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Neural and metabolic mechanisms of excessive muscle fatigue in maintenance hemodialysis patients

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Johansen, Kirsten L., Julie Doyle, Giorgos K. Sakkas, and Jane A. Kent-Braun. Neural and metabolic mechanisms of excessive muscle fatigue in maintenance hemodialysis patients. *Am J Physiol Regul Integr Comp Physiol* 289: R805–R813, 2005. First published May 19, 2005; doi:10.1152/ajpregu.00187.2005.—Dialysis patients have severe exercise limitations related to metabolic disturbances, but muscle fatigue has not been well studied in this population. We investigated the magnitude and mechanisms of fatigue of the ankle dorsiflexor muscles in patients on maintenance hemodialysis. Thirty-three dialysis patients and twelve healthy control subjects performed incremental isometric dorsiflexion exercise, beginning at 10% of their maximal voluntary contraction (MVC) and increasing by 10% every 2 min. Muscle fatigue (fall of MVC), completeness of voluntary activation, and metabolic responses to exercise were measured. Before exercise, dialysis subjects exhibited reduced strength and impaired peripheral activation (lower compound muscle activation potential amplitude) but no metabolic perturbation. During exercise, dialysis subjects demonstrated threefold greater fatigue than controls with evidence of central activation failure but no change in peripheral activation. All metabolic parameters were significantly more perturbed at end exercise in dialysis subjects than in controls, including lower phosphocreatine (PCr) and pH, and higher P_i, P_i/PCr, and $H_2PO_4^-$. Oxidative potential was markedly lower in patients than in controls [62.5 (SD 27.2) vs. 134.6 (SD 31.7), $P < 0.0001$]. Muscle fatigue was negatively correlated with oxidative potential among dialysis subjects ($r = -0.52$, $P = 0.04$) but not controls. Changes in central activation ratio were also correlated with muscle fatigue in the dialysis subjects ($r = 0.59$, $P = 0.001$) but not the controls. This study provides new information regarding the excessive muscular fatigue of dialysis patients and demonstrates that the mechanisms of this fatigue include both intramuscular energy metabolism and central activation failure.

oxidative phosphorylation; central fatigue; electromyography; muscle activation; ^{31}P magnetic resonance spectroscopy

DIALYSIS PATIENTS have well-known exercise limitations. Maximal whole body oxygen consumption is approximately half that of gender- and age-adjusted norms for sedentary individuals despite widespread use of erythropoietin to control anemia (1, 19, 33, 45). Patients often cite muscle fatigue rather than cardiopulmonary limitations as the reason for terminating maximal exercise tests (32), and uremic myopathy has been hypothesized to contribute to the exercise limitations in this population (12, 40). Numerous investigators have reported the presence of muscle atrophy and weakness in dialysis patients (11, 15, 16, 22, 47). In addition, biopsy studies have described abnormal mitochondria (11, 31), and ^{31}P magnetic resonance spectroscopy (^{31}P MRS) studies have shown impaired oxidative capacity (13, 23, 35, 53, 54).

However, the link between these manifestations of myopathy and muscle fatigue, defined as the reduction in force with repeated or sustained contractions, has not been investigated. Moore et al. (39) reported that dialysis patients experienced greater muscle fatigue during static handgrip exercise than healthy control subjects, but these investigators did not examine the possible causes of this fatigue. Muscle fatigue can occur as a result of failure at one or more sites along the pathway of force production (4, 24, 25). Specific factors that have been implicated as contributors to fatigue in various conditions or disease states include central activation failure, impaired neuromuscular propagation, impairment of contractile function, or altered muscle metabolism.

The purpose of this study was to investigate the magnitude and mechanisms of fatigue [i.e., fall in maximum voluntary contraction (MVC) of the ankle dorsiflexor muscles] in patients on maintenance hemodialysis during a progressive, intermittent isometric exercise protocol that proceeds from a steady-state oxidative phase to a more glycolytic, fatiguing phase (27). The dorsiflexor muscles are functionally important for locomotion, posture, balance (56), and the prevention of falls in older adults (8). Furthermore, habitual use of the dorsiflexor muscles may make them less susceptible to disuse deconditioning than muscles more typically involved in high-power activities (e.g., quadriceps femoris), which may not be used as intensely by individuals on dialysis as by healthy subjects. To examine the mechanisms of fatigue, we obtained simultaneous measures of central and peripheral muscle activation and intramuscular energy metabolism, using a combination of voluntary and electrically stimulated muscle contractions, electromyography (EMG), and ^{31}P MRS. We hypothesized that the dialysis group would fatigue more than the control group as the result of limitations in skeletal muscle oxidative capacity.

METHODS

Subjects. Thirty-three dialysis subjects were recruited from University of California (UC), San Francisco-affiliated dialysis units, including the San Francisco Veterans Affairs (VA) Medical Center, the UC-Mt. Zion Dialysis Center, and the UC Renal Center at San Francisco General Hospital (Table 1). Entry criteria included receipt of chronic hemodialysis for 3 mo or longer with adequate dialysis delivery ($Kt/V \geq 1.2$). Subjects were excluded if they had reasons for being in a catabolic state such as a known malignancy, infection requiring intravenous antibiotics within 2 mo before enrollment, or

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Table 1. *Baseline characteristics of study subjects*

Variable	Dialysis	Control	*P* Value
n	33	12	
Age, yr	53.4 (SD 11.7)	56.5 (SD 14.2)	0.46
Sex, M/F (%male)	22M/11F (67)	7M/5F (58)	0.38
Mass, kg	74.4 (SD 18.6)	67.8 (SD 16.2)	0.28
Body mass index, kg/m^2	27.3 (SD 7.0)	23.3 (SD 3.9)	0.07
Physical activity, arbitrary units	70.3 (SD 49.6)	207.4 (SD 132.5)	<0.0001
Current smoker, *n* (%)	7 (21)	5 (42)	0.21
Comorbid conditions, *n* (%)			
Hypertension	28 (85)	2 (17)	<0.0001
Diabetes mellitus	19 (58)	1 (8)	0.003
Coronary artery disease	10 (30)	0	0.03
Peripheral vascular disease	4 (12)	0	0.20
Cerebral vascular disease	4 (12)	0	0.20
Ankle brachial index	1.14 (SD 0.46)	1.11 (SD 0.07)	0.89
Ankle dorsiflexor muscle CSA, cm^2	9.7 (SD 2.1)	10.8 (SD 2.1)	0.16
Time on dialysis, mo	37.1 (SD 37.5)		
Kt/V	1.43 (SD 0.31)		
Albumin, g/dl	3.9 (SD 0.3)		
Hemoglobin, g/dl	11.8 (SD 1.8)		
Calcium, mg/dl	9.3 (SD 0.8)		
Phosphorus, mg/dl	5.8 (SD 1.8)		
Parathyroid hormone, pg/ml	378 (SD 374)		

Values are presented as means (SD); *n* = no. of subjects. M/F, male/female; CSA, cross-sectional area; Kt/V, unitless measure of delivered dialysis dose.

corticosteroid treatment. Patients also were excluded if they had musculoskeletal limitations to mobility. Medical charts were reviewed and patients were interviewed to determine the presence of comorbid conditions. Twelve control subjects who reported no kidney disease were recruited from the community. Control subjects were required to be sedentary, defined as no participation in routine exercise or fitness-related activities within 2 mo of study enrollment.

All subjects gave informed consent for study participation. The study was approved by the Committee on Human Research at UC, San Francisco, the Clinical Research Subcommittee of the Research and Development Committee of the San Francisco VA Medical Center, and the Human Subjects Committee at the University of Massachusetts, Amherst.

Clinical measurements. Patients were studied in the Magnetic Resonance Unit at the San Francisco VA Medical Center and in the General Clinical Research Center at San Francisco General Hospital. Height and weight were recorded with subjects wearing only a hospital gown, and body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in meters). Dialysis subjects were weighed after a dialysis session. Routine monthly laboratory results were recorded for dialysis subjects, including serum albumin concentration, hemoglobin, and single-pool Kt/V calculated from pre- and postdialysis blood urea nitrogen measurements. To minimize the possibility of including subjects with latent peripheral vascular disease (38), we obtained the ratio of ankle to brachial systolic blood pressures for all volunteers. Physical activity was measured by accelerometry as previously described (21). Briefly, three-dimensional accelerometers (Tritrac R3D; Professional Products, Madison, WI) were worn for 1 wk during waking hours, and the vector magnitude was summed over the period and a daily average reported in arbitrary units.

Anterior compartment muscle area was measured using MRI, and these data have been previously presented (22). Proton T1-weighted magnetic resonance axial images of the anterior compartment of the leg were acquired at 1.5T (Siemens Vision) by using a 31-cm-diameter extremity coil with the subject in a supine position. The image parameters were an echo time of 14 ms, field of view of 210 mm^2, a matrix 256 × 256, slice thickness of 4 mm, 33 slices, and a total acquisition time of 13 min. The anterior compartment was identified and manually outlined. A customized software program written in IDL (Research Systems, Boulder, CO) was used to separately quantify contractile and noncontractile components of the anterior compartment of the leg. The largest muscle cross-sectional area (CSA) for each subject was used as a measure of muscle size.

Force measurements. All measures of ankle dorsiflexor muscle force, activation, and metabolism were acquired with the subject seated with one leg extended and the knee fixed at ~170° extension (24, 25). The foot was secured to a platform (ankle angle 120°) under which was mounted a nonmagnetic force transducer, which in turn was coupled to a computer. Before exercise, maximal isometric voluntary contraction (MVC) force was measured during three 3- to 4-s trials, each separated by 2 min of rest. To ensure accurate quantification of the MVC, we repeated any trial resulting in a force <90% of the other trials. The peak value from the three trials was used as the MVC, and the exercise protocol was scaled to this value.

Muscle activation. A stimulating electrode [pair of 10-mm nonmagnetic disks (Grass Instruments, West Warwick, RI) mounted on a plastic strip] was placed over the peroneal nerve ~1 cm distal to the fibular head. A copper ground plate was placed between the stimulating electrode and the EMG recording electrodes. For each subject, supramaximal intensity [15% greater than that necessary to elicit a maximal compound action potential (CMAP)] was determined and then used for all subsequent stimuli. The CMAP, which reflects the excitability of the neuromuscular junction and muscle membrane, was recorded at 2,500 Hz with nonmagnetic surface electrodes (10-mm disks) taped over the belly and distal tendon of the tibialis anterior muscle, as previously described (24, 25). The amplitude (in mV) of the CMAP negative peak was recorded at baseline, immediately after the preexercise MVCs (to determine the degree of potentiation of CMAP amplitude), and after exercise.

Central activation, defined here as that portion of neuromuscular activation located proximal to the stimulating electrode on the peripheral motor nerve, was quantified using the central activation ratio (CAR): CAR = MVC/total force, where total force = MVC + superimposed stimulated force (24, 25). The stimulated force was elicited from a supramaximal 50-Hz train of 25 stimuli, which was superimposed on the MVC when the MVC force had reached maximal and plateaued. The CAR was determined before and at the end of exercise.

Muscle metabolism. In a subset of 18 dialysis and 10 control subjects, phosphorus MRS was used to acquire information regarding muscle energy metabolism, as performed previously (24, 25). Data were acquired in a 30-cm-bore 1.9T superconducting magnet by using a 3 × 5-cm elliptical surface coil taped over the belly of the tibialis anterior muscle, just proximal to the EMG recording electrode. After acquisition of the baseline force and activation measures, the subject sat without moving while the magnet was shimmed using proton MRS to a water peak half height <40 Hz. Phosphorus data were then acquired from the resting muscle, and the exercise protocol was begun. The acquisition rate was 1.25 s, and the data were averaged over 1 min for the rest spectrum and every 30 s during exercise. To ensure accurate quantitation of overlapping peaks, all peaks in the spectra were fit [bone broad component, phosphomonoesters, inorganic phosphate (P_i), phosphodiesters, phosphocreatine (PCr), 3 peaks of adenosine triphosphate] using NUTS software (Acorn NMR, Livermore, CA). The data were then imported into a spreadsheet (Excel; Microsoft, Kirkland, WA), corrected for partial saturation, and used to calculate P_i (in mM), PCr (in mM), Pi/PCr, diprotonated inorganic phosphate ($H_2PO_4^-$, in mM), and pH, according to standard equations (52). Corrections for partial saturation of PCr and P_i were made using values obtained experimentally and from the literature (7), respectively. The oxidative potential, which reflects the muscle's ability to provide energy oxidatively (9, 27), was calculated from the initial, linear portion of the slope of force (%MVC) vs. P_i/PCr, because this reflects the steady-state portion of the exercise.

Exercise and recovery protocol. After baseline measures of force, activation, and metabolism were acquired, each subject briefly practiced several contractions at 10% MVC to become familiar with the target intensity and duty cycle to be used during the exercise protocol. The subject then performed up to 14 min of isometric contractions (4 s contract, 6 s relax, Fig. 1). Exercise started at 10% of MVC and was increased by 10% every 2 min. At the beginning of each 2-min stage and after the final contraction at the end of exercise, an MVC was obtained to quantify fatigue. Muscle fatigue was calculated as [(MVC preexercise − MVC postexercise)/MVC preexercise] × 100.

A secondary index of fatigue was the time to cessation of exercise. Although the protocol was designed to be completed in 14 min, many dialysis subjects could not complete the entire protocol. When this occurred, the end-exercise MVC was recorded and recovery proceeded. Recovery was monitored with measures of MVC taken immediately (*minute 0* of recovery) and 2, 5, and 10 min after exercise.

Statistical analyses. ANOVA with age and gender as covariates was used to examine differences between groups in preexercise force, peripheral activation (CMAP), and metabolic variables. Because of the nonnormal distribution of the CAR measure, which has a ceiling of 1.0, Mann-Whitney and Wilcoxon nonparametric procedures were used to detect differences across groups in pre- and postexercise CAR values. Paired *t*-tests were used to test for changes over time within each group, and repeated-measures ANOVA with age and gender as covariates was used to compare changes in force, peripheral activation, and metabolites before and immediately after exercise between groups. The difference in fatigue between groups was also examined with physical activity level as a covariate. The relationships among physical activity, oxidative potential, and fatigue were determined using linear regression analyses for both groups combined. Univariate and multiple linear regression were used to assess the contributions of muscle atrophy and peripheral activation to baseline force production and to assess the contributions of oxidative potential and central activation failure to muscle fatigue among dialysis subjects. Descriptive data in Table 1 are presented as means (SD); all other data are presented as means ± SE, and precise *P* values are given. Analyses were performed using Statistica software (StatSoft, Tulsa, OK).

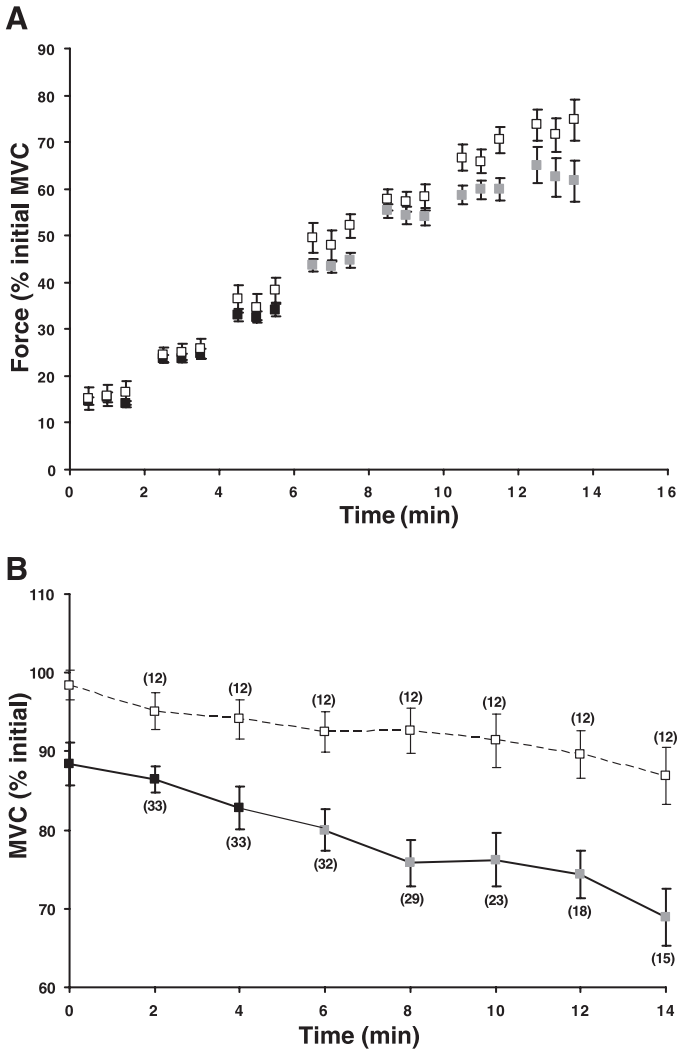

Fig. 1. Force and fatigue. Changes in target force (*A*) and maximal voluntary contraction (MVC; *bottom*) are shown for dialysis (solid squares) and control groups (open squares). Values are means ± SE. Fatigue was significantly greater in dialysis compared with control. Eighteen dialysis subjects failed to complete the 14-min protocol; the shift from solid to shaded squares indicates the point at which attrition began in the dialysis group. The number of subjects completing each stage of the protocol is shown in parentheses.

RESULTS

Baseline characteristics of the study subjects are presented in Table 1. The groups were well matched for age and gender; the dialysis group had marginally greater BMIs. The dialysis group had more comorbidity than the control group. In addition, the dialysis group was less active, as has been seen in other studies (21, 22). All patients were dialyzed three times per week with the use of biocompatible membranes. The average treatment time was 3.2 (SD 0.4) h. Patients had been receiving dialysis for a median duration of 37.1 mo (range 3–156 mo). Patients in the dialysis group had normal pulses at the ankle, were well dialyzed and well nourished, and had hemoglobin levels indicative of good anemia control (42, 43).

Before exercise, dialysis subjects' MVCs were ~20% lower than controls (Table 2). The dialysis group also showed evidence of impaired peripheral activation, with markedly lower CMAP amplitude at baseline and after potentiation from the

Table 2. *Force and activation data*

Variable	Dialysis	Control	*P* Value
n	32	12	
MVC, *n*			
Preexercise	176.9±59.4	220.3±67.8	0.04
End exercise	112.1±46.3	188.2±55.3	<0.0001
Fatigue, %	37.1±15.9	12.6±13.5	<0.0001
CAR			
Preexercise*	0.96±0.11	0.94±0.10	0.61
End exercise†	0.89±0.13	0.93±0.09	0.36
Change†	0.09±0.11	0.006±0.03	0.02
CMAP amplitude, mV			
Preexercise	4.87±1.53	7.19±1.64	0.0003
Potentiated	5.90±2.80	7.74±1.81	0.05
End exercise	5.36±2.16	7.87±1.86	0.002
Change	−0.45±1.35	0.13±0.97	0.21

Values are means ± SE; *n* = no. of subjects. MVC, maximum voluntary contraction; CAR, central activation ratio; CMAP, compound muscle action potential. Fatigue was calculated as [(MVC preexercise − MVC postexercise)/MVC preexercise] × 100. Change in CMAP amplitude was calculated as (CMAP end exercise − CMAP potentiated). *For dialysis subjects, *n* = 29. †For dialysis subjects, *n* = 26, and for controls, *n* = 11.

preexercise MVCs (Table 2). CMAP amplitude was not correlated with muscle CSA among the dialysis patients ($r = 0.22$, $P = 0.40$), suggesting that the lower CMAP was not a result of muscle atrophy. However, baseline MVC in the dialysis group was related to both muscle CSA and to CMAP amplitude in multiple regression analysis (overall $r = 0.68$), indicating a possible role for reduced peripheral excitability in the weakness of this group. Despite hyperphosphatemia in the dialysis subjects (Table 1), intracellular P_i, PCr, P_i/PCr, and pH were similar at rest in patients and controls (Table 3).

Whereas all control subjects completed the fatigue protocol, 18 dialysis subjects were unable to finish, stopping at 6–13.5 min of exercise because of exhaustion. Dialysis subjects demonstrated threefold greater fatigue than controls despite the performance of less work by about one-half of the dialysis subjects (Table 2). CAR declined in dialysis subjects but not in controls, indicating central fatigue in these patients. CMAP amplitude did not change significantly in either group as a result of exercise, suggesting that peripheral activation failure was not an important contributor to the fatigue that was observed.

In the subsets of subjects from whom metabolic data were obtained, all metabolic parameters were significantly more perturbed at end exercise in dialysis subjects than in controls, including lower PCr and pH and higher P_i, P_i/PCr, and $H_2PO_4^-$ (Table 3 and Fig. 2). These subsets showed the same differences in fatigability and change in CAR as the larger groups. Oxidative potential was markedly lower in patients than in controls (Table 3 and Fig. 3), indicating that dialysis subjects had an impaired ability to provide energy oxidatively as exercise proceeded. Muscle fatigue was negatively correlated with oxidative potential in the dialysis subjects ($r = -0.52$, $P = 0.04$) but not in controls ($r = -0.26$, $P = 0.53$), suggesting that poor oxidative capacity is an important mechanism of fatigue during intermittent, submaximal contractions in dialysis subjects. The change in CAR was also correlated with muscle fatigue in the dialysis group ($r = 0.59$, $P = 0.001$) but not in the control group ($r = 0.23$, $P = 0.50$). A combined model that included both oxidative potential and the change in central activation showed that these two factors explained 56% of the variation in fatigue among dialysis subjects ($r = 0.75$, $P = 0.014$).

In both groups combined, physical activity was correlated with oxidative potential ($r = 0.55$, $P = 0.006$), and there was a trend toward a correlation between activity level and muscle fatigue ($r = -0.30$, $P = 0.06$). Of note, muscle fatigue remained excessive in the dialysis group compared with the control group even after statistical adjustment for activity level ($P = 0.003$). There were no correlations between central activation or decline in central activation during exercise and physical activity level.

Dialysis subjects demonstrated delayed recovery of MVC force, returning to only 85 ± 3% of preexercise MVC after 10 min of rest (Fig. 4). Control subjects recovered fully by 10 min (99 ± 3%, $P = 0.006$ for the difference between groups).

DISCUSSION

The results of this study show that patients on hemodialysis fatigue to a much greater extent than healthy, sedentary individuals during performance of incremental isometric contractions of the ankle dorsiflexor muscles. This excess fatigue was due in part to poor oxidative metabolism and greater accumulation of metabolic by-products in the patients, with additional contribution from central activation failure. Even within this group of rather high-functioning patients, only half were able to complete the protocol, experiencing greater fatigue than controls even in response to significantly less absolute and relative work. Although the dialysis patients were weaker than the control subjects at baseline, the excess muscle fatigue was much greater in magnitude than the initial strength deficit.

Baseline measures. The dialysis group was ~20% weaker than controls, which was related to both muscle atrophy and reduced peripheral activation. The lack of difference between groups in the preexercise CAR provides additional evidence that this weakness was due to peripheral, rather than central, alterations in the muscle.

Table 3. *Metabolic data*

Variable	Dialysis	Control	*P* Value
n	18	11	
P_i, mM			
Rest	5.7±2.7	5.6±2.0	0.88
End exercise	28.5±6.4	21.4±5.9	0.006
PCr, mM			
Rest	36.8±2.7	36.9±2.0	0.88
End exercise	14.0±6.4	21.1±5.9	0.006
P_i/PCr			
Rest	0.16±0.09	0.17±0.06	0.88
End exercise	2.67±1.64	1.25±0.82	0.01
$H_2PO_4^-$, mM			
Rest	1.8±0.7	1.7±0.8	0.80
End exercise	13.6±5.3	8.6±4.1	0.01
pH			
Rest	7.05±0.08	7.09±0.08	0.23
End exercise	6.80±0.17	6.94±0.14	0.04
Oxidative potential	62.5±27.2	134.6±31.7	<0.0001

Values are means ± SE; *n* = no. of subjects. P_i, inorganic phosphate; PCr, phosphocreatine; $H_2PO_4^-$, diprotonated inorganic phosphate. For oxidative potential data, *n* = 16 for dialysis group and *n* = 9 for controls. Reasons for missing oxidative potential data include lack of steady state during exercise (*n* = 1 dialysis) and incomplete or missing central activation (*n* = 1 dialysis, *n* = 2 control).

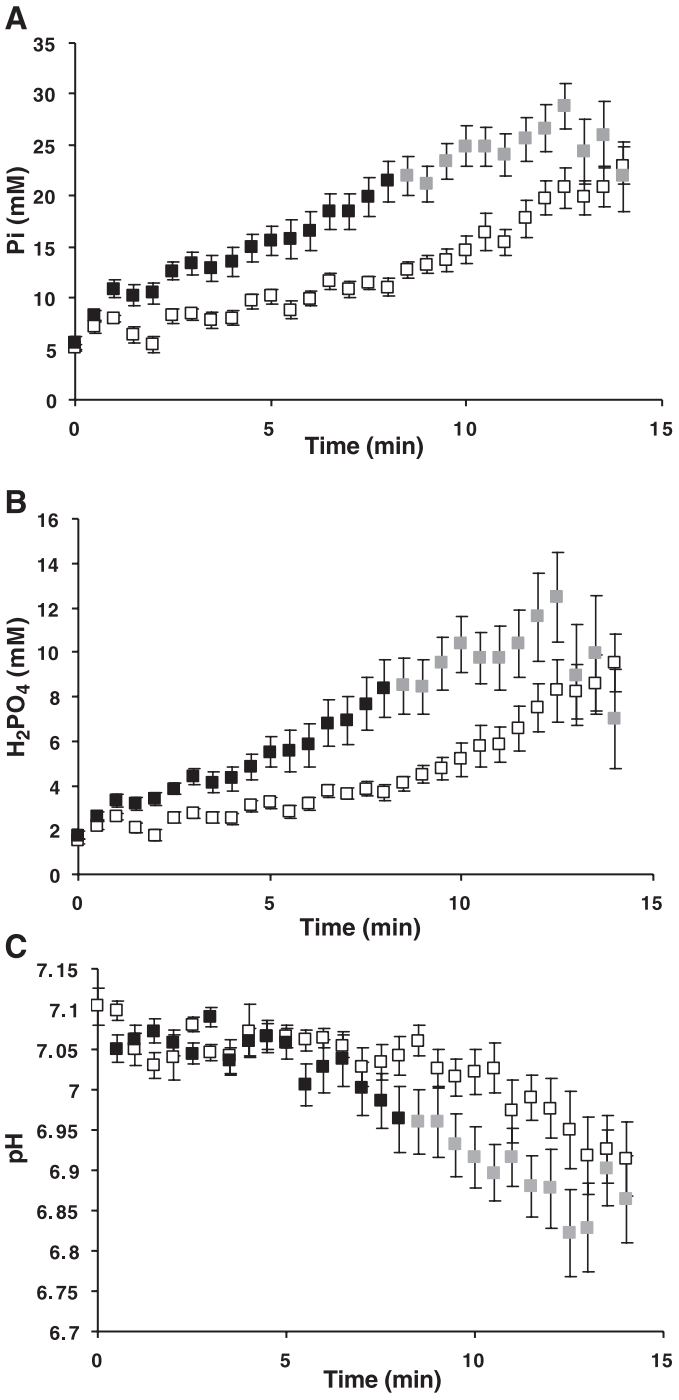

Fig. 2. Pi, $H_2PO_4^-$, and pH. Changes in P_i (*A*), $H_2PO_4^-$ (*B*), and pH (*C*) are shown for dialysis (solid squares) and control groups (open squares). Values are means ± SE. Whereas all subjects in the control group completed the entire protocol, subjects in the dialysis group began to drop out after 8 min of exercise. For each plot, the shaded squares represent the metabolic data from the remaining dialysis patients. Metabolic changes were greater in dialysis than control ($P < 0.05$, all), despite shorter exercise times and greater central activation failure in the dialysis group.

The amplitude of the unpotentiated CMAP was markedly reduced in the unfatigued muscle of the patient group (Table 2), suggesting an impairment in the excitability of the neuromuscular junction or muscle membrane. On the basis of previous work in the elderly (28), this decrease in CMAP amplitude would not be expected to arise from the rather modest degree of muscle atrophy observed in this study. This was confirmed by the lack of correlation between CMAP amplitude and muscle CSA among the dialysis subjects. After potentiation by the baseline MVCs, CMAP amplitude was increased in both groups, although the patient group remained depressed relative to control (Table 2). Little information is available with regard to the effects of renal disease or long-term dialysis treatment on skeletal muscle excitability, although there is some evidence to suggest that impaired Na^+-K^+ pump function may arise from long-term renal insufficiency (18, 51). Furthermore, Sangkabutra et al. (48) recently reported an

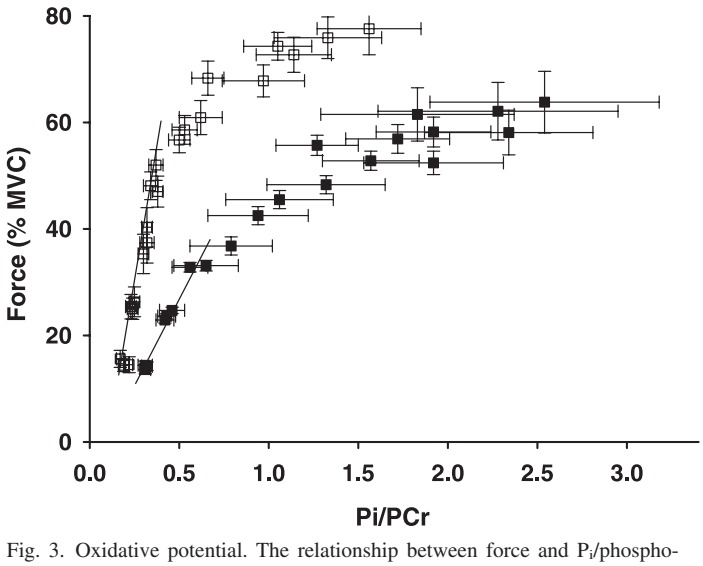

Fig. 3. Oxidative potential. The relationship between force and P_i/phosphocreatine (PCr) is shown for dialysis (solid squares) and control groups (open squares). Values are means ± SE. Note that at any given force level, the perturbation of P_i/PCr was less in the control than in the dialysis group, indicating an inability of the dialysis subjects to keep pace with the energy demand during exercise. The initial, linear slope of this relationship, which reflects the potential for oxidative metabolism, was significantly lower for dialysis compared with control ($P < 0.001$).

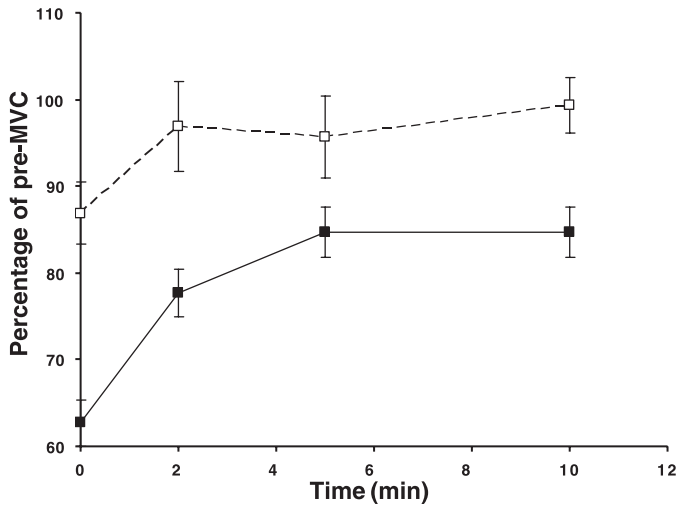

Fig. 4. Recovery of MVC. Changes in MVC in dialysis (solid squares) and control groups (open squares) during 10 min of recovery. Values are means ± SE. Whereas recovery was complete in the control group, dialysis subjects failed to return to preexercise strength levels, even after 10 min.

elevated plasma K^+ concentration that was associated with poor exercise performance in end-stage renal failure patients. These investigators suggested that impaired Na^+-K^+ pump function may arise from the poor K^+ regulation that accompanies long-term renal insufficiency, which in turn could contribute to fatigue in this population. Our data are consistent with this possibility, but we did not directly examine K^+ regulation or Na^+-K^+ pump function. This apparent disturbance of skeletal muscle membrane function in the dialysis group indicates a need for further research in this area.

The metabolic profile of the resting muscle was similar in both study groups (Table 3). In particular, the lack of difference in P_i/PCr between groups suggests a normal phosphorylation state in the dialysis group, which would not be expected if there were a significant defect in mitochondrial function, limitation of resting blood flow, or change in fiber type composition (26) in this group of patients. We observed no acidosis of the resting muscle in this reasonably well-dialyzed group of patients. These results are consistent with those of earlier investigators who examined comparable patient groups (13) and suggest that perturbations of energy metabolism were not so profound as to be evident in the resting muscle of the dialysis patients.

Protocol performance. As has been observed before (27, 29), this protocol is not particularly taxing to the control population, who had no difficulty completing the protocol and showed only a 12.6% loss of maximal force as a result of the 14 min of exercise (Table 2 and Fig. 1). In stark contrast, this reasonably well-managed dialysis group struggled to complete the protocol and had three times as much fatigue as the controls. Beyond the second stage in the larger group of patients and the fourth stage in the subset studied in the magnet, the dialysis patients began to reach exhaustion. Thus the greater fatigue observed in the dialysis group was in concert with the performance of less total "work" compared with controls (Fig. 1), despite the fact that the task was scaled to each individual's preexercise MVC force.

Metabolic response. The exercise protocol used in this study resulted in significantly greater perturbations of energy metabolites in dialysis compared with control subjects (Table 3 and Fig. 2). P_i and diprotonated inorganic phosphate, both of which have been implicated in the fatigue process (10, 24, 44, 55), increased to a greater extent in the dialysis group. Likewise, PCr fell more in the patients as a result of exercise (Table 3). Of note, mono- and diprotonated P_i increased at a greater rate in dialysis subjects than in controls from the outset of the protocol, whereas differences in pH were not apparent until ~5–6 min of exercise (Fig. 2). The rapid accumulation of these metabolites indicates a reduced capacity for keeping pace with the needed energy production by the muscle in the patients. It is likely that this accumulation resulted in direct inhibition of the contractile process (17), as well as provided negative feedback to central motor drive, with subsequent central activation failure (24).

The relationship between force and P_i/PCr during this incremental exercise protocol (Fig. 3) can be used to assess the progression from steady-state exercise, in which the overall energy needs of the muscle are met oxidatively, to the point at which the steady state is lost and fatigue ensues (27). The initial, linear portion of this relationship may be used to indicate the potential of the muscle for oxidative phosphorylation (9, 27). In the present study, this slope was reduced approximately twofold in the dialysis patients compared with the controls (Fig. 3 and Table 3), indicating poor oxidative capacity and an early loss of the steady state in the patient group. This was the case even though atrophy was accounted for by scaling the exercise to each individual's strength. The magnitude of this deficit is comparable to that previously observed in renal (13, 54) and heart failure patients (34). An important result of the present study was that a significant proportion of the observed fatigue in the patients could be accounted for by their low oxidative potential, with the remainder due to the accumulation of fatigue-related metabolites and the development of central activation failure as the exercise progressed.

The causes of the low oxidative potential during exercise in the patient group could be due to several factors. First, there may be a decrease in mitochondrial content in this group, whether due to disease or disuse (31). Second, there may be limitations to oxygen delivery to the mitochondria, due to either anemia, reduced blood flow, or low muscle capillary oxygen conductance (36). The dialysis group was reasonably well dialyzed and not anemic, as indicated by an average hemoglobin of 11.8 g/dl. Thus the oxygen-carrying content of the blood, which was comparable to the erythropoietin-loaded patients in Marrades et al. (35), seems unlikely to have been a limiting factor during exercise in this group. This improbability is supported by the observation that the patients were capable of establishing a metabolic steady state during the first few stages of the exercise (Fig. 3). Beyond that, however, the steady state was lost as the ability to keep pace with the energy demand by oxidative metabolism became limited.

With regard to the possibility of blood flow limitations, the lack of difference between groups in the ankle/brachial index at rest (Table 1) suggests that there was no obvious defect of the peripheral vasculature in either group (37). However, it is possible that a limitation of blood flow developed during exercise such that the dialysis group experienced difficulty distributing blood to the exercising muscle due to endothelial dysfunction, a poor muscle microcirculatory network, or capillary-to-myocyte mismatching due to uremic myopathy (47). Support for the possibility that exercise-induced muscle hyperemia is impaired comes from an earlier study in which plethysmography measures indicated that blood flow to the leg at rest was normal in dialysis patients but was markedly limited postexercise compared with healthy controls (6). The question of whether poor vascular function during exercise limits performance needs to be addressed. Reduced muscle oxidative potential accounted for a substantial portion of the excess fatigue observed in these dialysis patients. In turn, oxidative potential was associated with physical activity when the two study groups were combined. Thus it seems likely that the lower physical activity level of the patients in this study contributed to their increased muscle fatigue. Interestingly, however, the strong group effect on muscle fatigue persisted even after adjustment for physical activity, which suggests that other factors unrelated to physical activity are important in the etiology of fatigue in this population. The metabolic data reported support that likelihood.

In addition to lower physical activity levels, the patient group presented with more comorbidities than the control group. Clarification of the extent to which each comorbidity

contributed to the poor oxidative potential and excessive fatigue in this group is beyond the scope of the present study, but this question clearly warrants additional investigation.

In general, selective atrophy of type II muscle fibers and the resultant increase in reliance on type I fibers might be expected to result in a decrease in muscle fatigability; this pattern has been observed in healthy older adults (5, 29, 41). However, despite reports of a similar shift toward greater type I fiber content in dialysis patients (11, 31, 47), our dialysis group fatigued more than controls, due largely to a poor metabolic capacity. Likewise, the possibility that the smaller muscles of the dialysis group might be relatively better perfused than the larger muscles of the control group, which could postpone the onset of fatigue due to more oxygen delivery at higher relative force levels (2, 20, 29), seems not to be the case.

Central and peripheral activation. Although central activation failure was not the reason for the baseline muscle weakness in the patient group, central fatigue was responsible for some of their excessive muscle fatigue. On the basis of the feedback loop from the muscle to the central nervous system during fatigue (3, 24), it is likely that the greater metabolic perturbation observed in the dialysis group contributed to their development of central activation failure. It should be mentioned, however, that as with all in vivo assessments of central activation, the role of volitional changes cannot be determined here. Overall, the oxidative potential and central fatigue combined to account for ~60% of the variation in fatigue among the dialysis patients but only for 15% in the control subjects.

Although the CMAP was significantly lower in dialysis patients before exercise, there was no difference between the patient and control groups in the change in CMAP following fatiguing exercise (Table 2). Previously, submaximal contractions have not elicited peripheral activation failure in sedentary controls (29), healthy elderly (29), or patients with multiple sclerosis (30), postpolio syndrome (50), or amyotrophic lateral sclerosis (49). It can, however, be observed in healthy young adults as a result of high-intensity exercise that is associated with a large muscle metabolic response (46). In the present study, it did not appear that further peripheral activation failure was a mechanism of the excessive fatigue observed in the dialysis group.

Recovery. The incomplete recovery of force in the dialysis group was rather remarkable (Fig. 4), particularly given the fact that intramuscular acidosis was not excessive in this group at the end of exercise. A delayed force recovery has been suggested to result from excitation-contraction coupling failure (14), which can arise in part because of the accumulation of energetic by-products such as P_i and H^+ (17). Given the marked exercise intolerance of this patient population, it now becomes important to more fully understand the implications of the delayed force recovery of this group, because poor recovery could be expected to negatively impact the ability to fully participate in activities of daily living.

Implications. The profound dysfunction of the leg muscles in this patient group has implications for adequate functioning in activities of daily living. Poor dorsiflexor function has been implicated in the increased susceptibility to falls in the elderly (8). It seems reasonable to speculate that the reduced function and physical performance seen in this population may also be based on poor muscle function. Given that the typical reason these patients stop maximal exercise tests is leg fatigue (32), it seems likely that muscle fatigue may be important in their overall physical capacity. The baseline muscle weakness that we and others (12, 15, 16, 22) have described in patients on hemodialysis also should be taken into account when considering the possible functional consequences of muscle fatigue to these patients. Whereas acute muscle fatigue may only limit performance during vigorous activities in healthy subjects, patients on dialysis must use their muscles at levels closer to their maximum capacity during normal daily physical activities. Thus, although our fatigue protocol measures fatigue based on normalized force, the force required for normal daily activities will be higher in relative terms for many dialysis patients. Therefore, it is reasonable to expect that this population would benefit from resistance exercise training.

This study was conducted with a small group of fairly high-functioning individuals on dialysis treatment. These results probably underestimate the true degree of muscle fatigue among the hemodialysis population, because less able dialysis patients were precluded from participation. Therefore, the results likely underrepresent the degree of skeletal muscle abnormalities in the general hemodialysis population.

In conclusion, we provide new information regarding the excessive muscular fatigue of dialysis patients during relatively mild, submaximal contractions. Furthermore, we demonstrate that the mechanisms of this fatigue are both metabolic and neural in nature. Overall, the observations of excessive fatigue, central activation failure, poor metabolic response, and impaired recovery of force in the patient group suggest a range of neuromuscular impairments. The full consequences of these impairments require additional elucidation.

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