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 ^{18}F-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 a fractional uptake of only 3% and to an average 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

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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 NH_2 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

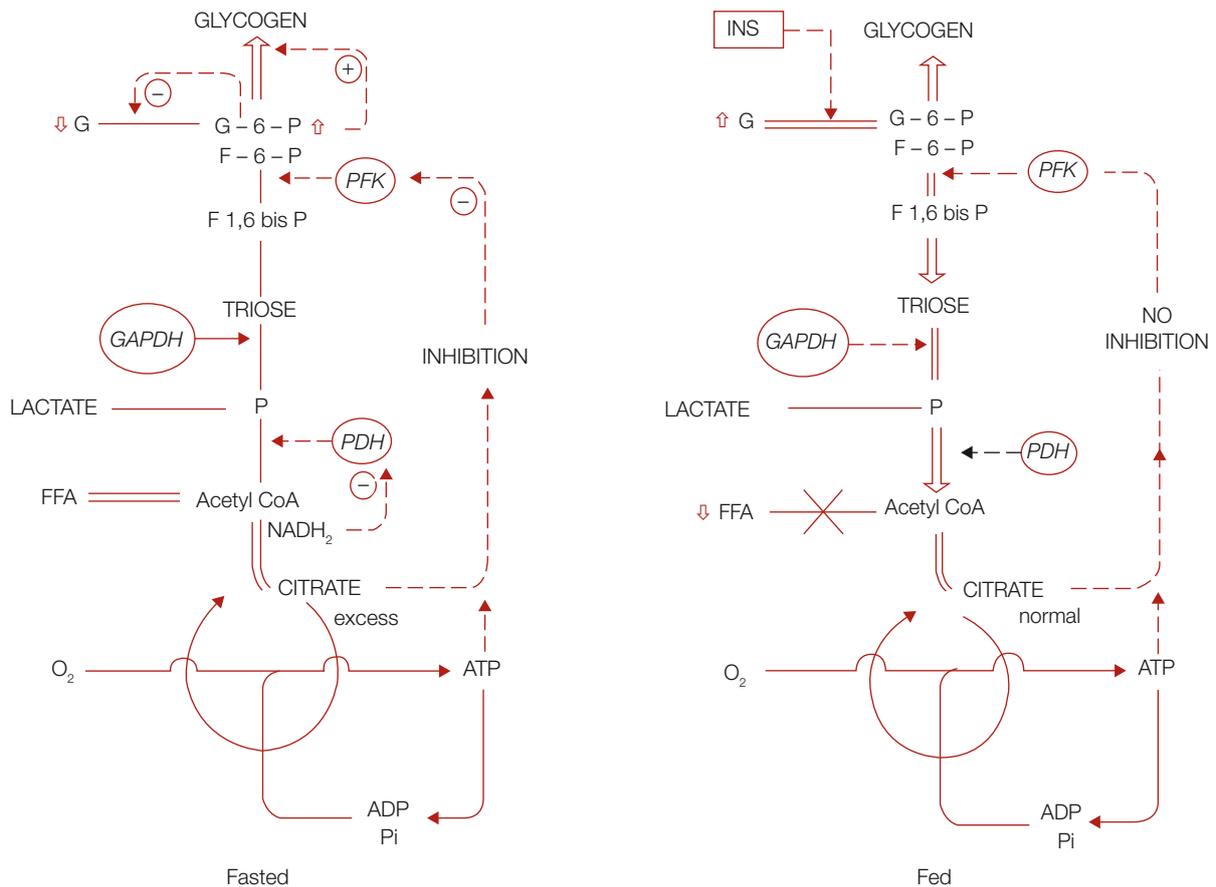The utilization of exogenous glucose by the myocardium can be assessed using positron emission tomography

Fasted

Fed

Fig. 1 **Left panel**: Inhibited glycolysis in fasted state. Overall control of pathways of glycolysis, which is taken as the conversion of G-6-P to P. The inhibition of glycolysis at the level of phosphofructokinase is the result of accumulation of excess citrate during oxidation of FFA. Pyruvate dehydrogenase is inhibited by accumulated $NADH_2$ the result of β-oxidation of fatty acids. **Right panel**: Overall patterns of glycolysis in the fed state. Besides direct acceleration of glucose uptake as a result of high circulating levels of glucose and insulin, there is indirect acceleration of glycolysis as blood FFA levels decrease, and the inhibition of phosphofructokinase by citrate is removed. G-6-P glucose-6-phosphate, P pyruvate, G glucose, F-6-P fructose 1,6 phosphate, PFK phosphofructokinase, F 1,6 bis P fructose1,6 diphosphate, GAPDH glyceraldehyde phosphate dehydrogenase, $NADH_2$ reduced form of nicotine edenine dinucleotide, PDH pyruvate dehydrogenase.
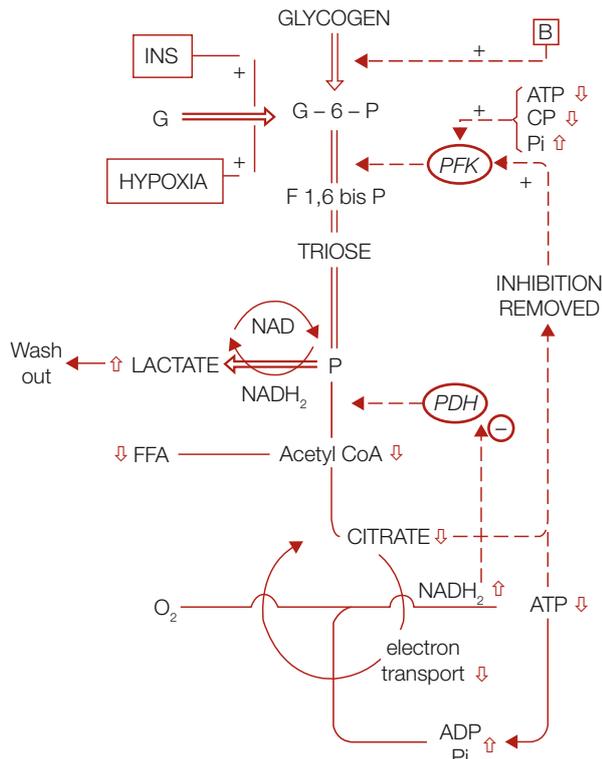
Fig. 2 *Mechanisms whereby mild ischemia increases glycolysis. Note especially a direct effect of hypoxia on glucose transport, and acceleration of phosphofructokinase (PFK) activity by decreasing adenosine triphosphate (ATP), creatin phosphate (CP) and an increase of inorganic phosphate (Pi) as well as a decrease of citrate. Note inhibition of pyruvate dehydrogenase (PDH) by NADH2*

(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 hydrolyses 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-sacolemmal 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-
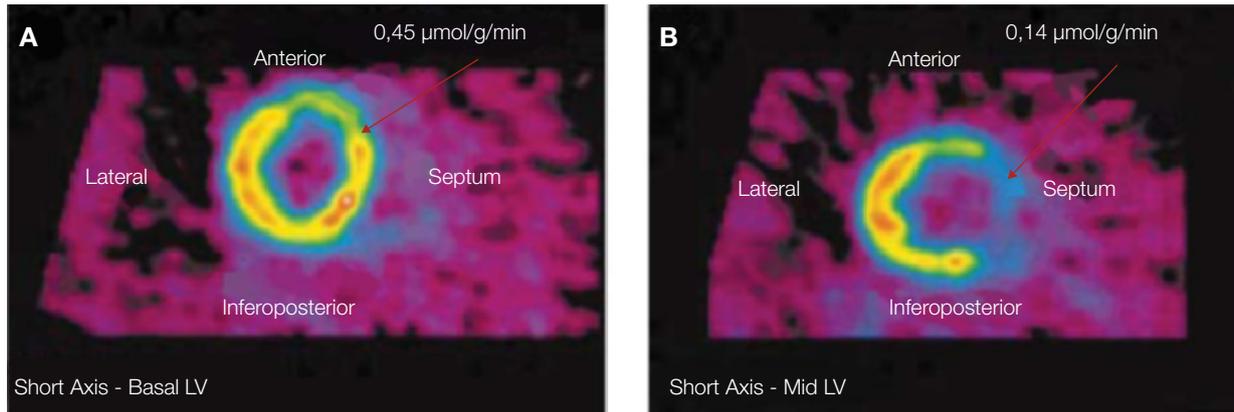
Fig. 3 *Myocardial viability in two patients with coronary artery disease and severe chronic left ventricular dysfunction assessed by PET with 18F-labelled fluorodeoxyglucose (FDG) during hyperinsulinemic euglycemic clamp. Both patients had previous myocardial infarctions. The scan illustrated in panel A shows that FDG uptake in the previously infarcted antero-septal segment is 0.45 μmol/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 μmol/min/g), suggesting absence of viability in this large area. A cut-off point of 0.25 μmol/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 μmol/min/g.*

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 (μmol/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. •

References

1. Camici PG, Ferrannini E, Opie LH (1989) Myocardial metabolism in ischemic heart disease: basic principles and application to imaging by positron emission tomography. Prog Cardiovasc Dis 32:217–238
2. Randle PJ, Hales CN, Garland PB et al (1963) The glucose fatty acid cycle. Its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. Lancet 1:785–789
3. Markham RV, Winniford MD, Firth BG et al (1983) Symptomatic electrocardiographic, metabolic, and hemodynamic alterations during pacing-induced myocardial ischemia. Am J Cardiol 51:1589–1594
4. Mudge GH, Mills RW, Taegtmeyer H et al (1976) Alter ations of myocardial amino acid metabolism in chronic ischemic heart disease. J Clin Invest 58:1185–1192
5. Brodan V, Fabian J, Andel M et al (1978) Myocardial amino acid metabolism in patients with chronic ischemic heart disease. Basic Res Cardiol 73:160–170
6. Araujo LI, Camici PG, Spinks T, Jones T, Maseri A (1988) Abnormalities in myocardial metabolism in patients with unstable angina as assessed by positron emission tomography. Cardiovasc Drugs Ther 2:41–46
7. Camici PG, Araujo L, Spinks T et al (1986) Increased uptake of F18-flurodeoxyglucose in postischemic myocardium of patients with exercise-induced angina. Circulation 74:81–88
8. Marinho NVS, Keogh BE, Costa DC, Lammertsma AA, Ell PJ, Camici PG (1996) Pathophysiology of chronic left ventricular dysfunction: New insights from the measurement of absolute myocardial blood flow and glucose utilization. Circulation 93:737–744
9. Camici PG, Wijns W, Borgers M, De Silva R, Ferrari R, Knuuti J, Lammertsma AA, Liedtke AJ, PaternostroG, Vatner SF (1997) Pathophysiological mechanisms of chronic reversible left ventricular dysfunction due to coronary artery disease (hibernating myocardium). Circulation 96:3205–3214
10. Wijns W, Vatner SF, Camici PG (1998) Hibernating myocardium. N Engl J Med 339:173–181
11. Tillisch J, Brunken R, Marshall R, Schwaiger M, Mandelkern M, Phelps M, Schelbert H (1986) Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. N Engl J Med 314:884–888
12. Camici PG, Prasad S, Rimoldi O (2008) Stunning, hibernation and assessment of viability. Circulation 117:103–114