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The Relationship in Man Between Plasma Free Fatty Acids and Myocardial Metabolism of Carbohydrate Substrates

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A number of animal studies of the interaction between free fatty acids (FFA) and carbohydrate substrates have suggested that enhanced myocardial oxidation of fatty acids can suppress the uptake and oxidation of glucose by the heart [6, 7]. Other experiments have indicated that, at least in part, FFA may exert its effect on glucose metabolism at the level of pyruvate decarboxylation [2], probably by an inhibition of pyruvate dehydrogenase due to increased levels of intracellular acetyl coenzyme A [3]. These observations have all been made in the isolated perfused rat heart. In order to see whether a similar relationship exists between plasma FFA and the myocardial metabolism of blood carbohydrate substrates in man, the arterial and coronary sinus concentrations and myocardial extractions (i.e. arterial-coronary sinus differences in concentration) of FFA, glucose, lactate and pyruvate were measured at rest in healthy, fasting male subjects [1, 4].

Table I shows that there were significant, negative linear correlations between arterial FFA concentration and the myocardial extraction of glucose, lactate and pyruvate. With arterial FFA concentrations above about 800 μmol/l significant efflux of pyruvate into the coronary sinus was observed. The negative correlation between glucose and lactate extraction and FFA concentration appeared to be independent of the arterial concentration of glucose and lactate since the extraction of these substrates was not related to their arterial concentrations. Although arterial pyruvate extraction and arterial pyruvate concentration were significantly correlated there was no relationship between arterial FFA and arterial pyruvate concentration ($r = -0.19$) – again indicating that the negative correlation between pyruvate extraction and FFA concentration was independent of pyruvate concentration.

This reciprocal relationship between arterial FFA concentration and glucose extraction suggests that FFA can depress glucose uptake in the human heart *in vivo* as it does in the isolated perfused rat heart. Furthermore, the negative correlation between FFA and pyruvate extraction with significant efflux of pyruvate at higher FFA concentrations, suggests that this depression may be due, at least in part, to inhibition of pyruvate dehydrogenase.

In addition, the reciprocal relationship between arterial FFA and myocardial lactate extraction indicates that FFA concentrations should be taken into consideration when using the percentage extraction of lactate by the human heart as an indicator of myocardial ischaemia or hypoxia – particularly when substances such as heparin or catecholamines which increase FFA concentrations are being used.

Table I. A Linear correlation analyses between arterial FFA concentration and myocardial extraction of carbohydrate substrates and *B* between arterial concentration and myocardial extraction of various blood substrates. $_a$ = Arterial; $\Delta_{(a\text{-}cs)}$ = arterial-coronary sinus difference in concentration; r = correlation coefficient

Arterial concentration	Myocardial extraction	r	n	p
A				
FFA_a	$\Delta_{(a-cs)}$ glucose	−0.51	28	<0.01
FFA_a	$\Delta_{(a-cs)}$ pyruvate	−0.46	32	<0.01
FFA_a	$\Delta_{(a-cs)}$ lactate	−0.62	32	<0.001
B				
FFA_a	$\Delta_{(a-cs)}$ FFA	0.57	32	<0.001
$Glucose_a$	$\Delta_{(a-cs)}$ glucose	0.24	28	ns
$Pyruvate_a$	$\Delta_{(a-cs)}$ pyruvate	0.86	32	<0.001
$Lactate_a$	$\Delta_{(a-cs)}$ lactate	0.33	32	ns

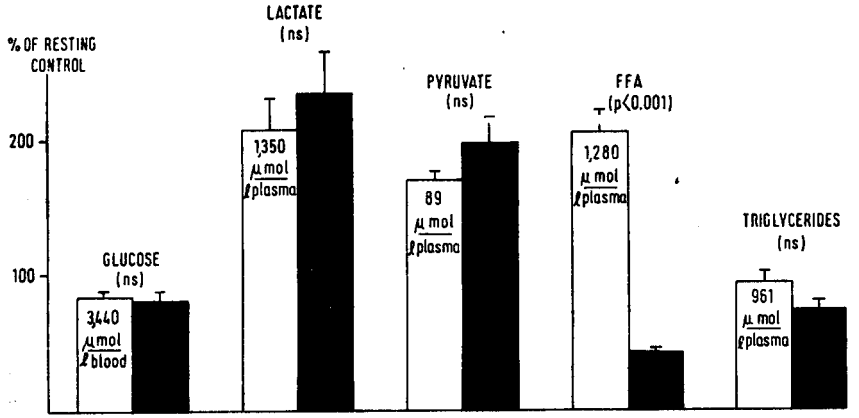

Fig. 1. The average arterial concentrations during prolonged exercise of the principle blood substrates for myocardial energy metabolism. A comparison between a group of 10 subjects receiving (■) a continuous i.v. infusion of nicotinic acid and a control group of 15 similar subjects not receiving (□) nicotinic acid (mean±SEM). The average resting concentration of each substrate in the control group was taken as 100% so that the bars represent the percentage change from this level with exercise. The actual average concentration during exercise for the control group is also included within the bars.

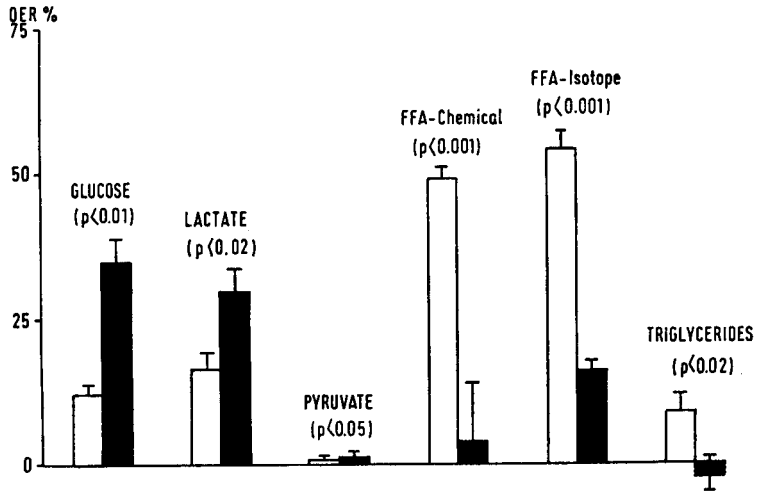

Fig. 2. A comparison between the same two groups shown in figure 1 of the average oxygen extraction ratios (OER) for the various energy substrates. □ Control group, ■ nicotinic acid group (mean ± SEM).

Additional evidence of the effect of arterial FFA concentration on myocardial extraction of blood carbohydrate substrates was obtained in a study of the effect on myocardial substrate metabolism of inhibiting the elevation of arterial FFA which is produced by prolonged exercise [5]. A continuous infusion of nicotinic acid was administered to 10 fasting subjects and their response to 2 h of supine leg exercise was compared with that of a similar group of 15 subjects who did not receive nicotinic acid. Arterial and coronary sinus substrate concentrations were measured during the final minutes of exercise and myocardial extractions and oxygen extraction ratios were calculated. Figure 1 compares the average arterial substrate concentrations during exercise in the two groups, and figure 2 their oxygen extraction ratios. It can be seen that although the arterial FFA concentration during exercise was very much lower in the nicotinic acid group, the concentration of glucose, lactate and pyruvate did not differ significantly. In keeping with the reduced arterial FFA concentration the myocardial extraction and oxygen extraction ratio for FFA were very much lower in the nicotinic acid group. However, despite the similarity between the two groups in the arterial concentrations of glucose, lactate and pyruvate, the myocardial extraction and oxygen extraction ratios for all three substrates were significantly higher in the nicotinic acid group. Thus the suppression of the exercise induced rise in arterial FFA concentration was associated with increased myocardial extraction of glucose, lactate and pyruvate, again suggesting that a reciprocal relationship exists in man between arterial FFA concentration and myocardial metabolism of carbohydrate substrates.

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