

Electrical stimulation of human lower extremities enhances energy consumption, carbohydrate oxidation, and whole body glucose uptake

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Hamada, Taku, Tatsuya Hayashi, Tetsuya Kimura, Kazuwa Nakao, and Toshio Moritani. Electrical stimulation of human lower extremities enhances energy consumption, carbohydrate oxidation, and whole body glucose uptake. *J Appl Physiol* 96: 911–916, 2004. First published October 31, 2003; 10.1152/jappphysiol.00664.2003.—Our laboratory has recently demonstrated that low-frequency electrical stimulation (ES) of quadriceps muscles alone significantly enhanced glucose disposal rate (GDR) during euglycemic clamp (Hamada T, Sasaki H, Hayashi T, Moritani T, and Nakao K. *J Appl Physiol* 94: 2107–2112, 2003). The present study is further follow-up to examine the acute metabolic effects of ES to lower extremities compared with voluntary cycle exercise (VE) at identical intensity. In eight male subjects lying in the supine position, both lower leg (tibialis anterior and triceps surae) and thigh (quadriceps and hamstrings) muscles were sequentially stimulated to cocontract in an isometric manner at 20 Hz with a 1-s on-off duty cycle for 20 min. Despite small elevation of oxygen uptake by 7.3 ± 0.3 ml·kg⁻¹·min⁻¹ during ES, the blood lactate concentration was significantly increased by 3.2 ± 0.3 mmol/l in initial period (5 min) after the onset of the ES ($P < 0.01$), whereas VE showed no such changes at identical oxygen uptake (7.5 ± 0.3 ml·kg⁻¹·min⁻¹). ES also induced enhanced whole body carbohydrate oxidation as shown by the significantly higher respiratory gas exchange ratio than with VE ($P < 0.01$). These data indicated increased anaerobic glycolysis by ES. Furthermore, whole body glucose uptake determined by GDR during euglycemic clamp demonstrated a significant increase during and after the cessation of ES for at least 90 min ($P < 0.01$). This post-ES effect was significantly greater than that of the post-VE period ($P < 0.01$). These results suggest that ES can substantially enhance energy consumption, carbohydrate oxidation, and whole body glucose uptake at low intensity of exercise. Percutaneous ES may become a therapeutic utility to enhance glucose metabolism in humans.

exercise; glucose transport; euglycemic clamp; insulin sensitivity; oxygen uptake

IT HAS BEEN RECOMMENDED THAT, for the greatest improvement in glycemic control and insulin sensitivity, exercise intensity needs to be set at 50–80% of maximal aerobic capacity in Type 2 diabetes (1). An acute bout of physical exercise increases glucose disposal into the contracting muscles, leading to clinically significant decreases in blood glucose concentrations. This is due partly to the translocation of GLUT4 glucose transporters to the cell surface via insulin-independent mechanism (11, 23). In addition, after a single exercise session at intensity of 60–85% maximal oxygen uptake ($\dot{V}O_2$), substantial glucose utilization continues to occur at a significantly elevated

level in the previously exercised muscles, primarily functioning to restore muscle glycogen concentrations (8, 25). This postexercise effect has been well characterized by a substantial increase in insulin-stimulated whole body glucose uptake (insulin sensitivity), as demonstrated by the hyperinsulimic-euglycemic clamp (8, 25). These clinically important effects of insulin-independent and -dependent stimulation by exercise have widely been accepted as a useful modality to prevent and treat Type 2 diabetes.

However, attention has not been given to those individuals who are restricted from voluntary physical activity and in a bedridden state because of chronic illness or other forms of disability. It is quite difficult to require the recommended exercise intensity for those individuals. Lipman et al. (22) have shown that a chronic lack of physical activity is associated with reduced peripheral glucose uptake due to insulin resistance. More recently, Mikines et al. (24) and Stuart et al. (35) have demonstrated that physical inactivity caused by bed rest for as little as 7 days is associated with a substantial reduction in insulin sensitivity in inactive skeletal muscle without changing the effect of insulin on hepatic glucose production. In addition, prolonged physical inactivity has been shown to decrease the oxygen transport capacity of skeletal muscle (32). Thus it is important to develop a new way of enhancing energy and glucose metabolism in individuals who are unable to exercise.

Electrical stimulation (ES) produces skeletal muscle contractions as results of the percutaneous stimulation of peripheral nerves. Clinically, the use of ES has been shown to potentially improve or compensate for disadvantages in disabled or chronic patients with physical inactivity. In fact, ES of skeletal muscles might not only improve cardiovascular function for tetra- or paraplegic individuals but may also increase the strength and endurance of their paralyzed muscles during daily activity, such as wheelchair locomotion or body transfer (5, 18). Furthermore, there is substantial evidence that the anaerobic metabolism in the glycolytic pathway with the formation of lactate and hydrogen ions and through the degradation of phosphocreatine (PCr) is more pronounced in ES than in voluntary exercise when the exercise protocols were performed at identical low intensity (17, 21, 33, 37). In addition, previous studies in rat have shown that glucose transport activity can be higher in type II than type I fibers when ES is employed (19, 31). Unlike the orderly recruitment of motor units during low-intensity voluntary exercise in which type I slow-twitch fibers are utilized first (10), during ES, large and fatigable fast-twitch motor units with glycolytic fibers are

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activated first because of their larger axons, which in turn have much lower electrical resistance for a given externally applied electrical current (4, 34), suggesting "reversed-size principle" of motor unit recruitment by ES. It is thus reasonable to assume that ES may become a better approach to enhance the glucose transport activity in skeletal muscle, without requiring vigorous voluntary exercise, that ensures the activation of type II fibers with subsequent enhancement of postexercise glucose uptake, particularly for those individuals who are unable to exercise because of orthopedic problems or other complications. Although functional and enzymatic adaptations in response to chronic low-frequency ES of skeletal muscle has been obtained in human subjects (3, 26, 28, 36), the clinical relevance of percutaneous ES for therapeutic purposes of glucose metabolism has not yet been well established in humans.

In our laboratory's earlier communication (14), we demonstrated in human subjects that ES significantly increased the glucose disposal rate (GDR) during euglycemic clamp. The present study was, therefore, undertaken to investigate the acute metabolic effect of ES of lower extremities compared with voluntary cycle exercise (VE) under experimental condition of identical intensity ($\dot{V}O_2$). Our hypothesis was that ES would induce greater glycogen utilization than VE at identical $\dot{V}O_2$. We have employed a new way of giving involuntary exercise induced by percutaneous electrical muscle stimulation. This was performed by means of rhythmic muscle contractions of lower leg and thigh muscles of both lower extremities. The present follow-up study provided further fundamental evidence for a possible therapeutic potential associated with ES-induced enhancement of energy consumption and whole body glucose uptake in humans.

METHODS

Subjects. Eight men served as subjects. Their age, height, and body mass were 24.8 ± 0.6 (SE) yr, 172.4 ± 2.8 cm, and 68.3 ± 4.7 kg, respectively. They were not taking medications, were free of metabolic, neuromuscular, cardiovascular disorders or recent illness, and were not engaging in any regular endurance and resistance training exercise program at time of study. All the subjects signed an informed consent after being fully informed about all aspects of the experimental protocol and were asked to abstain from alcoholic beverages, exercise, and caffeine for 24 h before experiments. The Ethical Committee of Kyoto University Graduate School approved the experimental protocol.

Experimental procedure. On each of two occasions after an overnight fast, the subjects came to laboratory at 8:30 AM and were instrumented with ECG electrodes and then quietly rested for at least 30 min before the beginning of the experiment. All subjects were then asked to lie in the supine position with the lower legs extended over the end of the bed. Two trials of experiment were performed on a day separated by a minimum of 1 wk.

The initial trial required subjects to complete involuntary muscle contraction by percutaneous ES of lower extremities. Two rubber stimulation surface electrodes (6.5×8.5 cm) were placed over the lower legs (tibialis anterior and triceps surae) and thigh (quadriceps and hamstrings) muscles. Before application of stimulation electrodes, underlying skin was prepared by shaving, sanding, and application of isopropyl alcohols. We adopted the appropriate stimulation parameter, which consisted of square-wave biphasic pulses of 0.2-ms duration at a frequency of 20 Hz with a duty cycle of 1-s stimulation/1-s pause, because our laboratory has previously reported that parameters used can induce the highest $\dot{V}O_2$ with this procedures (14). Both muscle

groups (lower legs and thigh) were sequentially stimulated to cocontract in an isometric manner elicited from an electrical stimulator (Omron, Kyoto, Japan). Stimulator output voltage was limited to 80 V without discomfort. In the second trial, the same subjects performed voluntary supine exercise for 20 min using a cycle ergometer (model 771, Monark) that was adjusted for each subject so that a knee angle at maximal leg extension was consistent for all tests. Exercise intensity was individually adjusted according to the subject's corresponding levels of $\dot{V}O_2$ observed during percutaneous ES, and all of the subjects were requested to maintain a pedal cadence of 50 rpm for the duration of exercise by using a metronome.

Respiratory gas measurement. Our methods for measuring respiratory gas exchange parameters online have been fully described in our laboratory's previous studies (14, 27). Briefly, gas measurement was continuously performed for a total period of 35 min, including before (5 min), during (20 min), and after (10 min) exercise periods, with respiratory gas exchange ratio (RER) and $\dot{V}O_2$ being calculated online every 15 s. Subjects breathed through a low-resistance valve, and expired gas was sampled in synchrony with the breath cycle from a mixing chamber. Analog signals of fractional concentrations of oxygen and carbon dioxide and flow rate from AE 280 analyzer (Minato Medical Science, Tokyo, Japan) were continuously digitized at a sampling rate of 50 Hz by a 13-bit analog-to-digital converter. Simultaneously, heart rate (HR) was recorded from a bipolar lead (CM5) ECG. Blood lactate measurement was performed every 5 min and was measured by the lactate oxidase method with an automated analyzer (Lactate Pro, Arklay, Kyoto, Japan).

Glucose uptake measurement. We measured glucose uptake in whole body by the hyperinsulinemic-euglycemic clamp, according to the method of DeFronzo et al. (7), with the aid of a blood glucose monitoring and glucose-insulin infusion system (Artificial pancreas model STG22, Nikkiso, Tokyo, Japan) (14). After an overnight fast, subjects arrived at a clinical research room in Kyoto University Hospital and were kept in the supine position with both knees extended. A polyethylene catheter was placed into an antecubital vein in the right side and connected to the STG22 for continuous monitoring of blood glucose with glucose oxidase method, and the hand, forearm, elbow and brachial regions were kept warm by disposable warmers to provide an arterialized venous blood source. A second catheter was inserted into the left antecubital vein for continuous infusion of insulin and glucose. After 15–20 min, baseline blood samples were drawn for the determination of fasting glucose and insulin concentrations. Insulin (Humulin R, Eli Lilly, Indianapolis, IN) was continuously infused at a rate of $1.12 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ throughout the experimental period after priming insulin infusion (0–1 min, $3.56 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 1–2 min, $3.17 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 2–3 min, $2.82 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 3–4 min, $2.52 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 4–5 min, $2.24 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 5–6 min, $1.99 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 6–7 min, $1.77 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 7–8 min, $1.58 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 8–9 min, $1.41 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 9–10 min, $1.25 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) followed by constant insulin infusion at $1.12 \text{ mU}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Priming of glucose infusion with the use of a 20% glucose solution was also performed (4–10 min, $2.0 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 10–15 min, $2.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 15–16 min, $4.0 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), and thereafter, baseline plasma glucose level was maintained by adjusting the glucose infusion rate. At 100 min, at least [ES, 104 ± 4 (SE) min; VE, 107 ± 3 min], after the start of insulin infusion, ES or VE trial was performed for 20 min as described above. GDR was determined as the average value of every 5 min throughout the experiment period, and its values are expressed as milligrams per kilogram per minute. Blood samples for insulin measurements were obtained at the beginning and the end of ES and every 30-min during the poststimulation period of 90 min and were determined by blood enzyme immunoassay (Eiken Chemical, Tokyo, Japan), and GDR data were collected in only seven subjects because of analytic difficulty with blood sample for insulin in one subject. During the entire clamp procedures, subjects were in a prone

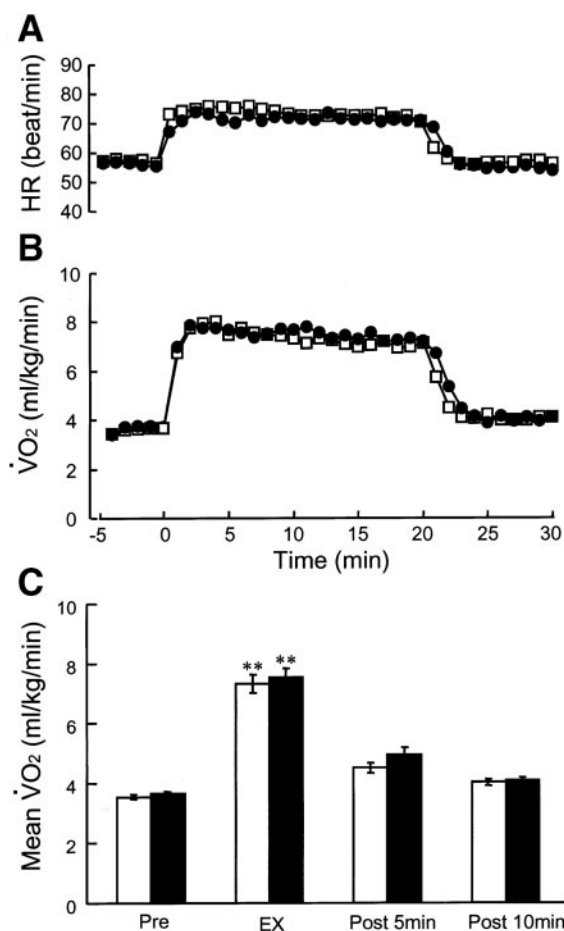


Fig. 1. Time course of changes in heart rate (HR; A) and whole body oxygen uptake ($\dot{V}O_2$; B). $\dot{V}O_2$ was continuously determined by respiratory gas exchange analysis in electrical stimulation (ES) of lower extremities (\square) and voluntary cycle exercise (VE, \bullet). Values are means \pm SE for 8 subjects. Error bars have been omitted for clarity. Mean $\dot{V}O_2$ (C) was nearly identical before, during, and after ES (open bars) and VE (solid bars). Ex, exercise (ES and VE); Pre, preexercise; Post, postexercise. **Significantly different from preexercise, $P < 0.01$.

position with both hands kept flat on the table and instructed not to move and contract upper arms.

Statistical analysis. All data are expressed as means \pm SE. A one-factor (time) repeated-measures ANOVA was used to test whether a single bout of ES and VE increased respiratory gas parameters, blood lactate concentration, and GDR from baseline values. A two-factor ANOVA (between, ES and VE condition; within, time) was used for comparison of gas parameters, blood lactate concentration, and GDR. Tukey's post hoc test was used to determine the significant difference when the significant interaction was found. The probability level for statistical significance was set at $P < 0.05$.

RESULTS

Figure 1 is a time course of the changes in $\dot{V}O_2$ and HR throughout the pre-ES and VE (5 min), during ES and VE (20 min), and post-ES and VE period (10 min). HR and $\dot{V}O_2$ were rapidly increased with the onset of ES to lower extremities, maintained fairly constant throughout the ES, and then returned to the prestimulation level immediately after the cessation of ES. Mean $\dot{V}O_2$ during ES was significantly increased from 3.6 ± 0.1 to 7.3 ± 0.3 ml \cdot kg $^{-1}\cdot$ min $^{-1}$ ($P < 0.01$). On a

separate day, when the same subjects performed VE using a supine cycle ergometer for 20 min, exercise intensity (work rate) was individually adjusted, and thereby $\dot{V}O_2$ was increased to the same level as observed during ES (7.5 ± 0.3 ml \cdot kg $^{-1}\cdot$ min $^{-1}$, not significant vs. ES; Fig. 1).

Figure 2 is a time course of the change in blood lactate concentration and RER. As we expected, lactate significantly increased at initial period (5 min) after the onset of the stimulation period (lactate, pre 1.2 ± 0.1 vs. ES 3.2 ± 0.3 mmol/l; $P < 0.01$), whereas no such drastic changes were observed during VE, despite the identical $\dot{V}O_2$ (lactate, pre 1.2 vs. VE 1.4 mmol/l; not significant). Similarly, it was found that RER rose sharply and significantly at 5 min after the onset of ES far greater than during VE (RER, pre 0.80 ± 0.02 vs. ES 0.99 ± 0.03 , $P < 0.01$; pre 0.79 ± 0.02 vs. VE 0.83 ± 0.03 , $P < 0.01$).

Figure 3 indicates changes in whole body glucose uptake determined by GDR in euglycemic clamp. Steady-state clamp concentration of plasma glucose was quite satisfactory in both ES and VE conditions. The coefficient of variation was found to be 2.5% for ES and 2.6% for VE. Serum insulin concentration throughout both clamp experiments was constant within the range of physiological hyperinsulinemia that was sufficient to suppress endogenous glucose production (30) (Table 1). GDR was significantly increased in response to ES and VE ($P < 0.01$). However, there was a significant requirement for glucose during the post-ES period (20–50 min, 3.9 ± 0.4

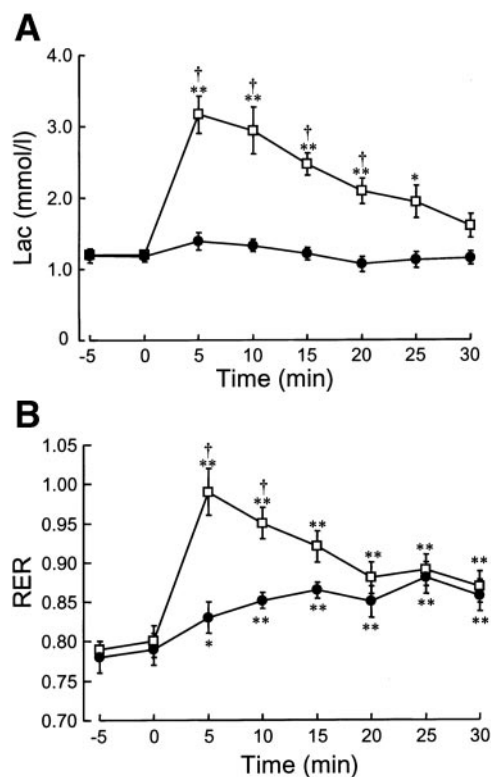


Fig. 2. Comparison of time course of changes in blood lactate concentration (Lac; A) and respiratory gas exchange ratio (RER; B). Data are indicated in a time point of every 5 min before, during, and after ES (open bars) and VE (solid bars). Values are means \pm SE for 8 subjects. **Significantly different from preexercise (0 min), $P < 0.01$. *Significantly different from preexercise (0 min), $P < 0.05$. †Significantly different from VE, $P < 0.01$.

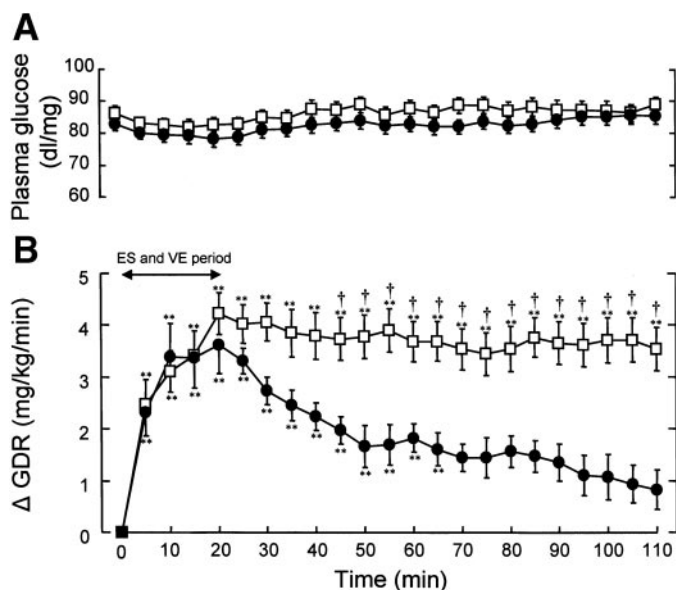


Fig. 3. Mean time course of changes in plasma glucose (A) and glucose disposal rate (GDR; B) during steady-state euglycemic clamp in both ES (open bars) and VE (solid bars) conditions. Change in GDR (Δ GDR) data determined every 5 min are indicated as increasing time point from preexercise period (ES and VE). Values are means \pm SE for 7 subjects. **Significantly different from preexercise (0 min), $P < 0.01$. †Significantly different from VE, $P < 0.01$.

$\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 50–80 min, $3.7 \pm 0.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 80–110 min, $3.7 \pm 0.5 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ above pre-ES). Thus the stimulatory effect of ES on GDR persisted not only during but also after the stimulation. In contrast to the recovery period after ES, GDR decreased rapidly during the recovery period after VE (20–50 min, $2.6 \pm 0.4 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 50–80 min, $1.7 \pm 0.3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; 80–110 min, $1.2 \pm 0.3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ above pre-VE). The difference in GDR during the recovery periods was statistically significant ($P < 0.01$).

DISCUSSION

The significant finding of this study was that a single bout of ES to lower limb muscles induced significantly greater carbohydrate utilization than VE when the same subjects were compared at the identical intensity and duration of exercise. It is well known that, unlike during voluntary contraction, the large motoneurons innervating fast-twitch fibers are the first ones to be activated, owing to their large nerve axons with low-input resistance against external stimulation current (4).

The present findings seem to support this notion. In fact, we found a larger concomitant increase in blood lactate concentration and RER in response to ES compared with VE, and this appears to reflect increased carbohydrate utilization. It has been shown in humans that there is a greater reliance on anaerobic glycolysis for energy production together with the degradation of PCr and the formation of lactate during electrically elicited muscle contractions. Greenhaff et al. (13) have found that the rates of glycolysis in contracted muscles during ES of human quadriceps muscles were twofold higher in type II fibers than type I fibers. Furthermore, the most recent evidence has shown that, for identical low-intensity level (10% maximal voluntary contraction), ES to quadriceps muscle induced a faster decline of intracellular pH together with the degradation of PCr after the onset of ES, whereas no such changes resulted from voluntary contraction (37). Our finding and these earlier observations seem to suggest that differential metabolic response to VE and ES could be primarily due to a large activation of glycolytic type II fibers by ES. One may consider the possibility that our findings of quite high RER together with considerable blood lactate concentration might have been a result of involvement of small amounts of muscle during ES, leading to much smaller overall blood flow than during VE. Therefore, lactate transport to other tissues would likely be less in the ES trial, resulting in higher blood lactate as well as RER values. Although we are not able to discard such a possibility, the nearly identical $\dot{V}\text{O}_2$ during ES and VE trials suggests the similar blood supply to the working muscles in addition to a potentially higher venous blood pumping action by simultaneous and quite rhythmic contractions by ES. The higher RER values during ES could also result from hyperventilation. However, it is unlikely that such a hyperventilation continues for more than 10 min. The nearly identical time course changes in lactate and RER during constant $\dot{V}\text{O}_2$ also seem to refute such a possibility.

In the present study, the most novel aspect of the present finding was that the acute stimulatory effect of ES to lower extremities on whole body glucose uptake persisted not only during but also for at least 90 min after ES under physiological hyperinsulinemia that was sufficient to suppress endogenous glucose production. This further supports our laboratory's previous findings on possible beneficial effects of ES to quadriceps alone (14), and we consider the present results as more encouraging.

Table 1. Plasma glucose, serum insulin, and glucose disposal rate during euglycemic clamp

	Preinfusion	Pre-Ex (–30–0 min)	Ex (0–20 min)	Post-Ex (20–50 min)	Post-Ex (50–80 min)	Post-Ex (80–110 min)
ES						
Plasma glucose, mg/dl	86.6 \pm 2.4	85.0 \pm 1.9	82.5 \pm 1.5	84.9 \pm 2.4	86.4 \pm 2.3	86.8 \pm 2.7
Serum insulin, $\mu\text{U}/\text{ml}$	6.4 \pm 1.0	88.3 \pm 5.0	91.2 \pm 4.6	89.4 \pm 4.1	92.4 \pm 6.8	91.8 \pm 5.9
GDR, $\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$		8.8 \pm 0.6	12.1 \pm 0.8*	12.7 \pm 0.8*	12.5 \pm 0.9*	12.5 \pm 0.9*
VE						
Plasma glucose, mg/dl	84.9 \pm 1.0	82.1 \pm 1.0	81.1 \pm 0.7	81.8 \pm 1.3	82.6 \pm 1.1	84.8 \pm 1.6
Serum insulin, $\mu\text{U}/\text{ml}$	5.3 \pm 0.8	83.1 \pm 5.3	81.7 \pm 4.0	82.7 \pm 4.5	82.8 \pm 5.7	81.4 \pm 4.4
GDR, $\text{mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$		8.7 \pm 0.7	11.9 \pm 0.9*	11.3 \pm 0.8*	10.4 \pm 0.7†	9.9 \pm 0.7

Values are means \pm SE for 7 subjects. Plasma glucose and glucose disposal rate (GDR) were continuously determined, and mean values of the indicated time period are shown. Serum insulin was determined at the end of the indicated time period. ES, electrical stimulation; VE, voluntary cycle exercise; –30–0 min, preexercise (Ex) period (ES and VE); 0–20 min, during Ex period; 20–50, 50–80, and 80–110 min, post-Ex period. *Significantly different from pre-Ex, $P < 0.01$. †Significantly different from pre-Ex, $P < 0.05$.

One effect, evident during exercise and for a relatively short period after exercise, is an insulin-independent stimulation of glucose uptake. The second effect, which becomes evident while the acute effect of exercise on glucose uptake disappears, consists of a large increase in the insulin-dependent stimulation (insulin sensitivity). Although increased glycogenolysis was not necessarily associated with glucose disposal (9, 15), there is substantial evidence to suggest that, for glycogen repletion after a single exercise session, both insulin-independent and insulin-dependent glucose uptake may play a role. In fact, Price et al. (29) showed in humans that postexercise glycogen repletion occurred in an insulin-independent manner for ~ 1 h after exercise, and thereafter insulin-dependent glycogen repletion became significant. In line with this, Wallberg-Henriksson et al. (38) have shown in isolated rat skeletal muscle that the activity of insulin-independent glucose uptake is maximally enhanced immediately after exercise and then gradually wears off but that $\sim 34\%$ of the initial activity is still present over 180 min. Because our data are limited to 90 min post-ES, it appears that acute and persistent enhancement of GDR during and after ES is likely due, at least in large part, to the insulin-independent-mediated effect and that the insulin-dependent effect may come into play, particularly during the latter part of the post-ES period. In addition, it has been recently suggested that 5'-AMP-activated protein kinase (AMPK) may have a regulatory role in contraction-stimulated (insulin-independent) glucose transport in skeletal muscle (16). AMPK is stimulated by various glycogen-depleting stimuli, including contraction, with a close correlation to glucose transport activity in rat skeletal muscle (15). In fact, contraction-induced activation of AMPK and GLUT4 translocation and glucose uptake is impaired in glycogen-supercompensated muscles of exercised rats (20). With regard to insulin sensitivity, carbohydrate deprivation after exercise results in delayed glycogen restoration and prolonged increase in insulin sensitivity in rat skeletal muscle (2), and, furthermore, insulin-stimulated GLUT4 translocation and glucose uptake are impaired in supercompensated muscles of exercised rats (20). It thus seems that exercise-induced increase in carbohydrate depletion may have provided the stimulus for increased glucose uptake in the postexercise period. Muscle fuel and energy state in contracted muscles may play an important role in regulating the acute and persistent effect of contraction on glucose transport and may partly explain different persistent duration of increased glucose uptake.

It is interesting to note that the post-ES increase in GDR was as high as that observed by bicycle exercise at 40% of maximal $\dot{V}O_2$ for 30 min under similar hyperinsulinemia ($\sim 77 \mu\text{U/ml}$) (6). DeFronzo et al. (6) have demonstrated that exercise and insulin actually act synergistically on glucose uptake in whole body under physiological hyperinsulinemia. The synergism could be attributed to the fact that exercise enhances blood flow, which increases glucose supply to contracting muscles, thereby reinforcing the effect of infused insulin. It has been shown that ES can increase lower limb blood flows, leading to enhanced stroke volume and cardiac output by activation of venous muscle pump when ES was used to induce rhythmic muscle contractions of calf and thigh in able-bodied and paraplegic patients (5). It thus appears that acute increase in GDR during ES and VE condition could be due to a better perfusion of the peripheral tissue within contracted muscles.

However, the results obtained from physiological hyperinsulinemia must be interpreted in light of the fact that exercise (or almost every other condition in which the insulin clamp has been applied) is not normally characterized by hyperinsulinemia and euglycemia. Indeed, DeFronzo et al. (6) have shown that the effect of combined insulin and exercise on the peripheral glucose uptake is much greater than of either one alone and is more likely to have an impact throughout exercise and postexercise period. If the effects of exercise and insulin were purely additive, then the acute stimulatory effect of ES alone on glucose uptake in the whole body would have been a smaller magnitude than that with combined insulin.

Additionally, it has been shown that increase in epinephrine may partly enhance carbohydrate utilization in humans. Because epinephrine enhances the rate of muscle glycogenolysis as well during short-term ES (12), it might have resulted in an enhanced glyconeogenesis after ES. It is unlikely that significant epinephrine spill out would have occurred during a low-intensity exercises, such as the ones employed in the present study (i.e., 10% maximal voluntary contraction of ES). We could, however, only speculate such a possibility in the absence of no epinephrine data.

Recent therapeutic studies have shown that ES-assisted training can increase muscle GLUT4 content and improve insulin sensitivity in patients with spinal cord injury (3, 26). It has also been reported in humans that chronic low-frequency ES to leg muscles increased $\dot{V}O_2$ at anaerobic threshold as an improvement in muscle function due to its enhanced oxidative capacity (28). In addition, chronic low-frequency ES can induce improvement in the aerobic-oxidative metabolism of skeletal muscle (36). Those previous therapeutic findings, together with the present study, seem to suggest that ES may have a great potential for medical applications, e.g., counteracting the effects of disuse, decreased oxygen transport, and reduced peripheral glucose uptake due to insulin resistance in immobilized or bedridden patients, without requiring vigorous voluntary exercise.

In summary, we have demonstrated that a single bout of ES to lower extremities can significantly enhance energy consumption, carbohydrate oxidation, and whole body glucose uptake at low-intensity exercise. This could be partly due to a larger contribution of type II fibers in ES compared with in VE at identical intensity. Enhanced carbohydrate oxidation by ES may partly influence the post-ES effect on enhanced GDR. Thus percutaneous ES may become an important part of therapy in enhancing energy and glucose metabolism for those individuals who are unable to exercise because of orthopedic problems or other complications.

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