THE NATURE AND CONTROL OF MYOCARDIAL SUBSTRATE METABOLISM IN HEALTHY MAN

B. W. LASSERS, L. A. CARLSON, L. KAIJSER, AND M. WAHLQVIST

THE myocardium has a continual demand for energy which is normally satisfied by the oxidation of substrates ultimately derived from the blood. Investigations of the nature of these substrates and of the regulation of their supply were first made using isolated perfused heart preparations. Early studies established that the myocardium could take up and catabolize glucose, lactate, pyruvate, fatty acids and ketone bodies.[1,2] Subsequent studies with the isolated heart have indicated the importance of substrate concentrations, hormones, and free fatty acids (FFA) in the control of substrate utilization by the heart.[3,4]

The introduction of the technique of coronary sinus catheterization with the measurement of arterio-venous differences in concentration across the heart allowed the investigation of these problems in the intact animal including man. During the past 25 years much has been learned about the nature of the substrates extracted by the heart from the blood in healthy subjects or patients at rest.[4] However, relatively little is known about the effect of physiological changes such as exercise on the pattern of myocardial substrate utilization. In addition, although it has been recognized for some time that intracellular or endogenous substrate stores are an important source of energy in exercising skeletal muscle, there is virtually no information about their role in the human myocardium. Furthermore, little has been done to establish the role in man of factors which have been found to control substrate utilization by isolated hearts, apart from the demonstration of a general relationship at rest between substrate concentration and myocardial extraction.

The purpose of this communication is to review those aspects of our own studies in healthy fasting men[5-11] which are concerned with (a) the pattern of utilization of blood substrates at rest and during prolonged exercise, (b) the role of endogenous substrate in

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myocardial energy metabolism and (c) the control of substrate uptake.

Material and methods

The subjects were 42 healthy men each of whom had been fasting overnight. Seventeen of them were studied only at rest; the other 25 were investigated both at rest and during approximately 2 hours of supine leg exercise. In order to examine the effect of lowering plasma FFA on the pattern of substrate metabolism, ten of the latter group received a continuous intravenous infusion of nicotinic acid throughout the study (Fig. 14, 1). The details of these studies, the catheterization and sampling techniques, analytical methods and calculations have been described.[6 8 9]

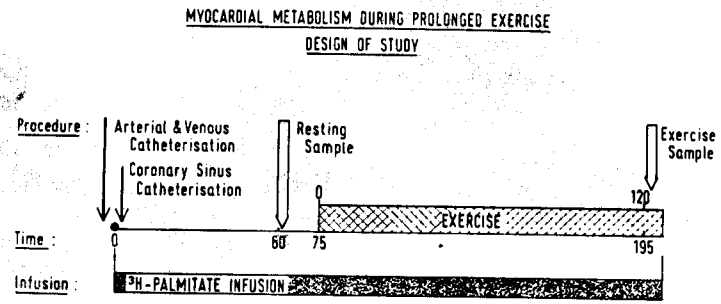

FIG. 14, 1. Design of studies of myocardial metabolism during prolonged exercise. After insertion of arterial and venous catheters a constant infusion of ^{3}H-palmitate was begun as an FFA tracer. The coronary sinus was catheterized and at 60 min resting samples were collected. The subjects then performed two hours of supine leg exercise and further samples were collected during the final minutes of this period. The design of the nicotinic acid investigation was identical except that the subjects received a constant intravenous infusion of nicotinic acid throughout the study.

The pattern of substrate utilization at rest and during prolonged exercise

The pattern of substrate utilization (as assessed by calculation of the oxygen extraction ratios of the various substrates[6]) which we found in our subjects at rest is shown in Table 14, 1. This pattern only differs substantially from that found by other workers[4] in that we were able to demonstrate a significant extraction of plasma triglycerides.[5] Prolonged exercise was accompanied by a decrease

in the relative contribution of glucose to myocardial energy metabolism, a concomitant increase in the contribution of lactate and no significant change in that of FFA or triglycerides (Table 14, 1). Thus there was no difference between rest and prolonged exercise in the relative importance of total blood lipid and total blood carbohydrate as fuel for myocardial energy metabolism. In this respect prolonged exercise would appear to differ from short periods of submaximal exercise. The marked rise in the arterial concentration of lactate and the fall in that of FFA which occur in the first half hour or so of exercise enhance the contribution of lactate to myocardial energy metabolism and decrease that of FFA. Hence, during this period, carbohydrate is a quantitatively more important source of energy for the heart than it is either at rest or when exercise has been prolonged.[8 12]

The role of endogenous substrate as a source of energy for myocardial metabolism

A considerable proportion of the energy requirements of exercising skeletal muscle is derived from the metabolism of endogenous glycogen and triglycerides.[13 14] Endogenous substrates are also metabolized by the isolated perfused heart and changes in the glycogen and triglyceride content of the intact rat heart are known to occur with physiological changes such as ageing, exercise, and dietary alterations and with the administration of drugs such as nicotinic acid. However, because it is difficult to obtain biopsy material from the human heart, the significance of these stores in myocardial energy metabolism in man is not clear. Nevertheless, inferences about the stores can be drawn from data on oxygen extraction ratios, and for the endogenous glyceride pools, from measurement of arterial coronary sinus differences in free glycerol concentration.

It can be seen from Table 14, 1 that at rest, both with and without nicotinic acid, the total oxygen extraction ratio for blood substrates did not differ significantly from 100 per cent. Measurements of substrate extraction by the heart obviously do not indicate whether a substrate is immediately oxidized or stored for catabolism later, but as the total oxygen extraction ratio was very close to 100 per cent it follows that in the resting fasting state there is little change in

Table 14, 1. *The relative contribution of various blood substrates to myocardial oxidative metabolism as assessed by their oxygen extraction ratios at rest and during prolonged exercise in: (A) a control group of 15 subjects not receiving nicotinic acid and: (B) a group of 10 subjects receiving a continuous intravenous infusion of nicotinic acid. FFA = free fatty acids; TGFA = triglyceride fatty acids.*

SUBSTRATE	OXYGEN EXTRACTION RATIO %							
	A. CONTROL GROUP				B. NICOTINIC ACID GROUP			
	REST		EXERCISE		REST		EXERCISE	
FFA	49 ± 4	64 ±6	49 ± 2	58 ±4	11 ± 3	22 ±7	4 ± 10	2 ±10
TGFA	15 ± 5		9 ± 3		11 ± 6		−2 ± 3	
Glucose	25 ± 5	33 ±5	13 ± 2	30 ±5	48 ± 5	72 ±5	35 ± 4	67 ±6
Lactate	8 ± 2		16 ± 3		22 ± 2		30 ± 4	
Pyruvate	0 ± 1		1 ± 0		2 ± 1		2 ± 0	
TOTAL	97 ± 8		88 ± 6		94 ± 9		69 ± 12	

(mean ± SEM)

the total energy content of endogenous myocardial substrate pools, although shifts between the various pools could, of course, occur.

During prolonged exercise the average total oxygen extraction ratio for the control group fell to 88 per cent. This fall was not significant, and the total ratio does not in fact differ significantly from 100 per cent. Nevertheless, it does raise the possibility that during prolonged exercise energy is being derived from sources other than the blood substrates which were measured. It seems very unlikely that other blood metabolites such as ketone bodies or amino acids are a significant source of energy in this circumstance[8] and, therefore, it could be that there is a net decrease in the total energy content of endogenous substrate pools. On the other hand, it is clear from the magnitude of the contribution of blood substrate

that if the myocardium does indeed derive energy from endogenous pools during exercise, it is very much less dependent on them than is skeletal muscle which may obtain as much as 70 per cent of its energy from intracellular stores.[14]

In the case of the nicotinic acid group during prolonged exercise, the total oxygen extraction ratio of 69 per cent was significantly less than 100 per cent. Again it is unlikely that this deficit can be accounted for by other blood metabolites, and it is probable that there has been a reduction in the total energy content of endogenous myocardial substrate pools.[9] Evidence that the substrate is in fact lipid stems from a comparison of estimates of the relative utilization of carbohydrate and lipid derived in two different ways: from the oxygen extraction ratio data, and from the myocardial RQ's (Table 14, 2). In both the control and nicotinic acid groups at rest and in

Table 14. 2. *The relative contribution of blood carbohydrate (CHO) and lipid to myocardial oxidative metabolism as assessed by the oxygen extraction ratios (OER), compared with the contribution predicted from the average myocardial RQ's (RQm) (given in brackets)*

	CONTROL		NICOTINIC ACID	
	OER	RQm	OER	RQm
REST		(0·76)		(0·91)
Lipid	64 ± 6%	82%	22 ± 7%	31%
CHO	33 ± 5%	18%	72 ± 5%	69%
TOTAL	97 ± 8%	100%	94 ± 9%	100%
EXERCISE		(0·81)		(0·91)
Lipid	58 ± 4%	65%	2 ± 10%	31%
CHO	30 ± 5%	35%	67 ± 6%	69%
TOTAL	88 ± 6%	100%	69 ± 12%	100%

(mean ± SEM)

the control group during prolonged exercise the percentage participation of carbohydrate and lipid as measured by the oxygen extraction ratios are in good agreement with those predicted by the average myocardial RQ's. In the nicotinic acid group during prolonged exercise, the two methods give concordant estimates for carbohydrate, whereas in contrast, for lipid there is a considerable

discrepancy between the oxygen extraction ratio value of 2 per cent and the RQ one of 31 per cent. This implies that in this rather extreme condition of prolonged exercise combined with inhibition of FFA mobilization, lipid is the principal type of endogenous substrate from which the heart is deriving energy.[9]

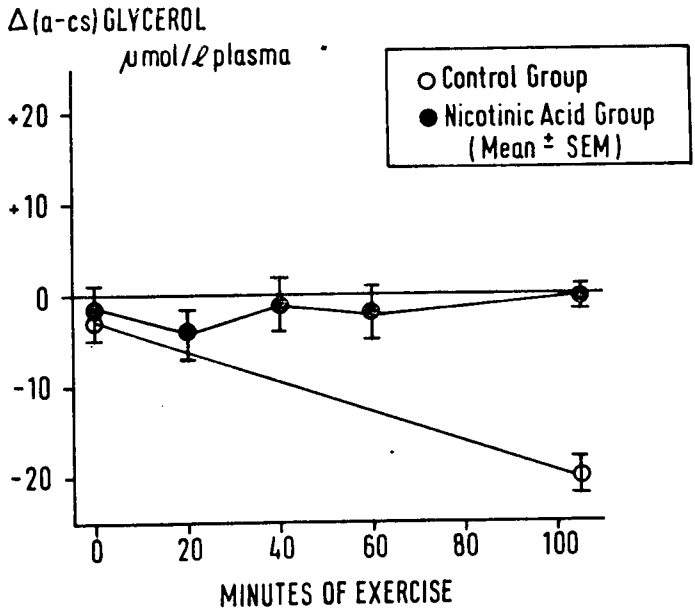

FIG. 14, 2. Arterial-coronary sinus differences in free glycerol concentration ($\Delta_{(a-cs)}$ Glycerol) at rest and during prolonged exercise in the control and nicotinic acid groups. Positive differences indicate myocardial extraction of glycerol and negative differences the release of glycerol into the coronary sinus blood.

Further evidence that endogenous lipid pools are metabolically active in man comes from measurement of arterial-coronary sinus differences in free glycerol concentration (Fig. 14, 2). At rest, in both the control and nicotinic acid groups, there was no evidence of either myocardial uptake of free glycerol or release of it into the coronary sinus. However, during prolonged exercise there was marked efflux of glycerol into the coronary sinus blood in the control group, but not in the nicotinic acid one. For a number of reasons it seems that the most likely source of free glycerol entering the

coronary sinus is endogenous myocardial glycerides.[8 9] Thus it would appear that during prolonged exercise without nicotinic acid, in contrast to the situation at rest or during exercise with nicotinic acid, the rate of glyceride hydrolysis has exceeded the capacity of the myocardium to reutilize glycerol. On the other hand, when nicotinic acid was administered, prolonged exercise was not accompanied by an efflux of glycerol from the heart. These somewhat paradoxical results present a problem of interpretation. However, if glycerol release reflects the turnover of endogenous glycerides rather than changes in actual pool size, then these findings could be consistent with the oxygen extraction ratios. As described above, these suggested that during prolonged exercise without nicotinic acid there was very little, if any, depletion of endogenous energy stores, but that with the combination of nicotinic acid and exercise there was net utilization of intracellular lipid pools. Thus, in the normal circumstance in which exercise is accompanied by increased plasma FFA concentrations, the turnover rate of endogenous glycerides could exceed the myocardial capacity for reutilization of glycerol while in the situation of exercise with very low FFA concentrations, and therefore, possibly a reduced rate of synthesis of endogenous glycerides, the rate of utilization of endogenous lipid may have been greater than the rate of its formation without being sufficiently great to exceed the ability of the heart to metabolize glycerol.

The control of myocardial substrate uptake

In intact man, the investigation of factors affecting or controlling myocardial substrate uptake is dependent on inferences made from the relationships found between substrate and hormone concentrations and substrate extraction by the heart which do not, in themselves, imply a causal relationship. The inability to make precise measurements of coronary blood flow severely restricts the examination of these relationships under different physiological circumstances. Thus, although valid information about substrate uptake (extraction × flow) can probably be obtained by comparing extractions among healthy individuals at rest when coronary flow rates are likely to be very similar, a comparison of resting and exercising extractions could be misleading. Similarly, since there may well be substantial differences among individuals in coronary flow during

exercise—even when they are performing similar work loads in relation to their physical fitness[6]—it is difficult in this circumstance to make inferences about control of substrate uptake which are quantitatively meaningful from measurements of substrate extractions alone.

For example, one factor known to be of importance in the uptake of many substrates is the arterial concentration. Thus we found, like other workers, that at rest there is a significant linear relationship between extraction and arterial concentration of FFA but that during exercise this was not so (Fig. 14, 3). One interpretation of

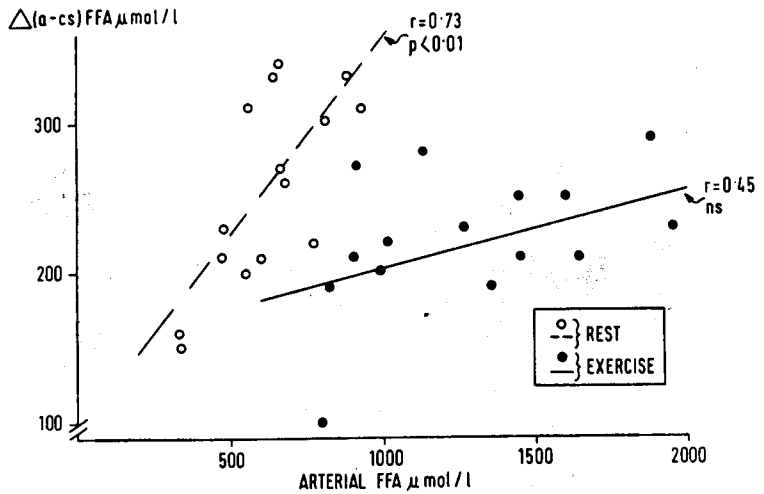

FIG. 14, 3. The relationship, both at rest and during prolonged exercise, of myocardial FFA extraction ($\Delta_{(a\text{-}cs)}$ FFA) and arterial FFA concentration.

these data is that, at the higher FFA concentrations found during prolonged exercise, FFA uptake had become saturated and no longer dependent on concentration. On the other hand, if those individuals with the higher FFA concentrations during exercise also had higher coronary flow rates, then uptake could still be dependent on arterial concentration.

For glucose similarly a close linear relationship was found at rest, but not during exercise (Fig. 14, 4). However, in this instance the exercising values all lie close to or above the regression line for the

relationship at rest. Since coronary flow was probably two to three times greater during exercise of the type performed by our subjects,[8] this implies that the rate of myocardial glucose uptake must be considerably greater for a given arterial glucose concentration during exercise. This acceleration of glucose uptake occurred despite the fact that arterial insulin concentration had fallen[11] and FFA concentrations had risen.[8] This observation suggests that exercise may, in fact, augment glucose uptake in man in a manner analogous to that found when the isolated perfused rat heart is made to perform at increased work loads.[15]

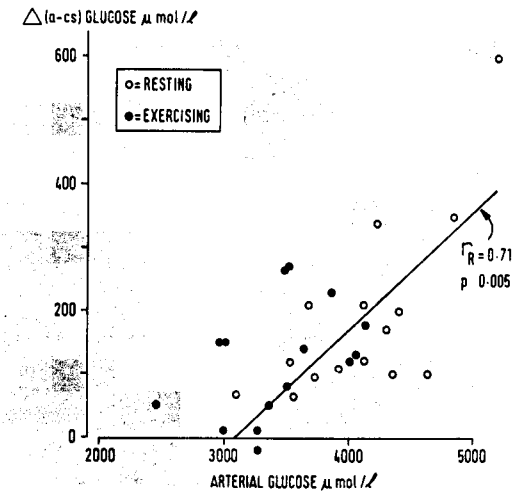

FIG. 14, 4. The relationship at rest and during prolonged exercise between myocardial glucose extraction ($\Delta_{(a\text{-}cs)}$ glucose) and arterial glucose concentration. Since the variables were not significantly correlated during exercise, the regression line has been drawn for the resting points only (r_R = correlation coefficient for resting points).

Studies with the isolated perfused rat heart have also shown that FFA may inhibit glucose utilization[16,17] and our investigations in man support this idea.[6,7,9,10] We found that there were significant, negative correlations between arterial FFA concentration and myocardial extraction of glucose, lactate and pyruvate: as FFA concentration increased, extractions of these substrates fell, and in the case of pyruvate there was net efflux from the heart at higher

FFA concentrations. This inhibition disappeared when FFA concentrations were reduced with nicotinic acid. Not only do these findings support the general concept of an inhibiting effect of fatty acids on myocardial glucose utilization, but the observation of pyruvate efflux also supports the idea that at least in part this inhibition may occur at the level of pyruvate dehydrogenase.[18]

An additional relationship between FFA concentrations and

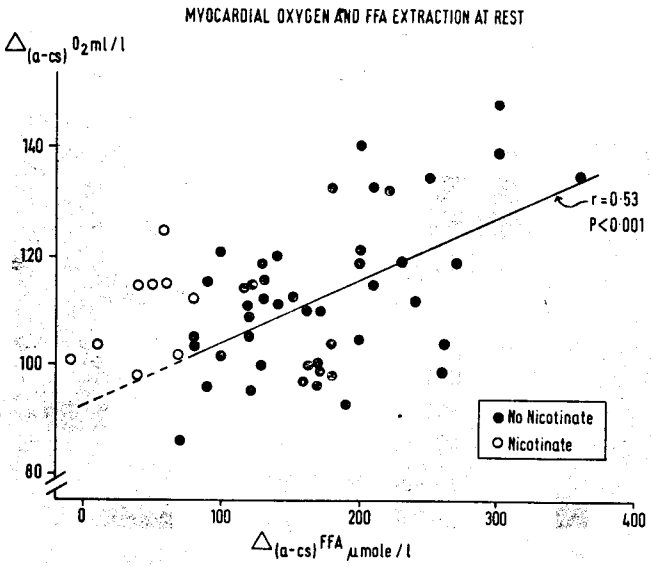

FIG. 14, 5. The relationship at rest between myocardial oxygen ($\Delta_{(a\text{-}cs)}O_2$) and FFA ($\Delta_{(a\text{-}cs)}$ FFA) extractions. The regression line has been drawn only for the measurements in subjects not receiving nicotinic acid.

myocardial metabolism is seen in Figure 14, 5. Here, there is a significant correlation between the myocardial extractions of FFA and oxygen.[10] Thus, increased FFA extraction by the heart is associated with increased myocardial oxygen utilization—unless there has been a concomitant fall in coronary blood flow. On the other hand, it can also be seen that lowering FFA extraction below the normal range by decreasing FFA concentrations with nicotinic acid is not associated with a parallel decrease in oxygen extraction.

One possible explanation for this association between FFA and oxygen extraction is that fatty acid metabolism increases myo-

cardial oxygen requirements in man as it appears to do in the isolated rat heart[19] and in the intact dog.[20] An alternative explanation is that some third factor such as catecholamines has increased myocardial oxygen utilization but not coronary blood flow and at the same time has produced increased plasma FFA concentrations.

The inter-relationships between the various factors affecting myocardial uptake of blood substrates is obviously complex. It is always possible that the apparent relationship between two variables is really a function of some third variable or a number of other variables (for example, as discussed above for oxygen and FFA extractions). Conversely, it is also possible that a genuine relationship may be obscured by the interaction of other factors.

Table 14, 3. *Various factors which were found on partial correlation analysis to be significant determinants of glucose extraction. The magnitude of their effect is illustrated in the table by showing the predicted effect on glucose extraction of a 10 per cent increase in each variable, the remaining variables being held constant.*[10]

10% INCREASE IN:	EFFECT ON GLUCOSE EXTRACTION:
Arterial insulin	24% increase
FFA extraction	17% decrease
Arterial glucocorticoid	13% decrease

Thus, for example, although glucose extraction and arterial insulin concentration were not directly correlated with each other at rest, when the effect of other variables was allowed for by multiple regression and partial correlation analysis, extraction was found to increase with insulin concentration. At the same time, however, the significant relationship between glucose extraction and concentration disappeared.[10] Table 14, 3 summarizes the factors which were found to be significant determinants of glucose extraction in resting fasting man.

SUMMARY

1. Prolonged exercise is associated with a decrease in the contribution of glucose, and an increase in the contribution of lactate to myocardial energy metabolism. However, there is no change in the relative importance of blood lipid and carbohydrate as sources of energy for the heart in this circumstance.

2. Neither at rest nor during prolonged exercise, do endogenous myocardial energy stores appear to be important net sources of energy for the heart. Only in the rather extreme situation of prolonged exercise and low FFA concentrations produced by nicotinic acid infusion is there any indication of net depletion of endogenous myocardial energy pools: under these circumstances it is probable that the heart derives energy from intracellular lipid.

3. At rest myocardial extraction of FFA and glucose increased with their respective arterial concentrations. A negative correlation between glucose extraction and arterial FFA concentration supports the contention that FFA can inhibit glucose uptake. The observation that myocardial oxygen extraction increased with increasing FFA concentration is consistent with the hypothesis that fatty acid metabolism increases myocardial oxygen requirements.

ACKNOWLEDGMENTS

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DISCUSSION

Mjøs. You measured glycerol in some of your experiments both during rest and exercise. Did you see any output of glycerol from the myocardium? When patients were pretreated with nicotinic acid and then exercised, did they then show any release of glycerol from the myocardium? Is it possible to inhibit myocardial lipolysis by nicotinic acid?

Lassers. Figure 14, 2 of the text shows the arterial coronary sinus difference in concentration of free glycerol at rest and during exercise in the control group of subjects (open circles). You will see that, although there was no significant extraction or release of glycerol in the control group during rest, there was a marked efflux of glycerol from the heart during exercise. For a number of reasons we think that the most likely source of this glycerol was endogenous myocardial glyceride and that this efflux probably reflects increased turnover of this pool rather than its net depletion. Now, when nicotinic acid was administered continuously throughout the study, glycerol release was completely inhibited. These observations may seem paradoxical in view of the oxygen extraction ratio and RQ predictions which suggested that endogenous glycerides are being utilized. The answer may be that the glycerol release reflects rates of turnover of endogenous glyceride pools and that, in the nicotinic acid group, this has not exceeded the capacity of the myocardium for reutilization of the glycerol. In the control group, on the other hand, the rate of glycerol production may have exceeded the rate of reutilization without any change in pool size.

Carlson. It is unfortunate that the myocardium in contrast to adipose tissue has an active glycerokinase. This means that glycerol made available during lipolysis of myocardial triglycerides does not necessarily need to be released into plasma but could be reutilized by the heart.

Randle. We have recently reported (Neely, Denton, England and Randle, *Biochem. J.* (1972), **128,** 147) the results of a study of the effects of cardiac work on the regulation of the citrate cycle in rat hearts and this is relevant to Dr Carlson's observations on the utilization of myocardial triglyceride. In these studies we increased cardiac work acutely by raising the perfusion pressure abruptly from 50-120 mmHg in rat hearts perfused (a) with glucose + insulin and (b) with glucose + insulin + acetate. The hearts were thus deprived of exogenous sources of long chain fatty acids. The experimental period employed involved an 8 min period of perfusion at either 50 mmHg followed by a further 12 min of perfusion at either 50 mmHg or 120 mmHg. At low perfusion pressure, rates of oxygen consumption were essentially constant at 25 μmol/min/g dry heart with glucose and 29 μmol/min/g dry heart with glucose

+ acetate (the higher rates with acetate are attributed to the lower P : O ratio for oxidation of this substrate as compared to glucose). Increasing the perfusion pressure led to an abrupt increase in oxygen consumption to a new steady state level (2·5 times) within 2 min.

The most striking change in substrate utilization was in the oxidation of fatty acids derived from muscle glyceride. This increased ninefold in perfusions with glucose and tenfold in perfusions with glucose+acetate. This was shown in two ways (a) by measurement of the concentration of muscle glycerides and (b) by calculation of the fraction of the oxygen consumption which was not accounted for by the oxidations of glucose or of glucose + acetate. The two methods of calculation showed close agreement. Other changes noted were a twofold increase in glycolytic rate with glucose or glucose acetate; and a twofold increase in oxidation of glucose with glucose alone but no increase when glucose and acetate were present. In the latter situation there is little if any oxidation of glucose by the heart. The rate of acetate oxidation showed little change on increasing cardiac work. These studies indicate that work stimulates lipolysis of muscle glycerides and are in general agreement with Dr Carlson's *in vivo* findings. They also indicate that an apparently abundant supply of certain fuels (in this study glucose and acetate) may not be adequate to support increased cardiac work and to prevent utilization of endogenous triglyceride. Consequently, it may be unwise in the clinical situation to assume that glucose can substitute for long chain fatty acids when lipolysis is inhibited with nicotinate or other antilipolytic drugs. It might be advisable to consider supplying other substrates such as ketone bodies. The rates of oxidation of endogenous glycerides that we have seen in the rat heart could only continue for about 15 to 30 min at the most and by this time the triglyceride stores would have been utilized.

Lassers. It does seem that at least *in vivo,* unless there is a profound stress such as nicotinic acid and prolonged exercise, control mechanisms are such that other substrates become available : for example, lactate concentrations rise and lactate is taken up, or glucose concentrations rise. It seems that even during very prolonged exercise the heart still derives adequate energy from circulating substrates.

Allison. Working in Professor Randle's department, we have studied the dog heart *in vivo* and have shown striking effects of elevating free fatty acids by using Intralipid and heparin on the inhibition of uptake of lactate and pyruvate. Furthermore, we have studied the effects of two substances—bromostearate which has to be bound to albumin, and the water soluble sodium dichloracetate. Both block the oxidation of free fatty acids and cause a striking reversal of the inhibition of pyruvate, lactate and glucose uptake caused by free fatty acids. These results add further confirmation to the glucose fatty acid cycle *in vivo*.

A COMPARISON OF SUBSTRATE METABOLISM OF THE HUMAN HEART IN THE FASTING AND FED STATES

L. A. CARLSON, L. KAIJSER, B. W. LASSERS, S. RÖSSNER AND M. L. WAHLQVIST

AVAILABLE information about the metabolism of the human heart deals almost exclusively with the fasting state. Furthermore in the few non-fasting studies only glucose has been administered.[1,2] During most of the day the human heart is perfused by blood which from the substrate and hormonal point of view is quite different from that perfusing the heart in the fasting state. This report deals with two questions related to the substrate uptake of the human heart in the fed state.

1. Are exogenous plasma triglycerides extracted by the human heart and if so, what is the quantitative importance of that extraction compared to the extraction of endogenous plasma triglycerides?
2. Does the extraction of FFA and glucose differ in the fed and fasted states?

This report is based on data from several studies in our laboratories on the metabolism of the human heart.[3,4,5,6]

Material and methods

The general procedures for catheterization of the coronary sinus and the physiological and biochemical methods have been described elsewhere.[3,4,5,7] All catheterizations were started at about 8 a.m.,