(iii) During Prolonged Exercise

FFA parameters were not as good predictors of myocardial carbohydrate extraction as they were at rest. Of the three carbohydrate substrates examined, pyruvate was the only one whose extraction was predicted significantly from myocardial FFA extraction on multiple regression analysis. Little, in fact, is known about what regulates myocardial uptake of carbohydrate during exercise (21, 22, 39).

(b) In Parenterally-Fed Healthy Men

When infusions of glucose and the fat emulsion Intralipid^{R}-S were given to healthy men, myocardial glucose extraction was significantly and negatively related to plasma FFA concentration, but not to myocardial FFA extraction. It is therefore possible that FFA can affect myocardial extraction of glucose without actually entering myocardial cells. The presumed effect of FFA on pyruvate dehydrogenase may not be as evident in the presence of high blood glucose concentrations and of exogenous plasma triglycerides (see below).

(c) During Angina Pectoris

The myocardial extractions of glucose, lactate, pyruvate and FFA were estimated during angina pectoris induced by atrial pacing. Some of the patients were paced in the same way a second time during an infusion of nicotinic acid. The infusions had been in progress 90 minutes so that plasma FFA concentrations were low at the time of the second pacings. When the observations were considered together, myocardial lactate and pyruvate extractions, but not glucose extraction, were found to be significantly and negatively related to plasma FFA concentration and to myocardial FFA extraction. In the hypoxic heart, therefore, it may not be possible to improve glucose uptake and anaerobic metabolism by lowering plasma FFA concentrations. However, it is possible that, at low plasma FFA concentrations, more myocardial energy is derived

anaerobically by using the limited amount of oxygen available to oxidize lactate and pyruvate instead of FFA (74).

One limitation of the study was that the coronary sinus blood which was collected presumably drained both hypoxic and well-oxygenated myocardium. It therefore cannot be asserted that low plasma FFA concentrations actually increase the availability of lactate and pyruvate to hypoxic areas. Another potential limitation is that the observations at low plasma concentrations were made during a second pacing which may not have been analogous to the first in every way except for changes in FFA. Nevertheless, the investigation shows that it is possible to approach the problem of survival of ischaemic myocardium metabolically.

Free Fatty Acids and Myocardial Oxygen Metabolism (Paper I)

The finding of a significant positive relationship between myocardial oxygen and FFA extractions in healthy fasting subjects at rest is in agreement with work in the isolated perfused rat heart (17-19) and the intact dog heart (49). The part of myocardial oxygen consumption affected by FFA may be that concerned with basal or resting metabolism (65) and this could represent more than 15 - 20 % of the heart's oxygen consumption (17, 18). At least one of the factors related to non-basal myocardial oxygen metabolism, namely heart rate (65), was not involved in the relationship between oxygen and FFA extractions at rest, but was during prolonged exercise.

The Hormones Insulin, Growth Hormone and Glucocorticoid and Myocardial Carbohydrate Metabolism in Healthy Fasting Subjects (Paper II)

No significant correlations were found between myocardial glucose extraction and arterial concentrations of plasma insulin, growth hormone or glucocorticoid. Significant positive correlations were found between myocardial lactate extraction and arterial growth hormone concentration at rest and during prolonged exercise. A significant negative correlation was found between myocardial pyruvate extraction and arterial insulin concentration during

prolonged exercise. A significant positive correlation was found between pyruvate extraction and arterial growth hormone concentration at rest.

Equations for the myocardial extractions of glucose, lactate and pyruvate were written on the basis of multiple regression analysis. These included the substrate's own arterial concentration, the extractions of other myocardial substrates and the three arterial plasma hormone concentrations. It was found that myocardial glucose extraction was increased by insulin and decreased by glucocorticoid at rest in accordance with the known actions of these hormones in the isolated heart (34, 50, 52, 62) or on administration to man (29). Myocardial lactate extraction was increased by growth hormone during prolonged exercise; this effect may depend on inhibitions of hexokinase and phosphofructokinase with slowing down of glycolysis (52, 62). Myocardial pyruvate extraction was decreased by insulin and increased by growth hormone and glucocorticoid at rest; for insulin and glucocorticoid these effects were opposite to those on glucose extraction and may depend on them or the mechanisms underlying them.

Thus the complex interrelationships which exist in vivo among the various factors determining substrate uptake by the heart may obscure the effect of any one factor examined in isolation.

Uptake and Release of Hormones by the Heart in Healthy Fasting Men (Papers III and IV)

During prolonged exercise and also during the infusion of nicotinic acid in resting subjects, net release of insulin from the myocardium took place. ^{125}I-albumin data indicated that these findings could not be accounted for by haemoconcentration. There was a positive linear relationship between arterial-coronary sinus difference in insulin concentration and arterial

insulin concentration with the most marked release of insulin from the heart occurring at the lowest arterial concentrations. This would be in accordance with the view that interaction of insulin with its receptors on cell membranes follows the law of mass action (41). Both the infusion of nicotinic acid and prolonged exercise (39, 45, 46) increase myocardial glucose uptake, yet in both of these circumstances insulin release from the myocardium took place. This suggests that either insulin is released from a site such as the capillary (60) where it does not affect myocardial metabolism or other factors, such as fatty acids and exercise (21, 22, 39, 45, 46) play an important role in determining glucose extraction by the myocardium under these circumstances.

No significant relationship was found between arterial-coronary sinus difference in growth hormone concentration and arterial growth hormone concentration.

At rest, myocardial extraction of glucocorticoid was related significantly and positively to arterial concentration. To some extent, this depended on plasma insulin concentration, but the reason for this is not clear. Significant release of glucocorticoid from the heart took place during prolonged exercise in those subjects receiving nicotinic acid. This release was associated with a rise in plasma growth hormone concentration. The uptake or release of glucocorticoid could be expected to alter myocardial glucose metabolism (Paper II). The action of insulin to increase glucose uptake may be partly offset if insulin facilitates myocardial uptake of glucocorticoid. Furthermore, an increased glucose uptake, which might be expected to follow glucocorticoid release might be partly offset by the associated high growth hormone concentrations which may tend to reduce glucose uptake.

Parenteral Feeding and Myocardial Metabolism in Healthy Subjects (Paper V)

It was possible to maintain reasonably steady concentrations of exogenous plasma triglyceride and of blood glucose, from about 30 minutes after commencement of simultaneous infusions of these substrates, onwards. Thus a study of arterial-coronary sinus concentration differences was possible at 1, 2, 3 and 4 hours. The fed state created by the infusions would correspond to a meal rich in fat followed by a carbohydrate snack at about the time of peak fat absorption.

During the infusions, significant myocardial extraction of exogenous plasma triglyceride was demonstrated using the technique of nephelometry. Shifts in plasma water, as determined with ^{125}I-albumin, could not have given rise to apparent extractions. If completely oxidised, exogenous plasma triglyceride would have met about 40% of the heart's energy requirements at rest. Production of glycerol across the coronary circulation suggested that at least 50% of the exogenous plasma triglyceride which disappeared did so as a result of complete lipolysis. There was no significant extraction of endogenous labelled plasma triglyceride.

Probably due to lipolysis of infused Intralipid^{R}-S, plasma FFA concentrations were maintained at fasting concentrations in spite of the simultaneous infusion of glucose, which would have been expected to decrease plasma FFA concentrations. At similar plasma concentrations of FFA in fasting and parenterally-fed subjects, less FFA was extracted by the myocardium in the parenterally-fed. This might have been due to competition between triglyceride fatty acid and free fatty acid for uptake by the myocardium .

Some evidence that this might be so is provided by a study with the intact dog heart in which epinephrine increased myocardial extraction of endogenous plasma triglyceride and reduced that of plasma FFA (61). Another possi-

bility is that the elevated blood glucose concentration, and the rise in blood lactate concentration which accompanied the infusions, have decreased myocardial FFA extraction. Indeed, when fasting and fed state observations are considered together, significant negative relationships are found between myocardial FFA extraction and arterial concentration of glucose, lactate or pyruvate (Table 2). This is reflected in decreased FFA OER's and an increased lactate OER in the fed state relative to the fasting state (Figure 8). These relationships are unaffected by the elimination, on partial correlation analysis, of arterial FFA concentration which is usually regarded as the major determinant of myocardial FFA extraction (Table 2). In fact, for the combined fasting and fed-state observations, FFA extraction was not significantly related to plasma FFA concentration (Table 1).

It appears therefore that there could be at least two kinds of relationship between myocardial lipid and carbohydrate metabolisms. One is as originally proposed by Randle and coworkers (59); that at rather constant blood glucose concentrations, a decrease in plasma FFA concentration leads to an increased myocardial glucose extraction. The other possibility is that,with relatively constant FFA concentrations , increase in blood glucose,lactate or pyruvate concentration can lead to decreased myocardial FFA extraction. Since both relationships involve at least glucose and lactate, they may both operate in part through pyruvate dehydrogenase.

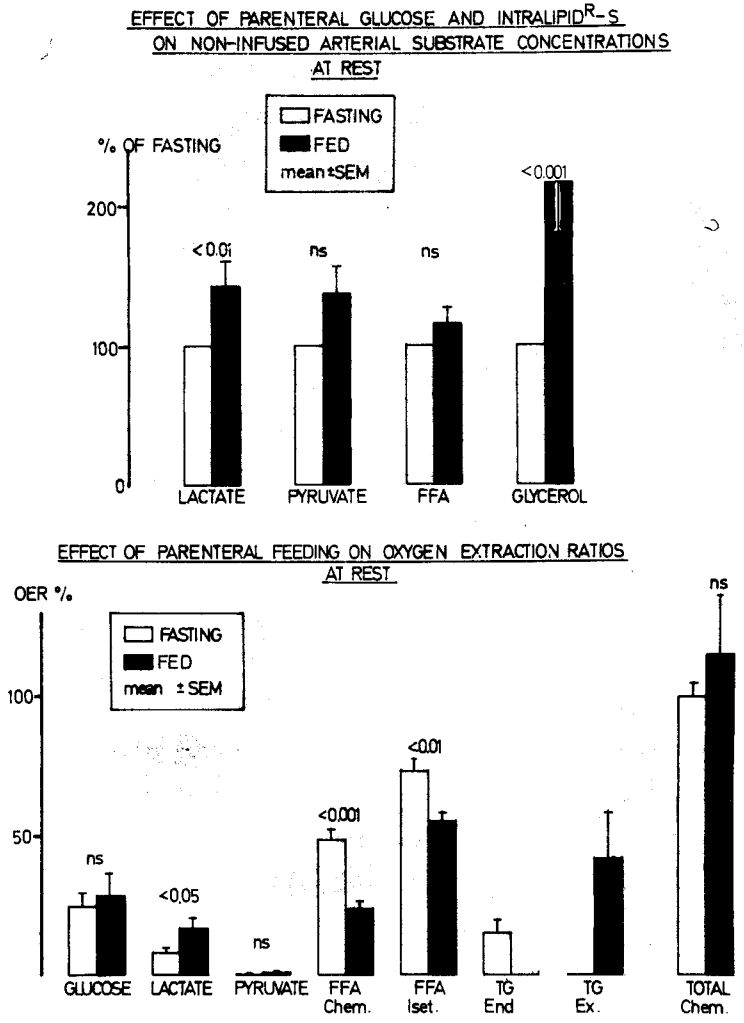

Figure 8: Effect of parenteral glucose and fat emulsion (Intralipid^{R}-S), administered simultaneously, on non-infused arterial substrate concentrations (upper figure) and on myocardial OER's (lower figure). TG end = endogenous plasma triglyceride; TG ex = exogenous plasma triglyceride; TOTAL chem = total OER calculated from chemically determined FFA extractions and either chemically or nephelometrically determined triglyceride extractions.

1 (a) The myocardial extractions of the blood carbohydrates glucose and lactate were significantly and negatively related to that of plasma free fatty acids (FFA) in healthy fasting men at rest. The relationships did not appear to depend on the effects of other substrates or on the plasma concentrations of the hormones insulin, growth hormone or glucocorticoid as evidenced by partial correlations and multiple regression analysis. Also, there were not significant negative relationships between plasma concentrations to correspond to those between extractions. An inhibition of pyruvate dehydrogenase following oxidation of fatty acid seems a likely explanation for the two negative relationships between carbohydrate and FFA extractions.

(b) During the infusions of a fat emulsion and glucose in healthy men, myocardial extraction of glucose was significantly and negatively related to arterial plasma FFA concentration, but not to myocardial extraction of FFA.

(c) In a series of observations during angina pectoris, induced by atrial pacing, in the absence and presence of nicotinic acid, myocardial lactate and pyruvate extractions, but not glucose extraction, were significantly and negatively related to plasma FFA concentration and myocardial FFA extraction.

2 The myocardial extraction of oxygen was significantly and positively related to that of FFA in healthy fasting subjects. At rest, this relationship did not depend on heart rate, although during prolonged exercise it did.

3 In healthy fasting subjects multiple regression analysis showed as far as hormones are concerned that:

(i) myocardial glucose extraction was increased by insulin and decreased by glucocorticoid at rest.

(ii) myocardial lactate extraction was increased by growth hormone during prolonged exercise.

(iii) myocardial pyruvate extraction was decreased by insulin and increased by growth hormone and glucocorticoid at rest.

4 (a) In healthy fasting subjects there was a positive linear relationship between arterial - coronary sinus difference in insulin concentration and arterial insulin concentration with the most marked release of insulin from the heart occurring at the lowest arterial concentrations.

(b) At rest, in healthy fasting subjects, a significant positive relationship between arterial - coronary sinus difference in glucocorticoid concentration and arterial glucocorticoid concentration was found. Significant release of glucocorticoid from the heart took place during prolonged exercise in those subjects receiving nicotinic acid.

5 (a) Significant myocardial extraction of exogenous plasma triglyceride during parenteral feeding was demonstrated nephelometrically. It could have met a substantial part of the heart's energy requirements at rest. Much of the exogenous plasma triglyceride which disappeared did so apparently as a result of lipolysis.

(b) Proportionately less FFA was extracted in parenterally-fed than in fasting subjects. This might have been due to competition between triglyceride fatty acid and free fatty acid for uptake by the myo-

cardium. Since, when fasting and fed state observations were considered together, significant negative relationships were found between myocardial FFA extraction and blood glucose, lactate or pyruvate concentrations, it is also possible that elevated blood carbohydrate concentrations may depress myocardial FFA uptake.

ACKNOWLEDGEMENTS

Professor Lars A. Carlson has met and exceeded each of my expectations of him as one of those scientists with whom it is a privilege to work. He has proven to be an efficient and perceptive teacher, generous and flexible. The facilities he has provided have been exceptionally good.

Professors Gunnar Birke and Torgny Sjöstrand, in providing facilities at the King Gustaf V Research Institute and the Department of Clinical Physiology, Karolinska Hospital, Stockholm, have been of much assistance.

Dr. Lennart Kaijser was, with his clinical tact, catheterisation skill and background in physiology, much of the reason for the success of the studies. Dr. Ben Lassers collaborated enthusiastically and energetically and with a considerable knowledge of the subject. Dr. Hans Löw added his endocrinological facilities and critical faculty to the work. Dr. Stephan Rössner contributed unsparingly with his clinical resources, research facilities and administrative ability.

Miss Britt Elving has, as much as anyone, by her ability and dependability in the laboratory, by her kindness and encouragement, been responsible for the successful conclusion of this work. There are others too, who rendered much technical assistance.

In one way or another, Dr. Jonas Boberg, Mrs. Kerstin Carlson, Dr. Brita Eklund, Dr. Martin Ericsson, Dr. Sven Fröberg, Dr. Iván Håkansson, Dr. Ted Nye and Göran Walldius have helped and to them I am also grateful.

The investigations have been carried out as an Overseas Research Fellow of the Life Insurance Medical Research Fund of Australia and New Zealand and with the support of the Swedish Medical Research Council.

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Gamla Brogatan 26
STOCKHOLM, SWEDEN

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