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The effect of elevated arterial free fatty acid concentrations on hemodynamics and myocardial metabolism and blood flow during ischemia*)

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With 2 figures and 4 tables

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Summary

In the present investigation the effect of elevated arterial free fatty acid (FFA) concentrations on regional myocardial blood flow (MBF), myocardial metabolism and hemodynamics during ischemia was studied in anesthetized dogs.

Ischemia was induced by stenosis of the left interventricular coronary artery. Mean poststenotic coronary artery pressure was kept constant during ischemia. FFA concentrations were elevated by intravenous injection of heparin (group I), intralipid (group II) or both substances (group III).

After elevation of FFA concentrations by heparin alone or together with intralipid, heart rate gradually increased, while aortic pressure tended to decrease.

Slight elevation of arterial FFA levels (up to 0.30 mM, group I, and up to 0.53 mM, group II) had no significant effect on total MBF and uptake of glucose, FFA, and oxygen or release of lactate in the ischemic myocardium. However, elevating arterial FFA levels up to 0.81 mM (Group III), significantly decreased total MBF (6 %), endo/epicardial blood flow ratio (13 %), and oxygen uptake (34 %) in the ischemic myocardium and resulted in release of lactate from this area. The release of potassium, inorganic phosphate and H^+ as well as plasma CO_2 concentration were not influenced. Neither was the uptake of glucose and FFA.

These findings suggest that elevated arterial FFA concentrations can decrease MBF and augment lactate production in the ischemic myocardium.

Introduction

High arterial free fatty acid (FFA) concentrations are considered to be harmful for the ischemic myocardium (8, 16, 31). In these investigations positive relations were found between arterial FFA levels on the one hand and infarct size, ventricular arrhythmias and ventricular fibrillation on the other. In other studies, however, these relations could not be confirmed (3, 26).

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Although the occurrence of arrhythmias and of left ventricular failure in relation to elevated plasma FFA levels has been studied extensively, only limited information is available about myocardial metabolism and regional myocardial blood flow under these circumstances, especially during ischemia.

In the present investigation carbohydrate, FFA and oxygen utilization of the ischemic myocardium as well as the release of potassium and inorganic phosphate from this tissue at normal and elevated arterial FFA levels was studied in anesthetized dogs. Left ventricular hemodynamics and regional myocardial blood flow were measured as well. Myocardial ischemia was induced by partial occlusion of the left interventricular artery, using an inflatable cuff and a servo-motorpump with an autoregulating feedback system, controlled by the poststenotic coronary artery pressure. FFA concentrations were elevated by intravenous injection of heparin, intralipid or a combination of these substances.

Materials and methods

Animal preparation

The experiments were performed on 24 mongrel dogs of either sex and unknown age, ranging in weight from 18 to 48 kg. The animals were premedicated with fluanisone (10 mg/kg body weight) and fentanyl citrate (0.315 mg/kg body weight) as described by Marsboom et al. (10). Anesthesia was induced with sodium pentobarbital (10 mg/kg body weight I.V.) and, after endotracheal intubation, was maintained with oxygen nitrous oxide and a continuous infusion of sodium pentobarbital (2 mg/kg/hour I.V.) Ventilation was kept constant during the experiments with a positive pressure respirator (Pulmonat). During thoracotomy succinylcholine (2 mg/kg I.M.) was injected to prevent muscle movements caused by electrocoagulation.

Hemodynamic measurements

ECG was derived from the limb leads. Ascending aortic pressure was measured through the femoral artery with a poly-ethylene catheter connected to a pressure transducer (Ailtech). The chest was opened through the left fifth intercostal space and the pericardium was incised over the antero-lateral aspect of the heart. The pressure in the left interventricular coronary artery distal to the site of stenosis (see below) was measured through a small side branch of this artery (32) with a polyethylene catheter (P.E. 50, Clay Adams) connected to a pressure transducer (Ailtech). Left ventricular pressure was measured through the left brachial artery with a catheter-tip micromanometer (Millar) and its maximal first derivative (LV dP/dt max) was determined with an analog differentiator (27). The hemodynamic variables were recorded continuously on a multichannel Schwarzer recorder. Through a jugular vein a Swan-Ganz balloon guided thermistor catheter was placed in the pulmonary artery to measure cardiac output, using the thermodilution technique as previously described in detail (29). Thermodilution curves were registrated on a Linseis series 2000 recorder. The surface under the curve was measured by planimetry. Cardiac output was calculated manually according to the log-normal assumption (29).

An inflatable cuff was placed on the left interventricular coronary artery (formerly called anterior descending branch of the left coronary artery) just distal to the diagonal branch. The cuff was through silastic tubing connected to a micrometer. The whole system was filled with distilled water so that the cuff could be inflated

carefully until the desired degree of stenosis, i.e. a mean coronary artery pressure distal to the stenosis of approximately 3.3 kPa (range of median values of 24 experiments 3.2–3.4 kPa) was obtained. This degree of stenosis could be maintained during the experimental period, using a servo-motorpump with an autoregulating feedback system controlled by the mean coronary artery pressure. In previous experiments with this degree of stenosis a decrease in electromagnetically measured flow of 75–95 % was found.

Metabolic measurements

Arterial blood samples were collected through the catheter used for aortic blood pressure measurements. Local venous blood samples were obtained through a poly-ethylene catheter (P.E. 60, Clay Adams) inserted into the concomittant vein of the left interventricular coronary artery with a Seldinger technique. From the blood samples 0.6 ml was used for determination of blood gases and blood pH, and 4.0 ml was immediately centrifuged. The supernatant of these samples were quickly frozen in dry ice and stored at – 80 °C for biochemical analysis. The catheters used for pressure measurements and sampling of blood were kept patent with a continuous infusion of physiological saline (6 ml · hr^{-1}), using a Harvard infusion pump or a Sorensen infusion system (Sorensen Research Company, Salt Lake City, USA).

Glucose, lactate, inorganic phosphate and potassium (K^+) were measured with a Technicon-Auto-analyzer, the last variable in combination with a Technicon Auto-analyzer Flame Photometer IV. Blood gases and blood pH were assessed with an IL 413. Hemoglobin (Hb) content and oxygen saturation were determined with a Radiometer OSM-2. Oxygen (O_2) content was calculated from the latter variables.

The assay of free fatty acids was started immediately after the samples were thawed. For each determination 0.1 ml of supernatant was used. Concentrations of free fatty acids were assessed by colorimetry using a standard Boehringer test kit (Boehringer, Germany). The intra-assay variation was 4 % (s.d.).

Experimental procedure

The dogs were allotted to 3 groups of 8 animals each. In each group the same protocol was followed during the control period and the first 60 min of stenosis. Thereafter, heparin (5000 I.U.) was injected intravenously in group I, whereas in

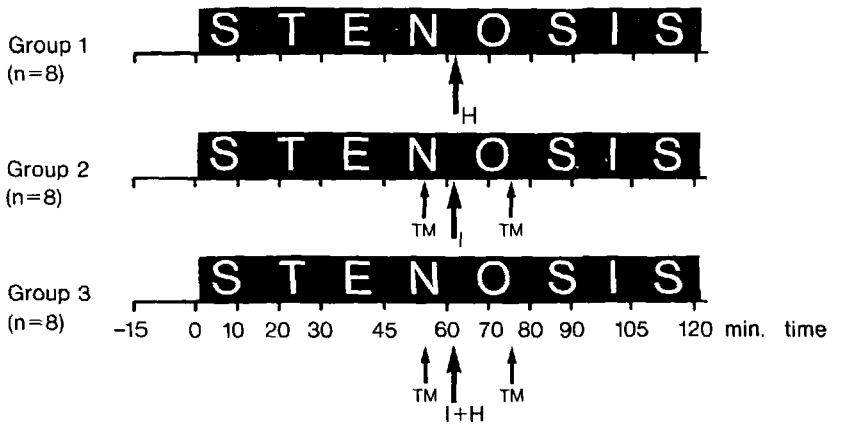

Fig. 1. Schematical representation of the experimental protocol. H = heparin 5000 I.U. i.v., I = intralipid 50 ml 20 % i.v., TM = injection tracer microspheres. The dashes on the time axis represent the sample time for biochemical and hemodynamic variables.

group II and III respectively intralipid (50 ml 20 % I.V., Vitrum, Stockholm) and heparin together with intralipid were administered. The last procedure is comparable with the method of elevating arterial FFA concentrations used by Opie and co-investigators (19). Both in group II and III the compounds were injected slowly (within 1–2 min). Arterial and venous blood samples were taken 15 min and just before, and 10, 20, 30, 45, 60, 70, 80, 90, 105 and 120 min after inducement of the stenosis. The continuously recorded hemodynamic variables and cardiac output were also determined at these moments (fig. 1).

Measurement of myocardial blood flow

In group II and III regional myocardial blood flow (MBF) was determined just before and 20 min after administration of intralipid, and heparin and intralipid, respectively, using tracer microspheres (15 ± 3 μm). The microspheres were labelled with I^{125}, Ce^{141}, Cr^{51}, Sr^{85} or Nb^{95} (3M Company, USA). At each determination 4.10^6 microspheres were injected into the left atrium. A reference sample was taken from the brachial artery at a rate of 22.6 ml · min^{-1}, using a Harvard suction pump. Withdrawal of blood started 5 s before the injection of the microspheres and was continued during at least one min. After the experiment, the heart was excised, rinsed and stored in formaldehyde 5 %. The free wall of the left ventricle was cut into five slices (parallel to the base of the heart). Each slice was cut into five pieces of approximately 3 gram. Each piece was divided into a subendocardial, middle and subepicardial layer. The tissue and blood samples were weighted and subsequently counted in a gammacounter (Packard Multichannel Analyzer). From these data regional myocardial blood flow was calculated with the MIC II program (28).

The main purpose of this study was to investigate the effect of elevated FFA levels on blood flow and metabolism in ischemic and non-ischemic myocardium. The ischemic area was considered to be the zone perfused by the left interventricular coronary artery which was identified macroscopically. For the determination of total flow in this ischemic zone, only samples in which flow in the subendocardial part of the transmural section before elevating FFA was reduced by at least 40 % as compared with the non-ischemic zone, were taken into account. The non-ischemic area was considered to be the zone of tissue along the circumflex coronary artery and along the marginal branch of this artery. The tissue samples were grouped per layer, so that besides total flow, MBF in the three layers of the non-ischemic and ischemic zones could be calculated.

In-vitro effect of intralipid on Hb measurements

After administration of intralipid, Hb concentrations increased consistently. If this is an artefact due to the intralipid administration, mistakes are made in the calculations of MVO_2. To investigate whether this phenomenon was an artefact, various amounts of intralipid were added to freshly drawn arterial and venous blood, and the Hb concentration was determined as described below. The range of concentrations used *in vitro* was comparable with the blood concentrations of intralipid reached in the dog after injection of 50 ml 20 % of this substance.

Both *in vitro* and *in vivo* Hb values measured by the hemoxymeter increased with increasing concentrations of intralipid. O_2 saturation decreased proportionally so that O_2 content of the blood remained unchanged. This effect of intralipid is caused by absorption of light at the wavelengths used, as was found recently (2).

Biochemical calculations

Utilization of glucose and FFA by the ischemic myocardium as well as release of lactate from this area was approached by using the net uptake or release of these substances, defined as the product of the respective serum arterio-local venous (AV) differences, and total MBF in the ischemic area (μmol · min^{-1} · g^{-1}). The net

uptake as determined in this study does not fully cover the utilization since the use of substances released from endogenous stores is not taken into account. In this calculation it was also assumed that transport of glucose, lactate and FFA from the plasma into the erythrocyte and vice versa, was not influenced by the substances administered to elevate the arterial FFA concentrations. O_2 utilization (MVO_2) by the ischemic myocardium was determined from Hb concentration times AV difference for O_2 times total blood flow of the ischemic myocardium ($\mu mol \cdot min^{-1} \cdot g^{-1}$).

Data analysis

To compare the hemodynamics of the three groups just before onset of ischemia, differences between the values of heart rate and mean aortic pressure at time 0 min were evaluated for statistical significance by applying Wilcoxon's two-sample test.

Information about the effect of heparin, intralipid or the combination of heparin and intralipid during myocardial ischemia was obtained by comparison of the data within each animal. The choice of each dog serving as its own control, was made because of the large differences between the animals. Influences on the hemodynamic and biochemical variables were evaluated by comparing the values at time 70, 80, 90, 105 and 120 min with those just before injection of the substances (time 60 min). Information about the effect on MBF was obtained by comparing the values just before (time 60 min) and 20 min after injection of the substances. Differences between the values of the various variables were evaluated for statistical significance by applying Wilcoxon's matched-pairs signed-ranks test (two-tailed probability). In this paper, the data are presented as median values and 95 % limits. A value of $p < 0.05$ was considered to be a significant difference.

Results

Hemodynamics

At time 0 min (before onset of stenosis) the heart rate and mean aortic pressure were for group I, II and III: 110 (60–160), 135 (79–177), and 85 (75–115) beats $\cdot$ min^{-1}, and 10.8 (8.8–12.4), 10.3 (8.5–13.2) and 10.0 (8.0–10.3) kPa, respectively. These values were not significantly different. Intravenous injection of heparin resulted in a slight and gradual decrease in systolic (median fall maximally: 1.4 kPa [= 8 %]) and diastolic aortic pressure (median fall maximally: 0.7 kPa [= 10 %]). This decrease was significant 45 and 60 min after administration of heparin. Injection of intralipid (group II) or heparin and intralipid (group III) induced a transient increase in blood pressure (of 0.5–2.0 kPa) within the first min after injection. These changes were not significant anymore 10 min after injection. Heart rate gradually increased after administration of heparin as well as heparin and intralipid (maximum rise: 45 [39 %] and 23 beats $\cdot$ min^{-1}, [23 %] respectively). After administration of intralipid alone, the maximal rise in heart rate was only 4 beats $\cdot$ min^{-1} (2.5 %). In all three groups this increase became significant 45 min after injection.

Heparin, intralipid or the combination of these substances neither induced cardiac arrhythmias nor influenced occasionally existing arrhythmias such as nodal rhythms or atrial fibrillation.

Administration of the substances had no significant effect on end-diastolic left ventricular pressure, LV dP/dt max, and cardiac output.

Regional myocardial blood flow

After administration of intralipid (group II), total MBF significantly increased in the non-ischemic myocardium (median increase: 13 %). In the ischemic tissue MBF did not change significantly (table 1). After simultaneous injection of heparin and intralipid, total MBF did not change significantly in the non-ischemic myocardium, but decreased significantly in the ischemic part (table 1).

Table 1. Changes in total myocardial blood flow (MBF) and endo/epicardial blood flow ratio in ischemic and non-ischemic tissue after elevation of arterial FFA concentrations, expressed as percentage of the value before injection of the substances. * = $p < 0.05$.

Variable		Non-ischemic		Ischemic	
		intralipid	intralipid + heparin	intralipid	intralipid + heparin
Relative increase in total MBF	median	13*	11	10	−16*
	95 % limits	5–22	(−9)–27	(−8)–33	(−45)–0
Relative increase in endo/epicardial blood flow ratio	median	−0.8	−3.0	−2.9	−13.2*
	95 % limits	(−0.5)–2.3	(−7.2)–6.2	(−11.1)–12.5	(−52.2)–0

Table 2. Arterial values of various biochemical variables before and 20 min after administration of heparin, intralipid or both substances. For explanation of the signs, see table 1.

Variable		Heparin		Intralipid		Heparin + Intralipid	
		before	after	before	after	before	after
FFA	median	0.20	0.30*	0.33	0.53*	0.17	0.81*
(mmol/l)	95 % limits	0.16–0.32	0.24–0.42	0.27–0.37	0.38–0.85	0.14–0.20	0.66–1.23
Lactate	median	1.09	0.92	1.35	2.31*	1.70	3.43*
(mmol/l)	95 % limits	0.72–1.84	0.72–1.75	0.90–1.69	1.77–3.30	1.40–3.18	2.33–4.72
pH	median	7.43	7.43	7.39	7.37*	7.44	7.41*
	95 % limits	7.41–7.45	7.41–7.45	7.36–7.41	7.34–7.40	7.42–7.48	7.39–7.46
P_{CO_2}	median	3.9	3.9	4.4	4.3	3.7	3.6
(kPa)	95 % limits	3.3–4.4	3.5–4.0	4.0–4.5	4.1–4.4	3.2–3.9	3.3–5.7

In the non-ischemic myocardium, the transmural distribution of MBF was not significantly affected by the administration of intralipid or heparin and intralipid (table 1). In the ischemic myocardium the transmural distribution (endo/epicardial ratio) of MBF was not significantly changed after the injection of intralipid. After the administration of heparin together with intralipid, however, the subendocardial layers in the ischemic myocardium were underperfused as compared with the subepicardial layers in this area (table 1).

Biochemical variables

Intravenous injection of heparin (group I), intralipid (group II), or both (group III) elevated the arterial FFA concentrations from 0.20 to 0.30 mM, from 0.33 to 0.53 mM, and from 0.17 to 0.87 mM, respectively (table 2). The arterial FFA concentrations remained constantly elevated in group I and II, but gradually decreased in group III at the end of the experimental period (fig. 2). In each group, the concentrations 60 min after injection of the substances were still increased as compared to those before injection of the substances.

Immediately after injection of intralipid as well as intralipid and heparin, the arterial lactate concentrations increased to values 2–3 times higher than the control values. Arterial P_{CO_2} was not affected by the elevated arterial FFA concentrations (table 2).

The elevated arterial FFA concentrations did not result in a significant change in AV differences of FFA and glucose across the ischemic area (table 3). Yet the AV differences of lactate did not change in group I and II. In group III, however, the AV

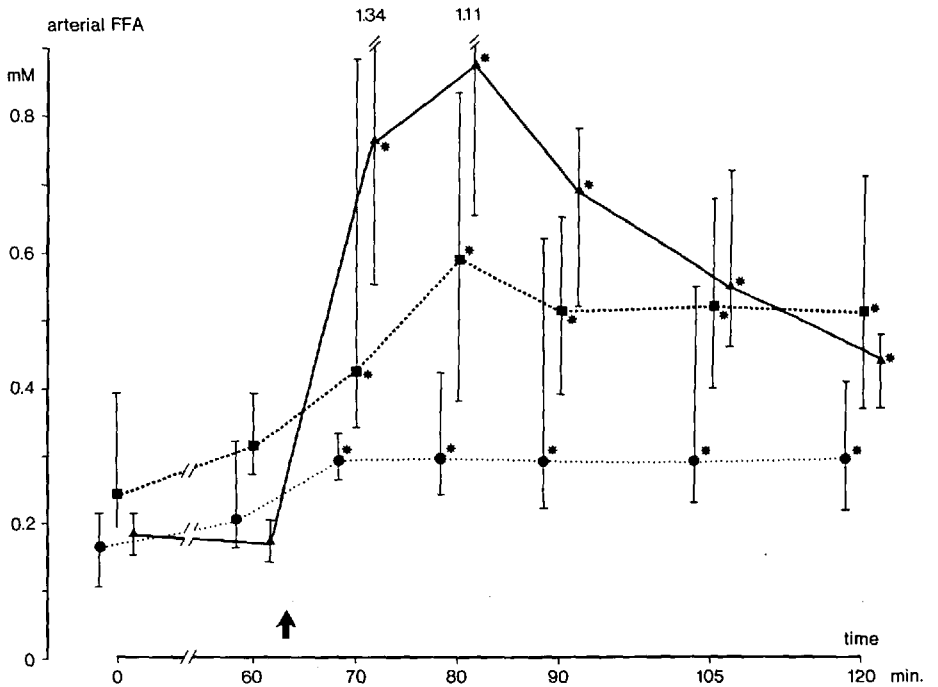

Fig. 2. Time course of arterial FFA concentration in the three experimental groups. The median values and 95 % limits are presented. ↑ = injection of the substances. * = $p < 0.05$. ● = heparin (group I). ■ = intralipid (group II). ▲ = heparin and intralipid (group III).

Table 3. MBF (ml · min^{-1} · g^{-1}), AV differences (mM) and net uptake (μmol · min^{-1} · g^{-1}) of various biochemical variables in the ischemic myocardium just before and 20 min after elevating FFA concentrations by injecting heparin, intralipid or both substances. For explanation of the signs, see table 1.

			Heparin		Intralipid		Heparin + Intralipid	
			before	after	before	after	before	after
	MBF	median	–	–	0.21	0.22	0.48	0.29*
		95 % limits			0.11–0.36	0.12–0.42	0.25–0.56	0.21–0.45
	Endo/epicardial ratio	median	–	–	0.40	0.35	0.52	0.35*
		95 % limits			0.16–0.56	0.18–0.57	0.29–0.59	0.22–0.58
FFA	AV difference	median	0.08	0.11	0.05	–0.01	0.02	0.10
		95 % limits	0.04–0.19	0.07–0.15	0.14–(–0.02)	–0.11–0.14	(–0.02)–0.06	0.04–0.20
	net uptake	median	–	–	0.01	0.00	0.01	0.02
		95 % limits			0.00–0.01	(–0.03)–0.03	(–0.01)–0.02	0.01–0.05
Glucose	AV difference	median	1.5	1.5	1.0	0.7*	0.4	0.7
		95 % limits	1.3–2.5	0.7–1.7	0.8–1.4	0.5–1.1	0.0–0.8	0.1–1.2
	net uptake	median	–	–	0.2	0.2	0.1	0.2
		95 % limits			0.1–0.3	0.1–0.3	0.0–0.2	0.0–0.3
Lactate	AV difference	median	–1.85	–1.11	–1.03	–1.29	–0.03	–0.50*
		95 % limits	(–3.21)–(–0.37)	(–1.39)–(–0.17)	(–1.73)–(–0.48)	(–3.75)–(–0.07)	(–0.23)–0.34	(–0.95)–(–0.27)
	net uptake	median	–	–	–0.18	–0.19	0.02	–0.13*
		95 % limits			(–0.36)–(–0.12)	(–1.56)–0.02	(–0.06)–0.18	(–0.31)–0.06
O_2	AV difference	median	5.6	5.6	6.1	6.6	5.8	5.8
		95 % limits	2.3–6.6	4.2–5.9	5.7–7.0	5.8–7.3	3.7–6.7	4.8–6.4
	MVO_2	median	–	–	1.4	1.4*	2.6	1.7*
		95 % limits			0.7–2.3	0.8–3.0	1.3–3.3	1.1–2.4

Table 4. AV differences of potassium, inorganic phosphate, pH, and P_{CO_2} across the ischemic myocardium before and 20 min after elevating arterial FFA concentrations by injection of heparin, intralipid or both substances. For explanation of the signs, see table 1.

		Heparin		Intralipid		Heparin + Intralipid	
		before	after	before	after	before	after
K^+ (mmol/l)	median	–0.10	–0.37	–0.53	–0.50	–0.33	–0.35
	95 % limits	(–0.60)–0.10	(–1.25)–0.05	(–0.65)–(–0.10)	(–0.90)–(–0.15)	(–0.50)–(–0.15)	(–0.60)–0.00
P_i (mmol/l)	median	–0.13	–0.02	–0.34	–0.24	–0.11	–0.15
	95 % limits	(–0.33)–(–0.03)	(–0.22)–0.03	(–0.40)–(–0.09)	(–0.41)–(–0.13)	(–0.21)–(–0.03)	(–0.33)–(–0.05)
pH	median	0.10	0.09	0.09	0.07	0.07	0.07
	95 % limits	0.07–0.15	0.05–0.13	0.05–0.18	0.06–0.11	0.05–0.08	0.06–0.09
P_{CO_2} (kPa)	median	–2.3	–3.3	–2.1	–2.5	–2.1	–1.9
	95 % limits	(–3.9)–(–1.7)	(–3.9)–(–1.6)	(–3.1)–(–1.7)	(–3.2)–(–1.6)	(–2.4)–(–1.3)	(–2.9)–(–0.09)

difference of lactate became negative and a significant net release of lactate occurred after injection of the substances. These changes were associated with a significant decrease in MVO_2 (table 3). In contrast with the elevated AV difference of lactate in group III (table 3), the AV differences of K^+, inorganic phosphate, pH and P_{CO_2} (table 4) were not significantly affected by the elevated arterial FFA concentration.

Discussion

In the present study, the effect of increased arterial FFA concentrations on MBF, myocardial metabolism and hemodynamics during ischemia was studied in anesthetized dogs. In this study mean coronary artery pressure, as measured distal to the stenosis in a small side branch of the interventricular coronary artery rather than the reduction of mean blood flow in this artery, was used to estimate the degree of coronary artery narrowing. Under these conditions, the determination of pressure is easier and more accurate (32). Moreover, coronary artery pressure takes into account the contribution of the collateral blood flow to the ischemic area. A further advantage of this system is that the servocontrol of this pressure corrects for possible movements of the cuff along the vessel causing changes in the degree of stenosis.

FFA concentrations were elevated by intravenous injection of heparin, intralipid or both substances. The higher plasma FFA concentrations reached after the administration of intralipid and heparin than after the injection of intralipid or heparin alone can be explained as follows. Intralipid causes primarily an increase of plasma triglycerides (22) and only secondarily of plasma FFA. The conversion into FFA is stimulated by lipoprotein lipase which is released from the endothelium into the blood under influence of heparin (6, 21).

It should be kept in mind that in group II and III no distinction can be made between the effect of high arterial FFA concentrations alone or together with heparin and high arterial triglyceride concentrations.

The findings in our study indicate that greatly elevated FFA levels (0.66–1.23 mM) result in a decrease of total MBF, endo/epicardial blood flow ratio and oxygen uptake in the ischemic area. The decreased oxygen uptake is associated with a more pronounced net release of lactate from the ischemic myocardium, suggesting the augmentation of anaerobic glycolysis.

Although FFA are known to have vasodilating properties in the coronary circulation (1, 5), it is unlikely that the decrease in MBF in the ischemic area results from a redistribution of blood flow in favor of non-ischemic areas. In our experimental set-up, after all, poststenotic coronary artery pressure is kept constant. Increased serum viscosity, resulting in elevated resistance to blood flow, might be an explanation for the decrease in MBF in the ischemic myocardium. The administration of intralipid and heparin indeed results in increased serum viscosity as determined by capillary viscometry (unpublished results). Whether the change in serum viscosity is less pronounced after the administration of intralipid alone, which could explain the non-significant alteration in ischemic MBF under these circumstances, is not known. Neither do we have information about the influence of FFA alone on serum or cellular viscosity.

It is unlikely that the differences in median values of ischemic MBF between group II and III before administration of the substances (table 2) influence the obtained results because no relation was found between these MBF values and changes in the determined variables after administration of the substances within these groups.

The decrease in endo/epicardial blood flow ratio can possibly be explained by the finding that during stenosis arterioles are fully dilated in the subendocardium but only partially in the subepicardium (4). In this light increased viscosity of the blood will affect subepicardial blood flow only to a limited extent because the arterioles in this layer can still dilate to compensate for the increase in resistance caused by the elevated viscosity. This dilation may even be stimulated by the increased concentration of FFA which are known to be coronary vasodilators (1, 5). The increased MBF in the non-ischemic area may also result from this property.

The increased net lactate release from the ischemic area is in agreement with previous findings (7) and indicates that acutely elevated arterial FFA concentrations do not inhibit anaerobic glycolysis in the ischemic myocardium.

Lactate, potassium and inorganic phosphate are commonly used as markers for ischemia. These markers are generally released simultaneously from the myocardium within 20 min after onset of ischemia (20, 33). In the present study, a more severe degree of ischemia, as indicated by the fall in MBF associated with increased net release of lactate, does not result in a more pronounced net release of potassium and inorganic phosphate. One explanation for this discrepancy might be that the cells are either retaining potassium and inorganic phosphate or are deprived of these markers after 60 min of ischemia. This theory is in agreement with the finding that the AV differences of these substances after one hour of ischemia do not significantly differ from those before ischemia, even when a significant lactate release exists (33). Another possibility is that we missed the release of potassium and inorganic phosphate because the majority of these markers is released within 10 min after inducement of ischemia (33).

After administration of heparin together with intralipid, net FFA uptake tended to increase while after intralipid administration net FFA uptake became negative in 5 out of 8 dogs. The latter can be explained by an increased intravascular lipolysis of serum triglycerides caused by an elevated concentration of this substance. In this way more FFA are formed than can be taken up by the myocardium and these FFA are released into the venous effluence. This does not occur after administration of intralipid together with heparin because heparin releases the lipoprotein lipase from the endothelium (see above).

The increased arterial lactate concentrations after the administration of intralipid as well as heparin together with intralipid, reflect a systemic effect and might result from release from skeletal muscle. The elevated arterial lactate concentrations might be responsible for the unchanged net FFA uptake of the ischemic myocardium, in the presence of elevated arterial FFA levels since experiments in non-ischemic hearts have shown that the uptake of FFA is diminished at elevated arterial lactate concentrations (30).

The increase in heart rate found after the administration of heparin as well as heparin and intralipid is probably caused by the former because heart rate did not change after the injection of intralipid alone. This is supported by the finding that intralipid administered to heparinized dogs had no significant effect on heart rate both in the non-ischemic (7, 11, 12, 13) and in the flowrestricted (7) heart. It is unlikely that our experimental design is responsible for the increase in heart rate because in a previous study without intervention no significant changes in heart rate were found during 2 hours of stenosis (33).

The present findings that elevated FFA concentrations do not induce arrhythmias, are in accordance with the data presented previously (9, 14, 15, 18, 21, 23, 25), but in disagreement with the findings of Oliver and Yates (17) and Yamazaki (34). This discrepancy is incompletely understood. A possible explanation might be that the FFA levels in our study were too low to induce arrhythmias (maximum 1.35 mM) because Oliver and Yates (17) described their effects at plasma FFA levels of 2.5 mM. On the other hand, Opie and co-investigators did not find an effect on arrhythmias at plasma FFA levels of 6 mM (18).

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Key words: myocardial ischemia, myocardial metabolism, myocardial blood flow, elevated FFA, hemodynamics, intralipid, heparin

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