European Journal of Radiology 85 (2016) 1900–1908

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Imaging of the myocardium using ^{18}F-FDG-PET/MRI

Jiří Ferda (M.D. Ph.D Prof.)[a,*], Milan Hromádka (M.D. Ph.D)[b], Jan Baxa (M.D. Ph.D)[a]

[a] Clinic of the Imaging Methods, University Hospital Plzen, Alej Svobody 80, 304 60 Plzeň, Czech Republic
[b] Department of Cardiology, University Hospital Plzen, Alej Svobody 80, 304 60 Plzeň, Czech Republic

ARTICLE INFO

Article history:
Received 23 March 2016
Received in revised form 17 July 2016
Accepted 19 July 2016

Keywords:
Myocardium
Positron emission tomography
PET/MRI
Fluorodeoxyglucose

ABSTRACT

The introduction of the integrated hybrid PET/MRI equipment creates the possibility to perform PET and MRI simultaneously. Depending on the clinical question, the metabolic conversion to glycolytic activity or beta-oxidation is performed before the application of FDG. Since FDG aids to evaluate the energetic metabolism of the myocytes and myocardial MRI reaches the imaging capabilities of perfusion and tissue characterization in the daily routine, FDG-PET/MRI looks to be a promising method of PET/MRI exploitation in cardiac imaging. When myocardial FDG uptake should be evaluated in association with the perfusion distribution, the cross-evaluation of FDG accumulation distribution and perfusion distribution pattern is necessary. The different scenarios may be used in the assessment of myocardium, the conversion to glycolytic activity is used in the imaging of the viable myocardium, but the glycolytic activity suppression might be used in the indications of the identification of injured myocardium by ischemia or inflammation. FDG-PET/MRI might aid to answer the clinical tasks according to the structure, current function and possibilities to improve the function in ischemic heart disease or to display the extent or activity of myocardial inflammation in sarcoidosis. The tight coupling between metabolism, perfusion and contractile function offers an opportunity for the simultaneous assessment of cardiac performance using one imaging modality.

1. Introduction

Hybrid imaging has brought a powerful tool to clinical practice that combines several advantages of both morphological and metabolic imaging. During the last two decades, ^{18}F-fluorodeoxyglucose (FDG) has changed the clinical spread of positron emission tomography (PET) imaging like no other molecule. The universal and achievable behaviour of FDG predicts it to be widely available every day and everywhere. Since its first years, PET/CT using FDG has played a crucial role in oncological imaging. Due to the technical difficulties in the co-existence of the PET acquisition system with the high magnetic field, the clinical use of PET/MRI was delayed for about fifteen years. Oncological imaging using FDG also still looks dominant in the current indications of PET/MRI. The introduction of the integrated hybrid PET/MRI equipment creates the possibility to perform PET and MRI simultaneously. The advent of this new technique has introduced the idea of new concepts in myocardial imaging [1,2], respecting all contraindications of the MRI in patients with incompatible implants or claustrophobia. As magnetic resonance is the gold standard *in vivo* technique in the assessment of the myocardial structure, positron emission tomography has become the gold standard of the *in vivo* investigation of its metabolism. The synergy in myocardial imaging should be the driving force of myocardial PET/MRI concept. Due to the advantage of the choice, the selection of the most effective way to assess myocardial perfusion, metabolism and function has to be evaluated and the possible role of myocardial PET/MRI has to be claimed. Since FDG aids to evaluate the energetic metabolism of the myocytes [3] and myocardial MRI reaches the imaging capabilities of perfusion and tissue characterization in the daily routine, FDG-PET/MR looks to be a promising method of PET/MRI exploitation in cardiac imaging, even if other tracers like ^{13}N-ammonium, ^{15}O-water, ^{82}Rb-rubidium-chloride, ^{18}F-flurpiridaz or ^{11}C-palmitate may be used in cardiac PET.

2. Myocardial energy metabolism and FDG uptake

A major role of FDG use in PET myocardial imaging is played by the relationship between β-oxidation or oxidative glycolysis based energy metabolism [4]. Myocardial energy metabolism depends on the oxidation of various substrates. Under fasting conditions, the myocardium uses almost all energy for the production of adenosine

* Corresponding author.
E-mail addresses: ferda@fnplzen.cz (J. Ferda), hromadkam@fnplzen.cz (M. Hromádka), baxaj@fnplzen.cz (J. Baxa).

http://dx.doi.org/10.1016/j.ejrad.2016.07.014
0720-048X/

triphosphate (ATP) during the oxidation of free fatty acids [5]. Fasting decreases plasma glucose levels rapidly, and the free fatty acids levels become high. The extraction of fatty acids by the myocardium is enhanced, and long-chain acyl-coenzym A (CoA) is increasingly formed. Even the activated fatty acids could be used in triacylglycerol or phospholipids building, as fasting facilitates their role in energy metabolism. Fatty acid energy-based metabolism takes place inside the mitochondrion. Acyl-CoA is useful as a source of substrate of β-oxidation and the majority is used in ATP synthesis. However, the molecule of acyl-CoA is too large to be transported into the mitochondria, the carnitine shuttle aids to pass the long-chain fatty acids with more than 15 acetate parts. The product of the β-oxidation acetyl-CoA then enters the cycle of Krebs (tricarboxylic acid cycle), the final pathway of the oxidative metabolism of all substrates. When the insulin plasma level is low and free fatty acids levels increase, only a small amount of the glucose is extracted by the myocardium [6,7]. However, when the glucose level increases, the energetic role of the oxidative glycolysis becomes more important. In a postprandial state, one-third to one-half of energy used by the myocardium depends on oxidative glycolysis [8].

Beyond the physiological conditions, the state after myocardial ischemia is the situation in which the up-regulation of the oxidative glycolysis becomes the one-way energetic pathway [9–11]. Nonetheless, not only the acute situation of the ischemia enhances the glycolysis; the glucose metabolism also remains for several weeks after the ischemic episode, partially due to inflammatory cell immigration into the insulted myocardium, partially when the myocardium is hibernating, even if the myocardium is recovering in normal perfusion conditions and functional ability (Fig. 1).

The FDG molecule looks very similar to that of glucose, only the OH group is replaced by the fluorine. A very similar molecular appearance is responsible for FDG behaviour [3]. FDG accumulates in the myocardial tissue proportionally according to the glucose transport and phosphorylation, and even FDG exhibits a slightly different affinity to transporters and phosphatase compared to glucose. The utilization of the glucose does not have a uniform pattern in the entire heart, and, consequently, the inhomogeneous FDG uptake distribution is obvious [8]. Copying the glucose metabolism, the lateral wall of the left ventricle exhibits a more homogenous and more intense distribution of FDG [9,12].

Because of the outlined variability of the energetic sources, the major role in myocardial metabolic conversion belongs to the patient's dietary preparation and pharmacological intervention. As during fasting conditions, the glucose levels are decreasing, therefore the metabolism of the myocardium converts towards fatty acid β-oxidation. This fact makes the PET images after intravenous administration of FDG poor and of unstable quality [13]. However, the fasting state before the imaging has been applied to detect the ischemic myocardium after physical exercise. Fasting helps to identify myocardial infarction, infarcted tissue exhibits an increased level of glucose metabolism not only due to the myocardial glucose conversion, but also due to the migration of inflammatory vectors such as macrophages and/or activated fibroblasts. To be able to delineate the normal myocardium, it is necessary to make its glucose metabolism as low as possible. An effective way to suppress glycolytic activity in normal myocytes is a low carbohydrate and high fat diet (the Atkins diet) [14]. There is also an alternative way to myocardial conversion to fatty acid exploitation. The intravenous administration of un-fractioned heparin leads to rapid conversion to β-oxidation in the myocardium. Having a direct impact on lipoprotein lipase activation, the heparin causes the elevation of the plasma free fatty acids levels and switches the normal myocytes almost exclusively to β-oxidation [15].

The metabolic switch almost exclusively to glucose is the important challenge in the assessment of myocardial viability. The main strategy is to offer to the myocardium such a glucose overload that myocytes are able to diminish the β-oxidation and the forced glucose extraction results in high FDG uptake. There is a traditional approach and an alternative one. Some centres advocate the hyperinsulinemic-euglycemic clamp – to intravenously administer insulin and glucose simultaneously under control of normal glucose plasma levels. The main intent is to standardize the glucose metabolism within the whole myocardium, but the most important disadvantage is the complicated procedure [16]. An easier way to convert the myocardium to glycolysis is the oral glucose load. Oral glucose administration increases plasma insulin level and accelerates the glycolytic activity and decreases the plasma fatty acid level. Oral glucose load very effectively forces the conversion in non-diabetic patients. In diabetics, there are two main problems in myocardium glycolytic conversion. High glucose plasma levels lead to the limited ability of the myocardium to extract FDG. The second very important problem could be the insensitivity of some diabetics to insulin, which has a key role in metabolic switching [6,7].

The classic approach of the FDG uptake evaluation is based on proportional assessments according to myocardial perfusion [16,17]. Proven concepts include the perfusion evaluation using PET tracers such as ^{15}O-H_2O, ^{13}N-NH_3 or ^{82}Ru. PET-based perfusion imaging could be successfully replaced by SPECT imaging using ^{99m}Tc labelled methoxy-lisobuthyl-isonitril or ^{201}Tl. However, cardiac magnetic resonance offers perfusion imaging based on the first pass of the gadolinium contrast agent (Fig. 4).

3. Myocardial gadolinium imaging during PET/MRI

Gadolinium-based contrast agents have been used for thirty years to involve the tissue behaviour in T1 weighted images (with a known influence also in T2 weighted images). Gadolinium based contrast agents (GBCA) have also been used in myocardial imaging for the past two decades, and the possibilities of myocardial imaging using magnetic resonance and the GBCA application have been studied intensively. Concerning the myocardium, multiparametric ECG synchronized cardiac magnetic resonance imaging (CMRI) included kinetic studies, the first past perfusion imaging and the evaluation of the myocardial structure, including the late gadolinium enhancement evaluation. Using the basic sequences, the associate findings such as pericardial fluid or valvular disease could be found at the same time. With respect to specific questions like flow quantification, valve regurgitation or contractile myocardial function, the sequences targeting blood flow (phase contrast imaging) or myocardial contractility (myocardial tagging) may be used.

Multiple studies assessed the clinical relevance of flow-limiting coronary artery disease (CAD). CMRI detected more cases of obstructive coronary artery disease without increasing the false-positive rate; however, the sensitivity of nuclear stress testing is significantly lower than had previously been published. Very few centres now use CMRI for the diagnosis of CAD given the lack of experienced clinicians able to perform the study, the inability to perform exercise stress CMRI, and patient issues including claustrophobia and relatively long imaging times. Nevertheless, studies were able to show that CMRI can serve as an alternative to stress echocardiography and nuclear stress testing when evaluating patients for obstructive CAD (Fig. 7).

When myocardial FDG uptake should be evaluated in association with the perfusion distribution, the cross-evaluation of FDG accumulation distribution and perfusion distribution pattern is necessary. Modelling of the myocardial flow using GBCA is completely different than that used in PET. PET flow modelling is based on indicator extraction by cardiomyocytes, so it uses intracellular uptake of the tracer. Because neither the time resolution nor