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.,

In: Effect of acute ischaemia on myocardial function. Edited by KW Donald, DG Julian, MF Oliver. London: Churchill Livingstone, 1972.

when the young healthy male subjects reported to the laboratory. An *oral* fed state was induced by eating 200 ml of cream (40 per cent fat), 15 g cheese and 50 g of bread. An *intravenous* fed state was created by the infusion of Intralipid-S[1] (containing sorbitol instead of glycerol as in Intralipid) and glucose. The advantage of the intravenous fed state is that fairly steady blood levels of exogenous triglycerides and of glucose can be reached.

Results

The human heart extracted exogenous triglycerides when they were present in blood either as chylomicrons or Intralipid emulsion (Table 14a, 1). Earlier studies have shown that the kinetics for

Table 14a, 1 *Arterial (A) concentration and arterial-coronary sinus difference (A-Cs) of exogenous plasma triglycerides and oxygen extraction ratio (OER) for the extracted exogenous triglycerides*

	ORAL FED STATE	INTRAVENOUS FED STATE
	μmol per l	μmol per l
A	1190 ± 160	2580 ± 160
A-Cs	70 ± 20	80 ± 20
OER (per cent)	51 ± 14	43 ± 17

Mean ± SEM of 6 determinations in 3 subjects (one determination at 3 hr and one at 4 hr after the meal for the oral fed state and of 38 determinants in 12 subjects for the intravenous fed state.

removal of Intralipid[R] from blood are identical to those for chylomicrons and that the elimination below a certain plasma concentration (C) is a first order reaction and above this concentration it is a zero order reaction.[8] The value for C is usually around 1000 μmoles of exogenous triglycerides per litre plasma. Above that concentration, removal follows zero order kinetics, which means that a constant amount of exogenous triglyceride is cleared from blood per unit time regardless of the plasma level of triglycerides. This kinetic

[1] Kindly supplied by Dr Iván Håkansson, AB Vitrum, Stockholm, Sweden.

behaviour with an apparent saturation of the removal mechanism above 1000 μmol/l may explain why the same amount of exogenous triglyceride was extracted by the heart in the two fed state conditions (Table 14a, 1) despite the fact that the plasma level of exogenous triglycerides was about twice as high in the intravenous as in the oral fed state.

The mechanism for the uptake of exogenous triglycerides by the human myocardium has been discussed in detail elsewhere.[5] The significant production of glycerol by the heart in the fed state, which does not occur in the fasting state (Table 14a, 2), suggests that hydrolysis of the exogenous triglycerides had occurred. If certain assumptions are made, it can be calculated from these glycerol

Table 14a, 2. *Comparison of myocardial extraction of FFA, glucose and glycerol in the oral fed state, the intravenous fed state and the fasting state*

		FFA	GLUCOSE	GLYCEROL
		μmol per 1 plasma	μmol per 1 blood	μmol per 1 plasma
Oral fed n=3	A	1070±70	4370±80	47±23
	A-Cs	170±50	70±70	−17±8
	OER (%)	31±7	10±4	
I.v. fed n=12	A	720±40^{ns}	8330±330^{xxx}	100±14^{xxx}
	A-Cs	80±10^{xxx}	280±60^{ns}	−26±3^{xxx}
	OER (%)	24±3^{xxx}	29±8^{ns}	
Fasting n=15	A	620±50	4110±140	46±4
	A-Cs	170±20	190±40	−3±2
	OER (%)	49±4	25±5	

ns and xxx indicate that the difference between the i.v. fed and fasting groups are not significant ($p>0.05$) and significant ($p<0.001$) respectively.

values that at least about 50 per cent of the exogenous triglycerides taken up by the heart had been completely hydrolyzed (presumably by lipoprotein lipase) to fatty acids and glycerol before the triglyceride fatty acids were extracted.[5]

The quantitative importance of the exogenous triglycerides to myocardial energy balance is apparent from the fact that their oxygen extraction ratio (OER) was about 50 per cent (Table 14a, 1). In our two fed state conditions, exogenous plasma triglycerides were

the substrate with the highest OER (Table 14A, 2), and this was just as high as the OER for FFA in the fasting state (Table 14a, 2). In the fasting state, the OER for endogenous plasma triglycerides is about 15 to 20 per cent.[4,7]

In the intravenous fed state, the uptake of plasma FFA by the human heart was significantly less than in the fasting state in spite of the fact that the arterial levels of FFA were quite similar (Table 14a, 2). That the reduced extraction was not due to release of triglyceride fatty acids is evident from the fact that the uptake of ^{3}H-palmitate was also decreased.[6] In the fasting, resting state we, as others, have observed a positive linear relationship between the extraction of FFA and the arterial FFA level (Table 14a, 3). Such a relation was not present in the fed state (Table 14a, 3). One possible

Table 14a, 3. *Linear correlation coefficient (r) between the extraction of FFA and arterial FFA concentration in the fasting and the fed state.*

STATE	FASTING	FASTING	I.v. FED
r	$0{\cdot}57^{xx}$	$0{\cdot}66^{xx}$	$0{\cdot}28^{ns}$
n	30	15	38
Ref no.	(8)	(3)	(5)

n=number of observations; ns=not significant ($p>0{\cdot}05$); xx=significant ($p<0{\cdot}01$).
Ref no=Reference number.

explanation for this change in the relationship between FFA extraction and concentration from the fasting to the fed state is competition between triglyceride fatty acids and FFA. In the fasting state 170 μmoles of FFA were extracted per litre plasma by the heart and at the same time 50 μmoles of triglyceride fatty acids were extracted.[3,4] In the intravenous fed state the corresponding figures were (Table 14a, 1 and 2) 80 and 240. Comparing FFA uptake in the fasting and in the oral fed state, FFA extraction was the same in both despite the fact that arterial FFA were twice as high in the oral fed state. Thus, in the oral as in the intravenous fed state, the relationship between FFA concentration and extraction is altered from

that found in the fasting state. Glucose concentration would not seem to be an important factor in the depressed FFA extraction associated with feeding, since it occurred not only in the intravenous fed state but also in the oral fed state when glucose concentration was not significantly different from that found during fasting (Table 14a, 2).

Glucose extraction was not significantly different in the intravenous fed and in the fasting state in spite of the fact that arterial glucose and insulin levels had doubled. As in the fasting state,[4] glucose extraction was negatively correlated ($r=-0.50$) with the arterial concentration of FFA. It is likely that the exogenous triglyceride fatty acids as well as FFA have had an influence on glucose uptake, since chylomicra reduce glucose uptake in the isolated, perfused rat heart.[9]

It is interesting to see that in the fasting and in the fed states, when both lipid and carbohydrate are available, lipid appears to be the preferred substrate. In the fasting state, FFA were the dominant substrate for the human heart; in our fed states, however, exogenous triglycerides appeared on the stage as the dominant substrate for the energy supply of the human heart. It is clear that if one would like to lower the extraction of fatty acid by the heart, in certain clinical situations, restriction of FFA mobilization from adipose tissue and of the supply of exogenous triglycerides need to be considered.

Summary

We have compared the extraction of lipid and carbohydrate substrates for the normal human heart in the fasting and in the fed state.

In the fed state, the heart extracts exogenous triglycerides in amounts sufficient to cover about 50 per cent of the heart's energy requirement. The release of glycerol, which does not exist in the resting fasting state, suggests that at least half of the triglycerides removed by the heart are completely hydrolyzed before extraction.

In the fed state less FFA is extracted by the heart at a given FFA level than in the fasting state, possibly because of the pronounced uptake of exogenous triglyceride fatty acids.

Glucose extraction did not differ significantly between the fasting

and fed states, although both glucose and insulin levels had doubled.

In both the fasting and fed states, lipid appears to be the dominant substrate for the human heart.

ACKNOWLEDGMENT

Supported by grants from the Swedish Medical Research Council (19x--204).

REFERENCES

1 BING, R. J., SIEGEL, A., VITALE, A., BALBONI, F., SPARKS, E., TAESCHLER, M., KLAPPER, M. & EDWARDS, S. (1953). Metabolic studies on human heart *in vivo*; studies on carbohydrate metabolism of human heart. *American Journal of Medicine* **15**, 285-296.

2 GOODALE, W. T., OLSON, R. E. & HACKEL, D. B. (1959). The effect of fasting and diabetes mellitus on myocardial metabolism in man. *American Journal of Medicine* **27**, 212-220.

3 KAIJSER, L., LASSERS, B. W., WAHLQVIST, M. L. & CARLSON, L. A. (1972). Myocardial lipid and carbohydrate metabolism in fasting men during prolonged exercise. *Journal of Applied Physiology* **32**, 72-80.

4 LASSERS, B. W., KAIJSER, L. & CARLSON, L. A. (1972). Myocardial lipid and carbohydrate metabolism in healthy, fasting men at rest. *European Journal of Clinical Investigation* **2**, 348-358.

5 CARLSON, L. A., KAIJSER, L., RÖSSNER, S. & WAHLQVIST, M. L. (1972 in press). *Acta Medica Scandinavica.*

6 WAHLQVIST, M. L., RÖSSNER, S., KAIJSER, L. & CARLSON, L. A. *To be published.*

7 CARLSON, L. A., KAIJSER, L. & LASSERS, B. W. (1970). Myocardial metabolism of plasma triglycerides in man. *Journal of Molecular and Cellular Cardiology* **1**, 467-475.

8 CARLSON, L. A. & HALLBERG, D. (1963). Studies on the elimination of exogenous lipids from the blood stream. *Acta Physiologica Scandinavica* **59**, 52-61.

9 ONTKO, J. A. & RANDLE, P. J. (1967). Inhibition of glucose utilization by perfusion with chylomicrons in rat heart. *Biochemical Journal* **104**, 43C-44C.

DISCUSSION

Opie. Data suggesting that triglyceride can substantially inhibit glucose metabolism have been obtained in rat heart studies.

Do your experiments really mimic the fed state?

Carlson. Yes, for the oral fed state but of course not for the intravenous when the gastrointestinal tract is bypassed. But the increase in exogenous triglycerides corresponds closely to what you see with alimentary lipaemia. The purpose of the intravenous route of administration was to achieve a steady state in arterial levels of triglycerides.

Wallace. You both discuss the metabolism of the heart. You, Dr Carlson, have plotted on the vertical axis the arterial coronary

sinus difference for various substrates and then used the term uptake. It seems to me that in the absence of a knowledge of flow, you cannot use that term. Dr Lassers, you showed that the AV difference for glucose decreased in proportion to the free fatty acid concentration in arterial blood. Can we draw any interpretation from that without knowledge of what the coronary flow was?

Lassers. Obviously one cannot measure rates of uptake unless one knows flow. On the other hand, I think one can compare xtractions among healthy individuals at rest. All of our subjects were of similar physical fitness and in a similar dietary state and had been resting for an hour: the differences in coronary flow rates among such a group are probably relatively small. I have tried to avoid the word ' uptake ' when I mean ' extraction '. It is, as you point out, an extremely important point since rate of uptake is a different variable.

Carlson. I agree entirely. There are, however, two valid comments: (1) You may talk about ' uptake ' if you consider the uptake (disappearance) from the blood per unit volume. (2) You can avoid the need to measure flow when you study, at the same time, the relation between uptake of two different blood substrates—then flow cancels out.

Wallace. Do you have any idea about changes in coronary blood flow during your nicotinic acid experiments?

Lassers. Coronary blood flow has not been measured in man after nicotinic acid administration. But we do know that the haemodynamic variables such as heart rate and blood pressure, which are of importance in determining coronary flow, return to basal values after about 30 min of continuous infusion of nicotinic acid.

Maseri. Were you measuring the arteriovenous difference of free fatty acids from radioactive palmitate?

Lassers. In all the data presented, we determined arterial-coronary sinus differences in FFA from chemical estimates: these are, therefore, net differences. Our radioisotope data suggest that there is efflux of unlabelled FFA into the coronary sinus blood. If this is the case, then there is both extraction and release of FFA during passage of blood across the heart.

Maseri. Yes, that is exactly the point I wanted to make. When you measure the concentration difference between the artery and

coronary sinus you are measuring something that takes into account both uptake and release, whereas if you inject labelled palmitate and measure initial extraction of palmitate you only take release into account.

Lassers. Net extraction is what is required in order to calculate the oxygen extraction ratio.

Maseri. Did you infuse C^{14} palmitate during exercise following nicotinic acid?

Lassers. Yes, ^{3}H-palmitate actually. If you follow the time course of change in the specific activity of fatty acids in the artery and coronary sinus in the control group, the activity in coronary sinus blood gradually approaches that in arterial blood. However, during prolonged exercise, there continues to be a difference in the two specific activities and this difference is greater in the nicotinic acid than in the control group.

Maseri. Does this mean that the isotope infusion was started too early to allow calculation of the net extraction? The data seem to suggest that during exercise in the presence of nicotinic acid, there is a greater extraction of labelled palmitate.

Lassers. The differences in specific activities indicate an *apparent* increase in the extraction of labelled FFA. In fact, this is due to the entrance of unlabelled fatty acid into the coronary sinus from some pool with a lower specific activity. As time proceeds and this pool becomes labelled, the difference decreases.