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Myocardial lipid and carbohydrate metabolism in fasting men during prolonged exercise

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KAIJSER, L., B. W. LASSERS, M. L. WAHLQVIST, AND L. A. CARLSON. *Myocardial lipid and carbohydrate metabolism in fasting men during prolonged exercise.* J. Appl. Physiol. 32(6): 847–858. 1972.— Myocardial metabolism was studied at rest and during prolonged exercise in 15 healthy subjects by measurement of arterial-coronary sinus concentration differences and the intravenous infusion of palmitate-^{3}H as a free fatty acid (FFA) tracer. During prolonged exercise the relative participation of total blood lipid and carbohydrate substrates in myocardial oxidative metabolism, as assessed by the oxygen extraction ratios, did not differ from the pattern at rest. Arterial-coronary sinus difference in oxygen content increased with exercise and was significantly correlated with heart rate. Myocardial extractions of FFA, glucose, and pyruvate, but not lactate, were significantly correlated with their respective arterial concentrations at rest. During prolonged exercise myocardial extractions of pyruvate and lactate, but not FFA and glucose, were correlated with their arterial concentrations. However, the results suggested that rate of glucose uptake might be enhanced during exercise. Radiopalmitate measurements were interpreted as indicating efflux of fatty acids into the coronary sinus blood from endogenous lipid stores. The release of free glycerol during exercise raised the possibility of increased turnover of these stores during exercise.

myocardial substrate uptake; energy metabolism; coronary sinus; free fatty acids; triglycerides; glycerol; glucose; lactate; pyruvate; myocardial oxygen metabolism; palmitate-^{3}H

EXERCISE IS ACCOMPANIED by both increased myocardial energy requirements and a marked alteration in the metabolic environment of the heart. Changes occur in the arterial concentrations of a number of important energy substrates, and alterations take place in both local sympathetic activity (28) and in the levels of circulating hormones (13, 20, 31). For these reasons exercise might be expected to modify the pattern of utilization of energy substrates by the heart. There have been a number of studies of myocardial metabolism in fasting man performing short periods of submaximal exercise (6–20 min) (8, 14, 15, 24), when the arterial concentrations of free fatty acids (FFA) have fallen below resting levels (4) and peak levels of arterial lactate have been reached (11). During this early period of exercise it has been found that the relative contribution of FFA—which is the principal myocardial energy substrate at rest (see 29)—to myocardial oxidative metabolism falls, and that of lactate increases so that oxidation of this substrate can account for as much as 30–60% of the heart's oxygen uptake, depending on the work load (23). However, if exercise is continued, FFA concentrations rise to levels above those found at rest (4), and lactate concentrations fall from the peak levels which occur during the first 10–20 min of exercise (11). There have been no studies of myocardial metabolism in man during this type of exercise when the increased myocardial energy requirements have been prolonged and when the concentrations of arterial energy substrates not only differ from those found during the early minutes of exercise, but are also more constant so that the metabolic environment of the heart is closer to a steady state.

In a previous study we have used both chemical and radioisotope techniques to measure myocardial extraction and oxygen extraction ratios of blood substrates in healthy fasting men at rest (25). The purpose of the present investigation was to use these techniques to examine the effect of prolonged exercise on myocardial metabolism of oxygen and of lipid and carbohydrate substrates in a similar group of subjects.

METHODS

Subjects. Fifteen male volunteers, of average physical fitness, between the ages of 22 and 42 years, were studied. In addition to having no past history or symptoms suggesting cardiovascular or metabolic disease, all subjects had normal resting and exercising electrocardiograms. Their physical characteristics are shown in Table 1.

Design of study (Fig. 1). Each subject was investigated without sedation after an overnight fast. A Teflon catheter was inserted into the right brachial artery for blood sampling and a cannula into an adjacent vein. A continuous infusion of a total dose of 190 μc of palmitate-^{3}H bound to human albumin prepared as previously described (25) was then begun via the venous cannula to provide a tracer for the plasma free fatty acids (FFA) and to produce endogenous labeling of the plasma triglycerides (TG). This infusion was continued at a constant rate for the duration of the study. The coronary sinus was then catheterized from a left arm vein (25). 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 continuous slow infusion of 0.5% citrate in isotonic saline (25).

TABLE 1. *Physical characteristics of subjects; exercise loads and duration of exercise; resting and exercising heart rates, oxygen uptakes, respiratory quotients, and albumin-^{125}I measurements*

Subj	Age, yr	Ht, cm	Wt, kg	Work Load, kpm/min	Duration of Exercise, min	Sample	Heart Rate, beats/min	Oxygen Uptake liters/min	RQ		Albumin-^{125}I, counts/min per ml	
									Whole body	Myocardial	a	Δ(a−cs)
SA	24	176	89	300	85	R	94	0.340	0.78		330 ± 4.6	10 ± 5.1
						E	120	1.001	0.78		314 ± 1.8	−4.8 ± 2.7
JN	30	173	80	400	120	R	92	0.273	0.88		257 ± 2.8	1.4 ± 3.4
						E	159	1.298	0.84		244 ± 3.0	−2.0 ± 4.0
POB	31	183	81	500	105	R	78	0.281	0.78		201 ± 2.4	−4.6 ± 3.2
						E	159	1.441	0.80		204 ± 2.6	3.2 ± 3.6
LEA	24	178	66	450	85	R	68	0.209	HV		306 ± 1.8	−6.8 ± 2.1*
						E	120	1.360	0.82		337 ± 2.0	−3.2 ± 2.5
AH	29	183	74	500	115	R	63	0.232	HV		290 ± 1.8	−2.6 ± 2.4
						E	137	1.328	0.86		306 ± 1.8	2.4 ± 2.6
RGJ	33	179	70	500	125	R	86	0.258	HV	0.76		
						E	144	1.272	0.90	0.80		
RHS	28	183	80	450	100	R	62	0.230	0.77	0.75	617 ± 1.4	−18.4 ± 4.0*
						E	138	1.311	0.83	0.81	629 ± 1.8	1.6 ± 5.0
SN	25	178	85	750	110	R	55	0.277	0.78	0.74	690 ± 5.8	0.6 ± 6.6
						E	163	2.035	0.77	0.77	761 ± 3.2	−10 ± 5.2
FG	29	184	71	450	120	R	60	0.201	0.76	0.61	578 ± 2.4	4 ± 3.6
						E	136	1.043	0.82	0.79	583 ± 3.2	3.2 ± 7.4
GB	42	192	78	500	90	R	60	0.308	HV	0.62	265 ± 1.6	−1.6 ± 2.2
						E	136	1.430	0.76	0.82	283 ± 4.1	1.2 ± 4.4
ER	35	186	72	600	90	R	76	0.308	0.87	0.90	599 ± 2.6	−3.4 ± 4.0
						E	141	1.664	0.90	0.82	621 ± 3.8	0.4 ± 4.4
BR	35	188	92	550	100	R	71	0.287	0.78	0.90	663 ± 2.8	−4.4 ± 4.8
						E	161	1.610	0.82	0.74	671 ± 5.8	−32.4 ± 9.0*
JR	26	183	84	750	120	R	68	0.296	0.86	0.80	482 ± 1.6	3.0 ± 2.8
						E	156	1.985	0.82	0.88	519 ± 2.0	−4.8 ± 2.6
JK	24	175	72	400	105	R	76	0.301	0.84	0.54	693 ± 3.2	−6.2 ± 5.4
						E	147	1.299	0.80	0.77	688 ± 2.6	2.0 ± 4.0
AK	22	176	73	450	105	R	81	0.344	0.87	1.00	595 ± 2.2	−5.8 ± 2.8
						E	108	1.279	0.85	0.88	624 ± 3.4	−15.8 ± 4.6*
Mean	29	181	78	500	105	R	73	0.276	0.815	0.762	469	−2.4
						E	142	1.424	0.825	0.808	484	−4.2
± SEM	±1.4	±1.4	±1.9	±30	±3	R	3	0.011	0.01	0.04	49	1.8
						E	4	0.076	0.01	0.01	51	2.6
n	15	15	15	15	15	R	15	15	11	10	14	14
						E	15	15	15	10	14	14
P (R vs. E)							<0.001	<0.001	NS	NS	<0.025	NS

R = resting; E = exercising. Exercising measurements are measurements made during final minutes of exercise period. *P* values calculated by method of paired comparisons. HV = subject hyperventilating during expired gas collection. Albumin-^{125}I radioactivity: a = arterial; Δ(a−cs) = arterial-coronary sinus difference in radioactivity. Values are mean ± SEM. * Significant Δ(a−cs) ($P < 0.05$).

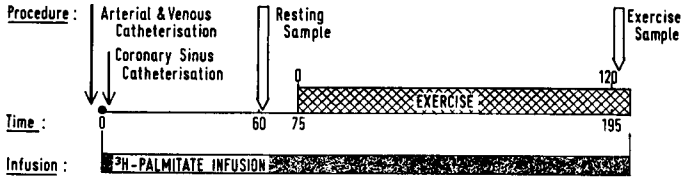

FIG. 1. Design of study. Zero-time was taken as the beginning of the palmitate-^{3}H infusion and the time after this is given in min.

The subjects rested until the palmitate-^{3}H infusion had been in progress for 60 min. Expired air was then collected in a Douglas bag for measurement of whole body oxygen uptake and respiratory quotient (RQ), and paired samples of arterial and coronary sinus blood were drawn simultaneously for chemical and radioisotope estimations. Samples for coronary sinus oxygen measurements were drawn both at the beginning and the end of the sampling period to ascertain whether the catheter had remained within the coronary sinus throughout this period. After the samples had been collected, the subjects performed supine leg exercise at a fixed, predetermined work load (see below) on an electrically braked cycle ergometer designed so that, within certain limits, work load and pedaling rate are independent (18). It was intended that exercise should continue for 2 hr. However, all but four subjects became exhausted before the end of this period (Table 1). In 12 of the 15 subjects paired samples of arterial and coronary sinus blood were drawn 10 min after the start of exercise, for measurement of lactate, pyruvate and blood gas levels. During the final 5 min of exercise, expired air was again collected and further paired arterial and coronary sinus blood samples were drawn for chemical and radioisotope measurements. Heart rate was calculated from an electrocardiogram recorded continuously throughout the study.

Work intensity. In order to choose work loads of comparable intensity in relation to the differing degrees of physical

fitness of the subjects, a preliminary exercise test was carried out 2 days before each study. In this preliminary test, exercise was performed in the sitting position on a cycle ergometer. Work loads were increased in a stepwise fashion and the subject's working capacity was determined as the work load (kpm/min) which produced a heart rate of 170/min after 6 min (35, 37). During the metabolic exercise study itself he exercised at 50% of this load. The circulatory and ventilatory response to prolonged exercise in the supine position at work intensities related to the individual's working capacity in this manner have been reported (11).

Treatment of samples and analytic methods. The treatment of the paired arterial and coronary sinus blood samples and the analytic methods used have been described in detail previously (25). Samples for enzymatic determination of blood glucose (16), lactate (27), and pyruvate (3) concentrations were deproteinized immediately with perchloric acid. Samples for the estimation of plasma FFA, TG, and free glycerol concentrations and for radioactivity measurements were immediately transferred to heparinized test tubes and placed in an iced water bath. These samples were centrifuged, and aliquots of the pooled arterial and pooled coronary sinus plasma were extracted within an hour of the sample being drawn (25). FFA were measured according to Trout et al. (36), and the heptane phase was washed twice with 0.05% H_2SO_4. Plasma TG concentrations were measured in triplicate on 10 extracts of each blood sample with an AutoAnalyzer technique (22). TG values were corrected for free glycerol (2) determined by a modification of the method of Chernick (9). Electrophoretic separation of the serum lipoproteins was carried out according to Lees and Hatch (26) on a resting sample of arterial serum to check, by the absence of chylomicra, that the subject had been fasting and to ensure that no abnormality of the lipoprotein pattern was present.

Radioactivity in the plasma FFA and TG fractions was determined on 10 extracts from each blood sample according to the method of Boberg (1). The lipids were separated by thin-layer chromatography and the radioactivity counted in a Packard model 3375 liquid scintillation spectrometer. Quench corrections were carried out with internal standards (25). The radioactivity in the palmitate-^3H infusate was determined from samples taken from the infusion syringe at the end of the study. These were added to aliquots of plasma, extracted, separated by thin-layer chromatography, and the radioactivity in the FFA spot was measured (25).

The oxygen content of the blood samples was calculated from the hemoglobin concentration, the oxygen saturation measured spectrophotometrically (19), and the oxygen tension measured with a polarographic electrode (Instrumentation Laboratory model 113). The values used for the coronary sinus oxygen measurements were the average of the samples drawn at the beginning and end of each sampling period. Samples of expired air were taken from the Douglas bag and analyzed for oxygen and carbon dioxide by the Haldane technique. The whole-body oxygen uptake and RQ values were calculated from these data. The myocardial RQ was calculated from the arterial-coronary sinus difference in carbon dioxide and oxygen content, which were determined by the Van Slyke technique. Arterial and coronary sinus hematocrit values were measured on 10 replicates from each blood sample.

Plasma water shifts. Any systematic redistribution of plasma water which occurred during the passage of blood across the heart or during the collection of samples would affect estimates of myocardial substrate extraction based on measurements of arterial-coronary sinus concentration differences. Particularly sensitive estimates would be those for substances with a small fractional extraction such as plasma TG. Therefore, to establish if a significant shift of water did in fact occur, albumin-I^{125} was used as a tracer for plasma albumin. Each subject was given an oral dose of iodine in the form of Lugol's solution followed by an intravenous injection of 5 or 8 μc of albumin-I^{125}. These were administered at the time of the preliminary exercise test 2 days prior to the metabolic study. ^{125}I radioactivity was subsequently determined on 10 replicates from each pooled arterial and pooled coronary sinus plasma sample (2).

Calculations. Arterial and coronary sinus specific activities were calculated from the respective radioactivities and concentrations, as previously described (25). Myocardial extraction of a substrate was determined from the chemical measurements as the arterial-coronary sinus (a-cs) difference in concentration. FFA and TG extraction was also calculated from the radioisotope data by dividing the (a-cs) difference in radioactivity by the arterial specific activity. The plasma FFA turnover rate (μmoles/min) was calculated by dividing the product of the infusate radioactivity (counts/min per ml) and infusion rate (ml/min) by the arterial FFA specific activity (counts/min per μmole). In order to relate substrate extraction to the energy requirements of the heart, the fraction of the (a-cs) difference in oxygen content which could be accounted for by complete oxidation of a particular substrate (the oxygen extraction ratio or OER) was calculated after correcting plasma concentrations by the hematocrit (25). The method of paired comparisons was used for statistical evaluation of changes from rest to exercise.

RESULTS

At Rest

The performance of a number of replicate analyses of concentration and radioactivity for each sample allowed an estimate to be made of the significance of arterial-coronary sinus differences in the individual subjects. For this reason the metabolic data for each subject have been presented in Tables 2 and 3 and for convenience, summarized in Table 4. The results at rest did not differ significantly from those obtained in our earlier study of myocardial metabolism in healthy, fasting men at rest (25). In this earlier study we found that it was not possible to calculate meaningful (a-cs) differences in TG concentration from differences in (a-cs) TG radioactivity using the specific activity of the total plasma TG, and postulated that this might be due to differing rates of change of specific activities in various subfractions of the plasma TG pool. For this reason we have only used chemical measurements to estimate TG extraction and OERs in the present study.

TABLE 2. *Plasma free fatty acids and triglycerides: measurements during resting and exercise*

Subj	Sample	Free Fatty Acids									Triglycerides		
		Chemical			Radioisotope								
		C_a	Δ(a−cs)C	OER, %	FFA TOR	SA_a	$\frac{SA_{cs}}{SA_a}$	Δ(a−cs)A	Δ(a−cs)C	OER, %	C_a	Δ(a−cs)C	OER, %
SA	R	600±20	170±20*	56	561	807±22	0.92	166±9*	210±10*	68	1,206±8	7±9	7
	E	1,130±30	140±30*	37	1,143	396±12	0.86	111±7*	280±20*	74	1,111±8	22±10*	17
JN	R	810±10	200±30*	64	561	876±15	0.84	260±5*	300±10*	95	1,758±13	4±15	4
	E	1,950±20	200±30*	49	1,409	349±5	0.98	81±8*	230±20*	57	1,461±11	20±12	15
POB	R	660±0	300±10*	62	489	1,120±19	0.89	380±13*	340±10*	70	1,430±6	1±8	1
	E	1,350±20	250±20*	48	1,192	459±10	1.05	89±12*	190±30*	37	1,146±6	−9±8	−5
LEA	R	680±10	160±10*	48	432	3,174±32	0.80	834±12*	260±10*	80	1,091±4	81±5*	74
	E	990±0	170±10*	43	1,060	1,293±10	0.96	259±14*	200±10*	50	938±5	17±6*	13
AH	R	550±10	170±20*	52	443	2,498±29	0.92	502±13*	200±10*	62	539±6	−24±9*	−23
	E	1,460±20	230±20*	55	1,286	860±12	0.98	214±12*	250±10*	59	460±6	23±8*	16
RGJ	R	660±0	140±20*	34	467	1,717±12	0.76	457±7*	270±10*	64	550±4	25±4*	18
	E	1,260±10	240±30*	50	1,181	679±8	1.01	155±8*	230±10*	47	463±8	5±10	3
RHS	R	330±0	100±10*	29	313	2,485±33	0.74	396±9*	160±10*	47	822±3	15±5*	13
	E	900±10	200±10*	47	1,074	724±11	0.98	155±8*	210±10*	51	858±6	−8±10	−6
SN	R	480±10	180±20*	55	445	2,021±48	0.85	454±15*	230±10*	69	1,774±13	22±15	20
	E	1,450±10	170±20*	36	1,528	589±7	0.97	124±10*	210±20*	44	1,768±11	51±13*	32
FG	R	770±10	120±20*	40	575	1,900±22	0.84	424±17*	220±10*	75	875±3	24±5*	24
	E	1,640±20	210±30*	64	1,583	690±10	1.00	146±19*	210±30*	65	811±2	−12±6	−11
GB	R	930±10	260±10*	84	880	1,269±14	0.92	398±11*	310±10*	102	787±4	−7±5	−7
	E	1,010±20	230±20*	66	1,251	893±22	1.01	196±9*	220±10*	63	910±5	1±6	1
ER	R	340±10	70±10*	28	491	2,250±62	0.69	347±8*	150±10*	61	471±5	12±7	14
	E	790±20	130±20*	38	961	1,150±25	0.87	118±11*	100±10*	34	486±6	39±7*	34
BR	R	560±10	200±10*	51	446	1,927±44	0.70	594±22*	310±10*	78	851±5	34±6*	26
	E	910±0	280±20*	52	1,087	791±8	1.01	216±12*	270±20*	54	927±6	31±7*	18
JR	R	640±10	120±10*	33	605	1,826±30	0.60	595±8*	330±10*	89	1,019±8	13±11*	11
	E	1,880±40	230±40*	51	2,002	552±11	0.96	162±9*	290±20*	65	1,146±5	12±7	8
JK	R	890±10	260±10*	71	566	1,678±20	0.89	551±22*	330±10*	89	1,044±5	35±7*	29
	E	1,600±0	240±10*	51	1,262	752±4	1.00	189±13*	250±20*	54	991±5	17±9	11
AK	R	470±0	80±10*	26	430	2,226±24	0.68	458±9*	210±10*	67	1,087±4	12±6	12
	E	820±10	170±10*	47	772	1,240±14	0.96	240±10*	190±10*	54	933±8	−7±9	−6
Mean	R	620±50	170±20	49±4	514±33	1,852±167	0.80±0.03	454±40	260±20	74±4	1,020±103	17±6	15±5
± SEM	E	1,280±100	210±10	49±2	1,253±76	761±75	0.97±0.01	164±14	220±10	54±3	961±91	13±5	9±3
P (R vs. E)		<0.001	<0.02	NS	<0.001	<0.001	<0.001	<0.001	<0.05	<0.001	NS	NS	NS

R = resting; E = exercising (final samples); a and cs = arterial and coronary sinus. C = concentration in μmole/liter plasma; A = radioactivity in counts/min per ml; SA = specific activity in counts/min per μmole; Δ (a − cs) = arterial-coronary sinus difference; OER = oxygen extraction ratio; TOR = turnover rate in μmoles/min. Individual values are presented as mean ± SEM of replicate measurements made on each sample. Means ± SEM at foot of table are for the group as a whole (i.e., $N = 15$). P values for rest vs. exercise measurements calculated by method of paired comparisons. NS = not significant ($P > 0.05$). *(a − cs) difference is significant at confidence level at 95% or greater.

During Exercise

The average work load and duration of the exercise are shown in Table 1. This level of exercise increased the heart rate from the average resting value of 73 ± 12 to 120 ± 12 (SD) beats/min after 10 min of exercise and to 142 ± 15 (SD) beats/min during the final minutes of exercise. The average oxygen uptake during the final minutes of exercise had increased to 5.2 times the resting value (Table 1).

Blood oxygen and pH values (*Table 5*). Arterial oxygen content increased significantly owing to an increase in hemoglobin concentration and coronary sinus oxygen content decreased significantly so that the average (a-cs) difference in oxygen content of the final exercising samples was 21% higher than the average resting value. There was a significant linear correlation between heart rate and both coronary sinus oxygen saturation (Fig. 2*B*) and (a-cs) difference in oxygen content (Fig. 3*B*).

Respiratory quotients (*Table 1*). The average whole body RQ during the final 5 min of exercise did not differ significantly from the resting value. There was no significant change in the average myocardial RQ during exercise.

Arterial substrate concentrations. During the first 10 min of exercise, the arterial concentration of lactate rose to 2,160 ± 240 (SEM) μmoles/liter (3.3 times the resting level) and pyruvate to 108 ± 10 (SEM) μmoles/liter (2.1 times the resting level), but by the final minutes of exercise lactate had fallen to about twice the resting level and pyruvate to 1.7 times the resting level (Table 3). At this time the average FFA turnover rate had increased 2.4 times, with a doubling of the arterial FFA concentration (Table 2) and a fivefold increase in arterial free glycerol concentration (Table 3). At the same time glucose concentration fell significantly to 83% of the resting level (Table 3) and arterial TG concentration had not changed significantly (Table 2).

TABLE 3. *Blood glucose lactate, and pyruvate and plasma glycerol: measurements during resting and exercise*

Subj	Sample	Glucose, μmoles/liter blood			Lactate, μmoles/liter blood			Pyruvate, μmoles/liter blood			Total CHO OER, %	Glycerol, μmoles liter plasma	
		C_a	Δ(a−cs)C	OER, %	C_a	Δ(a−cs)C	OER, %	C_a	Δ(a−cs)C	OER, %		C_a	Δ(a−cs)C
SA	R	3,550±30	70±40	9	1,270±80	40±100	3	42±5	−33±6	−2	10	62±1	−1±2
	E	3,360±20	50±30	6	2,160±30	740±50	42	97±7	65±16	4	52	150±1	−18±2*
JN	R	4,230±20	340±30*	44	410±0	40±10*	2	62±4	17±5*	1	47	69±2	−5±2
	E	3,280±20	−20±30	−2	1,230±40	220±50*	11	96±4	27±4*	1	10	487±9	−42±9
POB	R	3,530±40	120±60	12	570±20	160±20*	8	77±7	25±8*	1	21	44±1	−3±1
	E	2,990±30	10±40	1	1,300±10	440±10*	20	113±1	37±4*	2	23	269±2	−31±3*
LEA	R	3,090±20	70±30*	9	750±20	160±60*	10	52±4	−6±6	0	19	61±1	−19±3*
	E	2,460±20	50±20*	5	500±40	−60±30	−5	80±8	48±8*	2	2	210±1	−15±2*
AH	R	3,680±30	210±50*	27	440±30	120±30*	8	32±6	2±7	0	35	44±1	−1±1
	E	3,010±20	150±20*	15	1,460±20	260±20*	13	76±4	22±4*	1	29	255±3	−25±4*
RGJ	R	3,710±30	90±40	10	450±10	120±40*	7	48±8	−15±8	−1	16	44±3	−4±3
	E	3,270±20	10±30	1	1,000±30	50±70	2	110±5	0±5	0	3	312±8	0±9
RHS	R	5,200±70	600±80*	77	510±50	20±80	1	26±1	−24±2*	−2	76	26±0	−4±1*
	E	4,130±20	180±40*	18	740±40	240±40*	12	64±4	21±2*	1	31	207±3	−8±5
SN	R	4,350±30	100±40*	13	600±30	220±40*	14	51±2	4±2	0	27	28±1	1±1
	E	3,870±20	230±30*	22	1,760±40	530±50*	25	69±4	−12±2*	−1	46	413±2	−28±2*
FG	R	3,910±50	110±60	15	430±40	−100±70	−7	35±5	−2±2	0	8	50±1	−2±2
	E	2,960±20	150±40*	18	1,000±30	100±30*	6	67±7	−5±7	0	24	200±1	−2±2
GB	R	4,120±30	210±50*	26	510±0	80±10*	5	36±2	−6±3	0	31	83±0	15±1*
	E	3,500±50	80±60	9	970±80	10±80	1	89±1	27±4*	2	12	179±1	−6±2
ER	R	4,820±30	350±40*	54	880±40	280±40*	22	62±3	37±8*	3	79	37±1	0±1
	E	4,050±30	130±60	16	2,400±60	540±60*	33	105±3	31±3*	2	51	129±4	−51±5*
BR	R	4,120±40	120±40*	14	740±20	80±20*	4	35±3	19±7*	1	19	46±1	−4±1*
	E	3,510±20	270±60*	24	1,540±40	480±40*	22	74±4	27±6*	1	47	100±5	−36±5*
JR	R	4,300±30	170±40*	20	1,080±20	340±30*	20	75±5	24±6	1	41	33±1	−3±2
	E	3,530±30	270±40*	26	1,630±40	380±60*	18	97±3	5±4	0	44	215±2	−5±2
JK	R	4,640±30	100±70	14	340±50	50±90	3	23±1	−29±2	−2	15	46±1	−1±1
	E	3,640±20	140±40*	16	760±0	160±20*	9	88±2	27±4	2	27	152±3	−27±6*
AK	R	4,400±40	200±50*	26	800±0	320±30*	20	119±1	46±3	3	49	21±1	−15±1*
	E	4,000±30	120±30*	14	1,860±0	620±80	35	116±4	35±4	2	51	99±1	−6±2
Mean ± SEM	R	4,110±140	190±40	25±5	650±70	130±30	8±2	52±6	4±6	0±0.4	33±6	46±4	−3±2
	E	3,440±120	120±20	13±2	1,350±140	310±60	16±3	89±4	24±5	1±0.3	30±4	225±28	−20±4
P (R vs. E)		<0.001	NS	<0.05	<0.001	<0.005	<0.01	<0.001	<0.05	NS	NS	<0.001	<0.005

Abbreviations: as in Table 2; CHO = carbohydrate.

Myocardial extraction. After 10 min of exercise lactate extraction had increased 5.6 times to an average of 730 ± 160 (SEM) μmoles/liter and pyruvate extraction 7.5 times to 30 ± 7 (SEM) μmoles/liter. By the final minutes of exercise extraction had decreased to 2.1 times the resting level for lactate and 6.0 times for pyruvate. At this time glucose extraction was 63% of the resting value, but this apparent fall was not significant (Table 3). TG extraction did not change significantly. FFA extraction estimated chemically increased significantly by 23% with prolonged exercise while that derived from the radioisotope data fell significantly to 85% of the resting value (Table 2).

At rest the specific activity of the coronary sinus FFA was always less than that of the arterial FFA and the ratio of the two, SA_{cs}/SA_a, was significantly less than unity. This resulted in the radioisotopic estimate of FFA extraction being, on the average 90 μmoles/liter plasma greater than the chemical estimate. During exercise, however, the specific activity of the coronary sinus FFA approached that of the arterial FFA. Thus the ratio of the two was close to unity and the average radioisotope estimate of FFA extraction was only 10 μmoles/liter plasma greater than the chemical estimate (Table 2).

At rest there were significant linear correlations between *a*) myocardial extraction of FFA (chemical) and arterial FFA concentration and *b*) myocardial extraction of radiopalmitate and arterial FFA concentration (Fig. 4; Table 6). However, during exercise the slope of the regression line relating radiopalmitate extraction to arterial FFA concentration (Fig. 4) *a*) was significantly different from that at rest and *b*) did not differ significantly from zero (Table 6). This was also the case for chemical FFA extraction.

At rest there was a significant, positive linear correlation between arterial glucose concentration and glucose extraction, but this was not the case during exercise (Fig. 5; Table 6). In the case of lactate (Fig. 6) there was a significant correlation between arterial concentration and myocardial extraction during exercise, but not at rest (Table 6). Arterial pyruvate concentration and pyruvate extraction were significantly correlated both at rest and during exercise. The regression and correlation parameters in Fig. 7 were calculated from the pooled data for resting and exercising (Table 6).

Oxygen extraction ratios. The altered myocardial extraction of oxygen and substrates during exercise resulted in a number of changes in the OERs of the various substrates. After 10 min of exercise the OER for lactate had increased to an average value of 38 ± 9 (SEM) %, but by the final minutes

TABLE 4. *Myocardial substrate metabolism at rest and during prolonged exercise*

Substrate	(a-cs)		OER, %	
	R	E	R	E
FFA				
Chemical	170 ± 20	210 ± 10†	49 ± 4	49 ± 2
Isotope	260 ± 20	220 ± 10*	74 ± 4	54 ± 3§
Triglycerides	17 ± 6	13 ± 5	15 ± 5	9 ± 3
Glucose	190 ± 40	120 ± 20	25 ± 5	13 ± 2*
Lactate	130 ± 30	310 ± 60‡	8 ± 2	16 ± 3*
Pyruvate	4 ± 6	24 ± 5*	0 ± 0.4	1 ± 0.3
Total			97 ± 8	88 ± 5
Lipid			64 ± 6	58 ± 3
CHO			33 ± 5	30 ± 3

Average (± SEM) arterial-coronary sinus differences in concentration and oxygen extraction ratios. Abbreviations: as in Table 2; CHO = carbohydrate. FFA and triglycerides: μmoles/liter plasma; glucose, lactate, pyruvate: μmoles/liter blood. Totals calculated from chemical FFA OERs. *P* values, calculated by method of paired comparisons, refer to significance of change from rest to exercise. * $P < 0.05$. † $P < 0.02$. ‡ $P < 0.005$. § $P < 0.001$.

TABLE 5. *Effect of prolonged exercise on arterial and coronary sinus oxygen, pH, and hematocrit values*

Measurement	Rest	Exercise	*P*
Pa_{O_2}, mm Hg	92 ± 3	83 ± 1	<0.005
Pcs_{O_2}, mm Hg	22 ± 1	20 ± 1	<0.005
Sa_{O_2}, %	96.0 ± 0.6	95.7 ± 0.5	NS
Scs_{O_2}, %	35.9 ± 1.5	26.1 ± 1.4	<0.001
Ca_{O_2}, ml/100 ml	17.08 ± 0.41	17.83 ± 0.42	<0.001
Ccs_{O_2}, ml/100 ml	6.42 ± 0.34	4.92 ± 0.33	<0.001
pH_a	7.44 ± 0.01	7.43 ± 0.01	NS
pH_{cs}	7.40 ± 0.01	7.39 ± 0.005	NS
$C(a\text{-}cs)O_2$			
ml/100 ml	10.65 ± 0.33	12.90 ± 0.33	<0.001
μmoles/liter	4,753 ± 147	5,758 ± 148	
Hct_a, %	42 ± 1	43 ± 1	NS
Hct_{cs}, %	43 ± 1	44 ± 1	NS

Values are means ± SEM. *P* values for rest vs. exercise measurements calculated by method of paired comparisons. Abbreviations: a and cs = arterial and coronary sinus; Po_2 = oxygen tension; So_2 = oxygen saturation; Co_2 = oxygen content; $\Delta C(a\text{-}cs)O_2$ = arterial-coronary sinus difference in oxygen content; Hct = hematocrit.

of exercise this had decreased again, but not to resting levels (Table 3). The average OER for pyruvate was 1.3 ± 0.3 (SEM) % after 10 min of exercise not significantly different during the final minutes of exercise (Table 3). At this time the glucose OER had fallen significantly from the resting value, but the apparent change in TG OER was not significant (Table 3). Prolonged exercise produced no significant change in the average FFA OER calculated from the chemical measurements while that derived from the radioisotope data fell significantly (Table 2).

Thus with prolonged exercise, the total OER for blood carbohydrate substrates, the total OER for blood lipids, and the total OER for the blood energy substrates did not change significantly (Table 4).

Free glycerol (Table 3). At rest the average (a-cs) difference in free glycerol concentration did not differ significantly from zero. With exercise, all but two subjects showed a significant, negative (a-cs) difference in free glycerol concentration and the average was significantly below zero.

Plasma water shifts. The ^{125}I radioactivity measurements indicated significant hemoconcentration of coronary sinus plasma relative to arterial plasma in two subjects at rest and in two other subjects during exercise (Table 1). However, for the group as a whole the average (a-cs) differences in ^{125}I radioactivity at rest and during exercise were not significant. Thus there was no evidence either of a systematic shift of water into or out of the plasma during passage of the blood across the heart or of hemoconcentration or dilution due to differences in the techniques of sampling arterial and coronary sinus blood.

If 95% confidence limits are taken for the SEM of the average (a-cs) difference in ^{125}I radioactivity, then this

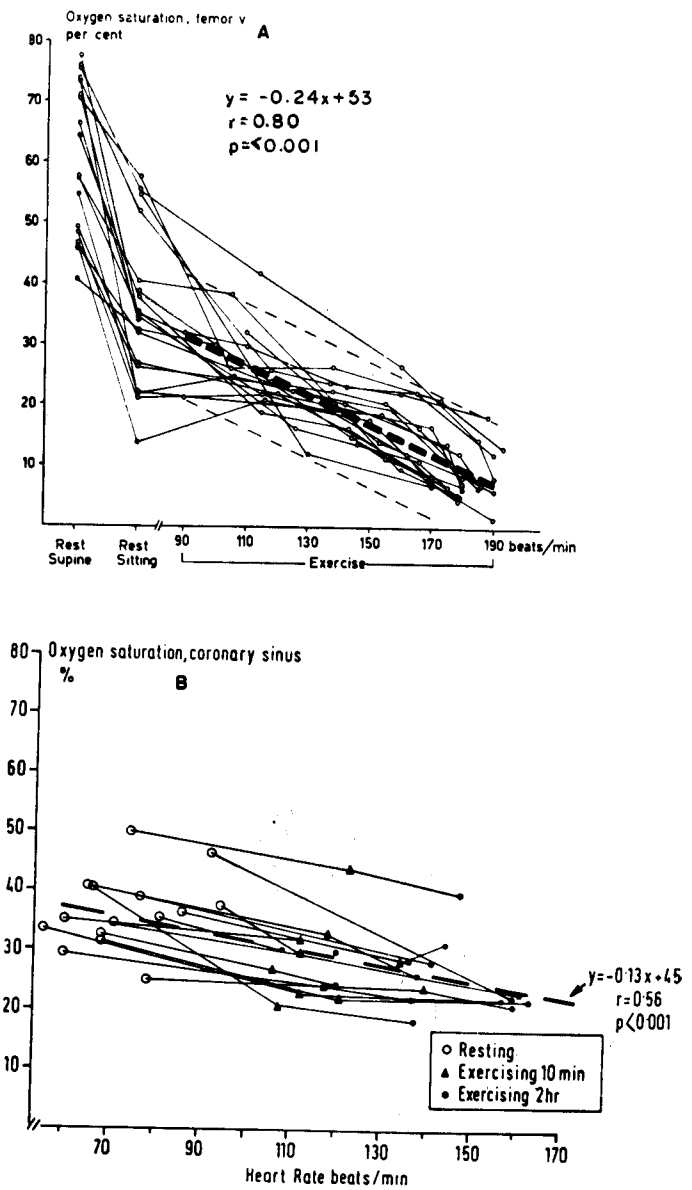

FIG. 2. A comparison of the effect of exercise-induced increase in heart rate on oxygen saturation in *A*) femoral venous blood [from Pernow et al. (30)] and *B*) coronary sinus blood.

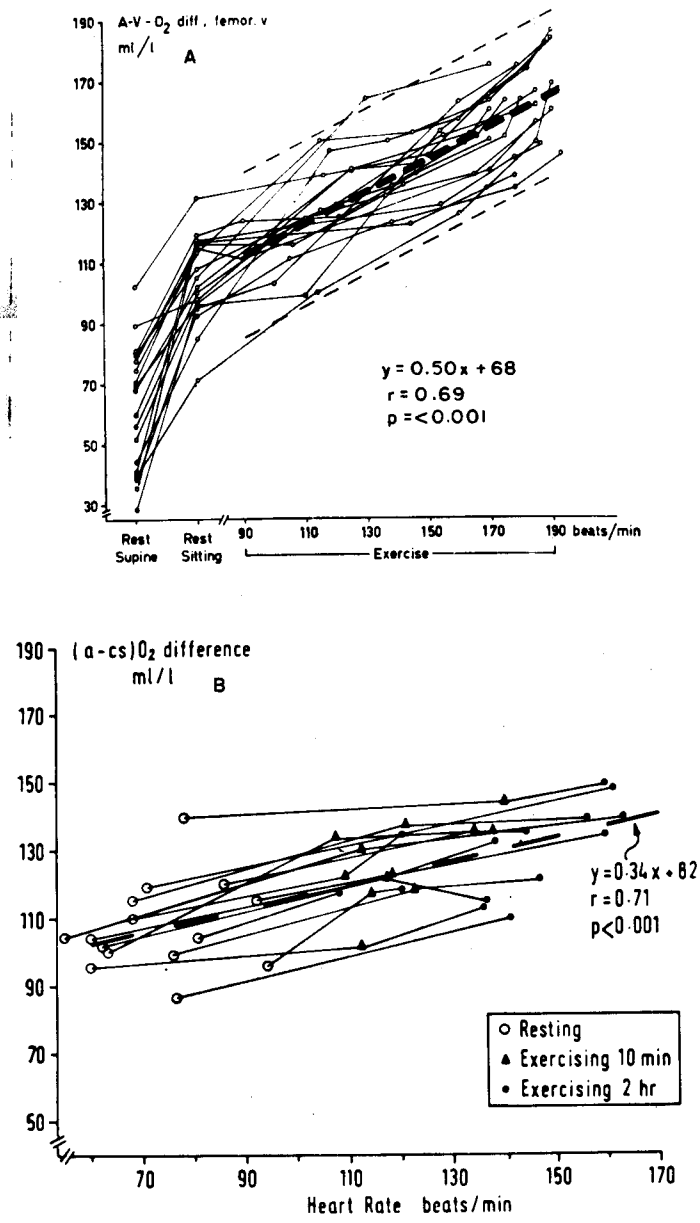

FIG. 3. A comparison of the effect of exercise-induced increase in heart rate on the arteriovenous difference in oxygen content of *A*) femoral blood [from Pernow et al. (30)] and *B*) coronary blood.

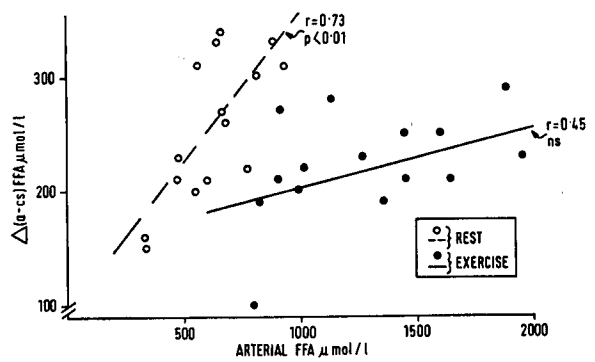

FIG. 4. Relationships, both at rest and during exercise, between arterial plasma FFA concentration and myocardial extraction (Δ(a-cs)) of FFA calculated from the radioisotope data (r = correlation coefficient) (see Table 6).

TABLE 6. *Regression and correlation analyses, both at rest and during exercise, of myocardial extraction of various substrates on their arterial concentration*

Y	Regression Analysis			Correlation Analysis		
	x	$B \pm SE_B$	$A \pm SE_A$	r	n	P
FFA extraction						
Chemical						
Rest	FFA_a	0.25 ± 0.08	10 ± 50	0.66	15	<0.01
Exercise	FFA_a	0.03 ± 0.03	160 ± 40	0.29	15	NS
Isotope						
Rest	FFA_a	0.26 ± 0.07	100 ± 40	0.73	15	<0.01
Exercise	FFA_a	0.05 ± 0.03	150 ± 40	0.45	15	NS
Glucose extraction						
Rest	$Glucose_a$	0.19 ± 0.05	−570 ± 210	0.71	15	<0.005
Exercise	$Glucose_a$	0.08 ± 0.05	−170 ± 170	0.43	15	NS
Lactate extraction						
Rest	$Lactate_a$	0.21 ± 0.11	−10 ± 80	0.47	15	NS
Exercise	$Lactate_a$	0.52 ± 0.06	−410 ± 110	0.87	27	<0.001
Pyruvate extraction						
Rest	$Pyruvate_a$	0.74 ± 0.17	−34 ± 10	0.77	15	<0.001
Exercise	$Pyruvate_a$	0.50 ±0.12	−25 ± 12	0.65	27	<0.001
Rest + exercise	$Pyruvate_a$	0.52 ± 0.08	−25 ± 7	0.73	42	<0.001

Parameters for lactate and pyruvate during exercise calculated from both 10-min and final exercise samples ($Y = Bx + A$). Abbreviations as in Table 2.

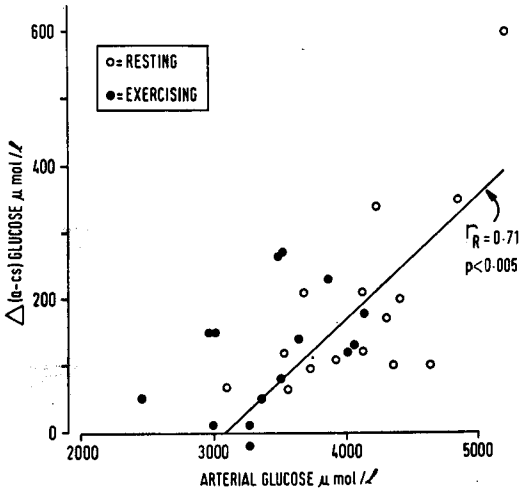

FIG. 5. Relationship between arterial blood glucose concentration and myocardial extraction (Δ(a-cs)) of glucose. Since concentration and extraction were significantly correlated only at rest, the regression line and correlation coefficient (r_R) have been calculated from these points (see Table 6).