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Effect of nicotinic acid on myocardial metabolism in man at rest and during exercise

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LASSERS, B. W., M. L. WAHLQVIST, L. KAIJSER, AND L. A. CARLSON. *Effect of nicotinic acid on myocardial metabolism in man at rest and during exercise.* J. Appl. Physiol. 33(1): 72–80. 1972.— The effect of nicotinic acid (NA) on myocardial metabolism was studied at rest and during prolonged exercise by giving the drug as a continuous intravenous infusion to 10 healthy subjects and comparing the findings with those in a control group of 15 similar subjects not receiving NA. Both at rest and during exercise NA reduced plasma free fatty acid (FFA) turnover rate and concentration. This was accompanied by reduced myocardial extraction of FFA and increased extraction of blood carbohydrate substrates. In both circumstances myocardial energy metabolism was shifted from a predominant utilization of blood lipid substrates to a predominant utilization of blood carbohydrate substrates. At rest NA reduced the total oxygen extraction ratio (OER) for blood lipids from 64 ± 6 to 22 ± 7 (SEM) % and increased the total OER for blood carbohydrate substrates from 33 ± 5 to 72 ± 5 (SEM) %. During prolonged exercise the total OER for blood carbohydrates was 67 ± 6 (SEM) % and that for lipids only 2 ± 10 (SEM) %. These observations, together with calculations based on myocardial RQ measurements, suggest myocardial utilization of endogenous lipid during prolonged exercise and NA administration.

human myocardial energy metabolism; triglycerides; FFA; glycerol; glucose; lactate; pyruvate; endogenous myocardial lipid metabolism; palmitate-^{3}H; coronary sinus

PLASMA FREE FATTY ACIDS (FFA) are an important source of energy for oxidative metabolism in muscle both at rest and during exercise. At rest, in the fasting state, plasma FFA accounts for about 25 % of the energy metabolism of skeletal muscle (23) and about 50 % of the energy metabolism of the myocardium (34, 37). During prolonged submaximal exercise mobilization of fatty acids from adipose tissue is stimulated and there is a consequent rise in plasma FFA concentration (8). The increased delivery of FFA to skeletal muscle results in an increase in its contribution to energy metabolism in this type of muscle (23). In contrast, it appears that during prolonged exercise there is no significant change in the relative contribution of plasma FFA to myocardial energy metabolism (34).

At rest nicotinic acid decreases mobilization of fatty acids from adipose tissue and produces a fall in plasma FFA concentration (12). If administered to fasted, exercising subjects, the exercise-induced increase in FFA mobilization is inhibited (11). This reduction in the availability of FFA as a source of energy metabolism does not affect the capacity of healthy, fasting men to perform either short periods of near-maximal exercise or prolonged submaximal exercise but does produce an alteration in skeletal muscle metabolism with an increased utilization of carbohydrates as energy substrates (1). Thus, after administration of nicotinic acid, exercise is accompanied by a rise in whole-body RQ (11) and increased utilization of muscle glycogen stores with higher respiratory quotients across the exercising muscles (1). The purpose of the present study was to investigate the effect of nicotinic acid in healthy, fasting men on myocardial metabolism of lipid and carbohydrate substrates both at rest and during prolonged exercise.

MATERIAL AND METHODS

Design of Study (Fig. 1)

Ten healthy male volunteers between the ages of 21 and 32 years were investigated after an overnight fast. Their physical characteristics are summarized in Table 1. A Teflon catheter was inserted into the right brachial artery and a control sample of blood was drawn for FFA estimation. A cannula was inserted into an adjacent antecubital vein and at zero time an intravenous injection of 200 mg of nicotinic acid was given as a 5 % solution of the sodium salt over a period of 5 min. Ten minutes later a bolus injection of approximately 10 μc of palmitate-^{3}H (New England Nuclear Corp.) bound to human albumin in a molar ratio of 1:7 (prepared as previously described (34)) was given, and a continuous infusion of a combination of labeled palmitate and nicotinic acid was begun. The palmitate-^{3}H was infused at a constant rate of about 0.7 μc/min to provide a tracer for plasma FFA. The rate of infusion of nicotinic acid was 3.8 mg/min in the first three subjects but was increased to 6.7 mg/min in the remaining seven in order to ensure adequate inhibition of adipose tissue lipolysis during exercise in all subjects. The coronary sinus was then catheterized from a left arm vein (34). Heparin was not administered to the subjects. Instead the arterial catheter was kept patent by intermittent flushing with isotonic saline and the coronary sinus catheter by a slow continuous infusion of 0.5 % citrate in isotonic saline (34).

The subjects rested until the palmitate-^{3}H, nicotinic acid infusion had been in progress for 60 min. At this time expired air was collected in a Douglas bag for measurement of oxygen uptake and whole-body respiratory quotient

(RQ), and paired samples of arterial and coronary sinus blood were drawn for chemical and radioisotope estimations. After these samples had been collected, the subjects performed supine leg exercise on an electrically braked cycle ergometer (27). It was intended that exercise should continue for 2 hr, but four of the subjects became exhausted before the end of this period. Paired samples of arterial and coronary sinus blood were drawn for estimation of free glycerol concentrations 20, 40, and 60 min after the start of exercise. During the final 5 min of exercise expired air was again collected and further samples of arterial and coronary sinus blood were drawn for chemical and radioisotope measurements. A total volume of approximately 400–500 ml of blood was drawn from each subject during the study. Heart rates were measured from an electrocardiogram which was recorded continuously throughout the study.

Work Intensity

To choose work loads of comparable intensity in relation to the differing degrees of physical fitness among the subjects, a preliminary exercise test was carried out as previously described (31) 2 days before each investigation. In this test the subject's working capacity was determined as the work load which produced a heart rate of 170/min after 6 min (46, 49). During the metabolic study 2 days later, he then exercised at 50% of this load.

Plasma Water Shifts

Any systematic redistribution of plasma which occurred during passage of the blood across the heart would affect estimates of myocardial substrate extraction based on measurements of arterial-coronary sinus (a-cs) concentration differences. To establish if a significant shift of water did in fact occur, albumin-^{125}I was used as a tracer for plasma albumin. It was given to each subject at the time of the preliminary exercise test as an intravenous injection preceded by an oral dose of iodine. ^{125}I radioactivity was subsequently determined in arterial and coronary sinus samples as previously described (31).

Treatment of Samples and Analytic Methods

The treatment of the blood and expired gas samples and the analytic methods used have been described in detail (31, 34). The following chemical estimations were made: plasma FFA (48), plasma triglycerides (32), plasma free glycerol (16), blood glucose (25), blood lactate (36), and blood pyruvate (5). Electrophoretic separation of the serum lipoproteins (22) was carried out on a sample of arterial serum taken before the administration of nicotinic acid, to check—by the absence of chylomicra—that the subject had been fasting. Radioactivity in the plasma FFA fraction was determined on 10 extracts of each sample in a liquid scintillation spectrometer after separation by thin-layer chromatography (4, 34). Plasma ^{125}I radioactivity was determined on 10 replicates from each sample as previously described (31). The blood oxygen content was calculated from the hemoglobin concentration, the oxygen saturation, and the oxygen tension as previously described (34).

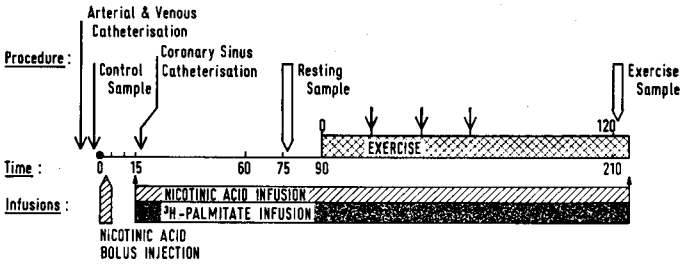

FIG. 1. Design of study (see text for explanation).

TABLE 1. *Physical characteristics and resting and exercising measurements: comparison between control and nicotinic acid groups*

Measurement	Control Group	Nicotinic Acid Group
Physical characteristics		
Age, yr	29 ± 1.4	26 ± 1.2
Ht, cm	181 ± 1.4	179 ± 2.0
Wt, kg	78 ± 1.9	76 ± 6.1
At rest		
Heart rate	73 ± 3	75 ± 3
Whole-body O_2 uptake, liter/min	0.276 ± 0.011	0.275 ± 0.011
Whole-body RQ	0.82 ± 0.01	0.84 ± 0.01
Myocardial RQ	0.76 ± 0.04	0.91 ± 0.05[a]
FFA turnover rate, μmoles/min	514 ± 33	264 ± 21[e]
Δ(a-cs) albumin-^{125}I, counts/min per ml	−2 ± 2	0 ± 4
Pa_{O_2}, mm Hg	92 ± 3	98 ± 3
Ca_{O_2}, ml/100 ml	17.08 ± 0.41	17.73 ± 0.32
Ccs_{O_2}, ml/100 ml	6.42 ± 0.34	6.75 ± 0.25
During exercise		
Work load, kg-m/min	500 ± 30	505 ± 30
Duration of exercise, min	105 ± 3	108 ± 7
Heart rate (10 min)	120 ± 3	124 ± 3
Heart rate (final)	142 ± 4	149 ± 6
Whole-body O_2 uptake, liter/min	1.424 ± 0.076	1.360 ± 0.074
Whole-body RQ	0.82 ± 0.01	0.88 ± 0.01[d]
Myocardial RQ	0.81 ± 0.01	0.91 ± 0.03[c]
FFA turnover rate, μmoles/min	1253 ± 76	376 ± 30[e]
Δ(a-cs) albumin-^{125}I, counts/min per ml	−4 ± 3	−8 ± 2
Pa_{O_2}, mm Hg	83 ± 1	88 ± 3[b]
Ca_{O_2}, ml/100 ml	17.83 ± 0.42	17.78 ± 0.38
Ccs_{O_2}, ml/100 ml	4.92 ± 0.33	5.04 ± 0.25

Values are means ± SEM. Δ(a-cs) albumin-^{125}I = arterial-coronary sinus difference in albumin-^{125}I radioactivity; Pa_{O_2} = arterial oxygen tension; Ca_{O_2} and Ccs_{O_2} = arterial and coronary sinus oxygen content. Heart rate (10 min) refers to heart rate after 10 min of exercise and (final) to heart rate during final minutes of exercise period. Level of significance of difference between control and nicotinic acid groups: [a] $P < 0.05$. [b] $P < 0.02$. [c] $P < 0.01$. [d] $P < 0.005$. [e] $P < 0.01$.

Calculations

Arterial and coronary sinus specific activities were calculated from the respective radioactivities and concentrations as previously described (34). The (a-cs) difference in concentration (i.e., myocardial extraction) was derived from the radioisotope measurement by dividing the (a-cs) difference in radioactivity by the arterial specific activity. The plasma FFA turnover rate (μmole/min) was calculated by dividing the product of the infusate radioactivity (counts/

TABLE 2. *Arterial concentrations, myocardial extractions, and oxygen extraction ratios of various substrates at rest and during exercise: comparison between control and nicotinic acid groups*

Substrate	Measurement	A: Resting			B: Exercising		
		Control	NA	P	Control	NA	P
FFA	Ca μmoles/liter plasma	620 ±50	250 ±20	<0.001	1,280 ±100	260 ±30	<0.001
	Δ(a-cs) chem	170 ±20	40 ±10	<0.001	210 ±10	20 ±10	<0.001
	Δ(a-cs) radio	260 ±20	120 ±10	<0.001	220 ±10	60 ±10	<0.001
	OER chem, %	49 ±4	11 ±3	<0.001	49 ±2	4 ±10	<0.001
	OER radio, %	74 ±4	33 ±2	<0.001	54 ±3	16 ±2	<0.001
TG	Ca, μmoles/liter plasma	1,020 ±103	803 ±94	NS	961 ±91	742 ±80	NS
	Δ(a-cs)	17 ±6	13 ±7	NS	13 ±5	−3 ±5	<0.05
	OER%	15 ±5	11 ±6	NS	9 ±3	−2 ±3	<0.02
Glucose	Ca, μmoles/liter blood	4,110 ±140	4,360 ±150	NS	3,440 ±120	3,350 ±240	NS
	Δ(a-cs)	190 ±40	390 ±40	<0.005	120 ±20	330 ±40	<0.001
	OER%	25 ±5	48 ±5	<0.01	13 ±2	35 ±4	<0.001
Lactate	Ca, μmoles/liter blood	650 ±70	880 ±80	<0.05	1,350 ±140	1,520 ±200	NS
	Δ(a-cs)	130 ±30	370 ±30	<0.001	310 ±60	580 ±90	<0.02
	OER%	8 ±2	22 ±2	<0.001	16 ±3	30 ±4	<0.02
Pyruvate	Ca, μmoles/liter blood	52 ±6	74 ±8	<0.05	89 ±4	103 ±10	NS
	Δ(a-cs)	4 ±6	37 ±8	<0.005	24 ±5	40 ±4	<0.05
	OER%	0 ±0.4	2 ±0.4	<0.02	1 ±0.3	2 ±0.2	<0.05
Glycerol	Ca, μmoles/liter plasma	46 ±4	13 ±1	<0.001	225 ±28	42 ±10	<0.001
	Δ(a-cs)	−3 ±2	−2 ±3	NS	−20 ±4	0 ±1	<0.001

NA = nicotinic acid group; C = concentration; a and cs = arterial and coronary sinus, respectively; (a-cs) = arterial coronary sinus difference in concentration; OER = oxygen extraction ratio; chem = chemical measurements; radio = radioisotope measurements; TG = triglyceride. Measurements are given as mean ± SEM for the groups of subjects and *P* values refer to significance of the difference between the means of control and NA groups.

min per ml) and infusion rate (ml/min) by the arterial FFA specific activity (counts/min per μmole). The relative contribution of different blood substrates to myocardial energy metabolism was estimated by the oxygen extraction ratio (OER) which was calculated after correcting plasma concentrations by the hematocrit as previously described (34).

Comparison with Control Group

Except for the administration of nicotinic acid, the design of the present study was similar to our earlier study of myocardial metabolism at rest and during exercise (31). The subjects in both studies were comparable in their physical characteristics, resting heart rates, and oxygen uptakes, the work loads which they performed, the duration of their exercise, and their physiological respnse to exercise as judged by increase in heart rate, whole-body oxygen uptake and myocardial oxygen extraction (Table 1). In view of this, the findings at rest and during exercise in the nicotinic acid group have been compared with those of the previous study (control group).

Statistical Analysis

The method of paired comparisons was used for statistical evaluation of the changes from rest to exercise within a group. The differences between the nicotinic acid and control groups were assessed by the *t* test for comparison of means of two small samples.

RESULTS

At Rest[1]

The average arterial concentrations, myocardial extractions, and OERs in the nicotinic acid group are compared with those for the control group in Table 2*A*.

Blood oxygen and pH. There were no significant differences between the two groups in the average arterial, coronary sinus, or (a-cs) blood oxygen measurements or in the arterial or coronary sinus pH values (Table 1).[1]

Arterial concentrations. The average FFA turnover rate in the nicotinic acid group was approximately half that of the control group (Table 1). This was associated with significantly lower arterial concentrations of both FFA and free glycerol in the nicotinic acid group and significantly higher concentrations of lactate and pyruvate (Table 2*A*). At rest there was no significant difference between the two groups in either triglyceride or glucose concentrations.

Myocardial substrate extraction. FFA extraction estimated from both chemical and radioisotope data was significantly lower in the nicotinic acid group, while glucose, lactate, and pyruvate were significantly higher than in the control group (Table 2*A*). The (a-cs) differences in triglyceride and free glycerol concentrations did not differ significantly between the two groups.

Oxygen extraction ratios. The average OER for FFA (both chemical and radioisotope estimates) was significantly lower in the nicotinic acid group, while the OERs for glucose, lactate and pyruvate were significantly higher than

[1] For complete tables giving data, for the individual subjects, on physical characteristics, work loads, duration of exercise, resting and exercising heart rates, oxygen uptakes, whole-body and myocardial RQs, albumin ^{125}I data, blood gas values, chemical and radioisotope measurements for FFA, chemical measurements for triglycerides glucose, lactate, pyruvate, and glycerol, order NAPS Document 01828 from ASIS National Auxiliary Publications Service, % CCM Information Corporation, 909 Third Ave., New York, N. Y. 10022, remitting $2.00 for microfiche or $5.00 for photocopies.

in the control group (Table 2*A*). The TG OERs did not differ significantly between the two groups.

Respiratory quotients. The average resting whole-body RQ in the nicotinic acid group did not differ significantly from that of the control group (Table 1). However, the myocardial RQ in the nicotinic acid group was significantly higher than that of the control group.

During Exercise[1]

The average arterial substrate concentrations, myocardial extractions and OER's in the nicotinic acid group are compared with those of the control group in Table 2*B*.

Blood oxygen and pH values.[1] Prolonged exercise produced slight but significant falls in arterial oxygen tension in both the nicotinic acid and control groups, but the fall in the nicotinic acid group was significantly greater than that in the control group (Table 1). Arterial oxygen saturation did not change in either group while arterial oxygen content rose significantly in the control group owing to an increase in hemoglobin concentration, but did not change in the nicotinic acid group (Table 1). Both groups had significant decreases in coronary sinus oxygen tension, saturation and content and in both groups exercise increased the (a-cs) difference in oxygen content: these changes were of a similar magnitude in both groups (Table 1).

Arterial concentrations. In the control group exercise increased the average FFA turnover rate 2.4-fold (Table 1), and this was associated with a doubling of the FFA concentration and a 5-fold increase in free glycerol concentration (Table 2*B*). In the nicotinic acid group exercise increased the FFA turnover rate only 1.4-fold. This was accompanied by a 3-fold increase in free glycerol concentration, but there was no significant change in arterial FFA concentration. The average arterial triglyceride concentration fell significantly to 92% of the resting level in the nicotinic acid group. Exercise produced significant decreases in glucose concentration and significant increases in lactate concentration in both groups. The magnitude of these changes was similar in both groups. In the control group the rise in pyruvate concentration to 171% of the resting level was significant, but in the nicotinic acid group the apparent rise to 139% of the resting value was not.

Myocardial substrate extraction and OERs. In the control group exercise produced a significant increase in the average FFA extraction estimated chemically, but because of the concomitant increase in oxygen extraction there was no change in the FFA OER (Table 2*B*). In the nicotinic acid group neither the average myocardial extraction of FFA nor the FFA OER fell significantly with exercise (Table 2*B*). During exercise the average FFA extraction and OER was significantly lower in the nicotinic acid group than in the control group (Table 2*B*).

Radiopalmitate. In the control subjects at rest the specific activity of the coronary sinus FFA was invariably less than that of the arterial FFA, so that the ratio, SA_{cs}/SA_a, was less than unity (0.80 ± 0.03) and FFA extraction derived from the radiopalmitate data was greater than that estimated chemically. During exercise the ratio approached unity in this group (0.97 ± 0.01), so that the chemical and radioisotope estimates of FFA extraction were similar

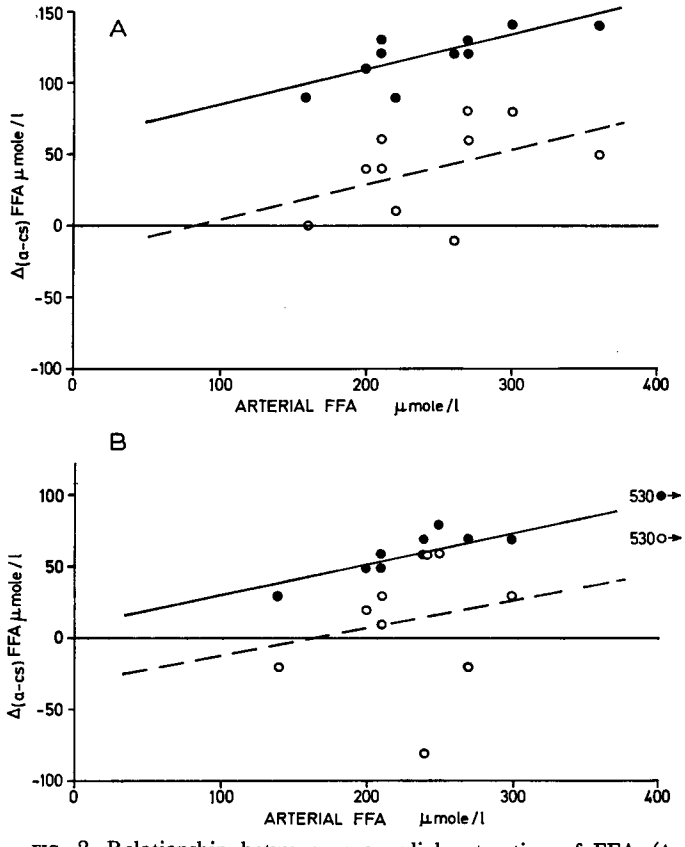

FIG. 2. Relationship between myocardial extraction of FFA (Δ-(a-cs)FFA) and arterial FFA concentration, (*A*) at rest and (*B*) during prolonged exercise in 10 subjects receiving a constant intravenous infusion of nicotinic acid. Myocardial extraction was estimated from same blood sample in each subject by both chemical (○) and radioisotope (●) techniques (see text). In both graphs, solid regression line (——) is that for the radioisotope data and broken line (– – –) that for the chemical data (see Table 3 for regression parameters).

(Table 2*B*). In the nicotinic acid group the ratio was less than unity at rest (0.61 ± 0.03), and although it increased significantly during exercise ($P < 0.01$), it still remained significantly less than unity (0.81 ± 0.04). Thus the radiopalmitate estimate of FFA extraction was greater than the chemical extraction in both circumstances (Fig. 2).

Relationship between Arterial Concentration and Myocardial Extraction of Substrates

In the nicotinic acid group there was a significant linear relationship between FFA extraction (estimated from the radioisotope data) and arterial concentration both at rest and during exercise (Fig. 2), and the slopes and intercepts of the regression lines for the resting and exercising data did not differ significantly (Table 3). In the case of the control group, although there was a significant linear relationship at rest, extraction and arterial concentration were not significantly related during exercise. The average myocardial extraction of glucose in the nicotinic acid group was almost three times, and the OER twice, that of the control group, although the average arterial glucose concentrations did not differ significantly between the two groups (Table 3). Similarly, although during exercise the average arterial

concentrations of lactate and pyruvate in the two groups were not significantly different, the myocardial extraction and OERs for these substrates were very much higher in the nicotinic acid group (Table 2*B*).

There was a significant linear relationship between glucose extraction and arterial concentration in the control group at rest, but this was not the case during exercise or in the nicotinic acid group either at rest or during exercise. In the case of lactate and pyruvate, there were significant linear relationships between extraction and concentration at rest in the nicotinic acid group and during exercise in both groups (Table 3).

TABLE 3. *Regression and correlation analyses, both at rest and during exercise, of myocardial extraction of various substrates on their arterial concentration: comparison between control and nicotinic acid groups*

y	*x*	Group		Linear Regression*		Linear Correlation	
				$B \pm$ SEM B	$A \pm$ SEM A	r	P
Δ(a-cs) FFA (chemical)	FFA_a	Control	R	0.25 ±0.08	10 ±50	0.66	<0.01
			E	0.03 ±0.03	160 ±40	0.29	NS
		Nicotinic acid	R	0.24 ±0.17	−20 ±40	0.46	NS
			E	0.19 ±0.14	−30 ±40	0.44	NS
Δ(a-cs) FFA (isotope)	FFA_a	Control	R	0.26 ±0.07	100 ±40	0.73	<0.01
			E	0.05 ±0.03	150 ±40	0.45	NS
		Nicotinic acid	R	0.24 ±0.07	60 ±20	0.76	<0.02
			E	0.16 ±0.03	20 ±10	0.88	<0.001
Δ(a-cs) glucose	$Glucose_a$	Control	R	0.19 ±0.05	−570 ±210	0.71	<0.005
			E	0.08 ±0.05	−170 ±170	0.43	NS
		Nicotinic acid	R	0.09 ±0.10	−10 ±440	0.32	NS
			E	0.01 ±0.06	−300 ±200	0.05	NS
Δ(a-cs) lactate	$Lactate_a$	Control	R	0.21 ±0.11	−10 ±80	0.47	NS
			E	0.52 ±0.06	−410 ±110	0.87	<0.001
		Nicotinic acid	R	0.33 ±0.08	80 ±70	0.83	<0.005
			E	0.39 ±0.05	−10 ±80	0.94	<0.001
Δ(a-cs) pyruvate	$Pyruvate_a$	Control	R	0.74 ±0.17	−34 ±10	0.77	<0.001
			E	0.50 ±0.12	−25 ±12	0.65	<0.001
		Nicotinic acid	R	0.83 ±0.17	−25 ±14	0.86	<0.005
			E	0.35 ±0.08	5 ±9	0.83	<0.005

Abbreviations as in Table 2; R = resting; E = exercise. * $y = Bx + A$; r = correlation coefficient.

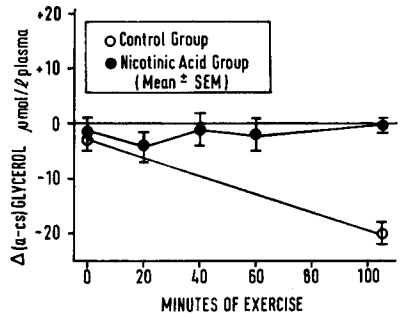

FIG. 3. Effect of prolonged exercise on arterial-coronary sinus differences (Δ(a-cs)) in free glycerol concentration. Resting samples were taken at rest (0 min) and during final minutes of exercise period in both groups and also at 20, 40, and 60 min of exercise in nicotinic acid group.

Free glycerol. At rest neither group had a significant (a-cs) difference in free glycerol concentration. During exercise, however, the control group showed a highly significant ($P < 0.005$) difference, whereas there was no significant difference in the nicotinic acid group (Table 2) (Fig. 3).

Respiratory quotients. In the control group exercise did not affect the whole-body RQ, and the increase in myocardial RQ was not significant (Table 1). In the nicotinic acid group exercise increased the whole-body RQ significantly but did not alter the myocardial RQ.

Plasma water shifts. The ^{125}I radioactivity measurements[1] indicated significant hemoconcentration of coronary sinus plasma in two subjects at rest and in two others during exercise. In the nicotinic acid group significant hemodilution of coronary sinus plasma was found in one subject at rest and significant hemoconcentration in three subjects during exercise. However, in the control group as a whole, both at rest and during exercise, and in the nicotinic acid group at rest there was no evidence of a systematic shift of water into or out of the plasma during passage of the blood across the heart. On the other hand, during exercise the nicotinic acid group had a significant (a-cs) difference in ^{125}I radioactivity equal to 1 % of the arterial ^{125}I level (Table 1). This indicates that significant hemoconcentration had occurred. Such hemoconcentration could arise, for example, from cardiac lymph flow, passage of plasma water into red blood cells or from differences between arterial and coronary sinus blood sampling techniques. The only blood substrate for which this degree of hemoconcentration could materially affect fractional extraction is triglyceride. During exercise the average (a-cs) difference in triglyceride concentration was −3 μmoles/liter; corrected for hemoconcentration, this becomes 4 μmoles/liter.

DISCUSSION

Effect of Nicotinic Acid on Myocardial Energy Metabolism

The results of the present study show that the administration of nicotinic acid had profound effects on myocardial lipid and carbohydrate metabolism in the fasting state. At rest the total contribution of blood lipid substrates to myocardial oxidative metabolism (as estimated by the OERs) was reduced from 64 to 22 % and the contribution of blood carbohydrates increased from 33 to 72 %. During