Myocardial ischaemia and metabolic memory

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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 reported arterial–venous (AV) differences 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 radiolabelling techniques in healthy volunteers have shown that, at the most, only about 30% of the glucose uptake is rapidly oxidised and about 15% is converted to lactate [1].

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 catheterisation technique, net uptake of FFA from the arterial circulation has been found consistently. At arterial FFA levels in the 0.5–0.9 mmol/l range, the reported AV difference is 0.14–0.20 μmol/ml, which corresponds to an oxygen extraction ratio 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 per 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 oxidised [1].

The oxidative use of lipid (FFA) and carbohydrate (glucose and lactate) fuels 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.

During conditions of reduced oxygen supply, the oxidation of all substrates is decreased while anaerobic metabolism is activated. In patients with coronary artery disease (CAD) and stable angina pectoris, net lactate release in the coronary sinus 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 ischaemia [3]. In patients with chronic angina, a significant release of alanine in the coronary sinus and 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 coronary sinus can be demonstrated following pacing in patients with stable angina.

Positron emission tomography (PET) has made it possible to study non-invasively regional myocardial perfusion and metabolism in patients with CAD and normal volunteers. Different patterns of myocardial glucose utilisation have been observed in patients with CAD studied using ^{18}F-fluorodeoxyglucose (FDG). In patients with stable angina studied at rest, after an overnight fast, regional myocardial glucose utilisation was found to be homogeneously low and comparable with that in normal subjects. In contrast, in patients with unstable angina, myocardial glucose utilisation at rest was increased even in the absence of symptoms and electrocardiographic signs of acute ischaemia [6]. In patients with stable angina, a prolonged increase in FDG uptake could be demonstrated in post-ischaemic myocardium in the absence of symptoms or perfusion abnormalities, which suggests a sort of post-ischaemic "metabolic memory" [7]. Subsequent studies in animals have indicated that this increased post-ischaemic glucose utilisation is mainly finalised to replenish myocardial glycogen stores depleted during ischaemia [1].

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FFA metabolism has been studied in patients with CAD and stable angina using PET with ^{11}C-palmitate. At rest, after an overnight fast, the washout of ^{11}C-palmitate, an index of FFA oxidation, was found to be uniform whilst during pacing-induced ischaemia a reduction in ^{11}C-palmitate oxidation could be demonstrated in the ischaemic regions [8].

In this issue of *Eur J Nucl Med Mol Imaging*, Kageyama et al. [9] report an interesting new observation on myocardial FFA metabolism in patients with stable angina obtained by combining PET and single-photon emission computed tomography (SPECT). They used PET with ^{15}O-labelled water to quantify regional myocardial blood flow (MBF) and flow reserve (CFR) whilst SPECT was used to measure the uptake of the FFA analogue ^{123}I-BMIPP. They observed regional deficits of ^{123}I-BMIPP uptake in the myocardium at rest in the absence of symptoms or electrocardiographic signs of ischaemia. The severity of the reduction in ^{123}I-BMIPP uptake was inversely related to both hyperaemic MBF and CFR. Unfortunately, the conclusions that can be derived from this study are limited by the fact that myocardial ^{123}I-BMIPP uptake was not quantified and the degree of uptake was based on visual assessment of the SPECT data. Still, the observation is of interest and is in line with the previous observation of a metabolic memory for glucose in the same type of patients after exercise-induced ischaemia using PET with FDG [7].

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