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FATTY ACID AS A DETERMINANT OF MYOCARDIAL SUBSTRATE AND OXYGEN METABOLISM IN MAN AT REST AND DURING PROLONGED EXERCISE

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Abstract. The relationship of fatty acids to the metabolism of the human heart has been investigated in 41 healthy fasting men. In some subjects low plasma free fatty acid (FFA) concentrations were produced by infusing nicotinic acid. There existed negative correlations between myocardial extraction of glucose, lactate and pyruvate and that of FFA. Furthermore significant negative linear relationships between myocardial extraction of glucose and lactate and that of FFA were also present on partial correlation analysis eliminating the influence of other carbohydrate substrates. Possible explanations for these findings were discussed. Myocardial extraction of oxygen was positively related to that of FFA at rest unrelated to heart rate. The possibility, and its clinical implications, that FFA may increase myocardial oxygen requirements was discussed.

Animal experiments have suggested that fatty acids might affect myocardial metabolism in at least two ways. Firstly, it has been shown that increased concentrations of free fatty acids (FFA) in the perfusate of the isolated rat heart decrease its glucose (31, 36) and pyruvate (13, 15) uptake and utilization. In the dog, extraction of lactate by the myocardium also appears to be reduced by increased plasma FFA concentrations (20). We have recently obtained evidence in support of these findings for the human heart as well (6, 27). A common explanation of these effects of FFA may be that myocardial fatty acid oxidation is stimulated, which leads to an increase in the intracellular level of acetyl coenzyme A relative to free coenzyme A, with consequent inhibition of pyruvate dehydrogenase (16) and thus reduction of the rate of glucose metabolism along the glycolytic pathway. Conversion of rat heart pyruvate dehydrogenase from an active to an inactive form by fatty acid has been reported (43). Moreover, as far as glucose is concerned, the phosphofructokinase and hexokinase reactions may be inhibited by fatty acids (31), with further reduction of glycolysis. The second way in which fatty acid might affect myocardial metabolism is to increase the oxygen need at a given level of myocardial work. The oxygen consumption of the isolated rat heart has been shown to be increased by perfusion with high concentrations of FFA (10). In dogs, myocardial oxygen consumption is increased when the plasma FFA concentration is elevated by i.v. heparin injection during i.v. infusion of fat emulsion (30).

In man, noradrenaline increases both oxygen consumption and FFA oxidation (18, 40). In the isolated perfused rat heart adrenaline increases oxygen consumption (9, 10, 13) and, in a situation where it does not perform work, intracellular FFA levels (11). Although increased FFA oxidation is thus accompained by increased oxygen consumption, increased glucose oxidation, produced by insulin in the perfusate of the isolated heart, is not accompanied by any change in oxygen consumption (14).

In the present study, relationships between fatty acid and myocardial carbohydrate and oxygen extractions in man, in situations with low, normal and high arterial FFA concentrations, have been investigated.

MATERIAL AND METHODS

Design of studies

To measure substrate and oxygen differences across the coronary circulation, referred to here as myocardial extractions, a brachial artery and the coronary sinus of

Table I. *Concentrations in arterial blood and myocardial extractions of various blood and plasma substrates in the four experimental categories*

Mean±S.E.M. and number of observations (within parentheses)

	Rest		Exercise	
	Without nicotinate	Nicotinate infusion	Without nicotinate	Nicotinate infusion
Concentrations (μmol/l)				
Plasma FFA	720±30 (47)	250±20 (10)	1 280±100 (15)	260±30 (10)
Blood glucose	4 200±90 (43)	4 360±150 (10)	3 440±120 (15)	3 360±250 (10)
Blood lactate	670±30 (47)	880±80 (10)	1 350±140 (15)	1 520±210 (10)
Blood pyruvate	51±3 (47)	74±8 (10)	89±4 (15)	103±10 (10)
Extractions (μmol/l)				
Plasma FFA	170±10 (47)	40±10 (10)	210±10 (15)	20±10 (10)
Blood glucose	180±20 (43)	390±40 (10)	120±20 (15)	330±40 (10)
Blood lactate	130±20 (47)	370±30 (10)	310±60 (15)	580±90 (10)
Blood pyruvate	7±3 (47)	37±8 (10)	24±5 (15)	40±4 (10)

41 healthy, fasting male subjects were catheterized as described elsewhere (5, 25, 26). Heparin was not administered. Instead the arterial catheter was kept patent by intermittent flushing with isotonic saline and the coronary sinus catheter by a continuous slow infusion of 0.5% citrate in isotonic saline. The beginning of a study was marked by the commencement of a constant infusion of ^{3}H-labelled palmitic acid complexed to human serum albumin (26) into an antecubital vein. The first blood sampling was made 60 or 90 min later. Observations were made at rest and during prolonged exercise, with and without a constant i.v. infusion of sodium nicotinate to block FFA mobilization from adipose tissue and hence decrease arterial FFA concentration.

The subjects exercised in the supine position on a bicycle ergometer at a constant, predetermined work load. The work load was 50% of that which produced a heart rate of 170/min after 6 min of exercise (W_{170}) (25, 37, 41). The exercise lasted for 65–125 min. It was intended to last for 120 min, a duration tolerated by most healthy subjects at the load used (1). However, since the subjects were fasting and some of them were infused with nicotinate, 15 of 25 stopped earlier because of fatigue. The exercise sampling was made during the last 5 min of work in all subjects.

On 16 subjects observations were made at rest at 90 and/or 120 min; on another 25 subjects one observation was made at rest at 60 min, then supine leg exercise was begun and a second observation was made during prolonged exercise. In 10 of these 25 subjects a constant i.v. infusion of sodium nicotinate (200 mg/h in 3 and 400 mg/h in 7 subjects) was maintained throughout, after a priming i.v. dose of 200 mg sodium nicotinate. This meant that during some observations plasma concentrations of FFA were in the normal fasting range, during others they were high, induced by prolonged exercise, and during others they were low at rest and during exercise because of the infusion of the antilipolytic agent sodium nicotinate (Table I).

Treatment of samples

Blood samples for estimation of oxygen content were drawn into heparinized glass syringes and other samples into unheparinized plastic syringes. Samples for determination of lactate and pyruvate were deproteinized immediately with perchloric acid. The absence of chylomicra, confirmation of the fasting state, was checked by paper electrophoresis of lipoproteins (28) from a sample of blood placed in an unheparinized tube. The remaining blood was transferred to heparinized tubes and aliquots for glucose determination were immediately deproteinized with perchloric acid. The heparinized whole blood was kept for 30–60 min in iced water and then centrifuged at 4°C. The plasma so obtained was either extracted immediately for determination of FFA concentration and also FFA radioactivity or stored at −20°C for subsequent determination of plasma glycerol, usually within one week.

Analytical methods

Oxygen saturation was measured spectrophotometrically (23). Oxygen tension was measured with a polarographic electrode (Instrumentation Lab. mod. 113). The oxygen content was calculated from oxygen saturation and Hb concentration together with oxygen tension (23).

Blood glucose was assayed in duplicate on each of 10 aliquots of whole blood from each sample, using a commercially available glucose oxidase method (Kabi, Stockholm) based on that of Hjelm (21). Blood lactate and pyruvate were assayed in duplicate by the enzymatic methods of Lundholm et al. (29) and Bücher et al. (3), respectively. Plasma FFA were assayed in quadruplicate according to Trout et al. (40): the heptane phase was washed with 0.05% H_2SO_4, once in the studies in which only resting observations were made and twice in those in which exercise observations were made as well. Radioactivity in the plasma FFA was determined according to the method of Boberg (2, 26). Glycerol was measured in quadruplicate on each of four extracts from each blood sample by an enzymatic fluorometric method (12).

Calculations and statistical analysis

The release of FFA into the coronary sinus was taken as the difference between FFA extraction measured radioisotopically and chemically. The radioisotopic FFA extraction was calculated by dividing the arterial-coronary sinus difference in radioactivity by the arterial specific radioactivity.

Correlation, partial correlation and linear regression analyses were made according to Snedecor (38).

RESULTS

Heart Rates

The heart rate (beats/min) at rest was 70 ± 1 (mean $\pm$ S.E.M.) without and 75 ± 3 with nicotinic acid infusion; at the end of exercise it was 142 ± 4 without and 149 ± 6 with infusion.

Substrate Metabolism

Mean values in four experimental categories

The means for the four categories—rest with and without nicotinate, exercise with and without nicotinate—indicate that myocardial extraction of plasma FFA follows plasma concentration (Table I). When mean FFA extraction is low during nicotinate infusion, mean glucose, lactate and pyruvate extraction is high. The order of difference in mean extraction of these carbohydrate substrates between the situations without and with nicotinate cannot be related to the difference between their mean plasma concentrations (Table I).

Correlation analysis for rest and exercise

Linear correlation coefficients for the relationship between the myocardial extraction of a substrate ($C_{(a\text{-}cs)}$) and its arterial concentration (Ca) are shown in Table II. For FFA, lactate and pyruvate significant positive relationships exist at rest, during prolonged exercise and for rest and exercise considered together. For glucose, however, a significant relationship is found only for the resting observations. A limitation of such an analysis in the case of the combined observations is that, for example, an increase in coronary blood flow could lead to an increased myocardial uptake (extraction × flow) of a substrate while blood concentration and extraction were unaltered.

However, this is not a problem where the extraction of one substrate is related to that of another, since the related extractions take place at the same blood flow. With this approach significant negative correlations are to be found between the myocardial extractions of glucose, lactate and pyruvate and that of FFA in all instances (Table III). With the exceptions of glucose/FFA overall and of pyruvate/FFA at rest, there are no significant relationships between plasma concentrations underlying the extraction relationships (Table IV).

The significant positive correlations, overall and at rest, between glucose extraction and the extractions of lactate and pyruvate could depend on their mutually negative correlations with FFA extraction (Tables III and V). The significant correlations to be found between the arterial concentrations of glucose and those of lactate and of pyruvate are actually negative (Table IV) and therefore cannot underlie the positive correlations for the extractions (Table III).

The significant positive correlations between lactate extraction and pyruvate extraction have

Table II. *Relationship between the myocardial extraction and the arterial concentration of a given substrate (correlation coefficients (r))*

Data from the categories with and without nicotinate infusion are combined. C_a = plasma concentration of free fatty acid and the concentration in whole blood of glucose, lactate or pyruvate; $C_{(a\text{-}cs)}$ = difference in concentration between arterial and coronary sinus blood, i.e. myocardial extraction from plasma for FFA and from whole blood for glucose, lactate and pyruvate. Number of observations within parentheses

$C_{(a\text{-}cs)}$	C_a	Rest and exercise	Rest	Exercise
FFA	FFA	0.72*** (82)	0.75*** (57)	0.84*** (25)
Glucose	Glucose	0.27^{ns} (78)	0.37** (53)	0.09^{ns} (25)
Lactate	Lactate	0.82*** (82)	0.54*** (57)	0.85*** (25)
Pyruvate	Pyruvate	0.79*** (82)	0.85*** (57)	0.53** (25)

ns, $p > 0.05$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table III. *Relationships between extractions from coronary blood of substrates for myocardial metabolism (correlation coefficients (r))*

Symbols and abbreviations as in Table II

$C_{(a\text{-}cs)}$	$C_{(a\text{-}cs)}$	Rest and exercise	Rest	Exercise
Glucose	FFA	−0.49*** (78)	−0.44*** (53)	−0.61** (25)
Lactate	FFA	−0.44*** (82)	−0.50*** (57)	−0.43* (25)
Pyruvate	FFA	−0.40*** (82)	−0.38** (57)	−0.46* (25)
Lactate	Glucose	0.29* (78)	0.44** (53)	0.32^{ns} (25)
Pyruvate	Glucose	0.26* (78)	0.34* (53)	0.14^{ns} (25)
Pyruvate	Lactate	0.62*** (82)	0.69*** (57)	0.47* (25)

Table IV. *Relationships between concentrations in arterial blood of substrates (correlation coefficients (r))*

Symbols and abbreviations as in Table II

C_a	C_a	Rest and exercise	Rest	Exercise
Glucose	FFA	-0.23^{*} (78)	-0.11^{ns} (53)	-0.10^{ns} (25)
Lactate	FFA	0.03^{ns} (82)	-0.25^{ns} (57)	-0.17^{ns} (25)
Pyruvate	FFA	-0.05^{ns} (82)	-0.34^{*} (57)	-0.22^{ns} (25)
Lactate	Glucose	-0.32^{**} (78)	0.20^{ns} (53)	-0.03^{ns} (25)
Pyruvate	Glucose	-0.43^{***} (78)	-0.02^{ns} (53)	-0.50^{*} (25)
Pyruvate	Lactate	0.68^{***} (82)	0.45^{***} (57)	0.62^{**} (25)

been observed by others (35). They could be accounted for in part by, or explain in part, mutually negative correlations of $C_{(a\text{-}cs)}$ lactate and $C_{(a\text{-}cs)}$ pyruvate with $C_{(a\text{-}cs)}$ FFA (Table III); the positive correlations that concentrations of lactate and pyruvate bear to each other (Table IV) could also underlie the positive correlations for the extractions (but see below and Table V).

Partial correlation analysis

Partial correlation analysis shows that the myocardial extractions of FFA and glucose are related irrespective of the extractions of lactate and pyruvate (Table V). The relationship between the myocardial extractions of FFA and lactate at rest also remains significant when the effects of both glucose and pyruvate extractions are eliminated; this does not apply, however, to the relationship during exercise, which becomes non-significant. Relationships between FFA and pyruvate extractions are not significant when both glucose and lactate extractions are held constant.

The extractions of pyruvate and lactate are closely related for the overall data and at rest when the extractions of FFA and glucose are held constant. The relationship between pyruvate and lactate extractions is not less significant when the arterial concentrations of both are held constant.

Although myocardial FFA extraction is closely related to plasma FFA concentration, it is of interest to examine the relationships between FFA extraction and concentrations of other substrates (Table VI). Apart from pyruvate concentration, for which the overall data show a weak correlation, carbohydrate substrate concentrations do not bear significant relationships to FFA extraction. This implies that either plasma FFA concentration or the myocardial extraction of FFA can be predictive of the myocardial extraction of carbohydrate.

Oxygen Metabolism

FFA

For the resting and exercise observations combined there is a significant positive correlation on

Table V. *Relationships between extractions from coronary blood of substrates for myocardial metabolism: partial correlation analysis (partial correlation coefficients)*

Symbols and abbreviations as in Table II

$C_{(a\text{-}cs)}$	$C_{(a\text{-}cs)}$	Eliminating $C_{(a\text{-}cs)}$	Rest and exercise ($n=78$)	Rest ($n=53$)	Exercise ($n=25$)
Glucose	FFA	Lactate + pyruvate	-0.41^{***}	-0.28^{*}	-0.59^{**}
Lactate	FFA	Glucose + pyruvate	-0.22^{ns}	-0.29^{*}	-0.13^{ns}
Pyruvate	FFA	Glucose + lactate	-0.15^{ns}	-0.03^{ns}	-0.38^{ns}
Lactate	Glucose	FFA + pyruvate	0.06^{ns}	0.20^{ns}	0.16^{ns}
Pyruvate	Glucose	FFA + lactate	0.04^{ns}	0.05^{ns}	-0.21^{ns}
Pyruvate	Lactate	FFA + glucose	0.53^{***}	0.61^{***}	0.37^{ns}
Pyruvate	Lactate	C_a pyruvate + C_a lactate	0.47^{***}	0.52^{***}	0.43^{*}

Table VI. *Relationships between the myocardial extraction of FFA and the concentrations in arterial blood of substrates (correlation coefficients (r))*

Symbols and abbreviations as in Table II

$C_{(a-cs)}$	C_a	Rest and exercise	Rest	Exercise
FFA	Glucose	-0.00^{ns} (78)	-0.09^{ns} (53)	-0.05^{ns} (25)
FFA	Lactate	-0.15^{ns} (82)	-0.10^{ns} (57)	-0.14^{ns} (25)
FFA	Pyruvate	-0.24^{*} (82)	-0.24^{ns} (57)	-0.21^{ns} (25)

Table VII. *Relationships between myocardial oxygen extraction and the extractions of various myocardial substrates (correlation coefficients (r))*

Symbols and abbreviations as in Table II

$C_{(a-cs)}$	$C_{(a-cs)}$	Rest and exercise	Rest	Exercise
Oxygen	FFA[a]	0.25^{*} (82)	0.45^{***} (57)	0.17^{ns} (25)
Oxygen	FFA[b]	0.57^{***} (62)	0.53^{***} (47)	0.55^{*} (15)
Oxygen	Glucose	0.04^{ns} (78)	0.07^{ns} (53)	0.08^{ns} (25)
Oxygen	Lactate	0.33^{**} (82)	0.04^{ns} (57)	0.19^{ns} (25)
Oxygen	Pyruvate	0.18^{ns} (82)	0.01^{ns} (57)	-0.01^{ns} (25)
Oxygen	Glycerol[c]	-0.26^{*} (82)	0.04^{ns} (57)	-0.15^{ns} (25)
Oxygen	"FFA release"[d]	-0.28^{*} (77)	-0.06^{ns} (52)	-0.02^{ns} (25)

[a] All data.
[b] All data excluding those with nicotinate.
[c] Becomes consistently negative during exercise without a nicotinate infusion, i.e. glycerol release into the coronary circulation occurs (25).
[d] The difference between actual FFA extraction measured radioisotopically (25, 26) and net FFA extraction measured chemically.

near regression analysis between the myocardial extractions of oxygen and FFA from coronary blood (Table VII). For the resting observations alone the relationship is highly significant (Table VII, Fig. 1), but for the exercise observations alone it is not significant. However, when only those observations where no infusion of sodium nicotinate was given are considered, the relationship at rest remains highly significant and that during prolonged exercise is significant (Table VII, Fig. 1). The observations which do not appear to conform to the general relationship are, therefore, those during prolonged exercise in the presence of an infusion of nicotinate.

Carbohydrate

Myocardial oxygen extraction is not significantly related to glucose or pyruvate extraction (Table VII). However, myocardial oxygen extraction is significantly and positively correlated with lactate extraction when the resting and exercise observations are considered together, but not when these observations are considered separately (Table VII).

Intramyocardial lipolysis

Myocardial oxygen extraction has a relationship to glycerol extraction (or glycerol release) which appears to be exercise-dependent (Table VII). The more glycerol released, as in exercise in the absence of nicotinate infusion, the greater the oxygen extraction. Glycerol release during exercise could be a reflection of intramyocardial lipolysis. "FFA release" into the coronary circulation, taken as the difference between actual FFA uptake estimated radioisotopically and net FFA uptake estimated chemically, is inversely related to myocardial oxygen extraction, and this relationship also appears to be exercise-dependent (Table VII). The rationale for regarding intramyocardial lipolysis as a source of glycerol in the coronary sinus and of fatty acid for myocardial metabolism is presented elsewhere (25).

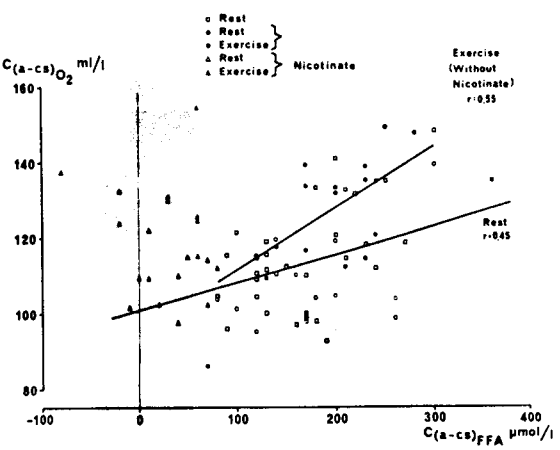

Fig. 1. Relationships between myocardial extractions of oxygen and FFA. Significance levels of regression lines drawn are shown in Table VII.

Table VIII. *Relationships between heart rate and either myocardial oxygen extraction or myocardial FFA extraction (correlation coefficients (r))*

Symbols and abbreviations as in Table II

$C_{(a-cs)}$	Rest and exercise	Rest	Exercise
Oxygen[a]	0.54***	0.14^{ns}	0.40*
	(82)	(57)	(25)
Oxygen[b]	0.52***	0.16^{ns}	0.62*
	(62)	(47)	(15)
FFA[a]	-0.10^{ns}	-0.01^{ns}	0^{ns}
	(82)	(57)	(25)
FFA[b]	0.31*	0.21^{ns}	0.52*
	(62)	(47)	(15)

[a] All data. [b] All data excluding those with nicotinate.

Heart rate

At rest, myocardial oxygen extraction is not related significantly to heart rate in the present investigation, but is so for the combined resting and exercise observations and for the exercise observations alone (Table VIII). Also, at rest, heart rate is not related to $C_{(a-cs)}$ FFA (Table VIII), so that the relationship $C_{(a-cs)}$ oxygen/ $C_{(a-cs)}$ FFA at rest does not arise through mutual dependence of $C_{(a-cs)}$ oxygen and $C_{(a-cs)}$ FFA on heart rate. This is confirmed by partial correlation analysis (Table IX). However, during prolonged exercise without nicotinate the relationship $C_{(a-cs)}$ oxygen $C_{(a-cs)}$ FFA does depend on changes in heart rate (Tables VIII and IX).

DISCUSSION

Substrate metabolism

From the viewpoint of cause and effect, it is of importance that sodium nicotinate has been used in these studies to induce a primary change in plasma FFA concentrations, so that differences in carbohydrate extraction between observations with and without nicotinate may be regarded as secondary to changes in FFA levels (4) although direct effects of nicotinic acid on carbohydrate metabolism has not been ruled out. The correlations, therefore, suggest that changes in myocardial FFA extraction may lead to altered extractions of glucose, lactate and pyruvate. For lactate extraction during exercise and pyruvate extraction at rest and during exercise, however, the relationships with FFA extraction (Table III) depend on interrelationships with other carbohydrate substrates (Table V).

Table IX. *Relationships between myocardial oxygen extraction and myocardial FFA extraction—partial correlation analysis eliminating heart rate (partial correlation coefficients)*

	Rest and exercise	Rest	Exercise
All data	0.36***	0.46***	0.18^{ns}
	(82)	(57)	(25)
All data excluding those with nicotinate	0.60***	0.52***	0.34^{ns}
	(62)	(47)	(15)

From the present study it is not possible to say to what extent FFA regulate carbohydrate extraction by the myocardium. The low correlation coefficients suggest that other factors are involved. One possibility is that the population studied is heterogeneous with respect to the effect of FFA on carbohydrate extraction. Especially for lactate and pyruvate and, to a lesser extent, for glucose, their own blood concentrations contribute to the determination of their respective extractions. Hormones, which have not been considered here, may also modify myocardial carbohydrate extraction.

Oxygen metabolism

For the resting observations the only extraction of a myocardial substrate which is related to myocardial oxygen extraction is that of FFA. It is known that the energy obtained from a given amount of oxygen is less for lipid than for carbohydrate oxidation (42). Thus the first possibility is that FFA extraction and subsequent oxidation may in part determine myocardial oxygen requirements. This view is supported by animal studies where an increased delivery of FFA to the heart has been followed by an increased myocardial oxygen consumption (10, 30). In the present study, myocardial oxygen extraction and not oxygen consumption was measured. However, since myocardial oxygen uptake seems to be increased, like that of other muscle tissue (7, 24), by increases in blood flow (22) and oxygen extraction (25) and, since these variables seem to increase in parallel (7, 24), increased oxygen extraction probably reflects increased oxygen consumption.

At rest the myocardial oxygen extraction in the absence of nicotinate (106.5 ± 3.3 ml/l) is

not significantly different from that in the presence of nicotinate (109.8 ± 2.6 ml/l), although the extraction of FFA is significantly lower in the presence of nicotinate. It is very likely, however, that there would be an extraction of FFA below which no further decrease in myocardial oxygen requirements could be observed.

The two other possibilities are that myocardial oxygen requirements determine myocardial FFA extraction and that a third factor determines both these extractions. The first of these cannot be excluded on the basis of the present series in vivo in man; but it is not compatible with the animal work to which reference has already been made, and there is no reason to believe that increased oxygen consumption should increase FFA but not carbohydrate uptake.

Substrate and oxygen metabolism

The biochemical basis for an action of FFA on both myocardial carbohydrate extraction and oxygen requirements may be its oxidation to acetyl CoA units. An increase in the ratio of these units to free CoA may lead to the inhibition of pyruvate dehydrogenase (16) and, by increasing citrate concentration, inhibit phosphofructokinase (34). Both these inhibitions will slow down glycolysis and may thus lower glucose uptake. At the same time increased oxygen uptake may in part be related to oxidation of extra citrate without formation of ATP (8, 17).

Inhibition of pyruvate dehydrogenase will not be followed by an increased intracellular pyruvate concentration and, it is assumed, decreased pyruvate extraction unless pyruvate is still formed from glycolysis and/or lactate. The dependence of the relationship $C_{(a\text{-}cs)}$ pyruvate/$C_{(a\text{-}cs)}$ FFA on $C_{(a\text{-}cs)}$ glucose and on $C_{(a\text{-}cs)}$ lactate indicates this.

An interesting possibility is that FFA might affect myocardial metabolism in part indirectly through the displacement of thyroxine from plasma proteins. Hillier (19) has shown that the isolated perfused rat heart takes up more thyroxine at higher concentrations of FFA in the perfusate. However, the dog heart in situ appears resistant to the uncoupling of oxidative phosphorylation by thyroxine (33). If this can be applied to the human heart, an effect of FFA on myocardial oxygen metabolism may not depend to any great extent on thyroxine.

During myocardial ischaemia the supplies of both oxygen and anaerobic fuel become critical. Since there is evidence that death after acute myocardial infarction is more frequent where plasma FFA concentrations are high (32), the present findings may prove of importance in the understanding and management of episodes of myocardial ischaemia.

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