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Short-term interruption of training affects both fasting and post-prandial lipoproteins

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Summary

Exercise training alters plasma lipoprotein profiles in a manner compatible with decreased coronary artery disease risk. The aim of this study was to ascertain whether interruption of training (detraining) was associated with potentially undesirable changes in the metabolism of post-prandial lipoproteins and plasma levels of Lp(a). Eight normolipidemic, male runners who ran 30–40 miles/week were studied in the trained state and after 14–22 days of detraining. Two of the subjects were studied in the reverse order to control for any confounding effects of exercise sequence. Detraining resulted in (1) a 12% ($P = 0.002$) reduction in the subjects' aerobic capacity, (2) a 7.7% ($P = 0.007$) reduction in fasting concentrations of high density lipoprotein cholesterol (HDL-C), (3) a 21% ($P = 0.01$) reduction in post-heparin lipoprotein lipase activity. Lp(a) concentrations did not change significantly (mean increase 15%, $P = 0.076$). Fasting plasma concentrations of total cholesterol (TC), triglycerides (TG) and low density lipoprotein-cholesterol (LDL-C) did not change in the detrained state. There was little fluctuation over 24 h in plasma concentrations of TC, LDL-C and HDL-C in either the trained or detrained states. TG concentrations fluctuated over the 24 h in accord with food intake, but there were no exercise-related changes. Exercise had a dramatic effect on chylomicron and chylomicron remnant metabolism as measured by retinyl palmitate measurements. The mean areas under the concentration vs. time curves (AUC) for chylomicron-retinyl esters increased by 41% ($P = 0.013$) and for chylomicron remnant-retinyl ester by 37% ($P = 0.058$) following detraining. Thus, brief intervals of detraining reduced fasting concentrations of HDL-C and decreased the metabolism of chylomicrons. These changes are associated with an increased incidence of atherosclerosis.

Key words: Exercise; Lipoproteins; Lipoprotein lipase; Hepatic triglyceride lipase; Lp(a)

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Introduction

Exercise-induced changes of plasma lipoprotein profiles and metabolism may contribute to the favorable effects of exercise in decreasing the risk of coronary artery disease. Regular and rigorous exercise training raises HDL-C, lowers TG and variably affects LDL-C concentrations in plasma [1,2]. In addition, exercise training also increases the plasma clearance of post-prandial lipoproteins, such as chylomicrons [3]. Chylomicrons transport dietary lipids from the intestine into the systemic venous system. During their circulation, chylomicrons are rapidly depleted of dietary triglycerides by the catalytic action of lipoprotein lipase (LPL), a triglyceride hydrolase located in virtually every capillary bed. The action of LPL generates fatty acids for tissue consumption or storage [4]. Lipolysis converts chylomicrons to chylomicron remnants which are cleared by the liver. Chylomicrons and chylomicron remnants can be identified in plasma either by the presence of apo B-48, the intestinal form of apo B, or by the presence of fatty acid esters of retinol [6]. Dietary retinol is esterified to fatty acids in enterocytes, incorporated into chylomicrons and circulates in plasma with post-prandial lipoproteins. In normolipidemic humans, it is possible to detect post-prandial particles in plasma for as long as 14 h following a single fat-rich test meal, but clearance of post-prandial lipoproteins is retarded in hypertriglyceridemia [6].

Chylomicron remnants and other related post-prandial lipoproteins such as β -VLDL and IDL, but not chylomicrons themselves, are thought to be atherogenic [7]. Therefore, conditions which minimize the amounts and transit times of these particles in plasma may be beneficial in reducing coronary artery disease risk. A previous study investigating the effects of a 7-week exercise training program in six normolipidemic subjects showed that exercise significantly reduced levels of chylomicrons but not chylomicron remnants following a fat-containing test meal [3].

Lipoprotein(a) (Lp(a)) is a macromolecular lipoprotein complex consisting of low density lipoprotein cholesterol linked to apolipoprotein(a). This particle has received increased attention since its association with premature coronary

artery disease and stroke was discovered [8,9]. There are few interventions that affect plasma levels of Lp(a). This study investigated the effects of exercise since no exercise related effects on Lp(a) have been reported.

This study investigated the effects of exercise training on lipoprotein metabolism by studying well-trained subjects who run 30–40 miles/week. Studies were performed before and after 14–22 days of stopping exercise (detrained state). Some subjects were studied in the reverse order to assess whether the effect of detraining seen in the majority of our subjects was compatible with the effect of training. Fasting lipoproteins, including Lp(a) and apolipoproteins were quantified and in addition, chylomicron metabolism was studied by measuring the appearance and disappearance of retinyl palmitate-labelled chylomicrons and chylomicron remnants from the plasma after the oral ingestion of test meals containing fat and vitamin A.

Ten to 14 days of detraining is known to be associated with significant declines in glucose tolerance, insulin sensitivity, various enzymes of energy metabolism and maximal oxygen consumption [10,11]. However, little is known about the effects of detraining on concentrations of plasma lipids. Since many people who exercise regularly are either forced through injury to stop exercising for short periods of time or take voluntary breaks in their exercise routine, it would be of interest to know whether the beneficial effect of exercise on fasting and post-prandial lipoproteins is reversible over a similar short period of time. The study design enabled us to assess both the effects of exercise and the effects of detraining on lipoprotein metabolism.

Methods

Study subjects

Eight normolipidemic, healthy male runners who were taking no medication and running 30–40 miles/week were studied after providing informed consent according to an IRB approved protocol (Tables 1 and 2). Subjects were studied in the trained state and then after 14–22 days of no exercise. Two of the subjects (No. 4 and No. 6) were studied in reverse order, i.e. after 14–21 days of detraining and after 15 days of retraining, to

TABLE 1

SUBJECT CHARACTERISTICS

Vo₂max, maximal O₂ consumption; BMI, body mass index; Apo AI, apolipoprotein AI; Apo B, apolipoprotein B; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; apo E, apolipoprotein E phenotype. These parameters were measured in the trained state upon recruitment into the study. ND indicates test not done.

Subject	Age years	Body fat % of body	Vo ₂ max ml/kg/min	BMI kg/m ²	Apo E phenotype	TC mg/dl	TG	LDL-C	HDL-C	Apo B	Apo AI	Lp(a)
1 (TA)	31	19.4	61	22.6	3,2	167	120	62	81	72	207	2.7
2 (DF)	39	22.7	52	25.5	3,3	162	76	91	56	75	181	1.5
3 (JM)	26	8.6	73	22.3	3,3	152	85	79	56	59	149	6.0
4 (KK) ^a	26	10.0	53	23.0	4,4	157	81	85	56	41	139	18.0
5 (JM)	40	13.9	60	22.3	3,3	143	82	83	43	50	101	8.0
6 (DW) ^a	33	12.8	58	22.5	3,3	183	94	100	64	55	121	2.0
7 (MS)	39	23.5	50	24.0	3,2	200	175	115	50	95	151	17.0
8 (JP)	40	12.7	59	21.8	ND	176	80	118	42	78	139	25.5
Mean	34	15.5	58	23		168	99	92	56	66	148	10.1
S.D.	6	6	7	1.2		18	32	19	13	18	33	9.0

^aSubjects studied in reverse order.

TABLE 2

EFFECTS OF DETRAINING ON PLASMA LIPOLYTIC ACTIVITY, MAXIMAL OXYGEN CONSUMPTION AND PLASMA LIPIDS

See Table 1 for column headings. T, trained; D, detrained. LPL activity and HTGL activity results represent means plus standard deviations of triplicate assays.

Subject	Lipolytic activity μmol FFA/ml/h				Detraining related changes		
	LPL activity		HTGL activity		VO ₂ max ml/kg/min	HDL-C mg/dl	Lp(a) mg/dl
	T	D	T	D			
1 (TA)	14.0 ± 0.7	11.8 ± 0.4	2.3 ± 0.3	2.0 ± 0.3	-1.75	-3	0
2 (DF)	19.1 ± 3.3	14.8 ± 1.2	3.7 ± 0.1	4.2 ± 0.1	-8	-5	0.25
3 (JM)	8.8 ± 0.4	5.6 ± 0.2	2.4 ± 0.1	2.7 ± 0.1	-12	-3.5	+4.0
4 (KK) ^a	10.1 ± 0.3	10.0 ± 0.5	3.4 ± 0.1	4.2 ± 0.8	0	-10	+4.0
5 (JM)	16.4 ± 2.7	11.4 ± 0.5	3.6 ± 0.1	4.4 ± 0.1	-11	-3	-1.5
6 (DW) ^a	8.9 ± 0.2	8.2 ± 0.3	1.3 ± 0.1	1.9 ± 0.1	-6	-1	+0.5
7 (MS)	7.1 ± 0.1	6.8 ± 0.1	3.6 ± 0.1	3.6 ± 0.2	-10	-8	+1.5
8 (JP)	7.4 ± 0.1	4.2 ± 0.1	3.7 ± 0.1	2.2 ± 0.1	-8	-1	+3.5
Mean	11.5	9.1**	3.0	3.2	-7.1***	4.3****	+1.5**
S.D.	4.5	3.6	1	1	4.3	3.2	2.1

^aSubjects studied in reverse order.

Significantly different from trained state by one tailed paired *t*-test, **P* = 0.05; ***P* = 0.0759; ****P* = 0.0023; *****P* = 0.0068.

control for any confounding effects of exercise sequence and one subject (No. 1) was studied in the trained state, after 14 days of detraining and then after 14 days of retraining. Plasma dilutional changes were estimated by calculating the plasma volume change using hemoglobin and hematocrit measured before and after training [12].

Percentage body fat and VO₂max

Percentage body fat was measured by underwater weighing and maximal oxygen consumption (VO₂max) was measured during treadmill testing utilizing standard open circuit spirometry.

Lipid, lipoprotein and apoprotein determinations

Blood was drawn after an overnight fast in either the trained or detrained state and the plasma was separated and frozen at -70°C. Plasma samples from the same individual in the trained and detrained states were assayed simultaneously. Cholesterol and TG were measured by enzymatic assays using commercially available kits (Wako

Chemical Company, Richmond, VA). HDL-C was measured after dextran sulphate precipitation of LDL and VLDL [13]. LDL-C was calculated from the Friedewald formula [14]. Apo A1 and apo B were measured by radio-immunoassay [15,16]. Plasma Lp(a) was measured by a commercially available ELISA kit (Terumo, Elkton, MD). Coefficients of variation for lipid and apolipoprotein measurements were < 5% and < 12%, respectively. Apo E phenotypes were identified by isoelectric focusing using the method of Weidman et al. [17] adapted to a commercially available slab gel system (PhastGel 4-6.5, Pharmacia, Piscataway, NJ). Plasma LPL activity was determined using an assay described previously [18] by subtracting HTGL activity (lipolysis in the presence of 1 M NaCl) from total plasma lipolytic activity.

Determination of plasma lipid concentrations over a 24-h period

TC, TG and HDL-C were measured over a 24-h period on subjects 2-8 in the trained and detrained

ed states. Studies were conducted on an inpatient basis at Washington University's General Clinical Research Center. Subjects reported after an overnight 12 h fast. Baseline blood samples were taken at 08:00 h and 2 hourly thereafter until 08:00 h the next morning. Subjects were given breakfast, lunch and dinner at 08:15, 13:00 and 19:00 h, respectively, and were instructed to eat their meals within 15 min. The meals consisted of 40% of daily calories as fat, 40% as carbohydrate and 20% as protein. The amount of calories given to each subject was calculated using the Harris Benedict equation [19]. Subjects received approximately 20% of total calories as breakfast, 30% as lunch and 50% as dinner. Each subject received the same calories in the trained and the detrained states. Subjects remained sedentary during the 24 h period and were allowed water ad libitum, but no food between meals.

Post-prandial triglyceridemia was quantitated from the plasma response curve by calculating the area between the curve and a horizontal line paralleling the abscissa drawn through the fasting plasma concentrations (zero hour concentration). Units are expressed in mg/h per dl.

Vitamin A fat loading studies

Vitamin A fat tolerance tests were conducted on subjects 1-7 on an inpatient basis at Washington University's General Clinical Research Center. Subjects were requested to refrain from exercise for at least 20 h before the vitamin A studies and fasted for 12 h prior to the studies. Baseline blood samples were taken and then subjects drank a milkshake containing a commercially available breakfast drink mix, 2 cups of skim milk, 100 g of corn oil and 120 000 IU of vitamin A (Armour Pharmaceuticals, Kankakee, IL). The milkshake was consumed within 10 min and venous blood was sampled at regular intervals over the next 12-24 h. Subjects fasted until the end of the study but drinking water was allowed ad libitum. All the meals were well tolerated.

Venous blood was drawn from the forearm into tubes containing EDTA. Samples were immediately centrifuged at $1500 \times g$ for 15 min and 0.5 ml plasma was stored wrapped in aluminum foil at -70°C for TG and plasma retinyl palmitate determinations. An aliquot of plasma (2.5 ml) was pipetted into a 0.5×2.5 inch polyallomer bell-top

tube (Beckman, Palo Alto, CA) and overlaid with 0.15 M NaCl, 1 mM EDTA solution (pH 7.4) (density 1.006 g/ml). Tubes were subject to preparative ultracentrifugation for $1.6 \times 10^6 g \cdot \text{min}$ in a Beckman 50.3 TI rotor to float chylomicron particles of $S_f > 1000$. The supernatant was removed by a tube slicer and brought to 1.25 ml with 0.15 M NaCl, 1 mM EDTA and the infranatant was then placed in a clean 0.5×2.5 polyallomer tube. The tube was filled with NaCl-EDTA solution and was subjected to preparative ultracentrifugation for $1.2 \times 10^8 g \cdot \text{min}$. The supernatant (remnant fraction) was removed by a tube slicer and brought to 1.25 ml. Samples from the remaining infranatant had $<10\%$ of total plasma retinyl palmitate. All samples were handled under reduced room light and stored at -70°C . As shown previously, this procedure appears to separate a predominantly chylomicron population from a predominantly remnant population [6].

Samples obtained in the trained and detrained states were analyzed simultaneously. Retinyl esters were extracted from plasma and ultracentrifugal fractions with hexane/methanol/water (4:3:3, v/v/v) and separated by reverse-phase HPLC using a C-18 column (Alltech; Deerfield, IL). The mobile phase was methanol and heptane (15:1 v/v) at a flow rate of 2 ml/min. The absorbance of the effluent was monitored at 326 nm. Peaks were identified by comparison with purified retinyl palmitate and retinyl acetate standards. Retinyl esters were quantified relative to the internal standard of retinyl acetate. Analyses of 14 identical samples yielded a coefficient variation of $<5\%$.

Concentrations of retinyl esters in chylomicrons and chylomicron remnants integrated over time were obtained by calculating the areas under the plasma concentration vs. time curves for the respective lipoproteins over the study period (see Fig. 1).

Statistical analyses

The differences between the trained and detrained states were analyzed for significance using a two-tailed paired Student's *t*-test with an α criterion of 0.05. Significance of Lp(a) was determined with a two-tailed paired *t*-test and due to the skewed distribution of Lp(a) concentrations, the Mann-Whitney non-parametric test was also

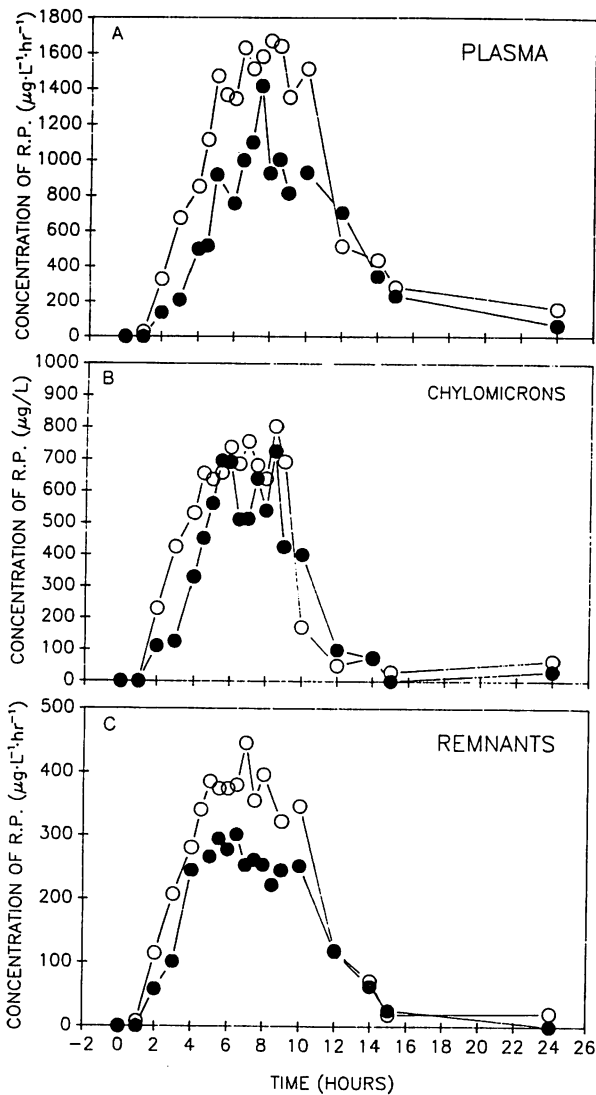


Fig. 1. The effects of detraining on chylomicron remnant metabolism. Curves represent levels of retinyl palmitate in whole plasma (A), chylomicrons (B) and chylomicron remnants (C) in the trained (●) and detrained (○) states in subject No. 4.

used. Results are similar by both tests. Correlations between all measured variables were calculated using a computer program (Instat, Graph Pad, San Diego, CA) by linear regression analysis with the least squares method.

Results

All subjects had normal plasma lipoprotein con-

centrations and were in good health (Table 1). Cessation of exercise for 14–22 days resulted in a significant change in the following metabolic parameters (Table 2): VO_2max decreased from 58 ml/kg per min to 51 ml/kg per min ($P < 0.002$); LPL activity decreased from 11.5 $\mu\text{mol/h}$ per ml to 9.1 $\mu\text{mol/h}$ per ml ($P < 0.01$) and HDL-C decreased from 56 mg/dl to 51.7 mg/dl ($P < 0.007$). Detraining did not result in a significant change in body weight (66.4 ± 6.4 kg vs. 65.8 ± 6.6 kg) ruling out effects of weight changes on lipoproteins [20].

No changes were seen in percentage body fat (15.5 ± 5.7 vs. 15.0 ± 5.5), plasma volume (as judged by hemoglobin and hematocrit determinations), Lp(a) (10.1 mg/dl vs. 11.6 mg/dl, $P = 0.076$), TG (99 ± 34 mg/dl vs. 113 ± 37 mg/dl), TC (167.5 ± 18.3 mg/dl vs. 175 ± 28 mg/dl), LDL-C (92 ± 19 mg/dl vs. 101 ± 24 mg/dl), apo A1 (148 ± 33 mg/dl vs. 134 ± 24 mg/dl), apo B (66 ± 18 mg/dl vs. 66 ± 13 mg/dl) or HTGL activity (3.0 ± 1 $\mu\text{mol FFA/ml}$ per h vs. 3.2 ± 1 $\mu\text{mol FFA/ml}$ per h) (Tables 1 and 2). There were no significant differences in the plasma lipids including HDL-C of 9 concurrent controls who did not change their exercise habits (data not shown).

The vitamin A fat tolerance test was performed

THE EFFECTS OF DETRAINING ON CHYLOMICRONS AND CHYLOMICRON REMNANTS

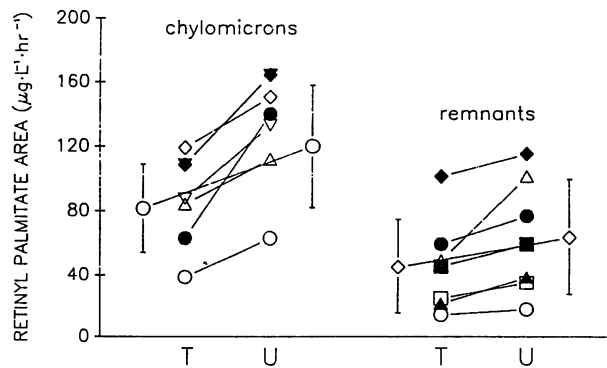


Fig. 2. Areas under the chylomicron and chylomicron remnant curves for individual subjects in the trained (T) and the detrained (U) states. The open circles and open diamonds with error bars represent means \pm S.D.

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CONCENTRATION (mg/dl)

Fig. poin ed st (D)

on 7 of the subjects. Curves illustrating the appearance and disappearance of retinyl palmitate in the whole plasma and in chylomicron and chylomicron remnant fractions of subject No. 4 are shown in Fig. 1. Retinyl palmitate levels tended to peak between 4 and 10 h and returned to baseline by 15 h. For the entire group mean AUCs calculated from the individual curves were higher in the detrained than in the trained state for both chylomicrons and chylomicron remnants (Fig. 2). Mean chylomicron AUC increased from 85.1 $\mu\text{g/l}$ per h to 120 $\mu\text{g/l}$ per h ($P = 0.013$) and mean remnant AUC increased from 43.1 $\mu\text{g/l}$ per h to 58.8 $\mu\text{g/l}$ per h ($P = 0.0580$). There was no statistically significant correlation between LPL activity and retinyl palmitate AUCs of either chylomicron or chylomicron remnants. Plasma triglyceride concentrations also were measured during these tests. No exercise-related differences were noted in AUCs for TGs (not shown).

Over the 24-h period, in either the trained or detrained states total cholesterol and HDL-C concentrations tended to be unaffected by the intake of meals, whereas triglyceride concentrations increased in the 2–4 h following meals (Fig. 3). No exercise-related significant differences for 24-h profiles were noted for TG (Fig. 3), TC, or HDL-

C, (not shown) as measured by the areas between the curve and a line drawn through the fasting plasma lipoprotein concentration. As noted above, AUCs for TGs from the fat tolerance tests also revealed no significant differences between the trained and the detrained states.

Discussion

This study examined the effect of exercise on fasting and post-prandial lipoproteins by studying well-trained runners before and after stopping exercise for 2–3 weeks. The detraining protocol used in this study enabled us to investigate several aspects of exercise and lipoprotein metabolism. We wanted to determine (1) whether short-term exercise detraining affects plasma lipids, (2) whether exercise significantly reduces plasma levels of chylomicrons and chylomicron remnants, (3) whether exercise affects post-prandial levels of TC, HDL-C and LDL-C and (4) whether exercise affects fasting plasma levels of Lp(a).

The study showed that there was no significant change in mean body weight, mean percentage of body fat or mean plasma volume, indicating that lack of exercise was probably the main factor causing the observed changes in lipid metabolism in this study.

Fourteen to 22 days of detraining in healthy male runners who usually run 30–40 miles/week resulted in a 12% decrease in maximal oxygen consumption, a 7.7% decrease in HDL-C and a 21% decrease in LPL activity. These results are the reverse of the effects seen when subjects train and are compatible with the known effects of exercise training [1–3]. Furthermore, the fact that the sequence of testing did not alter the results confirms that the effect seen was due to exercise training. These results are also consistent with studies evaluating the acute effects of prolonged exercise on lipoprotein metabolism [21,22]. Sady et al. [21] showed that male distance runners had enhanced clearance rates of exogenous fat, increased levels of LPL activity, lower fasting triglyceride levels and higher HDL-C levels following a marathon run. These effects lasted for several hours after the last bout of exercise. Others have shown that the acute effects of vigorous exercise may last up to several days [22]. In the current work, subjects

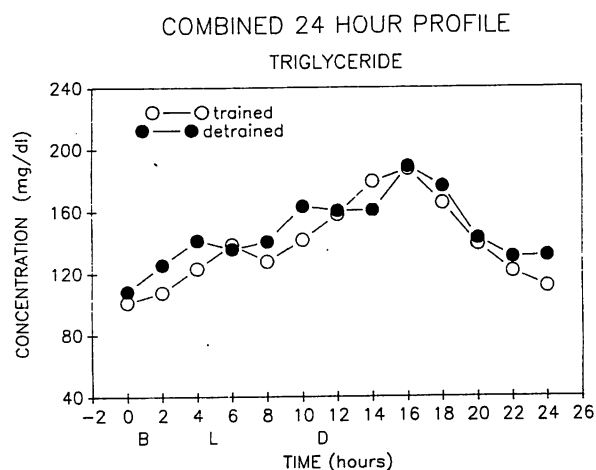


Fig. 3. Plasma triglyceride concentrations over 24 h. The data points represent means for 7 subjects in the trained and detrained states. Subjects received breakfast (B), lunch (L) and dinner (D) at 0 h, 5 h, 11 h, respectively. No food was allowed between meals.

were studied approximately 20 h after the last bout of exercise to attempt to avoid the acute effects of exercise on lipoprotein metabolism. However, because the acute effects of exercise may last longer than 20 h, part of what we noted in the detrained state could have been due to the absence of an acute bout of exercise. In any case, one implication of our study is that the favorable effects of exercise training on lipoprotein metabolism may decline rapidly after short-term detraining.

Since the effects of detraining seen in our study were consistent with the known effects of exercise and since the sequence of testing did not alter the results, it appears that detraining is an efficient and time-sparing technique to study the effects of exercise on lipoprotein metabolism.

One of the impressive findings in this study was the deleterious effect of detraining on chylomicron levels. Chylomicrons and chylomicron remnants increased by 41% and 37%, respectively, following 2–3 weeks of detraining. Weintraub et al. [3] showed that when sedentary men trained for 7 weeks, there was a significant decrease in plasma chylomicrons. Similarly, previous studies [21,23] have shown that exercise augments the clearance of both oral and intravenously administered triglycerides. However, in the latter studies chylomicron remnants were not studied [21,23]. In the study by Weintraub et al., exercise did not significantly affect chylomicron remnants [3]. Our results are compatible with theirs. The decrease in LPL activity and increase in fasting TG and chylomicron levels are compatible with the known effects of LPL on the metabolism of TG-rich lipoproteins [4].

Lipoprotein(a) has gained increased attention since the finding of its homology to plasminogen and its association with premature coronary artery disease and stroke [8,9]. It is unknown whether manipulating plasma levels of Lp(a) affects vascular disease risk, but based on the experience with the beneficial effects of lowering plasma LDL concentrations [24–26], it would seem logical that an intervention which lowers Lp(a) also would be beneficial. To our knowledge this is the first study to evaluate the relationship between exercise and Lp(a). Our study showed that mean plasma Lp(a) levels were 15% higher in the detrained state. However, this difference was at best marginally

significant. This is consistent with the unchanging nature of Lp(a) in the face of other perturbations. In sum, the effects of exercise on several aspects of lipoprotein metabolism are rapidly reversible, similar to the reversibility of the effects of exercise on glucose-insulin metabolism.

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