

## Catecholamine release, growth hormone secretion, and energy expenditure during exercise vs. recovery in men

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### Abstract:

We examined the relationship between energy expenditure (in kcal) and epinephrine (Epi), norepinephrine (NE), and growth hormone (GH) release. Ten men [age, 26 yr; height, 178 cm; weight, 81 kg; O<sub>2</sub> uptake at lactate threshold (LT), 36.3 ml · kg<sup>-1</sup> · min<sup>-1</sup>; peak O<sub>2</sub> uptake, 49.5 ml · kg<sup>-1</sup> · min<sup>-1</sup>] were tested on six randomly ordered occasions [control, 5 exercise: at 25 and 75% of the difference between LT and rest (0.25LT, 0.75LT), at LT, and at 25 and 75% of the difference between LT and peak (1.25LT, 1.75LT) (0900–0930)]. From 0700 to 1300, blood was sampled and assayed for GH, Epi, and NE. Carbohydrate (CHO) expenditure during exercise and fat expenditure during recovery rose proportionately to increasing exercise intensity ( $P = 0.002$ ). Fat expenditure during exercise and CHO expenditure during recovery were not affected by exercise intensity. The relationship between exercise intensity and CHO expenditure during exercise could not be explained by either Epi ( $P = 1.00$ ) or NE ( $P = 0.922$ ), whereas fat expenditure during recovery increased with Epi and GH independently of exercise intensity ( $P = 0.028$ ). When Epi and GH were regressed against fat expenditure during recovery, only GH remained statistically significant ( $P < 0.05$ ). We conclude that a positive relationship exists between exercise intensity and both CHO expenditure during exercise and fat expenditure during recovery and that the increase in fat expenditure during recovery with higher exercise intensities is related to GH release.

**Keywords:** epinephrine | norepinephrine | metabolism

### Article:

The “crossover concept” asserts that, during incremental exercise, as exercise intensity is increased, a shift in substrate utilization occurs, with an increase in carbohydrate (CHO) metabolism and a decrease in fat metabolism (4, 5, 20,27). This notion could be explicable by

increased recruitment of skeletal muscle, particularly fast-twitch fibers, and an increase in sympathetic nervous system (SNS) activity (4,5). The blood lactate response to exercise has been suggested as a particular marker of the “crossover” point (4, 5), given that the blood lactate and catecholamine responses to incremental exercise may be linked (24, 28, 37).

Other studies report that, after recovery from high-intensity exercise, there is a greater substrate shift toward fat oxidation (1, 39). This substrate shift occurs despite elevated catecholamine concentrations after high-intensity exercise and may be related to other driving forces, such as the growth hormone (GH) response to exercise. We recently reported that a linear dose-response relationship exists between exercise intensity and the GH secretory response in young men, with escalating GH release across the full range (sub- to supralactate threshold) of exercise intensities (29). Because GH has powerful lipolytic effects, we postulated that this may explain the increase in free fatty acid (FFA) utilization during recovery from high-intensity exercise.

In the present study, we examined the following hypotheses: 1) the shift in substrate utilization toward increased CHO metabolism with increasing exercise intensity is related to increased catecholamine release during exercise, and 2) the increase in fat oxidation during postexercise recovery is related to an elevation in GH release at the end of exercise and during recovery from exercise.

## METHODS

**Subjects.** Ten recreationally active men (age,  $26 \pm 1.1$  yr; height,  $178 \pm 1.7$  cm; weight,  $83.4 \pm 2.8$  kg; means  $\pm$  SE) provided voluntary written informed consent, as approved by the Human Investigation Committee of the University of Virginia, before entering the study. Each subject underwent a detailed medical history and physical examination, and no subject had a history of pituitary, renal, hepatic, or metabolic disease. The subjects were nonsmokers, did not abuse alcohol, and were not taking any medications known to affect GH secretion. Screening laboratory data revealed normal hematologic, renal, hepatic, metabolic, and thyroid function. Subjects refrained from exercise for 24 h before each evaluation.

**Experimental design.** Each subject completed a treadmill test to assess degree of cardiovascular fitness and underwent hydrostatic weighing to determine body density at the Exercise Physiology Laboratory of the General Clinical Research Center (GCRC). Subjects were then evaluated on six separate randomly ordered occasions, five with exercise and one at rest. Admissions were scheduled at least 7 days apart, and no more than two admissions per 2 mo were allowed (to fulfill guidelines for blood withdrawal). Exercise consisted of 30 min of constant-load exercise at a predetermined velocity. Treadmill velocity was set at 25% and 75% of the difference between the  $\dot{V}O_2$  uptake ( $\dot{V}O_2$ ) at the lactate threshold (LT) and  $\dot{V}O_2$  at rest (0.25LT and 0.75LT, respectively); at LT; and 25% and 75% of the difference between the  $\dot{V}O_2$  at LT and peak  $\dot{V}O_2$  ( $\dot{V}O_{2\text{peak}}$ ; 1.25LT and 1.75LT, respectively), based on results obtained during a prior LT- $\dot{V}O_{2\text{peak}}$  protocol (see below).

**Body composition.** Body density was assessed by hydrostatic weighing (21). Residual lung volume was measured by using an oxygen-dilution technique (38). The computational procedure of Brozek et al. (6) was used to determine percentage body fat.

**LT- $\dot{V}O_{2\text{ peak}}$ .** A continuous treadmill (Quinton Q 65) exercise protocol with increasing velocity until volitional fatigue was used to assess LT and  $\dot{V}O_{2\text{ peak}}$ . The initial velocity was set at 100 m/min with increases in velocity of 10 m/min every 3 min. Open-circuit spirometry was used for determination of  $\dot{V}O_2$  and carbon dioxide production ( $\dot{V}CO_2$ , SensorMedics model 2900Z metabolic measurement cart, Yorba Linda, CA). Blood samples were taken from a forearm vein at rest and during the last 15 s of each stage for the measurement of blood lactate concentration (Yellow Springs Instruments 2700 Select Biochemistry Analyzer, Yellow Springs, OH).

**Determination of LT.** The blood lactate-velocity relationship that was obtained from the LT- $\dot{V}O_{2\text{ peak}}$  protocol was used to estimate the LT, defined as the highest velocity obtained before the curvilinear increase in blood lactate concentration ( $\geq 0.2$  mM) with increasing velocities.  $\dot{V}O_2$  associated with velocity LT was then determined (35). The  $\dot{V}O_2$  and blood lactate data have been reported previously (29).

**Exercise/control days.** Subjects were admitted to the GCRC on the evening before the exercise/control studies and received a standardized snack (500 kcal, 55% CHO, 15% protein, and 30% fat) at 2000. Subjects then fasted until the end of the study (13, 15). At 2100, intravenous cannulas were placed in a forearm vein in each arm, and lights were turned off by 2300 (13, 15). At 0600 the next morning, basal metabolic parameters were measured for 30 min with a Delta-Trac bedside metabolic unit (SensorMedics, Anaheim, CA). Beginning at 0700, blood samples were withdrawn every 10 min until 1300 for later GH measurements. Beginning at 0800, blood samples were withdrawn every 20 min on ice until 1300 for later catecholamine analysis. Samples were assayed for FFA and  $\beta$ -hydroxybutyrate ( $\beta$ -OHB) at baseline (0830, 0900), during exercise (0910, 0920, 0930), and postexercise (1000, 1100, 1200, 1300). Subjects exercised from 0900 to 0930 or remained at rest (control). During exercise, blood lactate was measured every 10 min and  $\dot{V}O_2$  and  $\dot{V}CO_2$  were determined minute by minute (SensorMedics 2900Z Metabolic Measurement Cart). Measurements continued 30 min postexercise in seated subjects, after which bed rest was resumed and  $\dot{V}O_2$  and  $\dot{V}CO_2$  were measured during the last 30 min of each hour (Delta-Trac bedside metabolic unit, SensorMedics, Anaheim, CA) until 1300. On the nonexercise day, at 0900 subjects remained in their rooms and  $\dot{V}O_2$  and  $\dot{V}CO_2$  were measured from 0900 to 1000 at bed rest (as above).

**GH analysis.** GH concentrations (0600–1200) were measured by use of an ultrasensitive (0.005  $\mu\text{g/l}$  threshold) chemiluminescence-based assay (Nichols, San Juan Capistrano, CA) (10,17). Integrated serum GH concentrations (IGHC) were calculated as previously described (34).

**Catecholamine analysis.** Catecholamine analysis was performed by using a modification of the procedure published by Bioanalytic Systems (BAS; LCEC application note no. 14). We have recently reported a detailed description of this procedure (29).

**NEFFA and  $\beta$ -OHB analyses.** Nonesterified FFA (NEFFA) were assayed by use of a commercially available kit (Wako Kit, Richmond, VA), and  $\beta$ -OHB was assayed using the procedure described by Cahill et al. (8).

**Statistical analysis.** ANOVA with repeated measures was used to determine mean differences for  $\dot{V}O_2$  and blood lactate concentration, followed by comparisons of means (corrected for correlated data by use of Huynh-Feldt epsilons).  $\dot{V}O_2$  and respiratory exchange ratio were used to estimate kilocalories of fat and CHO utilized during exercise and recovery (25).

To examine the relationships among NE, Epi, GH, NEFFA,  $\beta$ -OHB, and fat and CHO expended during exercise and recovery, separate regression models were estimated for each of the 10 study subjects. These variables were regressed on intensity during exercise and recovery. Separate models were estimated within subjects because of the intraindividual correlation that existed between the responses across levels of exercise intensity. Such methods, although likely to be conservative, were thought to be appropriate because of the limited sample size that was available for estimating intraindividual correlation structures. Simple linear regression was also used, because, compared with more complex models that allow for curvature (e.g., quadratic), departures from linearity were not apparent. To determine whether a response changed significantly with exercise intensity, the 10 slopes associated with exercise intensity from the individual regression models were then subjected to a Wilcoxon signed-rank test against a null hypothesis of median zero slope (16).

To examine whether relations among individual responses were independent of intensity of exercise, multiple-regression models were employed and analyzed as described above.

All data are presented as means  $\pm$  SE, and  $P < 0.05$  was construed as statistically significant.

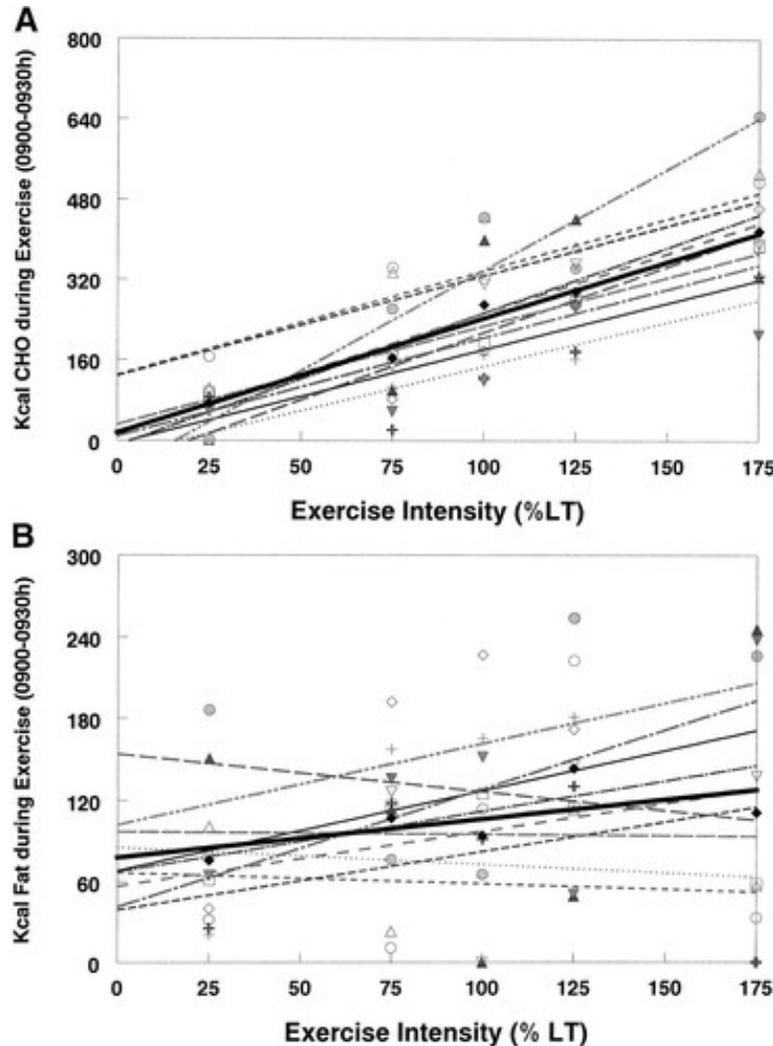
## RESULTS

**Subject characteristics.** Subjects'  $\dot{V}O_2$  at LT averaged  $2.72 \pm 0.18$  l/min ( $32.6 \pm 2.6$  ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>),  $\dot{V}O_{2\text{peak}}$  averaged  $3.93 \pm 0.19$  l/min ( $47.9 \pm 2.2$  ml  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>),  $\dot{V}O_{2\text{LT}}/\dot{V}O_{2\text{peak}}$  was  $0.68 \pm 0.04$ , and percentage body fat was  $19.3 \pm 1.9\%$ . As expected,  $\dot{V}O_2$  at LT and  $\dot{V}O_{2\text{peak}}$  were strongly correlated ( $r = 0.79$ ).

**$\dot{V}O_2$  and blood lactate concentration during constant-load exercise.** One-way ANOVA with repeated measures and post hoc analyses revealed that  $\dot{V}O_2$  and blood lactate concentrations increased ( $P < 0.05$ ) across all exercise intensities. The mean  $\dot{V}O_2$  values at different exercise intensities were  $1.01 \pm 0.08$  l/min at 0.25LT,  $1.85 \pm 0.14$  l/min at 0.75LT,  $2.45 \pm 0.18$  l/min at LT,  $2.98 \pm 0.21$  l/min at 1.25LT, and  $3.55 \pm 0.31$  l/min at 1.75LT. These  $\dot{V}O_2$  values corresponded to 26, 47, 62, 76, and 90% of  $\dot{V}O_{2\text{peak}}$ , respectively. Importantly, whether data were examined scaled relative to LT or relative to  $\dot{V}O_{2\text{peak}}$ , linear increments in  $\dot{V}O_2$  vs. exercise intensity were observed. Mean blood lactate values were  $0.65 \pm 0.05$  mM at 0.25LT,  $0.93 \pm 0.11$  mM at 0.75LT,  $1.52 \pm 0.16$  mM at LT,  $2.53 \pm 0.40$  mM at 1.25LT, and  $4.94 \pm 0.40$  mM at 1.75LT ( $P < 0.05$ ).

For the remaining analyses, we chose to express exercise intensity relative to the LT because of the following considerations: 1) the strong correlations observed in the present study and reported previously between LT and  $\dot{V}O_{2\text{peak}}$  (36) data that suggest that LT may be a marker for GH release (12,36) and 2) data that suggest that LT is an important marker of submaximal fitness and a strong predictor of endurance performance (36).

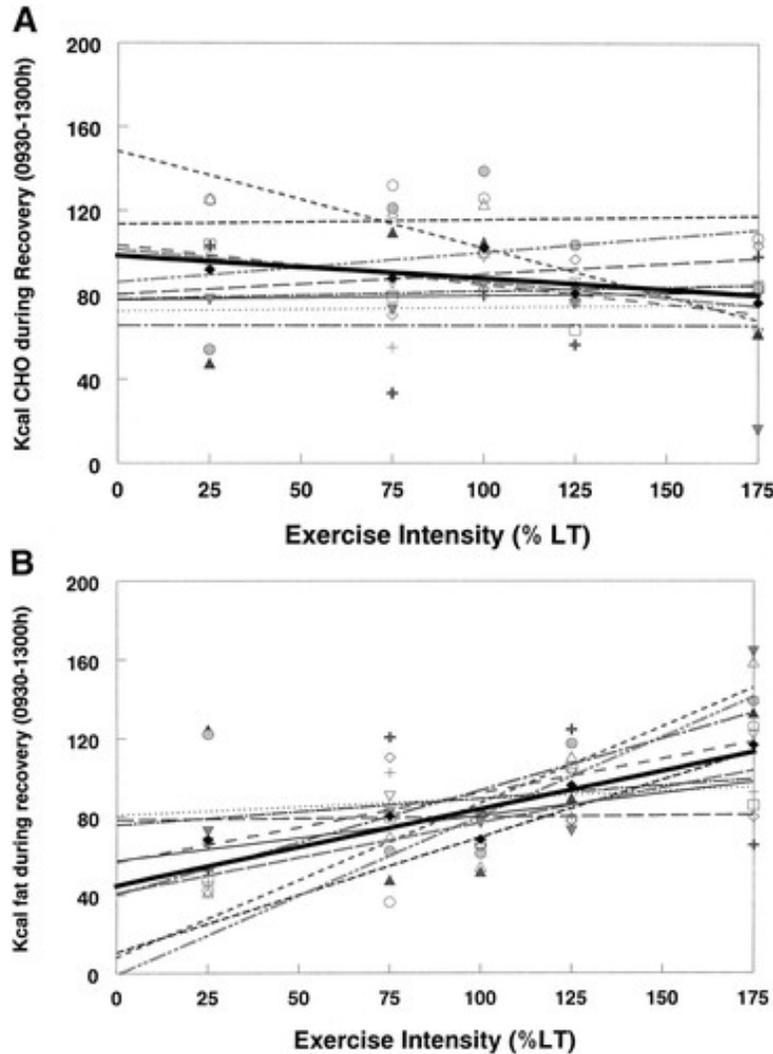
The absolute fat and CHO responses during exercise at the five different exercise intensities are shown in Fig. 1. CHO expenditure increased with increasing exercise intensity in all 10 subjects ( $P = 0.002$ , Fig. 1A). The relationship between fat expenditure during exercise and exercise intensity was not significant ( $P = 0.50$ ) or directionally consistent (5 subjects increased fat expenditure, 5 subjects decreased fat expenditure with increasing exercise intensity) (Fig. 1B). When CHO expenditure during exercise was modeled as the percentage of total energy expenditure during exercise, percentage CHO increased with increasing exercise intensity in 8 of 10 subjects ( $P = 0.009$ , data not shown).



**Fig. 1.** Absolute carbohydrate (CHO) (A) and fat (B) energy expenditure (kcal) responses [individual and group (solid line)] during 30 min of exercise at 5 different exercise intensities relative to the lactate threshold (LT).  $P = 0.002$  and  $P = 0.50$ , respectively.

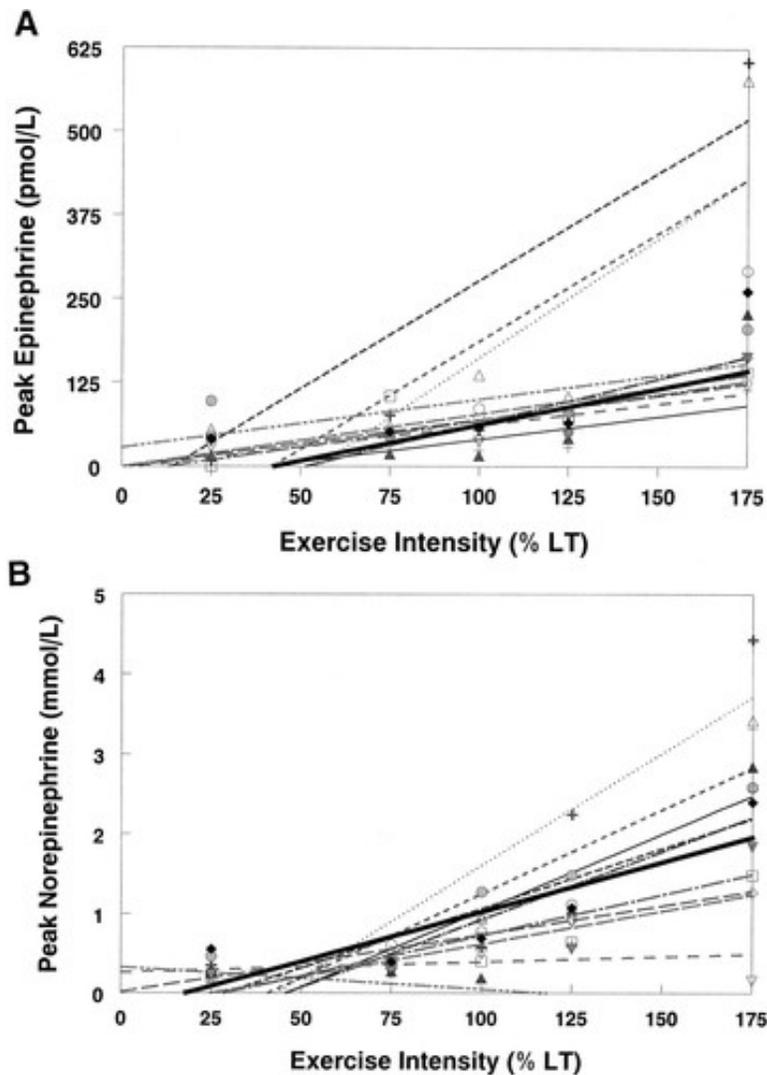
Figure 2 presents the same analysis for CHO expenditure and fat expenditure vs. exercise intensity during 3.5 h of recovery. The relationship between CHO expenditure during recovery and exercise intensity was not significant ( $P = 0.50$ , 5 subjects increased and 5 subjects decreased

CHO expenditure with increasing exercise intensity) (Fig. 2A). However, fat expenditure during recovery increased with exercise intensity in all 10 subjects ( $P = 0.002$ , Fig. 2B).



**Fig. 2.** Absolute CHO (A) and fat (B) energy expenditure responses [individual and group (solid line)] vs. exercise intensity during 3.5 h of recovery.  $P = 0.50$  and  $P = 0.002$ , respectively.

The individual relationships between exercise intensity and peak Epi or peak NE are shown in Fig. 3. Distinct peak Epi and peak NE values were evident during the exercise bout in all 10 subjects at 0920. Within-subject regression revealed that both peak Epi (Fig. 3A) and peak NE (Fig. 3B) increased significantly with each exercise intensity ( $P = 0.002$ ,  $P = 0.004$ , respectively). Figure 4 illustrates the relationships between exercise intensity and peak GH and between exercise intensity and 4-h IGHC. Peak GH always occurred within 10–50 min after the cessation of exercise. Within-subject regression revealed that both peak GH (Fig. 4A) and IGHC (Fig. 4B) increased significantly with each exercise intensity in all 10 subjects ( $P = 0.002$ ).

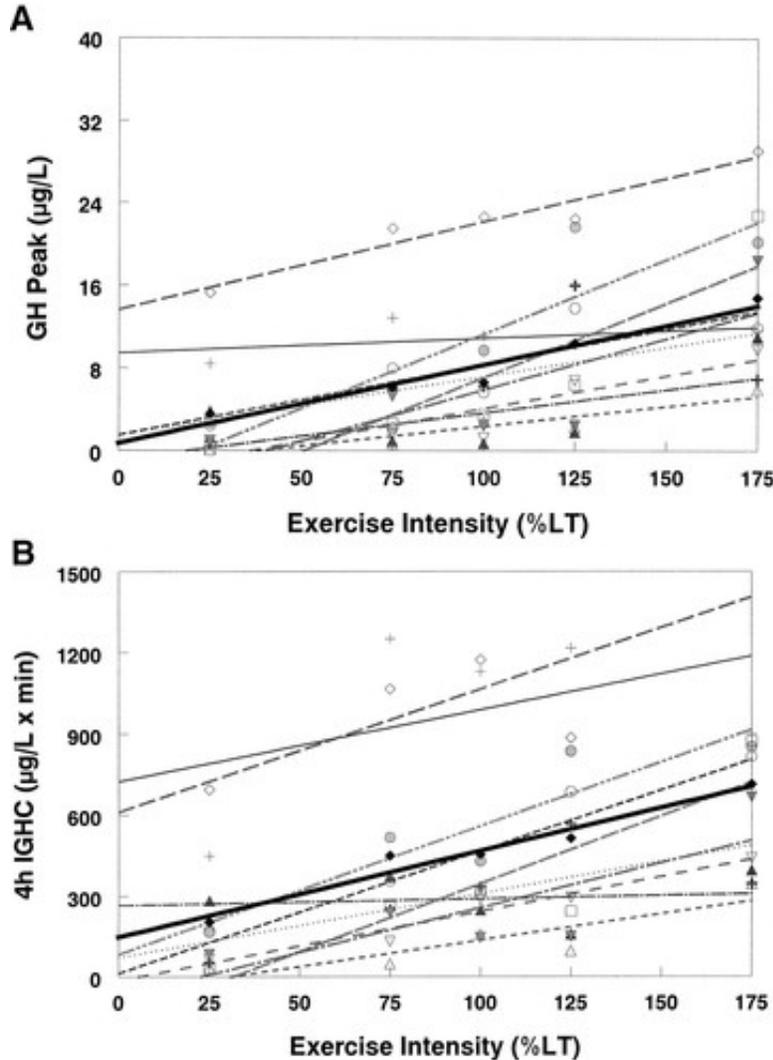


**Fig. 3.** Individual and group (solid line) relationships between exercise intensity relative to LT and peak epinephrine (A) or peak norepinephrine (B).  $P = 0.002$  and  $P = 0.004$ , respectively.

The relationship between mean NEFFA and exercise intensity was not significant ( $P = 0.50$ ) or directional (4 subjects positive, 6 subjects negative). For mean  $\beta$ -OHB, seven subjects showed a positive relationship with increasing exercise intensity, and three subjects exhibited a negative relationship ( $P = 0.13$ ).

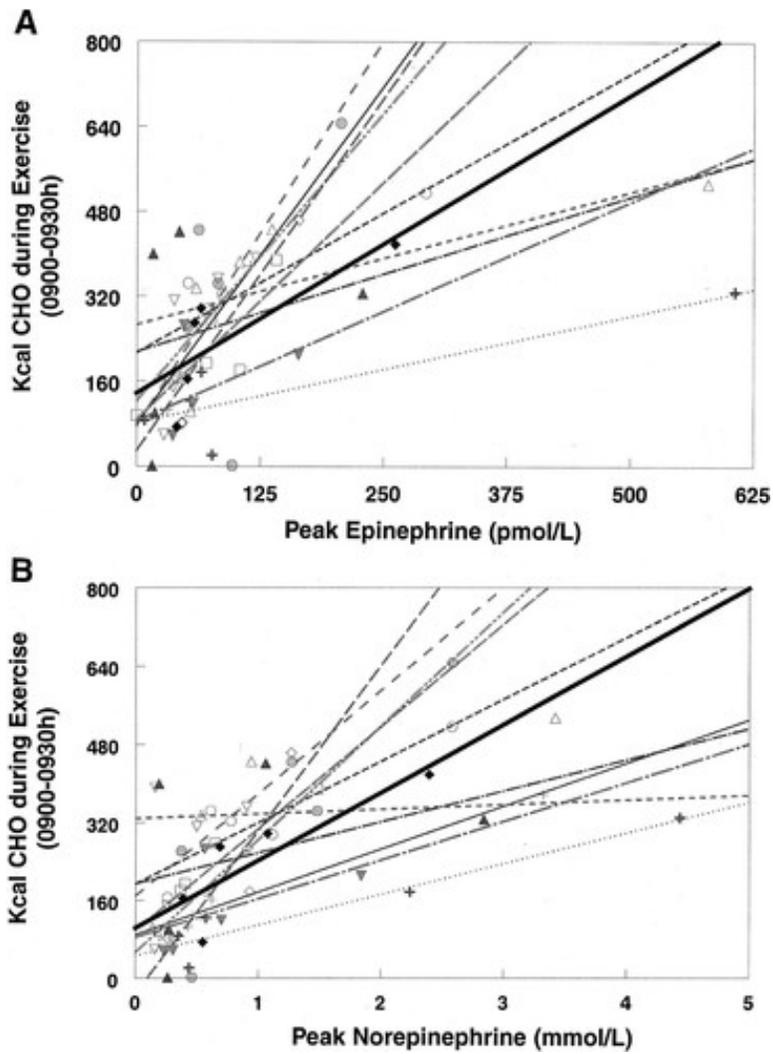
The individual relationships between CHO expenditure and Epi during exercise and between CHO expenditure and NE during exercise are shown in Fig. 5. We evaluated this relationship because both peak Epi and peak NE occurred during exercise and only CHO expenditure during exercise was related to exercise intensity. Within-subject regression revealed that CHO expenditure during exercise increased significantly with increasing Epi and NE during exercise ( $P = 0.002$  and  $P = 0.004$ , respectively). However, when CHO expenditure was examined against Epi, NE, and exercise intensity in a multiple-regression model, the relationships with Epi and NE were no longer statistically significant ( $P = 0.85$  and  $P = 0.50$ , respectively), suggesting that the effect of exercise intensity on increases in CHO expenditure during exercise cannot be explained

by Epi and NE. Therefore, other factors related to exercise intensity contribute to the increase observed in CHO expenditure.

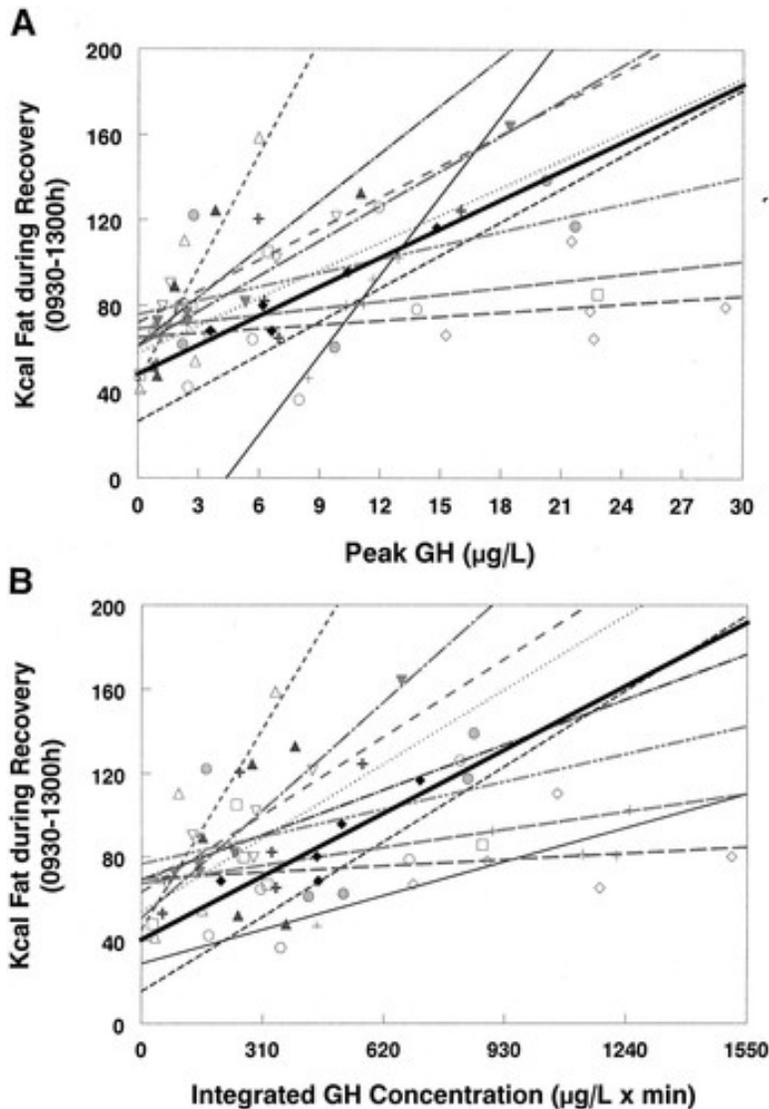


**Fig. 4.** Individual and group (solid line) relationships between exercise intensity relative to LT and peak growth hormone (GH; *A*) or 4-h integrated GH concentration (IGHC; *B*).  $P = 0.002$ .

The individual relationships between peak GH and IGHC and fat expenditure during recovery are presented in Fig. 6. We assessed this relationship because peak GH occurred during recovery from exercise, and fat expenditure during recovery was related to exercise intensity. Within-subject regression revealed that, in all 10 subjects, the increase in fat expenditure during recovery was significantly related to the increase in both peak GH and IGHC during recovery ( $P = 0.002$ ). When fat expenditure during recovery was examined against GH peak and exercise intensity and against IGHC and exercise intensity (in a multiple-regression model), the relationships for GH peak and IGHC remained statistically significant ( $P = 0.028$  and  $P = 0.032$ , respectively).

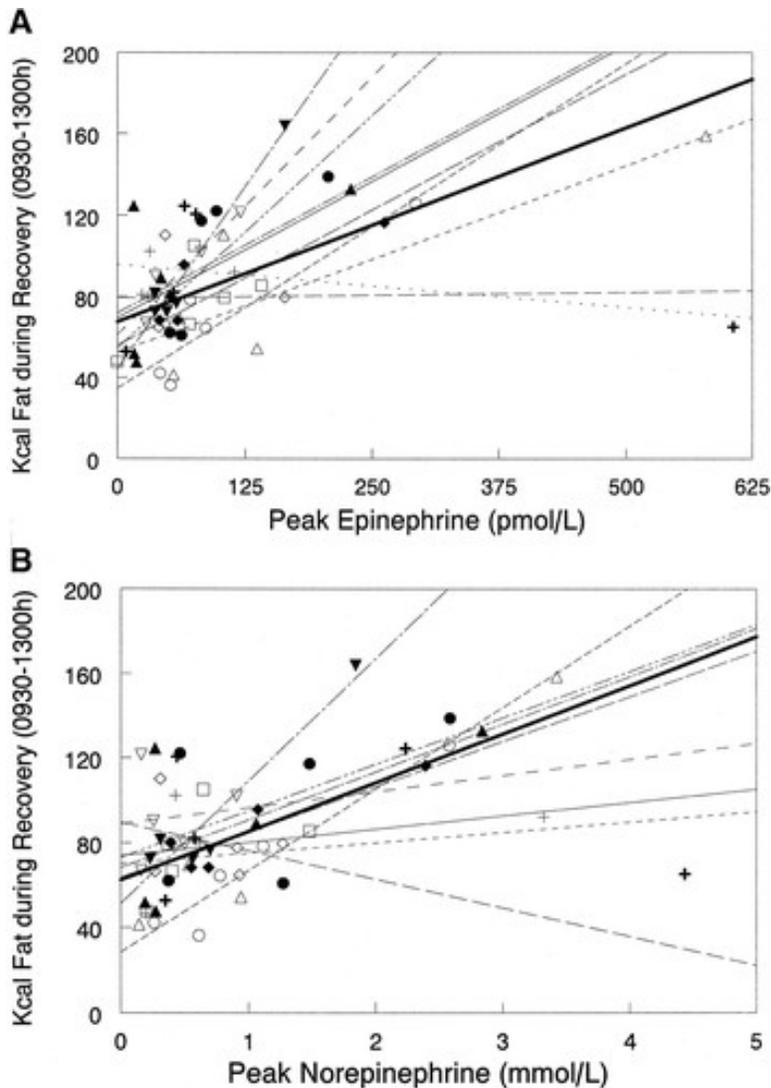


**Fig. 5.** Individual and group (solid line) relationships between epinephrine and CHO expenditure during exercise (*A*) and norepinephrine and CHO expenditure during exercise (*B*).  $P = 0.002$  and  $P = 0.004$ , respectively.



**Fig. 6.** Individual and group (solid line) relationships between peak GH and fat expenditure during 3.5 h recovery (*A*) and IGHC and fat expenditure during 3.5 h recovery (*B*) ( $P = 0.002$ ).

Figure 7 shows the individual relationships between Epi and fat expenditure during recovery and between NE and fat expenditure during recovery. Within-subject regression revealed that fat expenditure during recovery increased with increases in both peak Epi and peak NE ( $P < 0.01$  and  $P = 0.02$ , respectively). When fat expenditure during recovery was regressed against Epi and exercise intensity and against NE and exercise intensity, the relationship for Epi remained statistically significant ( $P < 0.05$ ), whereas the relationship for NE was no longer statistically significant.



**Fig. 7.** Individual and group (solid line) relationships between peak epinephrine and fat expenditure during 3.5 h recovery (A) and peak norepinephrine and fat expenditure during 3.5 h recovery (B).  $P < 0.01$  and  $P = 0.02$ , respectively.

Because both GH peak and peak Epi were related to fat expenditure during recovery, independent of exercise intensity, we regressed fat expenditure during recovery against Epi and GH. Results of this analysis revealed that the relationship for GH peak and fat expenditure during recovery remained statistically significant ( $P < 0.05$ ), whereas the relationship for Epi was no longer statistically significant, suggesting that GH is a primary correlate of fat expenditure during recovery.

## DISCUSSION

The exercise intensity (dose)-dependent nature of this randomly ordered metabolic study in young men allows us to explore the notion of a so-called metabolic crossover point in energy utilization during escalating exercise intensities (4, 5), standardized against the subject-specific LT. Unexpectedly, we report that absolute energy utilization from CHO increased progressively

according to a linear model, with increasing exercise intensity, whereas fat utilization was not affected under the same conditions (Fig. 1). An increase was also evident when CHO utilization during exercise was examined relative to total energy utilized during exercise. In addition, the present data reveal the novel insight that, during recovery from exercise, fat utilization correlated strongly with increasing exercise intensity (Fig. 2). Thus the present data do not fully support the crossover concept theory (4,5), which predicts a positive and negative curvilinear relationship between increased exercise intensity and utilization of CHO and fat, respectively. The rise in CHO energy expenditure with heightened exercise intensity corresponded only partially to elevated SNS activity (as reflected by blood concentrations of Epi and NE), whereas the fat expenditure during recovery from exercise related directly to Epi and GH release.

A corollary notion is that the blood lactate response to exercise may be related to increased CHO metabolism (4, 5) because elevated lactate can inhibit free fatty acid mobilization (18). Our data suggest that, although the blood lactate rise itself exhibits a threshold followed by a curvilinear increase with increasing exercise intensity (29), a simple linear relationship is evident between CHO energy utilized and exercise intensity (Fig. 1). Accordingly, the time course of the blood lactate response to exercise does not appear to correspond to (and thus may not mediate) substrate utilization.

A plausible interpretation is that increased SNS activity associated with incremental exercise may result in increased CHO utilization. At first glance, our data seem to support this view, because there was a progressive increase in Epi and NE with increasing exercise intensity (Fig. 3) and a similar relationship between Epi and NE and CHO expenditure during exercise (Fig. 5). Indeed, an individual's hormonal and metabolic responses to exercise are generally intensity dependent (11). Moreover, both NE and Epi appear to augment muscle lactate output during muscle contractions (11) and may, thus, in part govern the magnitude of the lactate response (24, 37). With increasing exercise intensity, SNS activity rises, resulting in an increase in glycolytic activity and a direct increase in absolute CHO expenditure. Concurrently, blood lactate accumulation inhibits lipolysis, facilitating a further increase in CHO expenditure. However, in the present study, when exercise intensity and catecholamines were examined together in a multiple-regression model, Epi and NE were no longer significant predictors of CHO expenditure during exercise independent of exercise intensity. According to this assessment, factors in addition to SNS activity participate in driving the increase in CHO expenditure observed with increasing exercise intensity.

Although the percentage of fat energy utilized decreased with increasing exercise intensity, total (absolute) fat utilization during exercise was not affected by exercise intensity. The mean slope of the 10 subjects tends to support only a slight increase in fat expenditure with increasing exercise intensity (Fig. 1).

Although the relative contribution of CHO to energy metabolism rises with increasing exercise intensity (3, 33), after recovery from high-intensity exercise, there is a greater substrate shift toward fat oxidation (1, 39). Thus strenuous exercise may evoke a persistent increase in the rate of FFA release from adipose tissue (14, 26). Elevated plasma FFA concentrations could restrict the rate of glycolysis in skeletal muscle via the glucose-fatty acid cycle, which would favor the repletion of muscle glycogen stores from available glucose (1, 19, 26). Triglyceride-fatty acid

substrate cycling may be important in mediating some of the effect of exercise on overall energy balance (39).

The present data relate the increase in fat oxidation observed during recovery from exercise to Epi and GH release (Figs. 4, 6, 7), with GH being a primary correlate of fat expenditure during recovery. In addition to exerting its own lipolytic effect, GH has been reported to potentiate the lipolytic response of adipose tissue to Epi (2). Acute bouts of exercise increase the plasma concentration of GH (22, 23,32), possibly, in part, via increased central nervous system sympathetic outflow (7, 9,22, 23, 31, 36). Recent observations from our laboratory (29; Fig. 4) indicate that the GH secretory response to exercise rises with increasing exercise intensities. The present study extends these findings and demonstrates a correspondingly positive relationship between fat expenditure during recovery and peak GH and IGHC (Fig. 6). This association may arise from the aforementioned direct lipolytic action of GH as well as from the effect of GH on the lipolytic action of Epi, possibly providing substrate for fat oxidation during recovery. Further support for this interpretation is the independent predictive value of GH levels in defining fat utilization during recovery when exercise intensity or peak Epi were covariates in the multiple-regression models.

The use of indirect calorimetry to estimate CHO expenditure and fat utilization during heavy exercise can be challenged (20). Because bicarbonate was not measured in the present study, it is possible that CHO utilization would be overestimated in the 1.75LT condition if non-steady-state blood lactate concentrations were present (30). However, 7 of the 10 subjects had steady-state blood lactate concentrations even during the 1.75LT condition. In the remaining three subjects, the mean blood lactate concentration increased by 3.46 mM between 5 and 30 min in the 1.75LT condition. This small increase in blood lactate concentration in only three subjects should not affect the overall estimation of energy expenditure or the linearity of the regression below 1.75LT.

In addition, it should be realized that several months were required to collect data in the present study (due to blood withdrawal guidelines). Thus, if fitness level or activity patterns changed over the course of the study, results could have been affected. To partially control for this possibility, only subjects who had a history of regular physical activity participated. In addition, the order of GCRC admissions was randomly assigned.

In summary, the present study indicates that CHO oxidation during exercise and fat oxidation during recovery increase significantly as a function of exercise intensity. Although a rise in SNS activity (as reflected by increased levels of Epi and NE) was evident with escalating exercise intensity, heightened SNS activity alone did not statistically explain the increase in CHO expenditure during exercise. In contrast, the increase in fat expenditure during recovery was directly related to GH release. In aggregate, these data point to a role of the SNS and other as yet unidentified factors in the regulation of CHO utilization during exercise and to a role for GH (perhaps both a direct lipolytic effect and an indirect effect through Epi) in the control of fat utilization postexercise. Further interventional experiments will be required to corroborate or refute these specific hypotheses.

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