Submaximal Exercise During Intravenous Hyperalimentation of Depleted Subjects

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The peripheral nitrogen wasting and loss of functional capacity caused by the malnutrition of disease and the immobilization of hospitalization may not be readily reversed by refeeding alone. In order to examine submaximal exercise as an adjunctive anabolic stimulus to intravenous refeeding (IVF) in depleted subjects, 14 volunteers were studied in the postabsorptive (PA) state, after 10 days of total starvation, and again after 10 days of nutritional repletion with I.V. feedings. The subjects were randomized to one group that received IVF alone and one group that performed 1 hour of submaximal (51% of $\dot{V}O_2$max) stationary bicycle exercise daily during IVF. The exercised group was not significantly different from the nonexercised group in urinary nitrogen balance, resting energy expenditure, extremity amino acid flux, or maximal oxygen consumption. Acute exercise did not induce significant derangements in electrolytes or counter-regulatory hormone concentrations. Ten days of submaximal exercise does not appear to be detrimental in this population recovering from moderate hospitalized malnutrition, but additional anabolic stimulae may be needed for improvements in protein accrual or functional capacity.

HOSPITALIZED SURGICAL patients often suffer from progressive muscle wasting and loss of functional capacity secondary to both malnutrition and immobilization. Reversal of the poor nutritional intake alone by limited periods of adequate protein and caloric supplementation does not completely reverse these detrimental changes.[1] Since recovery from disease and early rehabilitation is thought to be associated with restoration of skeletal muscle protein stores, identification of effective stimulae for preservation and restoration of muscle mass and function would provide important adjuvants to nutritional therapy in hospitalized patients.

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In isolated tissue studies and *in vivo* animal models, the stimulus that most consistently improves muscle protein balance is contractile activity.[2,3] Such activity reverses the ultrastructural changes seen with immobilization (loss of myofilaments and shrinkage of muscle fibers),[4] and may enhance protein synthesis even during unfavorable hormonal and nutritional conditions,[5] or in the presence of malignancy.[6]

Acute bouts of exercise can induce measurable changes in protein, carbohydrate, and lipid metabolism. These changes are characterized by an increase in body protein breakdown, a decrease in protein synthesis, and an increased utilization of protein for gluconeogenesis and lipids for oxidative fuel.[7-10] Chronic daily exercise, however, leads to adaptive processes that result in a net increase in total body as well as peripheral nitrogen stores.[11] Although the amount and frequency of exercise needed to bring about this adaptive process, or *training effect,* in normal humans is well studied, studies of the effects of chronic exercise in hospitalized humans are few.[12] Studies of exercise in the clinical setting of hospitalized, malnourished subjects during nutritional support are lacking.

The duration, intensity, and frequency of exercise that are needed for detectable improvements in either functional or metabolic parameters in this setting are unknown. Of perhaps equal importance is whether the acute or chronic effects of exercise in this setting would be detrimental to the subjects. These questions are important in planning physical rehabilitation of depleted patients.

In order to assess the impact of daily submaximal exercise on protein metabolism in this setting, we studied the effects of exercise on previously starved, healthy volunteers during IVF.

Methods

Subjects

Male volunteers were screened as outpatients by complete physical exam, blood count, and serum biochemistries. Fourteen subjects aged 21–31 years and within 10% of ideal body weight for age, sex, and height (Metropolitan Life Table, 1983) were admitted to the Adult Clinical Research Center (CRC) of the New York Hospital-Cornell Medical Center (NYH-CMC). The study was approved by the Institutional Review Board of the NYH-CMC, and informed written consent was obtained from each subject prior to enrollment in the study.

Study Protocol

The volunteers were admitted to the CRC for 24 consecutive days. Subjects were weighed daily at 6:00 AM after voiding. Daily 24-hour urine samples were collected. During the first 3 hospital days, each subject was fed orally with a defined formula diet (Sustacal, Mead-Johnson, Evansville, IN) in six equal portions daily. This diet was provided at 1.2 times the resting energy expenditure (REE) (33 ± 2 kcal/kg/d, 0.32 ± 0.01 gN/kg/d). Feedings were discontinued at 8:00 PM on hospital day 3 and at 7:00 AM on day 4, in the postabsorptive (PA) state; measurements of REE and extremity substrate flux were performed as outlined below.

From hospital days 4 to 14, a 10-day protein-calorie starvation period was achieved during which oral intake was limited to distilled water, no-calorie soft drink (provided *ad libitum*), and a tablet of sodium chloride (20 mEq/d). At 7:00 AM on hospital day 14 measurements of REE and substrate flux were repeated in the starvation (STV) state. A percutaneous catheter was then inserted into the antecubital vein and advanced into the superior vena cava (placement confirmed by chest roentgenography). All subjects received I.V. feeding from hospital days 14–24 with a commercially available amino acid source (aminosyn, 5%) and 100% of the nonprotein calories as D-glucose. The nutrients provided were 30 ± 2 nonprotein kcal/kg/d and 0.30 ± 0.02 gN/kg/d. Appropriate electrolytes, trace metals, and vitamins were added by previously described standards.[12]

From the time of admission until day 14 all subjects were allowed to ambulate within the ward but were restricted from any other physical activity. After beginning IVF the subjects were randomly selected to enter one of two physical activity groups. One group (−EX) (N = 7) continued to be restricted from any physical activity other than light ambulation within the hospital ward, while the other group (+EX) (N = 7) underwent 1 hour of daily upright bicycle exercise (Monarch Corp., Stockholm) at 51 ± 3% of $\dot{V}O_2$max. The exercise was performed between 5:00 PM and 6:00 PM each day during the I.V. feeding. On day 3 of the exercise regimen venous plasma electrolyte, glucose, catecholamine, glucagon, and cortisol levels were determined at 20-minute intervals during the 1-hour exercise period and at half-hour intervals for 1 hour after the exercise period.

On day 24 at 7:00 AM REE and substrate flux measurements were again made, this time under IVF conditions. On days 3, 13, and 23, maximal oxygen uptake ($\dot{V}O_2$max) determinations as described below were also made at least 12 hours before each metabolic study session.

Urinary Nitrogen Balance

Daily 24-hour urine collections were made. The samples were refrigerated and treated with sodium fluoride during collection and then frozen at −70 C immediately until analysis. After digesting the samples using a micro-Kjeldahl method, the total nitrogen was analyzed using the Technicon AutoAnalyzer-2 (Technicon, Tarrytown, NY). Urinary nitrogen balance was calculated as previously described.[13]

REE

Measurements of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were performed in the supine position with a Beckman Metabolic Measurement Cart-1 (Sensormedics Corp., Anaheim, CA). This system contained an OM-11 oxygen analyzer and LB-2 carbon dioxide analyzer. The instrument was calibrated before and after each test using a minimum of two standard calibration gases (100% nitrogen, and 16%:4% oxygen:carbon dioxide).[14] REE was estimated using the de V. Weir formula [REE(cal/min) = $3.941 \times \dot{V}O_2 + 1.106 \times \dot{V}CO_2$].[15]

Extremity Substrate Flux

Percutaneous radial artery and retrograde venous catheters (basilic or femoral) were placed on days 4, 14, and 24. Arterial and venous samples for substrate analysis were drawn simultaneously from the catheters. Blood flow to the extremity was determined before and after the blood sampling using electrocapacitance plethysmography.[16] Four of the nonexercised subjects had leg flux determinations while three had nondominant arm flux determinations. All exercised subjects had determinations of leg substrate flux only. Plasma amino acid flux was calculated as (arterial concentration − venous concentration) × blood flow × (1 − hematocrit). A posi-

TABLE 1. *Anthropometric Data and Liver Function Tests*

	PA	STV	IVF
Age (yr)			
−EX	28 ± 2	—	—
+EX	26 ± 1	—	—
Weight (kg)			
−EX	80 ± 3	73 ± 3 (−8% *vs.* PA)	78 ± 2 (−3% *vs.* PA)
+EX	73 ± 3	68 ± 2 (−7% *vs.* PA)	72 ± 2 (−2% *vs.* PA)
Albumin (g/dL)			
−EX	4.2 ± 0.1	4.1 ± 0.1	4.0 ± 0.1
+EX	4.2 ± 0.1	4.1 ± 0.1	4.0 ± 0.1
Alkaline phosphatase (U/L)			
−EX	66 ± 2	64 ± 4	60 ± 5
+EX	59 ± 6	58 ± 8	56 ± 3
Bilirubin (mg/dL)			
−EX	0.8 ± 0.1	1.1 ± 0.2	0.5 ± 0.2
+EX	0.6 ± 0.1	0.9 ± 0.3	0.6 ± 0.2
SGOT (U/L)			
−EX	29 ± 6	17 ± 3	41 ± 13
+EX	24 ± 4	17 ± 1*	28 ± 2†
Glucose (mg/dL)			
−EX	92 ± 3	60 ± 1*	107 ± 5*†
+EX	100 ± 8	69 ± 6*	107 ± 2*†

Values are given as mean ± SEM
* $p < 0.05$ *versus* PA.
† $p < 0.05$ *versus* STV.

tive value represents a relative uptake across the extremity whereas a negative value indicates a net efflux of amino acids out from the extremity.

Substrate Concentrations

Plasma amino acids, including glutamine,[17] were determined by column chromatography on a Beckman 119CL amino acid analyzer (Beckman Instruments, Fullerton, CA) using a three-buffer lithium system with ethyl-cysteine as an internal standard.[18] Cortisol was measured by radioimmunoassay.[19] Plasma for glucagon was collected with EDTA and aprotinin prior to analysis by radioimmunoassay.[20] Epinephrine, norepinephrine, and dopamine levels were determined by radioenzymatic assays.[21]

Blood count, electrolytes, glucose, and liver function tests were analysed using standard automated techniques available in the NYH-CMC Clinical Biochemistry Laboratories.

$\dot{V}O_2$max

$\dot{V}O_2$max was determined by stepwise bicycle ergometry (25–125 watts) using the linear relationship between $\dot{V}O_2$ and heart rate.[22] Subjects underwent continuous heart rate monitoring by ECG and $\dot{V}O_2$ determinations every 30 seconds for the study. Heart rate and $\dot{V}O_2$ were determined under basal conditions and during 4-minute intervals of incremental submaximal exercise. Mean heart rates (y axis) were plotted against $\dot{V}O_2$ (x axis) and linear regression analysis performed for each study. Using 220 − age as an estimated maximal heart rate,[23] $\dot{V}O_2$max was calculated as:

$$[(220 - \text{age}) - y \text{ intercept}]/\text{m},$$

where m is the slope of the linear regression line of the heart rate against $\dot{V}O_2$ under basal and submaximal exercise conditions.

Statistical Analysis

All data are expressed as mean ± SEM. Standard paired and unpaired Student's t-tests were used for single comparisons. ANOVA and Newman-Keuls tests, where appropriate, were used to identify statistical significance for multiple comparisons.

Results

Patient Groups

The average age of the volunteers in the exercised group was comparable to that in the nonexercised group (Table 1). The volunteers randomized to the nonexercised regimen had a higher average initial weight than those randomized to the exercise program (80 ± 3 kg *vs.* 73 ± 3 kg). However, both groups lost a similar per cent of body weight with 10 days of starvation (−8% *vs.* PA and −7% *vs.* PA). Both groups also exhibited similar weight recovery during IVF, reaching within 3% of initial weight in nonexercised subjects and 2% of initial weight in exercised subjects (Table 1). Thus, both groups demonstrated similar levels of depletion and subsequent repletion with the experimental regimen.

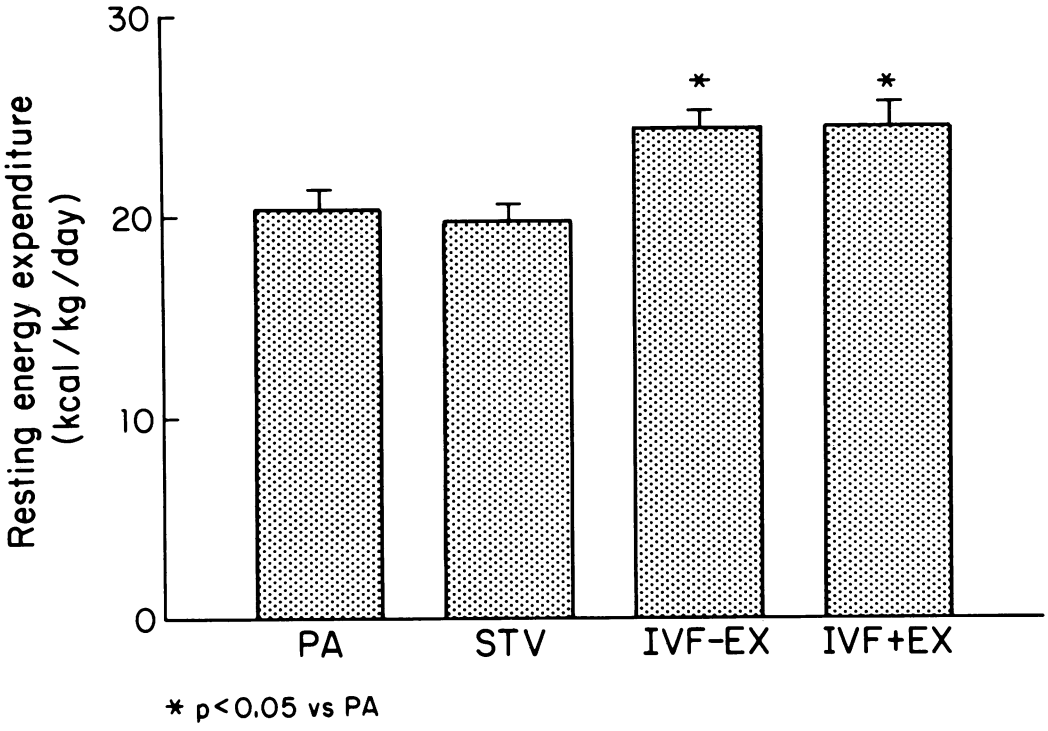

FIG. 1. REE was determined in the PA (N = 14), STV (N = 14), I.V. feeding without daily exercise (IVF − EX) (N = 7), and I.V. feeding with daily exercise (IVF + EX) (N = 7) conditions.

Serum Chemistries

Serum albumin levels were not significantly changed throughout the course of the experiment and were comparable in the exercised and nonexercised groups (Table 1). In agreement with previous reports, glucose levels decreased after 10 days of starvation and then rose during refeeding with the glucose-based parenteral feeding.[24] The values for both groups remained within the normal range for liver function tests throughout the study and were not statistically different between the groups.

REE

The REE was similar in the PA and the STV states (20.4 ± 0.9 and 19.8 ± 0.8 kcal/kg/d) (Fig. 1). REE rose significantly with IVF to 24.4 ± 0.9 in the nonexercised group and 24.5 ± 1.0 in the exercised group (both $p < 0.05$ *vs.* PA).

Urinary Nitrogen Balance

Negative nitrogen balance in the PA state (−0.12 ± 0.01 gN/kg/d) decreased significantly after starvation (−0.095 ± 0.009 gN/kg/d), indicating a degree of nitrogen sparing with starvation (Fig. 2). This is similar to levels previously reported in starved man.[13,25] With IVF both the exercised and nonexercised groups reached positive nitrogen balance by the second day of I.V. feeding. There were no significant differences of nitrogen balance between the two groups throughout the course of the study [0.12 ± 0.01 in the nonexercised (−EX) group and 0.11 ± 0.01 gN/kg/d in the exercised (+EX) group].

Extremity Amino Acid Flux

The total amino acid flux (TAA) across the extremity in the PA state was −950 ± 150 nmol/min/100 mL tissue (Table 2), similar to previous reports.[1] With starvation, efflux decreased to −700 ± 160 nmol/min/100 mL tissue, suggesting nitrogen sparing within the extremity. With refeeding, TAA flux in the group randomized to the exercise regimen and the group randomized to the nonexercise regimen, both rose significantly, to −39 ± 48 and +30 ± 160, respectively, but not statistically different between the two groups.

Only the flux of the amino acids serine and methionine showed significant differences between the exercised and nonexercised groups during IVF. All other amino acids, either alone or grouped as essential amino acids (EAA), branched chain amino acids (BCAA), or glutamine and alanine (G + A) were without significant differences in flux between the two groups during IVF (Fig. 3).

$\dot{V}O_2$

The group randomized to nonexercise had an initially higher $\dot{V}O_2$max (35 ± 1 mL/kg/min) than the group chosen to exercise (30 ± 3 mL/kg/min) (Fig. 4). Both groups demonstrated a similar percentage decline in $\dot{V}O_2$max with starvation (−10% *vs.* PA and −11% *vs.* PA). With IVF both groups showed a similar further

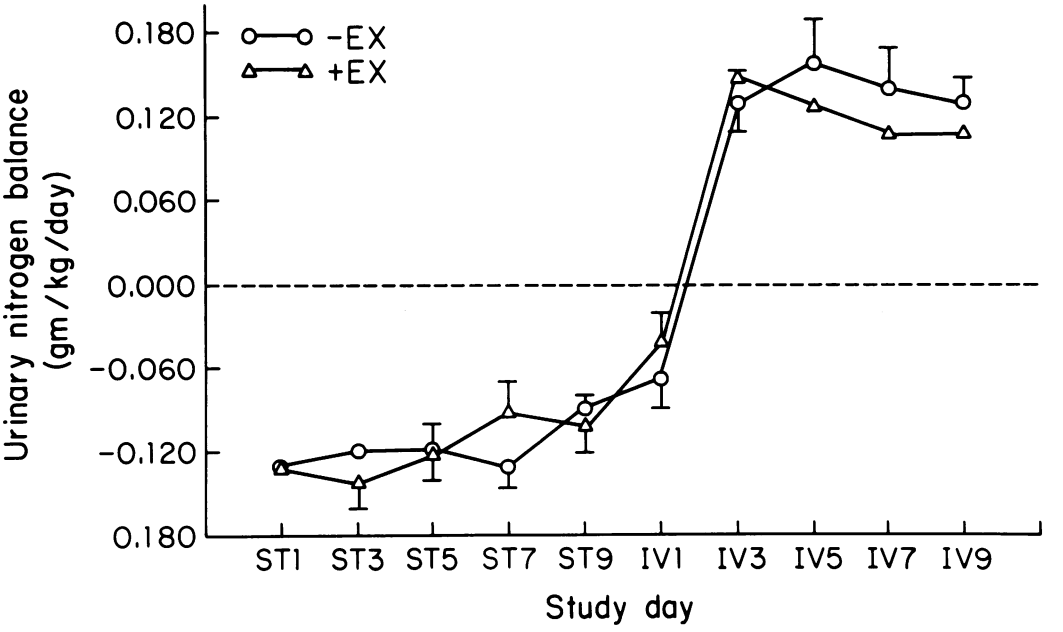

FIG. 2. Urinary nitrogen balance in exercised (+EX) and nonexercised (−EX) subjects. The data are plotted during ST and during IVF. Results are given as means ± SEM. There were no statistically significant differences between the two groups.

percentage decline in $\dot{V}O_2$max to −20% and −22% compared with the PA values.

Acute Electrolyte and Hormonal Changes with Exercise

There were no statistically significant changes in electrolyte or glucose levels during or immediately after an exercise session during IVF (Table 3). Venous epinephrine and dopamine levels rose significantly during the exercise session but remained in a low range and returned to pre-exercise levels within 1 hour of exercise. Serum concentrations of cortisol, glucagon, and norepinephrine also demonstrated slight increases during exercise, but these increased levels were not statistically different from baseline.

Discussion

It is estimated that 50% of all hospitalized patients exhibit overt clinical signs of malnutrition.[26] It is frequent in the surgical population, whether because of underlying disease or surgical procedures, that patients undergo periods of fasting and hospitalized immobilization. Significant total body and peripheral protein wast-

TABLE 2. *Extremity Amino Acid Flux*

	PA	STV	IVF − EX	IVF + EX
Taurine	4 ± 6	4 ± 2	−2 ± 3	4 ± 4
Aspartate	3.0 ± 0.4	0.9 ± 0.5*	3.3 ± 0.8†	2.6 ± 1.8
Threonine	−48 ± 8	−32 ± 12	15 ± 16*†	−14 ± 7*
Serine	11 ± 3	−20 ± 9*	44 ± 12*†	8 ± 6†‡
Asparagine	−54 ± 23	−31 ± 7	−23 ± 10	−14 ± 16
Glutamate	81 ± 31	57 ± 11	102 ± 36	114 ± 34
Glutamine	−321 ± 55	−200 ± 50	−187 ± 67	−101 ± 33*
Proline	−131 ± 20	−27 ± 21*	23 ± 62*	−16 ± 20*
Glycine	−65 ± 9	−73 ± 21	−55 ± 31	−51 ± 20
Alanine	−271 ± 39	−143 ± 25*	−137 ± 40*	−174 ± 57
Valine	−20 ± 8	−26 ± 19	79 ± 25*†	35 ± 17*
Cysteine	12 ± 5	3 ± 7	2 ± 2	5 ± 2
Methionine	−10 ± 3	−15 ± 3	6 ± 3*†	−1 ± 1*†‡
Isoleucine	−11 ± 2	−22 ± 7	53 ± 11*†	22 ± 10*†
Leucine	−17 ± 5	−46 ± 12*	59 ± 9*†	35 ± 11*†
Tyrosine	−17 ± 2	−16 ± 3	5 ± 2*†	1 ± 1*†
Phenylalanine	−15 ± 3	−17 ± 4	8 ± 3*†	1 ± 2*†
Ornithine	2 ± 1	−3 ± 4	21 ± 5*†	5 ± 8
Lysine	−53 ± 8	−72 ± 19	30 ± 14*†	15 ± 11*†
Histidine	−21 ± 4	−15 ± 5	−2 ± 3*	−1 ± 3*
Arginine	−24 ± 8	−26 ± 7	27 ± 11*†	17 ± 10*†

A positive value indicates uptake into the extremity while a negative value indicates efflux of amino acids from the extremity.

* $p < 0.05$ *versus* PA.

† $p < 0.05$ *versus* STV.

‡ $p < 0.05$ IVF − EX *versus* IVF + EX.

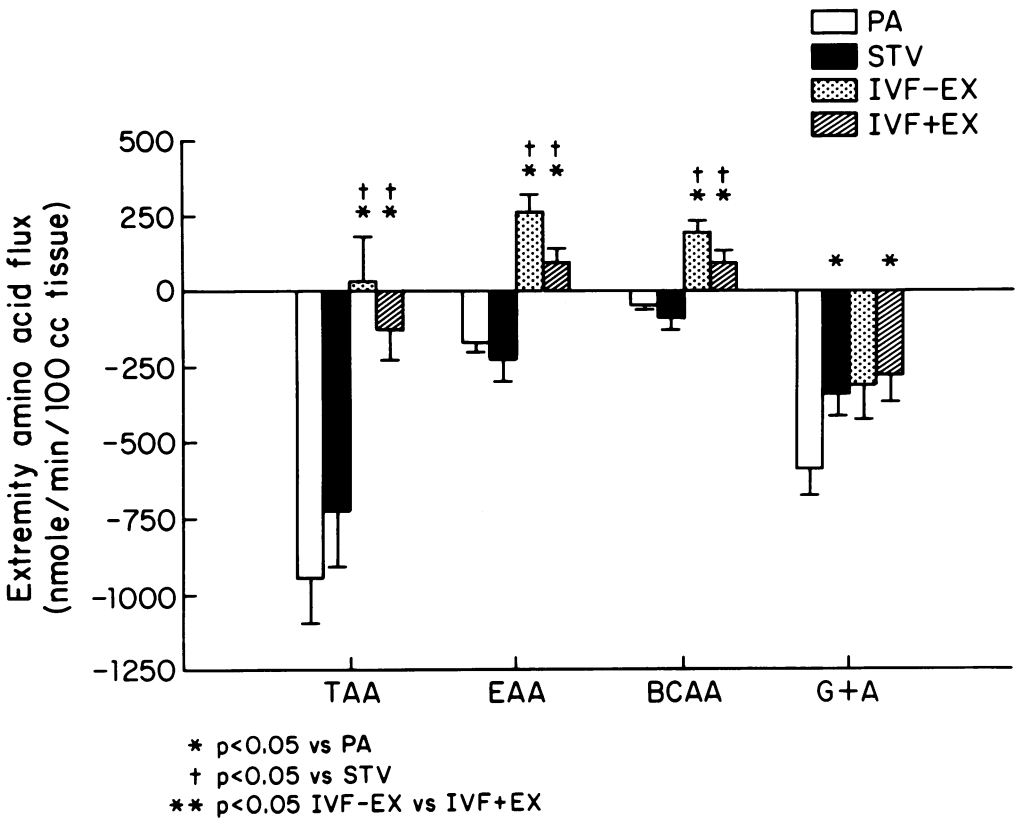

FIG. 3. Extremity amino acid flux of TAAs, EAAs, BCAAs, and the sum of glutamine and alanine (G + A). Measurements were performed in the PA, STV, I.V. feeding without daily exercise (IVF − EX), and I.V. feeding with exercise (IVF + EX) conditions. A positive value indicates extremity uptake of amino acids and a negative value indicates an efflux of amino acids from the extremity.

ing can be seen after as little as 4 days of in-hospital bed rest.[27]

Previous studies have examined the efficacy of chronic submaximal exercise used in conjunction with I.V. alimentation in reversing the negative effects of hospitalized immobilization.[12,28] In those studies, daily submaximal exercise in hospitalized but well nourished volunteers was observed to be associated with improve-

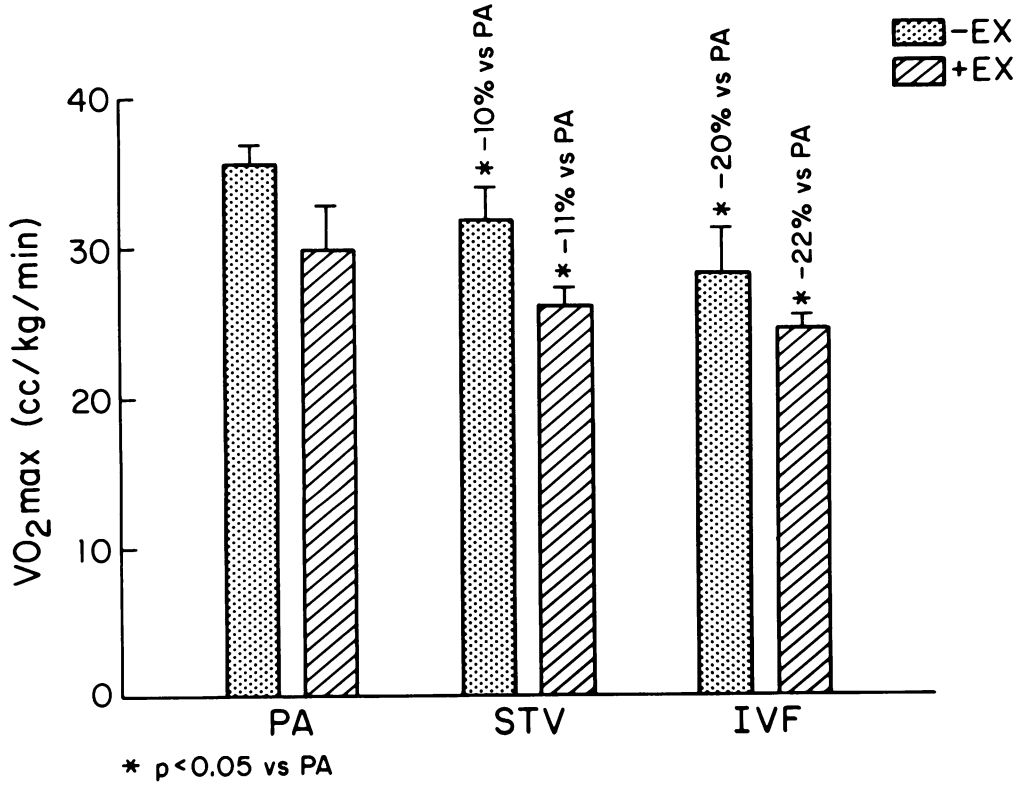

FIG. 4. Maximal oxygen uptake measured during PA, STV, and IVF conditions. The data are presented for nonexercised (−EX) and exercised (+EX) subjects. The per cent change *versus* the PA condition is indicated above the bars.

TABLE 3. *Hormone and Electrolyte Levels during and Immediately after Exercise*

	Baseline	20 Minutes	40 Minutes	60 Minutes	90 Minutes	120 Minutes
Glucagon (pg/mL)	104 ± 28	154 ± 38	165 ± 33	140 ± 33	109 ± 19	132 ± 16
Cortisol (ng/ml)	10 ± 3	10 ± 2	11 ± 2	13 ± 2	11 ± 2	10 ± 2
Epinephrine (pg/ml)	45 ± 3	127 ± 24*	100 ± 18*	132 ± 32*	69 ± 20	84 ± 25
Norepinephrine (pg/mL)	590 ± 250	1740 ± 660	1760 ± 860	1520 ± 490	490 ± 160	570 ± 230
Dopamine (pg/mL)	21 ± 3	47 ± 10*	54 ± 12*	99 ± 30*	25 ± 4	27 ± 7
NA	140 ± 1	142 ± 1	139 ± 1	139 ± 1	139 ± 1	139 ± 1
K	4.5 ± 0.1	4.7 ± 0.1	4.8 ± 0.2	4.7 ± 0.1	4.8 ± 0.1	4.6 ± 0.1
CL	106 ± 1	107 ± 1	107 ± 1	107 ± 1	107 ± 1	107 ± 1
CO_2	26 ± 1	22 ± 1*	22 ± 1*	23 ± 1	25 ± 1	25 ± 1
Glucose	106 ± 9	93 ± 16	93 ± 10	94 ± 9	97 ± 10	101 ± 9

Exercise was performed after the baseline (BL) measurements and continued through the 60-minute measurements. The subjects then rested for the 90- and 120-minute measurements.

* $p < 0.05$ *versus* baseline.

ments in total body and extremity nitrogen balance. The effects of such an exercise regimen, however, in the clinically relevant setting of immobilization compounded by malnutrition remained uncharacterized.

Since the amount of training improvement is known to be inversely related to the prior fitness level,[29] employing an untrained population allows the best opportunity for detecting any improvement brought on by the exercise regimen. Therefore, we chose to examine chronic submaximal exercise as an adjunct to IVF in a disease-free volunteer population subjected to hospitalized immobilization and malnutrition. The selection of healthy volunteers avoids the confounding variability inherent to comparisons of patients with different illnesses and differing degrees of stress-induced hypermetabolism.

The level of exercise in this study was chosen for its potential clinical applicability. It has been demonstrated[30] that this level of exercise has been able to bring about a training effect in well-nourished volunteers. It is also the most vigorous regimen that we thought can be reasonably expected of an ill, hospitalized, and possibly postsurgical population. However, 10 days of daily submaximal exercise at this intensity did not improve the total body or peripheral nitrogen accrual in the current study population.

We did verify that adequate nutritional supplementation via the I.V. route is able to abate the total body and peripheral nitrogen losses seen in otherwise unstressed but malnourished hospitalized subjects. While this supplementation is sufficient in promoting total body nitrogen accrual, we did not observe any net muscle-specific amino acid uptake.

Hospitalized patients demonstrate a progressive loss of functional capacity as measured by $\dot{V}O_2max$,[11] and this loss in functional capacity can be detected within 4 days.[27] Since early rehabilitation and return to premorbid and useful activity is thought to be facilitated by a preservation of functional capacity, methods of preserving or improving functional capacity have long been investigated. It has been demonstrated that nutritional supplementation alone, either in the form of hypocaloric glucose or amino acid supplementation,[31,32] was not effective in preserving functional capacity in postoperative patients. Intravenous hyperalimentation alone in hospitalized volunteers was also not effective in preserving functional capacity.[12]

The current study demonstrates that the immobilization of hospitalization and malnutrition are sufficient stimulae in bringing about a decline in $\dot{V}O_2max$. The degree of change is similar to a previous report of the change in $\dot{V}O_2max$ in an otherwise healthy volunteer population subjected to 20 days of bed rest alone without depletion.[33] In contrast to nondepleted subjects, however, the current study shows that 10 days of chronic submaximal exercise was not adequate in previously depleted subjects of alleviating the further detraining effects of hospitalization, even in the setting of adequate I.V. repletion. The REE, which is related to physical conditioning,[34] also demonstrated no detectable difference between the exercised and nonexercised groups at the end of the IVF period.

It is important to note that the exercise regimen explored in the current study did not produce significant acute or chronic detrimental effects in this population during refeeding. Previous investigators observed that unfed normal volunteers may develop hypoglycemia during acute exercise.[35] Counter-regulatory hormone rises have been observed with exercise and seem to be inversely related to the subject's level of physical conditioning.[36] Therefore, it is a legitimate concern that physical activity in a depleted, detrained population such as this may cause intolerable, detrimental hormonal or substrate changes. The present data, however, show that potassium and glucose levels remained unchanged during acute exercise and counter-regulatory hormone changes were acceptably small during the bouts of exercise. This suggests that the acute effects of exercise at the current level were well tolerated in this setting of recovery from the fasting-induced catabolic state. The cumulative effects of the 10 days of submaximal exercise also did not seem detrimental to the subjects in any of the

measured parameters. Thus, mobilization and physical rehabilitation might safely be initiated early in the recovery from hospitalization and moderate malnutrition.

Since training improvement seems to be directly related to training intensity and duration,[29] perhaps a higher level of exercise, longer daily bouts of exercise, or more days of exercise will produce detectable benefit in this population. Higher levels of exercise or longer bouts, however, are probably not clinically applicable options.

In summary, IVF in the setting of hospitalized immobilization was able to restore total body protein but was less successful in restoration of skeletal muscle mass. The addition of 10 days of daily submaximal exercise did not significantly impact upon the peripheral accrual of nitrogen in this previously depleted population. Therefore, additional anabolic stimulae might be used in an adjuvant setting both to affect earlier restoration of lean body mass as well as to supplement the functional response to submaximal exercise.

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