SUBSTRATE UPTAKE BY THE ISCHAEMIC HUMAN HEART DURING ANGINA INDUCED BY ATRIAL PACING

L. KAIJSER, L. A. CARLSON, B. EKLUND, E. R. NYE, S. RÖSSNER AND M. L. WAHLQVIST

IN healthy man the myocardial uptake of carbohydrate substrates has been shown to decrease with increased arterial concentration of free fatty acids (FFA)[1 2 3 4] in accordance with the 'glucose-fatty acid cycle' hypothesis of Randle and coworkers.[5] For a given amount of oxygen, less energy is liberated by lipid than by carbohydrate oxidation[6] and evidence has recently been presented indicating that the myocardial oxygen requirement at a given level of work increases with increased FFA uptake.[3 7 8] Thus the role of arterial FFA concentration as a determinant of myocardial substrate and oxygen metabolism might be especially important under ischaemic conditions.

The relationship between myocardial carbohydrate and fat metabolism is of interest for another reason. Normally the heart extracts lactate but, rendered hypoxic, it can liberate energy by anaerobic glycolysis. In this situation NADH accumulates and lactate is produced. Since the demonstration of lactate production can be of diagnostic value[9 10 11 12], it seems important to establish whether fatty acids affect lactate metabolism in the hypoxic heart. In the present study the myocardial extraction of substrates and oxygen was measured in patients with coronary heart disease at rest and during episodes of angina pectoris induced by atrial pacing. The effect of pacing was also studied under normal fasting conditions and after the infusion of nicotinic acid which decreased the arterial FFA concentration.

SUBJECTS

Twelve male patients with symptoms of ischaemic heart disease of more than two years duration were studied. Seven of them had been hospitalized for myocardial infarction 5 to 12 months before

In "EFFECT OF ACUTE ISCHAEMIA ON MYOCARDIAL FUNCTION" Edited by M. F. OLIVER, D. G. JULIAN, K. W. DONALD Churchill Livingstone, 1972.

the study: the remaining five had moderate or severe angina pectoris on exertion and a typical ECG of myocardial ischaemia during an exercise test.[13 14 15] Each subject underwent an exercise test on a bicycle ergometer[13 14] a few days before the study. Patients who could tolerate more than 500 kpm/min without angina were not included in the study. Known diabetics were excluded. No selection was made on the basis of serum lipid values.

Procedure

Treatment with anticoagulants, β-blockers and antilipolytic drugs was stopped 3 to 7 days before the study; glyceryl trinitrate was not taken on the day of the study. The patients were studied in the supine position without premedication after 15 hr fasting. Catheters were inserted percutaneously into the right brachial artery and the coronary sinus for blood sampling and arterial pressure recording. The coronary sinus catheter was kept patent by a continuous infusion of 0·5 per cent citrate at a rate of about 50 ml/hr; heparin was not administered. A bipolar electrode catheter (US Catheter and Instrument Corp., Glensfalls, N.Y.) was inserted percutaneously from the right femoral vein to the right atrium, and connected to an Elema Schönander, Model EM 145, external pacemaker unit. In those patients who were to receive an infusion of nicotinic acid. a catheter was inserted into another arm vein.

Each study started with blood sampling from the artery and coronary sinus, ECG recording (Leads CR_5 and CR_7) and arterial pressure measurements at rest. During continuous ECG and blood pressure recording, the heart rate was then increased every min by 10 beats/min by pacing up to a heart rate of 10 beats/min below the rate at which angina had developed during exercise. Thereafter the heart rate was increased every 2 min by 5 beats/min until the patient experienced angina of a moderate degree. Blood sampling from the coronary sinus and the artery was begun when 2 min had elapsed at that heart rate. Pacing was continued at the same rate until all sampling was completed about 3 min later. In 6 of the patients, sodium nicotinate was infused at a rate of 400 mg/hr for 90 min after a bolus injection of 200 mg. Thereafter a second period of pacing was carried out according to the same schedule as the first pacing. The remaining 6 patients served as

controls to determine the effect of repeated pacing on myocardial metabolism and were rested for 90 min without nicotinic acid before the second pacing period.

Two patients developed heart block as pacing rate was increased; this is not uncommon during atrial pacing in healthy, young subjects (own observations). Once the block had developed the pacing was stopped, 0·5 mg atropine was given intravenously and about 15 min later pacing was recommenced.

Treatment of Samples and Analytic Methods

Paired samples of atrial and coronary sinus blood were drawn into unheparinized plastic syringes. Samples for the estimation by enzymatic methods of blood glucose,[16] lactate[17] and pyruvate[18] were deproteinized immediately with perchloric acid. Samples for plasma FFA determinations were immediately transferred from the collection syringes to heparinized test-tubes, placed in iced water and centrifuged at 4° C within 1 hour.[19]

Oxygen saturation was measured spectrophotometrically.[20] Oxygen tension was measured with a polarographic electrode (Instrumentation Laboratory, Mod. 113). Oxygen content was calculated from the saturation and the haemoglobin concentration. For the estimation of the RQ of the myocardium, the oxygen and carbon dioxide content of arterial and coronary sinus blood were determined with the van Slyke technique.

Results

At rest

No patient had an arterial pressure above 170/95 mmHg. All subjects had normal arterial oxygen saturation. The average coronary sinus oxygen saturation was 28·8 ± 0·9 (S.E.) per cent, which is slightly lower than in healthy subjects,[21] and the oxygen tension was 22·7 mmHg.

The arterial FFA concentration was higher than in the above mentioned group of healthy subjects, and so was the arterial-coronary sinus difference in FFA concentration (FFA extraction). Myocardial FFA extraction was significantly and positively correlated with arterial FFA concentration and the regression line was

not significantly different from that found in normal subjects (Fig. 15, 1).

Pyruvate extraction, but not lactate extraction, was significantly and positively correlated with its arterial concentration and significantly and negatively related to the arterial FFA concentration. At a given arterial concentration, lactate extraction was in many patients smaller than in healthy subjects (Fig. 15, 2).

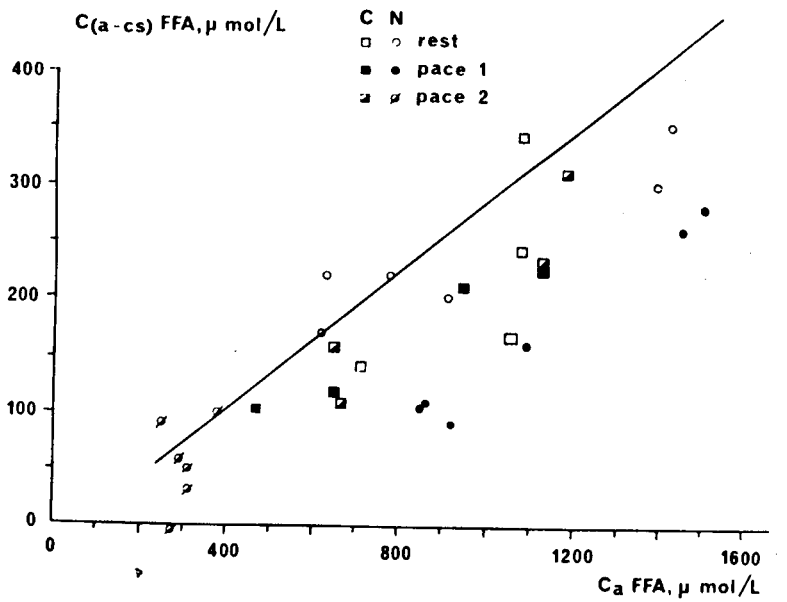

FIG. 15, 1. FFA extraction in relation to arterial FFA concentration. Symbols as in Figure 15, 2. The regression line is for healthy subjects at rest.[21]

The myocardial extraction of glucose was the same as that in normal subjects. It was neither significantly correlated with its own arterial concentration nor with the arterial FFA concentration.

The oxygen extraction ratio (OER) for FFA was 57·5 per cent, for glucose 21·4 per cent, for lactate 10·9 per cent, and for pyruvate 1·0 per cent—the total OER for these substrates was 90·8 per cent (Fig. 15, 3). Myocardial RQ was 0·78.

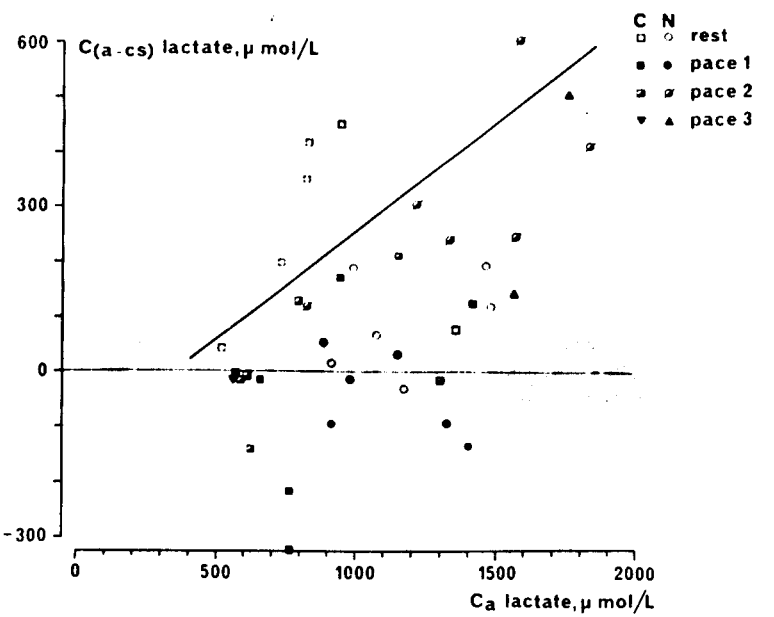

FIG. 15, 2. Lactate extraction in relation to arterial lactate concentration. C denotes patients not given nicotinate, N patients given nicotinate during their second pacing period. Pace 3 is the third pacing period at a higher heart rate in those patients who experienced less pain during pacing with than without nicotinate. The regression line for healthy subjects at rest and during exercise[22] is given for comparison.

During pacing

Chest pain, heart rate, arterial pressure. In all patients it was possible to increase the heart rate so as to produce moderate angina and keep the heart rate at that level for the time needed for blood sampling. During this time most patients experienced a slight increase in the degree of anginal pain. The average heart rate was 127 beats/min. For most patients the angina threshold was about 10 beats/min higher during pacing than during the exercise test. In all patients arterial mean pressure increased during pacing.

When pacing was repeated after 90 min rest without nicotinic acid, five out of six patients experienced the same degree of angina at the same heart rate, whereas one subject experienced less pain. This patient also had a lower arterial mean pressure before and during the second pacing, whereas the other five had approximately the same pressures during the first and the second pacing period.

Nicotinate infusion initially decreased the arterial pressure, which gradually increased again and in four of the six patients it had reached the preinfusion level by the start of the second pacing period. On pacing during the infusion of nicotinate, three out of six patients developed angina of approximately the same degree as during the first pacing period (without nicotinate), whereas one had angina of a milder degree and two felt no pain at all. After blood

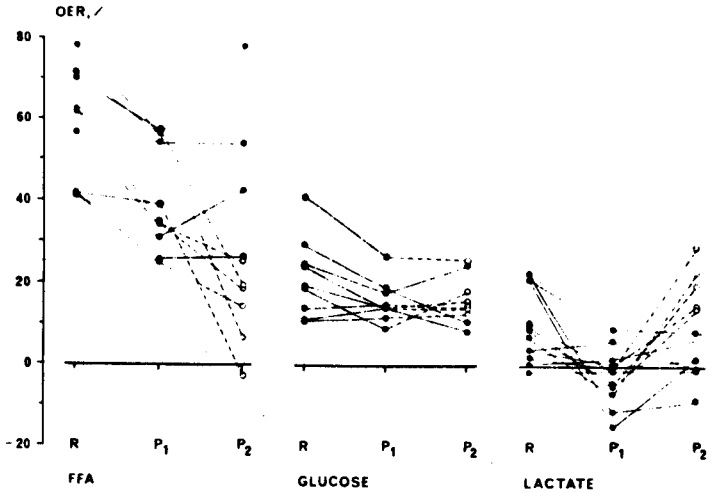

FIG. 15. 3. Oxygen extraction ratios for FFA, glucose and lactate for the individual patients at rest (R), during the first (P_1) and the second (P_2) pacing period. Filled circles: without nicotinate, unfilled circles connected with dashed lines: during nicotinate infusion.

sampling was completed, the heart rate was increased in the latter two subjects by 25 and 10 beats/min, respectively, to produce moderate angina. The arterial mean pressure during pacing was lower with than without nicotinate. This might be either the cause for or an effect of the reduced chest pain.

Oxygen extraction. Pacing did not change the coronary sinus oxygen saturation or tension or myocardial oxygen extraction, either without or with nicotinate infusion.

Lactate and pyruvate. During pacing, myocardial lactate extraction decreased in almost all patients and in 8 of them it changed from extraction to production (Figs 15, 2, 3). When pacing was repeated after nicotinate infusion, lactate was invariably extracted

and in all subjects the extraction was greater than during the first pacing. The increased lactate extraction could partly be explained by increased arterial lactate concentration. But it was greater than expected from the lactate concentration increase according to the relation between extraction and arterial concentration in normal subjects at rest and during exercise.[22] If observations during pacing with and without nicotinate are considered, the lactate extraction is correlated with its arterial concentration ($r=0{\cdot}50$, $p<0{\cdot}05$) as well as the arterial FFA concentration ($r=0{\cdot}75$, $p<0{\cdot}001$) and the FFA extraction ($r=0{\cdot}74$, $p<0{\cdot}001$). In the patients who were not given nicotinate infusion, lactate metabolism did not differ systematically during the first and the second pacing. Pyruvate extraction is not changed by pacing alone, but increased when pacing was repeated after nicotinic acid. This increase could be explained by an increased arterial pyruvate concentration since the pyruvate extraction was significantly and positively correlated with its arterial concentration; and the regression line was not different from that calculated at rest or that described for healthy subjects.[22] For observations at rest, during the first and the second pacing combined, the correlation coefficient was 0·61 ($p<0{\cdot}001$). The pyruvate extraction during pacing (without or with nicotinate) was correlated with the arterial FFA concentration ($r=0{\cdot}75$, $p<0{\cdot}001$) and the FFA extraction ($r=0{\cdot}64$, $p<0{\cdot}01$).

Glucose. The average myocardial glucose extraction remained unchanged during pacing and was not significantly smaller than in normal resting and exercising subjects. The glucose extraction did not change during nicotinate infusion.

FFA. During pacing, FFA extraction decreased in all patients, and was smaller in relation to its arterial concentration than in normal resting subjects. After nicotinate infusion, FFA extraction decreased further. In this situation the extractiin was the same as in normal subjects, in relation to arterial FFA concentrations (Fig. 15, 3). Considering all the observations in relation to pacing, FFA extraction was correlated with arterial FFA concentration.

OER, RQ. During the first pacing period the OERs for FFA were 41·6, for glucose 21·4, for lactate 0·6 and for pyruvate 0·6 per cent; the total was 63·0 per cent. The myocardial RQ was 0·78. When pacing was repeated during nicotinate infusion, the OER:s for FFA were 9·4, for glucose 17·1, for lactate 18·1 and for pyruvate

2·2 per cent; the total was 46·8 per cent. The myocardial RQ was 0·93.

Discussion

At rest, the patient group was characterized by a slightly lower coronary sinus oxygen saturation, a slightly higher FFA extraction (which was normal in relation to its arterial concentration), and a lower lactate extraction than in normal subjects: glucose and pyruvate extractions were the same as in normal. The sum of the OERs for the substrates studied was 90·8 per cent. Since triglycerides[23] and ketone-bodies[24] might contribute 10 to 15 per cent, the extracted substrates seem to cover the energy requirements. Since it was possible almost to double the heart rate by pacing in all patients, it is not likely that any major part of the myocardium was hypoxic at rest, and hence differences in myocardial metabolism between the patients and normal subjects are probably not attributable to oxygen lack *per se*.

When the heart rate was increased above the angina threshold, coronary sinus oxygen saturation did not decrease. This is surprising in view of the nature of the disease and the finding in normal subjects of decreasing saturation when the heart rate is increased by exercise.[22] However, the angina patients had a coronary sinus oxygen saturation which was at rest already as low as that found in normal subjects during exercise with a heart rate of about 145 beats/min. Furthermore, the heart muscles of the patients probably were unevenly perfused and, since the coronary sinus drains both well perfused and less well perfused myocardial areas, blood with extremely low oxygen saturation would be mixed with normally oxygenated blood. This is, at present, an insurmountable difficulty in the study of substrate and oxygen extraction in a heart with coronary disease.

When the myocardium was rendered hypoxic by pacing to the point of angina, lactate extraction was decreased or even changed into lactate production.[8 9 10 11] At the same time, FFA extraction was decreased. Apparently the hypoxic myocardium does not readily take up fatty acids. It must be pointed out, though, that the FFA uptake might have been unchanged or even slightly increased, since the coronary blood flow was presumably increased. For comparison, in normal subjects the myocardial extraction of FFA in

relation to its arterial concentration is smaller during exercise than at rest.[22] In our patients, the decreased FFA extraction was not compensated for by an increased glucose extraction, and since lactate extraction decreased, the total OER of carbohydrate substrates decreased. With a total OER for all substrates studied of 63·0 per cent, the substrate extraction was smaller than the total substrate oxidation. This is not seen in normal subjects except under extreme conditions, such as prolonged exercise, with reduced availability of FFA by nicotinic acid.[2 25] Apparently, coronary insufficiency is characterized not only by an insufficient oxygen supply to the myocardium, but also by an inability to extract substrates in amounts to match the oxidative capacity, and hence myocardial substrate stores must be utilized. Both the unchanged RQ (compared with resting conditions) and the unchanged relation between the OERs for fat and carbohydrates suggest that some of the stored carbohydrate and fat must have been oxidized. Lactate production presupposes carbohydrate breakdown and the lactate produced might to a substantial degree derive from extracted glucose as proposed by Most and coworkers,[26] who recently described a positive correlation between lactate production and glucose extraction in ischaemic human hearts. Such a relationship was not found in the present group of patients and seems unlikely unless the arterial FFA concentration is the same in the subjects studied, since both glucose and lactate extraction are positively correlated with FFA concentration,[1 2 3 4] and this would tend to produce a positive correlation between lactate *extraction* and glucose extraction. In our patients, the breakdown of myocardial glycogen seems to have contributed to the lactate production.

The present data do not answer the question as to why the total OER is reduced in the ischaemic heart. The availability of pyruvate dehydrogenase, held responsible for the interaction between fat and carbohydrate metabolism in the normal heart,[5] cannot be shown to be crucial since pyruvate extraction is unaffected by the pacing-induced ischaemia.

The decrease in FFA concentration produced by nicotinate infusion further reduced the uptake of FFA. However, the availability of FFA and not the capacity of the myocardium to metabolize it seem to limit its extraction, since the FFA extraction is the same in

relation to its arterial concentration as in normal resting subjects.[21] In this situation, lactate is invariably taken up. It is also taken up after nicotinic acid in patients whose heart rate was increased to a higher level during pacing. One important conclusion from this finding is that if lactate production is used as a diagnostic sign of myocardial hypoxia, it must be considered in relation to the arterial FFA concentration as well as its own arterial concentration.

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during ischaemia. This is a finding which has been shown by Dr Thomas and myself and co-workers, using an open-chest greyhound in which the blood going from the ischaemic area was sampled.

After arterial ligation there is a very distinct widening of the arteriovenous difference of glucose (Fig. 15, 4). The coronary sinus glucose value is unchanged during ischaemia. Arteriovenous difference for free fatty acids across the ischaemic section shows a small decrease, while the arterio-coronary sinus difference shows no decrease. We have attempted to increase the circulating free fatty acids by infusing Intralipid and heparin and then still find that there is increased glucose arteriovenous difference and still lactate output (see Table 15, 1).

Table 15, 1 *Effect of plasma free fatty acid concentration on arteriovenous difference of glucose across ischaemic myocardium*

In 8 starved greyhounds, glucose arteriovenous differences (using local vein sampling techniques) were measured 5 min before and 20 min after coronary artery ligation. Thereafter, circulating FFA was elevated by an infusion of Intralipid-heparin. Mean values ± SEM (number of observations).

EXPERIMENTAL CONDITION	ARTERIAL-LOCAL VENOUS PLASMA GLUCOSE DIFFERENCE: mg per 100 ml	ARTERIAL FREE FATTY ACID CONCENTRATION: mEq/litre
Pre-ligation (8)	12·6 ± 3·5	519 ± 122
Post-ligation (8)	25·6 ± 3·7	689 ± 110
Infusion of Intralipid-heparin (9)	22·3 ± 2·2	2900 ± 424

Our experimental work would fit in very nicely with the work from Dr Gorlin's group, using selective coronary sinus catheterization, showed an increased arteriovenous difference for glucose during human myocardial ischaemia at the same time as there was lactate output.

Mjøs What was the local arteriovenous flow in your preparation during coronary occlusion?

Thomas. The coronary sinus has, of course, a mixed flow from many areas. As the heart responds to any increase in demand, the

percentage of blood flow in the coronary sinus from non-ischaemic areas will become greater due to relative reduction of flow from ischaemic areas. This effect will become most marked with angina, unless there is some generalized change in coronary vasculature. Therefore, under high stress situations, the contribution of blood from ischaemic areas is not easy to detect in terms of A.V. differences.

Kaijser. In the coronary sinus, we sample mixtures of blood from better and from less well perfused parts of the myocardium and this is one of the major difficulties in metabolic studies of this kind. It seems likely that under conditions of increased myocardial oxygen demand, such as pacing, blood flow will increase in the less diseased areas. However, in most patients, coronary heart disease is not localized to a small area, but widespread, and hence coronary sinus blood represents blood from the ischaemic myocardium. In our patients this is quite evident, since all patients decrease their lactate extraction on pacing. Furthermore, data from patients, not presented here, whose chest pain increased profoundly on pacing, showed a successively increasing negative arterial-coronary sinus lactate difference.

Thomas. Goulding's group showed that regional sampling gives a very different answer if you place your catheter selectively. If samples are taken from the coronary sinus, they will represent a heterogenous area of the myocardium.

Livesley. I would like to take up Dr Thomas' point since it is my experience that selective coronary venous catheterization has little value.

I think that Dr Kaijser has been extremely fortunate in choosing, for investigation, patients who have developed angina as a result of the tachycardia during effort, since their symptoms can be readily produced by fast atrial pacing. In my own study, of more than seventy cases of patients with angina on effort, pacing-induced angina has always been coincidental with myocardial lactate production. I have also observed that fast atrial pacing has neither induced angina nor increased myocardial lactate production in patients whose angina occurred predominantly at rest. However, these patients have experienced angina during recorded attacks of

bradycardia. These observations have both clinical and biochemical importance, since patients may have to be divided into sub-groups if conflicting results are to be avoided in the biochemical study of ischaemic heart disease.