Glucose metabolism as a marker of myocardial ischemia

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Abstract
Although the heart is omnivorous, glucose becomes the key substrate under conditions of stress. The utilization of exogenous glucose by the myocardium can be assessed non-invasively using positron emission tomography (PET) with the glucose analogue 18F-fluorodeoxyglucose (FDG). Several studies have demonstrated that glucose utilization is increased at peak stress and during conditions of reduced oxygen supply. Moreover, glucose utilization remains elevated after an episode of transient ischemia, which constitutes a sort of “metabolic memory”. PET with FDG also permits the identification of “hibernating myocardium”. This allows a more accurate stratification of patients with post-ischemic left ventricular dysfunction and identification of those that might benefit most from coronary revascularization.

Keywords: coronary artery disease; myocardial metabolism; myocardial ischemia; positron emission tomography.

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Introduction
The human heart in the fasting state extracts free fatty acid (FFA), glucose, lactate, pyruvate, and ketone bodies from the systemic circulation. A small but consistent net uptake of circulating glucose by the heart is normally demonstrable in the fasting state with a reported arterial-venous (AV) difference ranging from 0.15 to 0.23 mmol/l, corresponding to an oxygen extraction ratio of ~27%. Measurements of the rate of glucose oxidation by radiolabelled techniques in healthy volunteers have shown that, at the most, only about 30% of the glucose uptake is rapidly oxidized, and about 15% is converted to lactate [1].

Cardiac glucose metabolism during fasted and fed states
There is a general consensus that FFA is the major fuel for cardiac muscle in the fasting, post-absorptive state. In various studies using the coronary sinus (CS) catheterization technique, net uptake of FFA from the arterial circulation has been found consistent. At arterial FFA levels in the 0.5 to 0.9 mmol/l range, the reported AV differences is 0.14 to 0.20 μmol/ml, which correspond to oxygen extraction ratios of up to 40%. If a total coronary blood flow of ~250 ml/min is assumed, then the heart of fasting subjects at rest consumes up to about 50 μmol/min of FFA, or up to 10% of the whole body FFA turnover (8 μmol/min/kg), despite receiving only 5% of cardiac output. In general, the fate of FFA is largely complete oxidation in the Krebs’ cycle with a lesser component undergoing re-esterification to tissue triglycerides. The fact that the
respiratory quotient of the heart in the fasting state is on average 0.74 indicates that the greater part of the extracted FFA is oxidized [1] (Fig. 1).

The oxidative use of lipid (FFA) and carbohydrate (glucose and lactate) fuel is reciprocally regulated through the operation of Randle’s cycle [2]. Feeding, by increasing both insulin and glucose concentrations shifts myocardial metabolism towards preferential carbohydrate usage, both for oxidative energy generation and for glycogen synthesis (Fig. 1).

Cardiac glucose metabolism during conditions of reduced oxygen supply

During conditions of reduced oxygen supply, the oxidation of all substrates is decreased while anaerobic metabolism is activated (Fig. 2). In patients with coronary artery disease (CAD) and stable angina pectoris, net lactate release in the CS can be demonstrated during pacing stress. However, this occurs in only 50% of patients, and no relationship can be demonstrated between lactate production and the severity of ischemia [3]. In patients with chronic angina, a significant release of alanine in the CS and an increased myocardial uptake of glutamate could be demonstrated at rest and following pacing [4–5]. These two phenomena result from increased transamination of excess pyruvate to alanine with glutamate serving as NH2 donor. In addition, release of citrate (a known inhibitor of glycolysis) in the CS can be demonstrated following pacing in patients with stable angina.

Positron emission tomography

The utilization of exogenous glucose by the myocardium can be assessed using positron emission tomography.
PET with the glucose analogue $^{18}$F-fluorodeoxyglucose (FDG). FDG is transported into the myocyte by the same trans-sarcolemmal carrier as glucose and is then phosphorylated to FDG-6-phosphate by the enzyme hexokinase. This is essentially a unidirectional reaction and results in FDG-6-phosphate accumulation within the myocardium, as no glucose-6-phosphatase (the enzyme that hydrolysates FDG-6-phosphate back to free FDG and free phosphate) has yet been identified in cardiac muscle. Thus, measurement of the myocardial uptake of FDG is proportional to the overall rate of trans-sarcolemmal transport and hexokinase-phosphorylation of exogenous (circulating) glucose by heart muscle.

A number of kinetic modeling approaches have been used for the quantification of glucose utilization rates using FDG. The major limitation of these approaches is that quantification of glucose metabolism requires the knowledge of the lumped constant, a factor that relates the kinetic behavior of FDG to naturally occurring glucose in terms of the relative affinity of each molecule for the trans-sarcolemmal transporter and for hexokinase. Unfortunately, the value of the lumped constant in humans under different physiological and pathophysiological conditions is not known, thus making precise in vivo quantification of myocardial metabolic rates of glucose practically impossible. Still current measurements of the uptake of FDG (particularly if obtained under standardized conditions) allow comparison of absolute values from different individuals and may help to establish the absolute rates of glucose utilization (in FDG units) in normal and pathologic myocardium.

FDG uptake in patients with CAD and stable angina
Different patterns of myocardial glucose utilization have been observed in patients with CAD studied using FDG. In patients with stable angina studied at rest, after overnight fast, regional myocardial glucose utilization was homogeneously low and comparable with that in normal subjects. In contrast, in patients with unstable angina, myocardial glucose utilization at rest was increased even in the absence of symptoms and electrocardiographic signs of acute ischemia [6]. In patients with stable angina, a prolonged increase in FDG uptake could be demonstrated in post-ischemic myocardium in the absence of symptoms or perfusion abnormalities, which suggests a sort of post-ischemic "metabolic memory" [7]. Subsequent studies in animals have indicated that this increased post-ischemic glucose utilization is mainly finalized to replenish myocardial glycogen stores which were depleted during ischemia [1].

PET with FDG for the identification of hibernating myocardium
In the current era of coronary revascularization and thrombolysis, it has become increasingly apparent that restoration of blood flow to asynergic myocardial segments may result in improved regional and global LV function [8–10]. The greatest clinical benefit is seen in those patients with the most severe forms of dysfunction. Initial studies indicated that myocardial ischemia and infarction could be distinguished by analysis of PET images of the perfusion tracer $^{13}$NH$_3$ and the glucose analogue FDG acquired after an oral glucose load. Regions which showed a concordant reduction in both myocardial blood flow and FDG uptake ("flow-
metabolism match") were labeled as predominantly infarcted, whereas regions in which FDG uptake was relatively preserved or increased despite having a perfusion defect ("flow-metabolism mismatch") were considered to represent jeopardized viable myocardium [11]. The uptake of FDG by the myocardium, however, depends on many factors such as dietary state, cardiac workload, and response of the tissue to insulin, sympathetic drive and the presence and severity of ischemia. These factors contribute to variability in FDG imaging in the fasted or glucose-loaded state, confusing data interpretation.

With the recent suggestion that semi-quantitative and quantitative analyses of FDG uptake may enhance detection of viable myocardium, there was an urgent need to rigorously standardize the study conditions. Furthermore, many patients with coronary artery disease are insulin resistant, i.e., the amount of endogenous insulin released after feeding will not induce maximal stimulation due to partial resistance to the action of the hormone. This may result in poor FDG image quality after an oral glucose load. To circumvent the problem of insulin resistance, an alternative protocol has been recently applied to PET viability studies. The protocol is based on the use of the hyperinsuline-mic euglycemic clamp, essentially the simultaneous infusion of insulin and glucose acting on the tissue as a metabolic challenge and stimulating maximal FDG uptake (see Fig. 3). This leads to optimization of image quality and enables PET studies to be performed under standardized metabolic conditions, which allows comparison of the absolute values of the metabolic rate of glucose ($\mu$mol/g/min) amongst different subjects and centers [12].

**Conclusion**

Although the heart is omnivorous, glucose becomes the key substrate under conditions of stress. Several studies have demonstrated that glucose utilization is increased at peak stress and during conditions of reduced oxygen supply. Moreover, glucose utilization remains elevated after an episode of transient ischemia, which constitutes a sort of "metabolic memory". PET with FDG also permits the identification of "hibernating myocardium". This allows a more accurate stratification of patients with post-ischemic left ventricular dysfunction and identification of those that might benefit most from coronary revascularization.

Fig. 3 Myocardial viability in two patients with coronary artery disease and severe chronic left ventricular dysfunction assessed by PET with $^{18}$F-labelled fluorodeoxyglucose (FDG) during hyperinsulinemic euglycemic clamp. Both patients had previous myocardial infarctions. The scan illustrated in panel A shows that FDG uptake in the previously infarcted antero-septal segment is 0.45 $\mu$mol/min/g, suggesting the presence of viable myocardium. In the scan illustrated in panel B the uptake of FDG in the anterior wall and the interventricular septum is significantly reduced (0.14 $\mu$mol/min/g), suggesting absence of viability in this large area. A cut-off point of 0.25 $\mu$mol/min/g is routinely used in our laboratory to differentiate between viable and non-viable myocardium. This cut-off value was derived from our database of patients with coronary artery disease and chronic left ventricular dysfunction who underwent FDG-PET and were subsequently revascularized. The proportion of dysfunctional segments that improved following revascularization increased linearly with FDG uptake. To determine the value of FDG uptake above which the best prediction of improvement in functional class of at least one grade could be obtained, a receiver-operator characteristic curve (ROC) was constructed. According to this analysis the optimal operating point on the curve (point of best compromise between sensitivity and specificity) was at the FDG uptake value of 0.25 $\mu$mol/min/g.
References