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News & Views

Prognostic value of global flow reserve assessed by cardiac ^{82}Rb PET

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Evaluation of: Fukushima K, Javadi MS, Higuchi T *et al*. Prediction of short-term cardiovascular events using quantification of global myocardial flow reserve in patients referred for clinical ^{82}Rb PET perfusion imaging. *J. Nucl. Med.* 52(5), 726–732 (2011).

This American retrospective study on 275 patients, tried to assess the global myocardial flow reserve (MFR) value as a marker of cardiovascular disease development and progression (death, myocardial infarction, coronary revascularization or hospital readmission) within the first 1–2 years after the test.

At present, global flow reserve of the coronary circulation is considered to be an important component of coronary artery disease (CAD) owing to its macroscopic flow limit and coronary microvascular dysfunction. However, in clinical practice, global MFR is not routinely measured. Some studies have demonstrated the potential of PET to quantify myocardial blood flow (MBF) and global MFR. MFR was determined with an experimentally validated approach as the ratio of stress MBF to corrected rest MBF.

Summed stress score and MFR were independent predictors of a cardiovascular adverse event and, if restricted to patients without any perfusion abnormalities, higher MFR was strictly associated with better outcome. Reduced global flow reserve was suggestive of short-term adverse events in the entire study population, including, most interestingly, a subgroup of patients who demonstrated no evidence of significant disease with other tests. This finding is thought to reflect microvascular dysfunction as a consequence of atherosclerotic risk factors and therefore represents an early stage of cardiovascular disease.

Some studies showed that impaired flow dynamics in patients with a single risk factor such as hyperlipidemia, insulin resistance or tabagism can be improved by different therapeutic approaches, suggesting that it is a reversible state.

Conversely, the situation of patients with obstructive and flow-limiting CAD is composite: in this setting, global flow reserve reflects a combined marker of macroscopic stenosis and microvascular dysfunction. These can be distinguished only with CT angiography or perfusion imaging. One more MFR application field could be the balanced ischemia in the absence of regional flow heterogeneity, identifying a state of high risk of adverse events.

In conclusion, this study suggested that global flow reserve has prognostic value in subjects referred for work-up of CAD. For this group of patients the calculation of MFR could be introduced for early detection of coronary artery disease.

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Myocardial perfusion reserve improvement in patients with ischemic cardiac disease after prolonged prostaglandin E1 administration

Evaluation of: Huang CL, Wu YW, Wang SS *et al.* Continuous intravenous infusion of prostaglandin E1 improves myocardial perfusion reserve in patients with ischemic heart disease assessed by positron emission tomography: a pilot study. *Ann. Nucl. Med.* doi: 10.1007/s12149–011–0487-x (2011) (Epub ahead of print).

This double-blind, placebo-controlled trial investigated the effects of prostaglandin E1 (PGE1) therapy in terms of reduction of perfusion abnormalities and increase of myocardial perfusion reserve (MPR) on patients affected by heart failure and myocardial ischemia. For 4 weeks, 11 randomly assigned patients were infused with PGE1 (eight patients) or saline (three patients), and underwent stress and rest ^{13}N-ammonia PET scans at baseline and 12 weeks after treatment completion.

The tissue effect of PGE1 is still blurred: studies on heart transplant candidates treated with PGE1 demonstrated significantly increased capillary density in explanted hearts, and benefits have been attributed to vasodilatation and antiproliferative effects on vascular smooth muscle cells. PET, compared with SPECT, offers the exclusive potential to measure the absolute value of myocardial blood flow (MBF) and, as a consequence, the MPR value (ratio of hyperemic to resting MBF). Contrary to MBF, a decrease of MPR is an early predictor of coronary stenosis. An abnormal MPR can be caused by thinning of the epicardial coronary arteries or may reflect impairment of microcirculation, which may be due to neurohormonal factors or endothelial dysfunction, without evidence of angiography alteration.

This study demonstrated that patients who underwent PGE1 therapy had mild but significant MPR improvement up to 12 weeks, while in the control group both the stress MBF and MPR significantly declined. On further examination, the majority of MPR improvement in the PGE1 group came from nonviable and ischemia segments. It has to be noted that persistence of MPR improvement could not be explained only by the well known vasodilator effect of PGE1.

Some studies have demonstrated a correlation between PGE1 and upregulation of VEGF in cardiac myocytes, therefore suggesting PGE1 has a role in angiogenesis. However, this study did not show any stress MBF improvement after PGE1 therapy and the majority of MPR improvement came from lowering MBF at rest. Nonetheless, considering the significant MPR improvement and its prognostic value, this study suggests that 4-week PGE1 therapy potentially reduces cardiovascular risk in patients with refractory angina.

Parametric perfusable tissue index images generation based on a ^{15}O-H_2O PET scan without an additional ^{15}O-CO blood-pool scan: a validation study

Evaluation of: Harms HJ, de Haan S, Knaapen P *et al.* Parametric images of myocardial viability using a single ^{15}O-H_2O PET/CT scan. *J. Nucl. Med.* 52(5), 745–749 (2011).

This is a validation study for the generation of parametric perfusable tissue index (PTI) images based on a ^{15}O-H_2O PET/CT scan without an additional ^{15}O-CO blood-pool scan. PTI is considered a validated indicator of viable hibernating myocardium. Hibernating myocytes, differently from death cells, are able to recuperate contractility following revascularization, leading to improved cardiac function and better prognosis ^{15}O-H_2O PET is considered the gold standard for obtaining a myocardial blood flow (MBF) value that, when integrated with a blood volume scan obtained by ^{15}O-CO, enables the calculation of PTI. PTI is described as the ratio of water perfusable tissue fractures (PTFs) and anatomic tissue fractions. PTF is, together with MBF, obtained from a ^{15}O-H_2O scan, while anatomic tissue fraction is calculated by

subtracting a normalized ^{15}O-CO blood-pool image from a transmission scan. Unfortunately, the ^{15}O-CO scan has no other clinical use.

The use of low-dose CT in cardiac PET has decreased overall scan time and thus risk of patient motion. In addition, an upgrade in detector efficiency and implementation of basis-function methods have permitted accurate estimation of MBF at a voxel level, resulting in parametric images of diagnostic quality.

When calculating MBF images, additional images of PTS, arterial and right-ventricular blood volume and spill-over fractions are also acquired. Being calculated from the same dynamic scan, all these images are not submitted to interscan patient motion. As a result, parametric PTI images of diagnostic quality are generated using blood volume fraction images through a fast 'low-dose' CT scan.

This validation study was carried out on 20 patients with known or suspected ischemic cardiopathy studied with both ^{15}O-H_2O and ^{15}O-CO scan on a standalone PET scanner plus ten patients investigated only with ^{15}O-H_2O PET/CT scan.

In conclusion, the proposed method provides parametric PTI images of diagnostic quality, enabling simultaneous imaging of myocardial viability and perfusion-based exclusively on a 10 min ^{15}O-H_2O PET/CT scan.

Comparison between myocardial and peripheral perfusion reserve assessed by ^{13}N-ammonia PET

Evaluation of: Scholtens AM, Tio RA, Willemsen A *et al.* Myocardial perfusion reserve compared with peripheral perfusion reserve: a [^{13}N] ammonia PET study. *J. Nucl. Cardiol.* 18(2), 238–246 (2011).

It is well known that conditions such as hypercholesterolemia and diabetes mellitus, are both risk factors for coronary artery disease (CAD), and induce a reduction in vasodilatation response to substances such as adenosine and dipyridamole. It is similarly known that PET is an accurate tool for the quantification of myocardial perfusion reserve (MPR), which is an important prognostic parameter in patients with CAD.

The aim of this Dutch study is to clarify if there is a correlation between peripheral and myocardial flow behavior during the same ^{13}N-ammonia PET scan rest and adenosine stress test. Since myocardial perfusion and peripheral perfusion were calculated in the same scans, all conditions, such as blood pressure and heart rate, were identical for both measurements. The amount of peripheral perfusion was obtained drawing six regions of interest around the upper limb (opposite to the injected arm) in six consecutive slices and then copied to the dynamic sequences to obtain time activity curves. MPR and peripheral perfusion flow reserves were then calculated as the ratio of stress and rest study perfusion results. Patients were collected from four different clinical situations: a documented CAD, a microcardiovascular disease (cardiac syndrome X), an idiopathic dilating cardiomyopathy and normal controls. Predictably, coronary perfusion increased more than two times in healthy controls in response to the adenosine infusion, while in the other three groups sufficient vasodilatation was prevented.

The results showed no significant correlations between peripheral perfusion reserve and MPR during adenosine infusion either for the group as a whole or any of the subgroups. A feasible rationalization for this difference has been described: as resting myocardial blood flow is approximately 20-times higher than in the periphery and total delivered dose of adenosine is flow dependent, the dose to the myocardial vessels will be approximately 20-times higher than peripherally. This may explain the minimal consequence of adenosine on the peripheral blood flow in all four patient groups, since a threshold dose may not be reached.

In conclusion, this study confirmed the different response of myocardial and peripheral blood flow to the vasodilative effects of adenosine infusion.