Effect of Norepinephrine on Myocardial Free Fatty Acid Uptake and Oxidation.* (29995)

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Although it has been found repeatedly that the myocardium is able to oxidize fatty acids, the effects of hormones on this process have not been completely elucidated. Many of the studies involving the metabolic effects of epinephrine (E) or norepinephrine (NE) on the heart have been conducted on perfused preparations or on tissue slices. The amounts of E or NE used have been frequently sufficiently high to cause marked hemodynamic changes.

The purpose of the present investigation was to measure the effect of NE on the myocardial removal and oxidation of FFA, and to attempt to separate the possible direct effect of NE from its influence through elevating the arterial FFA level.

Materials and methods. The results are based on observations of fasted mongrel dogs averaging about 20 kg weight. As described previously(1), morphine-chloralose anesthesia was employed and the dogs were given oxygen insufflation through a tracheal catheter during the experimental procedure. Catheters were placed in the coronary sinus and the pulmonary artery under fluoroscopic guidance. A double lumen catheter was placed in the aorta with the tip in the left ventricle and the side opening in the ascending aorta. Heparin was infused through the cardiac catheters throughout the experiment at the approximate rate of 12 units/min.

The electrocardiogram (Lead II) and mean aortic pressure were recorded continuously during sampling. Left ventricular pressure was recorded at appropriate intervals. Coronary blood flow, cardiac output, myocardial O_2 consumption, work and efficiency, blood oxygen, CO_2 and plasma FFA were estimated as described previously(1).

Palmitic acid-1-C^{14} was dissolved by heating with an excess of NaOH and promptly added to a 20% solution of Fraction V-human albumin. The rate of intravenous infusion was 0.2-0.5 μc/min with a specific activity of 9-12 mc/m mole. This corresponded to less than 0.1% of the total circulating plasma free palmitate.

After completion of the FFA titration the FFA was extracted by acidification of the lower phase after removal of the upper, as described previously(2). Radioactivity was assayed in a Packard liquid scintillation spectrometer using 0.5% 2,5-diphenyloxazole and 0.05% 2-p-phenylenebis-4 methyl-5 phenyloxazolone in toluene as the scintillation fluid. Analysis of $C^{14}O_2$ was performed according to the method of Passman, Radin and Cooper (3).

In all of the experiments, a control run (Run 1) was followed in approximately one hour by an experimental run (Run 2) on the same dog. An infusion of C^{14}palmitic acid was given for a period of approximately 35 minutes at which time blood samples were drawn for estimation of coronary blood flow and cardiac output. Approximately one hour later the identical procedure of Run 1 was repeated with addition of an intravenous infusion of norepinephrine simultaneously with the infusion of C^{14}palmitic acid. Occasionally the sequence of control and experimental runs was reversed.

The above design was carried out with 2 doses of NE. In one set of experiments the rate of infusion of norepinephrine was 0.2 μg/kg/min, in the other the rate was 0.4 μg/kg/min.

Simultaneous arterial and coronary sinus blood samples were drawn for determination of coronary blood flow, followed by samples used for analysis of FFA and C^{14}palmitic acid. In addition, samples for FFA and for C^{14}palmitic acid were also drawn immediately preceding the infusion of norepinephrine.

In the experiments where nicotinic acid was administered, dosage was 1 mg/kg/min and was given over 30 minutes before Run 2.

Results. Fig. 1 shows a correlation be-

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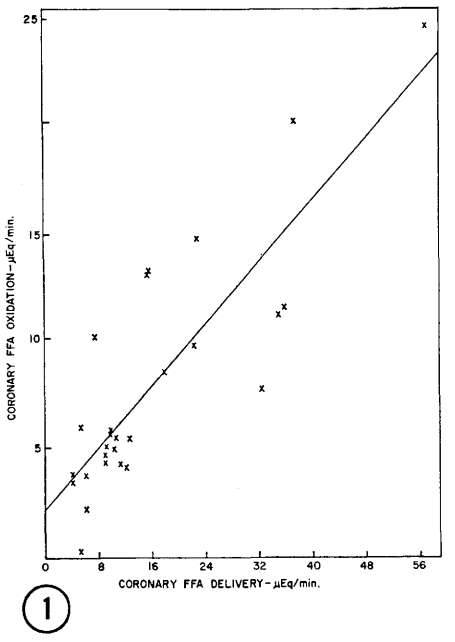

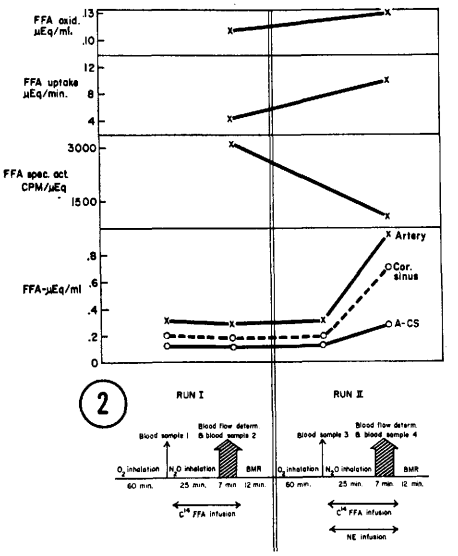

FIG. 1. Correlation between delivery of FFA and its oxidation by the myocardium. Each point represents one control dog. Correlation coefficient = 0.844.

FIG. 2. Outline of experimental design and changes during NE infusion.

tween delivery of FFA to the myocardium and its oxidation by this organ. Fig. 2 illustrates the course of the experiments and the mean changes occurring during the infusion of 0.4 μg/kg/min of NE.

Average changes in FFA metabolism during the infusion of NE, and the effect of nicotinic acid on these changes are shown in Tables I, II, and III. The directional changes caused by the lower dose of NE are similar to those brought about by the higher dose of NE, but are not consistent enough to be statistically significant. The higher dose of NE caused a marked elevation of arterial FFA, A-V difference and uptake. The specific activity of FFA decreased, as did the extraction ratio and the myocardial R.Q. A greater fraction of the CO_2 produced by the myocardium could be derived from FFA oxidation during the infusion of NE (last fraction in Table II). The mean changes in cardiac hemodynamics were relatively small.

When an infusion of nicotinic acid preceded administration of NE, all the above changes were eliminated.

Discussion. A significant correlation between FFA delivery and oxidation by the myocardium is presumably the consequence of the previously noted(1) dependence of myocardial FFA removal on arterial FFA level. After NE administration the elevated arterial FFA level is accompanied by an increased A-CS difference and oxidation of FFA. However, both the extraction ratio and the fraction of arterial FFA that was oxidized decreased significantly.

The increased removal of FFA tends to inhibit glucose oxidation(4) while there is a concomitant increase in fatty acid catabolism. These two effects are reflected in the diminished R.Q. and in the increase in the last fraction of Table II. This fraction expresses the maximal contribution of FFA oxidation to myocardial CO_2 production, assuming that the $C^{14}O_2$ counts derive from labeled plasma FFA, that all individual FFA are handled similarly, and that the "average" FFA molecule contains 17 carbon atoms.

Administration of nicotinic acid has been found to block FFA mobilization from the adipose tissue by NE(5). No direct effect of nicotinic acid on FFA metabolism was shown by Carlson *et al*(6). Nicotinic acid, by blocking FFA mobilization and the subsequent rise of arterial FFA by NE, eliminated all the changes of myocardial FFA oxidation observed in the NE infused dogs. Nicotinic acid when administered without NE, in 4

dogs, consistently lowered arterial FFA levels and increased the specific activity of plasma FFA, indicating a block of endogenous NE in adipose tissue.

It appears from the present data that the action of NE on myocardial FFA metabolism was an indirect one due to FFA mobilization from the adipose tissue. This is in agreement with the findings of Eaton and Steinberg(7) who found that the oxidation

TABLE I. Effect of Norepinephrine and Nicotinic Acid on Myocardial FFA Metabolism.

	Arterial FFA, μEq/ml	Artery-coronary sinus FFA, μEq/ml	Arterial FFA specific activity, cpm/μEq	FFA extraction ratio, $\frac{A-CS}{A} \times 100$	FFA uptake, μEq/min
	NE administered (0.2 μg/kg/min) during Run 2. N = 8				
Run 1	.535	.228	3173	44	6.27
" 2	.660 (.84)*	.285 (.055)	2671 (582)	47 (6.48)	7.53 (2.00)
	NE administered (0.4 μg/kg/min) during Run 2. N = 11				
" 1	.293	.109	3262	37	4.44
" 2	.966 (.076)‡	.268 (.034)‡	1148 (526)‡	29 (3)†	11.07 (1.45)‡
	Nicotinic acid (1 mg/kg/min) administered before, and NE (0.4 μg/kg/min) during Run 2. N = 9				
" 1	.518	.154	2413	30	6.53
" 2	.420 (.051)	.113 (.029)	2794 (760)	25 (5)	4.98 (2.16)

* ± SE calculated for paired variates; † $p < .05$; ‡ $p < .01$.

TABLE II. Effect of Norepinephrine and Nicotinic Acid on Myocardial FFA Metabolism.

	FFA oxidation (μEq/min)	$\frac{\text{FFA oxidation}}{\text{Arterial FFA}}$	Myocardial R.Q.	$\frac{\text{FFA oxidation} \times 17}{CS - A\ CO_2} \times 100$
	NE administered (0.2 μg/kg/min) during Run 2. N = 8			
Run 1	3.48	.30	.86	37
" 2	4.47 (.64)*	.25 (.034)	.85 (.07)	51
	NE administered (0.4 μg/kg/min) during Run 2. N = 11			
" 1	4.46	.38	.89	41
" 2	5.73 (1.10)	.14 (.037)‡	.73 (.059)†	68
	Nicotinic acid (1 mg/kg/min) administered before, and NE (0.4 μg/kg/min) during Run 2. N = 9			
" 1	6.79	.32	.82	56
" 2	5.97 (1.70)	.27 (.044)	.96 (.039)‡	47

* ± SE calculated for paired variates; † $p < .05$; ‡ $p < .01$.

TABLE III. Effect of Norepinephrine and Nicotinic Acid on Myocardial Hemodynamics.

	Plasma flow (ml/min/100 g/myocardium)	Heart rate (min)	Mean arterial blood pressure (mmHg)	Left ventricular O_2 consumption (ml/100 g myocardium)	Left ventricular work (kg/m²/min)
	NE administered (0.2 μg/kg/min) during Run 2. N = 8				
Run 1	27	85	90	8.20	3.48
" 2	26 (2.7)*	86 (12.9)	92 (5.9)	7.55 (.67)	2.91 (.70)
	NE administered (0.4 μg/kg/min) during Run 2. N = 11				
" 1	41	66	97	7.60	2.43
" 2	44 (7.5)	76 (7.1)	95 (4.4)	7.67 (.96)	2.57 (.37)
	Nicotinic acid (1 mg/kg/min) administered before, and NE (0.4 μg/kg/min) during Run 2. N = 9				
" 1	41	77	102	9.40	3.2
" 2	45 (5.6)	62 (11.6)	132 (4.8)†	8.00 (1.61)	3.1 (.78)

* ± SE calculated for paired variates; † $p < .01$.

of FFA by skeletal muscle was influenced by the FFA concentration of the medium, but not by the presence of epinephrine.

Summary. An intravenous infusion of labeled palmitic acid was repeated after an interval of about 90 minutes on the same intact anesthetized dog. During the second period, an infusion of NE (0.2 or 0.4 μg/kg/min) was also given. Arterial FFA, CS-A difference for FFA and myocardial uptake of FFA were increased by the higher dose of NE; the specific activity of arterial FFA, the extraction ratio of FFA and myocardial R.Q. were decreased. Infusion of nicotinic acid, preceding administration of NE eliminated the above changes. It appears that myocardial FFA oxidation is indirectly influenced by NE, through FFA mobilization and the elevated arterial level of this metabolite.

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Some Criteria for Removal of Skeletally Bound Radioactive Strontium.* (29996)

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It has been demonstrated that magnesium ions, in excess of normal requirement, can increase the overall elimination of radioactive strontium from the skeletons of rats. This occurs whether the isotope was administered 1 or 30 days previously. The increased elimination is by way of the kidney since fecal elimination is decreased(1). Magnesium ions also decrease uptake and retention of radioactive strontium by skeletons of rats fed a diet containing the isotope(2). Moreover, it has also been shown that the phosphate content of the diet has a marked influence on the removal of skeletally bound Sr^{89}(3,4,5). Since magnesium metabolism is intimately involved with that of calcium and phosphorus the following studies were designed to determine the mechanism whereby alterations in the dietary Ca/P ratio and in supplemental magnesium increase radiostrontium elimination and decrease skeletal uptake of the isotope.

Experimental. Male Holtzman rats weighing 90-100 g were injected with 30 μc of carrier free Sr^{89} intravenously and fed laboratory stock diet for 30-50 days before they were fed the experimental diets. During the balance period, the animals were housed in individual metabolism cages designed to separate urine and feces. They were kept in these cages for 16 days during which time their food, water and magnesium consumption were measured daily. The first 4 days were considered a pretreatment period to allow the rats to adjust to the different diets and the individual cages. From day 5, half of the animals received 10% glucose solution and the other half 10% glucose solution containing 2% $MgCl_2 \cdot 6H_2O$. The glucose solution

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