

# How should myocardial metabolism be measured in man?

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*Many variables, including food ingestion, circulating hormones, and cardiac workload, affect myocardial metabolism.*

*Important changes in myocardial metabolism are associated with myocardial ischemia.*

*The study of myocardial metabolism by means of different invasive and noninvasive techniques*

*allows a better understanding of both cardiac physiology and pathophysiology in humans.*



Any changes in cardiac function are associated with parallel changes in cardiac metabolism. Measuring such changes has important therapeutic implications in myocardial ischemia. This paper reviews the techniques available for measuring cardiac metabolism as well as the main findings in the normal and ischemic heart.

## TECHNIQUES FOR STUDYING MYOCARDIAL METABOLISM IN MAN

### Invasive procedures

In 1947, Bing<sup>1</sup> started to use coronary sinus catheterization for the study of myocardial metabolism in humans. This procedure implies the combined catheterization of the coronary sinus (CS) and an artery (A) with measurement of substrate concentrations in simultaneously drawn blood samples. From these, the extraction fraction [defined as (A-CS)/A] can be calculated, which reflects the ability of the heart to extract a substrate independently of its arterial level. Conversely, if the required information is the rate of absolute substrate uptake, then an estimate of coronary blood flow (CBF) is necessary, which is generally achieved by the thermodilution technique. This allows the use of the same catheter for blood sampling, CBF measurement, and if needed, for electrical pacing.<sup>2,3</sup> If CBF is known, net myocardial

substrate balance can be calculated as: (A-CS) × CBF.<sup>4</sup> If there is simultaneous uptake and release of a substrate, the A-CS difference will be the algebraic sum of the two processes. To obtain absolute rates of substrate uptake or release, the catheter technique must be combined with the use of labelled substrates.<sup>5</sup> Net rates of carbohydrate and lipid oxidation and myocardial energy expenditure can be calculated from classic calorimetric equations if myocardial exchange of oxygen and carbon dioxide is measured.<sup>6</sup>

### Positron emission tomography

Positron emission tomography (PET) is a radionuclide imaging technique which enables quantitative assessment of regional myocardial tissue function in vivo.<sup>7</sup> Using the appropriate tracers, labelled with positron emitting isotopes, a variety of functional parameters can be investigated. Because of the availability of positron emitting isotopes of elements which are commonly found in molecules of biological interest (eg, carbon 11, oxygen 15, and nitrogen 13), such compounds may be labelled without alteration of either their chemical structure or biological activity.

PET imaging has been used to probe a variety of cardiac biochemical pathways. Studies have been performed using labelled amino



acids to measure amino acid metabolism and protein turnover rates.<sup>8</sup> However, the majority of PET metabolic studies have focused upon investigation of the pathways involved in energy metabolism and the alterations which occur in disease.

The carbon 11-labelled free fatty acid palmitate ( $[^{11}\text{C}]$ palmitate) has been proposed as a tracer to probe beta oxidation. The clearance of  $[^{11}\text{C}]$ palmitate from the myocardium was found to be related to the degree of oxidative metabolism, though absolute quantification of utilization rates was not possible due to the over-complexity of the model required to explain the behavior of  $[^{11}\text{C}]$ palmitate in tissue. Interpretation of myocardial uptake and clearance of  $[^{11}\text{C}]$ palmitate is further complicated by the dependence of these two parameters on the prevailing blood flow and dietary state. In ischemic tissue the clearance rates were found to be reduced, suggesting reduced free fatty acid utilization in these regions.<sup>8,9</sup>

Carbon 11-labelled acetate ( $[^{11}\text{C}]$ acetate) has been advocated as a tracer of tricarboxylic acid cycle activity<sup>10</sup> and has been used as an indirect marker of myocardial oxygen consumption ( $\text{MVO}_2$ ) by PET in both experimental animals<sup>10-13</sup> and humans.<sup>14</sup> A number of studies have shown that the rate constant describing the clearance of  $[^{11}\text{C}]$ acetate from the myocardium correlates well with catheter measurements of oxygen extraction fraction (OEF) from analysis of arteriovenous differences of blood oxygen content using the Fick principle. Clinical studies using  $[^{11}\text{C}]$ acetate have demonstrated a decreased clearance rate from infarcted myocardium.<sup>15</sup>

A new method to quantify  $\text{MVO}_2$  by inhalation of oxygen 15-labelled molecular oxygen gas ( $^{15}\text{O}_2$ ) has

been developed recently.<sup>16</sup> The accuracy of this approach to quantify oxygen extraction fraction (OEF) and  $\text{MVO}_2$  has been successfully validated over a wide range of values in experimental animal studies.<sup>17</sup> Studies in six human subjects yielded mean OEF and  $\text{MVO}_2$  values of  $61 \pm 8\%$  and  $9.4 \pm 1.8$  mL/min/100 g, respectively,<sup>16</sup> which are consistent with those values previously reported in man using invasive techniques.

Extensive studies of glucose metabolism have been performed using PET, principally using  $[^{18}\text{F}]$ -2-fluoro-2-deoxyglucose (FDG). This tracer is transported into the myocyte on the same transsarcolemmal carrier as glucose and is then phosphorylated to FDG-6-phosphate by the enzyme hexokinase. This is essentially a unidirectional reaction, as no glucose-6-phosphatase has yet been identified in cardiac muscle,<sup>18</sup> and results in FDG-6-phosphate accumulation within the myocardium. Thus, although measurement of the myocardial uptake of FDG is proportional to the overall rate of transsarcolemmal transport and hexokinase phosphorylation of circulating glucose by heart muscle, no information about the further intracellular disposal of glucose can be derived from measurements of FDG uptake.

A number of kinetic modelling approaches have been used for the quantification of glucose utilization rates using FDG.<sup>19</sup> The major limitation of these approaches is that quantification of glucose metabolism requires the knowledge of the lumped constant, a factor which relates the kinetic behavior of the FDG to naturally occurring glucose in terms of the relative affinity of each molecule for the transsarcolemmal transporter and for hexokinase. Unfortunately,

the value of the lumped constant in humans under different physiological and pathophysiological conditions is not known, thus making true in vivo quantification of myocardial metabolic rates of glucose very difficult.

## METABOLISM IN THE NORMAL HUMAN HEART

Under normal circumstances, any increase in cardiac work is met by a parallel rise in coronary blood flow. If this is the condition sine qua non for a physiological increase of cardiac performance, other important adjustments in myocardial metabolism accompany and follow any given change in heart function. At rest, in the postabsorptive state, all the major circulating substrates, including free fatty acids (FFAs), lactate, pyruvate, and  $\beta$ -hydroxybutyrate, are extracted by the heart with the exception of alanine (which is released), glucose and glycerol,<sup>4</sup> for both of which net balances are not different from zero. The respiratory quotient (ie, the ratio between the carbon dioxide released in the coronary veins and the oxygen extracted from the coronary arteries) is approximately 0.7, indicating dominant reliance of heart muscle on lipid oxidation for energy production.<sup>6</sup> Camici et al,<sup>4</sup> showed that if cardiac workload is increased by rapid atrial pacing (heart rate was progressively increased from  $76 \pm 6$  to  $159 \pm 9$  bpm), myocardial oxygen consumption, which was  $301 \pm 53$   $\mu\text{mol}/\text{min}$  at baseline, increased to  $593 \pm 71$   $\mu\text{mol}/\text{min}$ . During pacing, both myocardial lactate and pyruvate uptake tended to increase before returning to baseline values during recovery. The uptake of  $\beta$ -hydroxybutyrate remained unchanged and alanine continued to be released. Myocardial glucose uptake increased linearly with

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pacing to a peak of 11  $\mu\text{mol}/\text{min}$ , from which it declined also linearly as a function of recovery time. The rate of change in myocardial glucose uptake followed heart rate closely during pacing, but not during the recovery phase when circulating glucose uptake was apparently in excess of the demand imposed by cardiac workload. In contrast, uptake of circulating FFAs was significant at baseline ( $10.0 \pm 2.5 \mu\text{mol}/\text{min}$ ), did not change during pacing, and fell significantly throughout the recovery phase.<sup>4</sup> Under most circumstances, oxidation of lipid fuel gave the major contribution to myocardial energy production. However, during maximal atrial pacing carbohydrate (glucose + lactate + pyruvate + alanine) oxidation rose significantly and contributed more than 62% of the energy produced during this phase. Accordingly, the respiratory quotient increased to almost 0.9. During this phase, carbohydrate oxidation was in excess of their uptake from the circulation, suggesting breakdown of myocardial glycogen stores. This shift can probably be explained by the greater caloric equivalent of oxygen for carbohydrate (5.02 kcal/L) than for lipid (4.66 kcal/L).

Feeding induces a series of metabolic changes in the whole body that have profound effects on myocardial metabolism.<sup>20</sup> Important substrate and hormonal changes are generated after food ingestion. Of these, by far the most important is the increase in the circulating levels of insulin. Concomitant with insulin-induced stimulation of glucose metabolism is a drastic reduction in FFA delivery to tissues due to inhibition of adipose tissue lipolysis by insulin. Therefore, the shift in myocardial substrate utilization which occurs with feeding is the result of the combined actions of insulin at a whole body level.

Recently, new insight into the direct effect of insulin on the human heart has been gained by the study of myocardial metabolism during hyperinsulinemic, euglycemic clamp.<sup>21</sup> In brief, these studies have shown that insulin: (i) specifically enhances myocardial glucose, lactate, and pyruvate uptake; (ii) converts cardiac fuel reliance from fat to carbohydrate (by suppressing lipolysis) with no change in oxygen consumption; and (iii) does not affect cardiac hemodynamics and external work.

### **EFFECT OF ISCHEMIA ON MYOCARDIAL METABOLISM**

Patients with coronary artery disease and stable angina pectoris have a resting myocardial metabolism similar to that in control subjects. All major substrates, including FFAs, glucose, pyruvate, lactate, ketones, and glutamate, are extracted, with the exception of alanine and citrate which are released in small amounts.<sup>22,23</sup> The fraction of energy supplied by lipid oxidation is more than 80%. Significantly, the uptake of carbohydrates exceeds their oxidation.<sup>23</sup> Regional utilization of FFAs and glucose at rest, as assessed with [<sup>11</sup>C]palmitate and FDG by means of PET, is homogeneous in patients with exercise-induced angina.<sup>24,25</sup>

In these patients, regional myocardial perfusion becomes inadequate during stress.<sup>25</sup> In the regions which demonstrated perfusion defects during exercise, an increased FDG uptake was observed. This is consistent with an increased glycolytic metabolism in the ischemic zone. Furthermore, the augmented glucose uptake in the ischemic territory is sustained well after the reversal of the perfusion defects and it is thought that the glucose is probably being

used to replenish glycogen stores which were depleted during the ischemic episode.<sup>25</sup>

During ischemia there will be accumulation of reduced coenzymes. Thus, despite the increase in myocardial glucose utilization, the pyruvate formed through anaerobic glycolysis will not be oxidized, but in the presence of increased amounts of reduced nicotinamide adenine nucleotide (NADH) will be converted to lactate. In addition, a greater amount of alanine will be released through transamination of pyruvate with glutamate serving as the  $\text{NH}_2$  donor.<sup>22</sup> In addition, glutamate may be used as an anaerobic fuel through conversion to succinate which is coupled with formation of GTP.<sup>20</sup>

In patients with unstable angina, resting glucose utilization is increased in the absence of symptoms and signs of ischemia.<sup>20</sup> These data suggest the presence of ischemia in these patients which can be alleviated by medical treatment, as evidenced by a decrease in resting myocardial FDG uptake.<sup>26</sup> Of interest was the finding that in patients with unstable angina, increased resting FDG uptake could be observed in myocardial territories subtended by epicardial coronary arteries with noncritical stenoses.

Studies by Marshall et al<sup>27</sup> have indicated that myocardial ischemia and infarction could be distinguished by qualitative PET imaging with FDG and nitrogen 13-labelled ammonia (<sup>13</sup>NH<sub>3</sub>), as a flow tracer, acquired after an oral glucose load. Regions which showed a concordant reduction in both <sup>13</sup>NH<sub>3</sub> and FDG uptake ("flow-metabolism match") were considered scarred, whereas regions in which FDG uptake was relatively preserved or increased despite having a <sup>13</sup>NH<sub>3</sub> defect ("flow-metabolism mismatch") were considered ischemic and thus



still viable. Further studies were performed so as to ascertain whether asynergic regions with a "flow-metabolism mismatch" represented reversibly injured myocardium. Preoperative PET scans were performed in 17 patients undergoing coronary artery bypass grafting. Regional wall motion increased after surgery in 35/41 segments displaying "flow-metabolism mismatch" and remained depressed in 24/26 segments demonstrating "flow-metabolism match."<sup>28</sup>

Recently, quantitative PET studies of myocardial blood flow (MBF) with oxygen 15-labelled water ( $H_2^{15}O$ ) and glucose utilization with FDG have been performed to study the pathophysiology of chronic left ventricular (LV) dysfunction in patients with coronary artery disease.<sup>29</sup> Regional MBF (mL/min/g of water-perfusible tissue) and glucose utilization (MRG,  $\mu\text{mol}/\text{min}/\text{g}$ ), during hyperinsulinemic euglycemic clamp, were measured in 30 patients before bypass. At baseline, 133 myocardial segments were normal (NOR) and 107 dysfunctional. After revascularization, 59/107 segments improved (IMP) while 48/107 were unchanged (UNC). MBF was  $0.92 \pm 0.25$  in NOR,  $0.87 \pm 0.31$  in IMP ( $P = \text{NS}$  vs NOR) and  $0.82 \pm 0.40$  in UNC ( $P < 0.05$  vs NOR). In 90% of the dysfunctional segments MBF was  $> 0.42$ , a cutoff value corresponding to the mean MBF minus 2 SD in NOR. The MRG was  $0.71 \pm 0.14$  in 9 age-matched normal subjects,  $0.45 \pm 0.19$  ( $P < 0.01$ ) in NOR,  $0.44 \pm 0.14$  in IMP ( $P = \text{NS}$  vs NOR), and  $0.34 \pm 0.17$  in UNC ( $P < 0.01$  vs NOR and IMP). The results of this study suggest that resting MBF, measured with  $H_2^{15}O$  in chronically dysfunctional segments is not reduced, that the myocardium of these patients is less sensitive to insulin than that

of normal subjects and that dysfunctional segments that improve after revascularization are characterized by higher glucose utilization rates.

## References

### 1. Bing RJ.

#### *The Metabolism of the Heart.*

Orlando, Fla/New York, NY: Academic Press Inc - Harvey Lecture Series 50; 1954:27-70.

### 2. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC.

*Measurement of coronary sinus blood flow by continuous and intermittent exercise to exhaustion.*

*J Appl Physiol.* 1971;44:181-195.

### 3. Pepine CJ, Metha JM, Webster WW, Nichols WW.

*In vivo validation of a thermodilution method to determine regional left ventricular blood flow in patients with coronary artery disease.*

*Circulation.* 1978;58:795-802.

### 4. Camici PG, Marraccini P, Marzilli M, et al.

*Coronary hemodynamics and myocardial metabolism during and after pacing stress in normal humans.*

*Am J Physiol.* 1989;257:E309-E317.

### 5. Gertz EW, Wisneski JA, Neese R, Bristow JD, Searle GL, Hanlon JT.

*Myocardial lactate metabolism: evidence of lactate release during net chemical extraction in man.*

*Circulation.* 1981;63:1273-1279.

### 6. Ferrannini E.

*The theoretical bases of indirect calorimetry: a review.*

*Metabolism.* 1988;37:287-301.

### 7. Phelps ME, Mazziotta JC, Schelbert HR, eds.

*Positron Emission Tomography and Autoradiography.*

*Principles and Applications for the Brain and the Heart.*

New York, NY: Raven Press; 1986.

### 8. Schelbert HR, Schwaiger M.

PET studies of the heart. In: Phelps ME, Mazziotta JC, Schelbert HR, eds.

*Positron Emission Tomography and Autoradiography.*

*Principles and Applications for the Brain and the Heart.*

New York, NY: Raven Press; 1986:581-662.

### 9. Schelbert HR, Henze E, Schon HR, et al.

*C-11 Palmitic acid for the noninvasive evaluation of regional myocardial fatty acid metabolism with positron computed tomography. IV. In vivo demonstration of impaired fatty acid oxidation in acute myocardial ischemia.*

*Am Heart J.* 1983;106:736-750.

### 10. Buxton DB, Schwaiger M, Nguyen A, Phelps ME, Schelbert HR.

*Radiolabeled acetate as a tracer of myocardial tricarboxylic acid cycle flux.*

*Circ Res.* 1988;63:628-634.

### 11. Armbrrecht JJ, Buxton DB, Schelbert HR.

*Validation of [ $^{11}C$ ]acetate as a tracer for noninvasive assessment of oxidative metabolism with positron emission tomography in normal, ischemic, postischemic, and hyperemic canine myocardium.*

*Circulation.* 1990;81:1594-1605.

### 12. Brown MA, Myears DW, Bergmann SR.

*Noninvasive assessment of canine myocardial oxidative metabolism with carbon-11 acetate and positron emission tomography.*

*J Am Coll Cardiol.* 1988;12:1054-1063.

### 13. Buxton DB, Nienaber CA, Luxen A, et al.

*Noninvasive quantitation of regional myocardial oxygen consumption in vivo with [ $^{11}C$ ]acetate and dynamic positron emission tomography.*

*Circulation.* 1989;79:134-142.

### 14. Armbrrecht JJ, Buxton DB, Brunken RC, Phelps ME, Schelbert HR.

*Regional myocardial oxygen consumption determined noninvasively in humans with [ $^{11}C$ ]acetate and dynamic positron tomography.*

*Circulation.* 1989;80:863-872.

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**15. Walsh MN, Geltman EM, Brown MA, et al.**

*Noninvasive estimation of regional myocardial oxygen consumption by positron emission tomography with carbon-11 acetate in patients with myocardial infarction.*

*J Nucl Med.* 1989;30:1798-1808.

---

**16. Iida H, Rhodes CG, Yamamoto Y, Jones T, De Silva R, Araujo LI.**

*Quantitative measurement of myocardial metabolic rate of oxygen (MMRO<sub>2</sub>) in man using positron emission tomography.*

*Circulation.* 1990;82:III-614.

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**17. De Silva R, Yamamoto Y, Rhodes CG, Iida H, Maseri A, Jones T.**

*Non-invasive quantification of regional myocardial oxygen consumption in anaesthetized greyhounds.*

*J Physiol.* 1992;446:219P.

---

**18. Gallagher BM, Fowler JS, Gutterson NI, MacGregor RR, Wan CN, Wolf AP.**

*Metabolic trapping as a principle of radiopharmaceutical design: some factors responsible for the biodistribution of [<sup>18</sup>F]2-deoxy-2-fluoro-D-glucose.*

*J Nucl Med.* 1978;19:1154-1161.

---

**19. Huang SC, Phelps ME.**

*Principles of tracer kinetic modeling in positron emission tomography and autoradiography. In: Phelps ME, Mazziotta JC, Schelbert HR, eds.*

*Positron Emission Tomography and Autoradiography. Principles and Applications for the Brain and Heart.*

New York, NY: Raven Press; 1986:287-346.

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**20. Camici PG, Ferrannini E, Opie LH.**

*Myocardial metabolism in ischaemic heart disease: basic principles and applications to imaging by positron emission tomography.*

*Prog Cardiovasc Dis.* 1989;32:217-238.

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**21. Ferrannini E, Santoro D, Bonadonna R, Natali A, Parodi O, Camici PG.**

*Metabolic and hemodynamic effects of insulin on human heart.*

*Am J Physiol.* 1993;264:E308-E315.

---

**22. Thomassen A, Bagger JP, Nielsen TT, Henningsen P.**

*Altered global myocardial substrate preference at rest and during pacing in coronary artery disease and stable angina pectoris.*

*Am J Cardiol.* 1988;62:686-693.

---

**23. Camici PG, Marraccini P, Lorenzoni R, et al.**

*Metabolic markers of stress-induced myocardial ischemia.*

*Circulation.*

1991;83(suppl III):III-8-III-13.

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**24. Grover-McKay M, Schelbert HR, Schwaiger M, et al.**

*Identification of impaired metabolic reserve by atrial pacing in patients with significant coronary artery stenosis.*

*Circulation.* 1986;74:281-292.

---

**25. Camici PG, Araujo LI, Spinks T, et al.**

*Increased uptake of F 18-fluorodeoxyglucose in postischemic myocardium of patients with exercise-induced angina.*

*Circulation.* 1986;74:81-88.

---

**26. Araujo LI, Camici PG, Spinks T, Jones T, Maseri A.**

*Beneficial effects of nitrates on myocardial glucose utilization in unstable angina pectoris.*

*Am J Cardiol.* 1987;60:26H-30H.

---

**27. Marshall RC, Tillisch JH, Phelps ME, et al.**

*Identification and differentiation of resting myocardial ischemia and infarction in man with positron computed tomography, <sup>18</sup>F-labeled fluorodeoxyglucose and N-13 ammonia.*

*Circulation.* 1983;67:766-768.

---

**28. Tillisch J, Brunken R, Schwaiger M, Mandelkern M, Phelps M, Schelbert HR.**

*Reversal of cardiac wall motion abnormalities predicted by using positron emission tomography.*

*N Engl J Med.* 1985;314:884-888.

---

**29. Marinho NVS, Keogh BE, Costa DC, Lammerstma AA, Ell PJ, Camici PG.**

*Pathophysiology of chronic left ventricular dysfunction: new insights from the measurement of absolute myocardial blood flow and glucose utilization.*

*Circulation.* 1996;93:737-744.

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