dipyridamole stress, suggesting that spinal cord stimulation is clinically effective due to homogenization of myocardial blood flow. Posma et al. [55] also reported a redistribution of myocardial flow during dual chamber pacing in a patient with non-obstructive hypertrophic cardiomyopathy by positron emission tomography, suggesting that early septal activation reduced septal fibre strain and blood flow and increased septal perfusion reserve.

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Disclosure of conflict of interest

None.

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