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Assessment of Vascular Reactivity with Positron Emission Tomography

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Positron Emission Tomography (PET) is the most advanced scintigraphic imaging technique developed for *in-vivo* assessment of cardiac (patho)physiology and biochemistry. The currently available PET technology allows the measurement of regional tracer activity with high spatial and temporal resolution. During recent years several radiopharmaceuticals have been developed to study myocardial perfusion enabling accurate diagnosis and risk stratification of coronary artery disease (CAD). The quantitative assessment of myocardial blood flow at rest and under stress conditions and the calculation of (regional) coronary flow reserve by N-13 ammonia, Rb-82 or O-15 water PET is the most sensitive means to detect any abnormal vasoreactivity which has already been found at very early stages of the atherosclerotic process before any angiographic or clinical evidence of CAD. Importantly, available flow tracers provide also quantitative information on the haemodynamic effects of any local, invasive (angioplasty) or systemic (risk factor modification) intervention supporting the use of PET methodology for drug research and evaluation in clinical cardiology. *J Clin Basic Cardiol 2001; 4: 135–138.*

Key words: PET, flow, coronary artery disease

For more than 10 years, positron emission tomography (PET) has been the most sophisticated scintigraphic imaging technique targeting on *in-vivo* quantification of cardiac (patho)physiology and biochemistry. Since its introduction into clinical medicine the use of PET has been rather restricted due to its limited availability and high costs. The role of clinical PET is being redefined due to (1) the increasing amount of data from clinical trials on its relevance for patient management and (2) better availability of this technique. This overview will focus on the current role of clinical applications of PET imaging in coronary artery disease (CAD) with a perspective on future developments.

Measurements of Myocardial Blood Flow

a) Blood flow tracers

Blood flow tracers (Table 1) can be classified based on their physiologic behavior. Oxygen-15 water for example represents a freely diffusible tracer, which washes in and out of myocardial tissue as a function of blood flow. The first pass extraction of O-15 water in the heart is neither diffusion limited nor is O-15 water tissue extraction affected by any metabolic pathways. Oxygen-15 water represents an almost ideal tracer for the assessment of myocardial blood flow over a wide flow range [1–3]. The time course of tissue O-15 activity can be modeled by a single tissue compartment using the blood pool activity as the input function. The second group of flow markers are tracers, which are retained in myocardial tissue proportional to myocardial blood flow. For these

radiopharmaceuticals the initial tracer extraction (first pass extraction) and their tissue retention are important factors defining their suitability as blood flow tracers. N-13 ammonia is highly extracted by myocardial tissue in the form of N-13 ammonia [4]. Within the tissue the tracer can either back-diffuse into the vascular space or be trapped in the form of N-13 glutamine whereby the relative activity retained in myocardial tissue following extraction varies from 60 % to 80 % [4, 5]. The rate limiting step for the tissue retention of N-13 ammonia is the glutamine synthetase reaction. This metabolic pathway is energy dependent and can be altered by extreme pathophysiological conditions (pH, ischaemia) as well as pharmacological interventions inhibiting transaminations. Ionic tracers among which rubidium-82 is most common, display similar tracer kinetics to thallium-201 [6]. Initial extraction of these compounds ranges between 50 to 70 %. For both N-13 ammonia retention and ionic tracer extraction, a nonlinear relationship exists between blood flow and tissue tracer extraction. With increasing flow rates the transport of radiopharmaceuticals into the cell or their metabolic trapping (N-13 ammonia) becomes rate limiting, resulting in reduced net tissue retention fraction. Such a nonlinear relationship between tracer tissue uptake and blood flow restricts the ability to quantitate myocardial perfusion based on tissue tracer concentration, alone, which is why correction factors or mathematical models were introduced to compensate for the known decrease of tracer extraction fraction at higher flow states [7, 8].

Rb-82 and N-13 ammonia are the tracers most commonly used. At the beginning most of the studies employed visual data analysis, as it has been clinical routine for Tl-201 and Tc-99m-SPECT imaging [4, 9]. The next step was the introduction of semiquantitative analysis [10–13]. Quantification of myocardial blood flow of attenuation corrected PET images by the use of volumetric approaches has opened up the spectrum for the clinical use of myocardial perfusion imaging [14].

b) Clinical applications of blood flow measurements in coronary artery disease

Measurements of myocardial blood flow at rest and under stress conditions allow the non-invasive determination of

Table 1. Tracers for routine cardiac PET studies

Radionuclide	Half-life	Radiopharmaceutical	Application
Rb-82	76 sec	Rubidium	Blood flow
O-15	2 min	Water	Blood flow
N-13	10 min	Ammonia	Blood flow
C-11	20 min	Acetate	Blood flow
F-18	110 min	Deoxyglucose	Oxygen consumption Glucose metabolism

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coronary flow reserve (CFR) [15]. CFR has been measured accurately, reproducibly, and non-invasively by N-13 ammonia, Rb-82 and O-15 water PET. Stress can be evoked by exercise, physically (cold pressure test) or pharmacologically. Most studies employed pharmacological stress using dipyridamole or adenosine. Resting myocardial blood flow reaches about 60–100 ml/100g/min in healthy subjects and is unchanged only in patients with mild to moderate coronary stenosis, while calculating CFR from rest and stress studies is a very sensitive means to detect vascular abnormalities [8, 16–21]. In fact, stenosis severity has been linked to the restriction in myocardial blood flow under stress and correlated with the decrease in CFR [19–21]. Even a 30 % to 40 % diameter stenosis has been associated with a reduction in CFR [19]. It is notable, that the extent of the reduction in CFR may be rather variable due to local vascular factors such as lesion geometry and concomitant changes in microvasculature and flow-dependent endothelium-mediated epicardial vasodilation [19, 22]. However, Demer et al. have demonstrated a close agreement between the severity of perfusion defects in PET and angiography [23]. These data underline that myocardial perfusion imaging with PET is more sensitive than SPECT leading to a 10 % gain in diagnostic accuracy. No differences in sensitivity could be found between the different tracers used. Thus, N-13 ammonia and Rb-82 PET have been shown to detect CAD with comparable sensitivity [23]. An improved sensitivity as compared to SPECT and the high accuracy has led to the assumption that rest-stress PET perfusion imaging might be more cost-effective in diagnosing patients with a low or intermediate likelihood of CAD as compared to conventional rest-stress myocardial perfusion scintigraphy.

Flow measurements with PET allow not only the documentation of a restricted CFR in patients with cardiovascular risk factors [17, 18, 24] and a familial history of CAD [16] but also the monitoring of therapeutic interventions (Table 2). Primary and secondary prevention studies have impressingly demonstrated an improvement in coronary events after intense risk factor modification [25–27]. The reduction in “hard” end points has been attributed to the stabilization of lipid-rich plaques, prevention of their formation, improvements on the microvasculature and flow-mediated vasodilation (endothelial function) rather than on stenosis regression [28, 29]. From several observations it seems rather plausible that both changes in microvasculature and flow-mediated vasodilation, an endothelium-dependent function, could be assessed by PET perfusion imaging. An improvement in CFR could be documented by PET imaging in patients with manifested CAD after a 4-week therapy with simvastatin, a mem-

ber of the HMG-CoA reductase inhibitor family [22]. The fact that improvements had been only seen in the stenosed vessel area led to the conclusion that mainly changes in flow-mediated vasodilation but not in the microvasculature were responsible for the documented improvement in CFR. Lipid lowering with fluvastatin, another synthetic HMG-CoA reductase inhibitor induced an improvement in CFR after 6 months of lipid lowering therapy while no effects were seen after 3 months of therapy [30]. It is interesting that the improvement in CFR relates to the observed statistical clinical benefit in lipid lowering trials after about 9 months. Altogether, these findings suggest that PET perfusion imaging might serve as a surrogate marker of cardiac vascular function. However, prospective studies are needed to determine whether (quantitative) perfusion imaging with PET provides prognostic impact in patients at increased risk for CAD.

c) PET and other new imaging modalities: competitive or additive?

Cardiac PET is the gold standard for the assessment of myocardial viability and for the non-invasive quantification of myocardial blood flow even when evaluating new, advanced imaging technologies [31]. The relation between coronary calcification and vascular reactivity is another major field of interest because electron beam computed tomography (EBCT) or ultrafast CT might be promising tools for the initial evaluation of asymptomatic subjects at risk for CAD facilitating risk stratification and, in consequence, the decision making on further diagnostic (scintigraphic) tests and therapeutic interventions [32]. Both exercise treadmill testing and conventional myocardial perfusion imaging with SPECT exhibited a low incidence of abnormal stress tests, which excludes their use as primary screening tests for early detection of CAD. In consequence these tests have limited value in the diagnostic work up of asymptomatic subjects and have been not recommended [33, 34]. Preliminary results might support the use of EBCT as a primary screening tool for the identification of high-risk subjects with subclinical CAD in whom early diagnosis and aggressive treatment seem advisable and cost-effective [32]. However, incertitude persists on the value of EBCT in asymptomatic subjects [35, 36]. Current evidence suggests (1) an increased prevalence of coronary calcium in adolescents and young adults with familial hypercholesterolemia [37, 38], (2) an association between increased coronary artery calcification and the development of clinically manifested CAD [39–40] and (3) an association between the severity of coronary calcification and the frequency of exercise-induced perfusion abnormalities [41]. It is im-

Table 2. Clinical applications of myocardial blood flow studies with PET

Application		Author
<i>Diagnosis</i> (Pre)clinical stage	Conditions with impaired vascular reactivity: positive history of CAD, familial hypercholesterolaemia, diabetes, mental stress	Dayanikli [16], Demer [23], Kao [46], Pitkanen [24], Yokoyama [45]
<i>Definition of extent</i> Risk stratification	Haemodynamic relevance of lesions, area at risk	Beanlands [21], DiCarli [19], Uren [20]
<i>Therapeutic monitoring</i> (Pre)clinical stage	Effects of: • Risk factor modification: hyperlipidaemia, cardiovascular conditioning • Pharmacological therapy (ACE inhibitors, Vitamin C) • Revascularization • Transplantation • Angiogenesis therapy	Gould [48], Guethlin [30], Huggins [22], Czernin [47] Kaufmann [49], Schneider [50], Stewart [51] Wolpers [52], Zhao [53] Udelson [54]

portant to note that the incremental value of EBCT over traditional multivariate risk assessment has not yet been established [42] while this has been the case for SPECT [43]. Taken together with the large evidence from studies using PET methodology, even in asymptomatic subjects it is plausible that the measurement of vasodilator reserve represents the most reliable functional parameter of coronary health.

Perspectives

The unique functional information provided by cardiac PET is increasingly relevant for a more effective management of patients with different cardiovascular diseases. The clinical acceptance, however, will depend on availability, cost and accuracy of scintigraphic information in comparison to other existing or developing alternative imaging modalities.

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