Non-invasive determination of myocardial oxygen consumption with ^{11}C-acetate and positron emission tomography

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(iii) Abstract

Assessment of myocardial metabolism with radiolabelled substrates and positron emission tomography (PET) provides a potentially sensitive technique to investigate physiological and pathological cardiac states *in vivo*. However myocardial substrate utilization is dependent on a number of variables, including prevailing substrate concentrations, the hormonal environment and the presence of pathological states such as myocardial ischaemia. Prior studies have indicated that overall metabolic activity cannot be estimated from rates of utilization of any one particular substrate, for example glucose or fatty acid. Oxygen consumption would provide an ideal assessment of metabolic activity, however technical considerations preclude assessment of this with oxygen-15 and PET. It was hypothesized that acetate labelled with carbon-11 would provide an index of oxidative metabolism, based on fundamental biochemical principles. Acetate is predominantly metabolized in the citric acid cycle, with limited alternative metabolic pathways. The rate of production of $^{11}CO_2$ from ^{11}C-acetate would reflect citric acid cycle flux, and could be measured from the externally assessed clearance of total ^{11}C-radioactivity from myocardium using PET. Citric acid cycle flux is known to be tightly coupled to oxidative phosphorylation, and hence would provide an index of oxidative metabolism.

This hypothesis is confirmed in studies using isolated perfused rabbit hearts and closed chest canine studies. The rate of production and clearance of $^{14}CO_2$, resulting from oxidation of ^{14}C-acetate, was closely correlated with oxygen consumption in isolated perfused rabbit hearts. Similarly the rate of production and clearance of $^{11}CO_2$, resulting from oxidation of ^{11}C-acetate, was closely correlated with myocardial oxygen consumption in canine studies. Production and clearance of $^{11}CO_2$ could be measured externally by PET from the rate of clearance of total ^{11}C-radioactivity from myocardium. The technique has been validated over a wide range of cardiac work loads and under conditions of myocardial ischaemia, myocardial reperfusion following ischaemia and hypoxia. ^{11}C-acetate kinetics were found to be insensitive to changes in myocardial substrate supply.

Changes in oxidative metabolism were then evaluated in acute and chronic animal models of myocardial infarction. Myocardial oxygen consumption was impaired by 26 to 97% following 1 hour of coronary occlusion in acute studies and to a lesser extent in chronic studies. Oxygen consumption and contractility are known to be dissociated in "stunned" myocardium following acute myocardial ischaemia. Recovery of oxidative metabolism and contractility following 1 hour of coronary occlusion were found to occur in parallel over a 4 week period.

Preliminary experience with ^{11}C-acetate was also obtained in normal subjects and patients following acute myocardial infarction. Oxidative metabolism was related to work load in normal subjects, and was impaired in patients with myocardial infarction.

In summary the technique offers non-invasive assessment of myocardial oxidative metabolism on a regional basis using PET. These measurements can be made on a serial basis and in situations where assessment of oxygen consumption was previously not possible, particularly with respect to human studies.

(iv) This thesis contains no material which has been accepted for the award of any other degree or diploma in any university and that, to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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