JCI The Journal of Clinical Investigation

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J Clin Invest. 1993;91(2):420-424. https://doi.org/10.1172/JCI116217.

Research Article

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^{31}P-Magnetic Resonance Spectroscopy Assessment of Subnormal Oxidative Metabolism in Skeletal Muscle of Renal Failure Patients

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Abstract

In hemodialysis patients, erythropoietin increases hemoglobin, but often the corresponding increase in peak oxygen uptake is low. The disproportionality may be caused by impaired energy metabolism. ^{31}P-magnetic resonance spectroscopy was used to study muscle energy metabolism in 11 hemodialysis patients, 11 renal transplant recipients, and 9 controls. Measurements were obtained during rest, static hand-grip, and rhythmic hand-grip; recoveries were followed to baseline. During static hand-grip, there were no between-group differences in phosphocreatine (PCr), inorganic phosphate (P_i), or PCr/(PCr + P_i), although intracellular pH was higher in hemodialysis patients than transplant recipients. During rhythmic hand-grip, hemodialysis patients exhibited greater fatigue than transplant recipients or controls, and more reduction in PCr/(PCr + P_i) than transplant recipients. Intracellular pH was higher in controls than either hemodialysis patients or transplant recipients. Recoveries from both exercises were similar in all groups, indicating that subnormal oxidative metabolism was not caused by inability to make ATP. The rhythmic data suggest transplantation normalizes PCr/(PCr + P_i), but not pH. In hemodialysis patients, subnormal oxidative metabolism is apparently caused by limited exchange of metabolites between blood and muscle, rather than intrinsic oxidative defects in skeletal muscle. (*J. Clin. Invest.* 1993. 91:420–424.) Key words: exercise intolerance • hemodialysis • transplant • erythropoietin

Introduction

The low exercise tolerance of renal failure patients is well documented, but the physiologic etiology of this condition remains unclear. The low peak oxygen uptake of hemodialysis patients commonly improves after exercise training, erythropoietin therapy (EPO),[1] or renal transplantation (1–3). However, the improvement mechanisms are obscure, and some patients enigmatically fail to improve after exercise training or EPO (4, 5). EPO often causes a large increase in hemoglobin, while the corresponding increase in peak oxygen uptake is disproportionately low (6, 7). Furthermore, peak oxygen uptake is better predicted by skeletal muscle strength than by hemoglobin (7, 8). These findings suggest skeletal muscle oxygen extraction, not oxygen delivery to muscle, limits exercise tolerance in many renal failure patients. We used magnetic resonance spectroscopy (MRS) to study oxidative energy metabolism in muscle of renal failure patients.

Application of ^{31}P-MRS to exercising skeletal muscle, in vivo, provides a method of directly examining intracellular concentrations of hydrogen ions (pH), phosphocreatine ([PCr]), and inorganic phosphate ([P_i]). In general, during exercise, intracellular pH correlates with glycolytic flux, while the [PCr] to [P_i] ratio correlates with energy available (as ATP) for muscle activity. Thus, ^{31}P-MRS noninvasively examines metabolic factors underlying myopathic exercise intolerance. Examining these myopathic factors during small muscle exercise (hand-grip) is advantageous over large muscle exercise, which can limit blood flow to the muscle being studied. Subnormal oxidative energy metabolism in muscle has been documented by ^{31}P-MRS for skeletal muscle enzyme deficiencies (9–12), congestive heart failure (13–15), and peripheral vascular disease (16).

The present study compared muscle energy metabolism responses to static and rhythmic hand-grip exercise in hemodialysis patients, renal transplant recipients, and normal controls. We hypothesized that renal failure patients treated with hemodialysis have skeletal muscle with reduced capacity for oxidative ATP generation, and this abnormality would be resolved in patients receiving successful renal transplant.

Methods

Patient selection. 22 patients were recruited from the chronic dialysis units and transplant clinic of Dallas Nephrology Associates. 11 patients were on chronic hemodialysis (11 males; aged 45±3 yr), and 11 patients were successful renal transplant recipients (10 males, 1 female; aged 36±16 yr). 9 healthy volunteers served as control subjects (3 males, 6 females; aged 35±4 yr). Each patient and control subject provided informed written consent before participation in the study, according to the protocol approved by the Institutional Review Board.

Dialysis patients were all on stable regimens of medication and hemodialysis, and had been on dialysis for 30±24 mo. Dialysis prescriptions ranged from 3 to 4 h, three times a week. No patient was on high flux or high efficiency dialysis, or on erythropoietin. Exercise testing was performed on nondialysis days, except for two patients who were tested before a dialysis treatment. Transplant recipients were 3–9 mo posttransplant (5±2 mo), which was chosen to avoid the cumulative effects of long-term prednisone therapy. Average prednisone dose was 12±5 mg/d, and all transplant recipients were taking both cyclosporin and azathioprine. Transplant recipients had lower serum creati-

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Received for publication 24 March 1992 and in revised form 26 June 1992.

1. *Abbreviations used in this paper:* EPO, erythropoietin; MRS, magnetic resonance spectroscopy; MVC, maximal voluntary contraction; NMR, nuclear magnetic resonance; [PCr], phosphocreatine; [P_i], inorganic phosphate.

J. Clin. Invest.

0021-9738/93/02/0420/05 $2.00
Volume 91, February 1993, 420–424

nine than hemodialysis patients (1.5±0.2 vs 19±4 mg/dl), and higher hematocrits (38±8 vs 26±3%).

Spectroscopy technique. ^{31}P-MRS was performed as previously described, with minor modifications (9). Briefly, a 1.89-Tesla/30-cm horizontal bore magnet (Oxford Instruments, Oxford, UK) was interfaced to a console (NT-80; GE NMR Instruments, Fremont, CA). The RF coil circuit was a pair of 2 cm diameter, single turn surface coils, inductively coupled to resonate at the ^{1}H and ^{31}P frequencies of 80.4 and 32.5 MHz, respectively, and mounted in a custom-designed housing. The coil was placed on the forearm over the flexor digitorum profundus, one-third of the distance from the humeral epicondyle to the pisiform, just volar to the ulna (17). Field homogeneity was optimized by manual adjustments of the room temperature shims until the water peak line-width was ≤ 30 Hz.

Nuclear magnetic resonance (NMR) data were acquired in 1- or 2-min blocks, containing 4,096 points, over a spectral width of ±2,000 Hz. Pulse repetition rate was 40/min, pulse width 20 μs (a pseudo 90° flip angle), and amplifier power output was 100 W. Raw NMR data were transferred to a computer (4/260; Sun Microsystems Inc., Mountain View, CA), processed, and analyzed using NMR1 software (New Methods Research Inc., Syracuse, NY). The free induction decays were apodized with baseline correction, trapezoidal multiplication (T1 = 4, T2 = 0), exponential multiplication (10 Hz line broadening), Fourier transformation, and phase adjustment in the zero-order only. The spectral peak areas were determined by Lorentzian curve fitting by nonlinear minimization using a modified Levenberg-Marquardt algorithm. After convergence, following at least 10 iterations, the areas under fitted curves were calculated ±5 line-widths. These peak areas and resultant chemical shifts were used to calculate relative metabolite concentrations. Calculated peak areas were referenced to the area under the β-ATP peak during rest (before the first exercise bout). Intracellular pH was calculated by measuring the chemical shift distance (δ) between PCr and P_i peaks, according to the equation:

$$pH = 6.75 + \log(\delta - 3.27)/(5.69 - \delta). \quad (18)$$

Peak saturation effects were determined by two point comparison, i.e., resting spectra collected during 40 pulses/min (1.5-s interpulse delay) versus 4 pulses/min (15-s interpulse delay). For each participant, the ratios in spectral peak areas were the basis for calculating saturation effects in all subsequent spectra. The PCr correction factor was ~ 1.4; the P_i correction factor was ~ 1.2. We had previously determined that there were no detectable saturation effects between spectra collected using 10-s, 15-s, or 30-s interpulse delays. Thus, this scheme adequately accounted for any saturation effects using a 1.5-s interpulse delay.

Exercise set-up and protocol. Hand-grip exercise was done on a custom designed hand-grip dynamometer. Force output was measured by an isometric load cell (Interface Inc., Scottsdale, AZ) and recorded on a multichannel chart recorder (Coulbourne Instruments, Lehigh Valley, PA). The patients performed hand-grip exercise in a seated position, with only the exercising arm inside the magnet. Arm position was confirmed by visual examination.

At the start of each study, patients performed three to five maximal hand-grip contractions. The greatest force was considered a maximal voluntary contraction (MVC). Static exercise consisted of 5 min isometric hand-grip, starting at 40% of MVC. Rhythmic exercise consisted of a 1-s isometric hand-grip alternated with 9 s of relaxation, for 10 min. Patients were instructed to attempt to equal their MVC with each contraction, thus yielding six peak contractions per min at a 10% duty cycle. Verbal feedback was used to motivate the patients. Results were expressed as percentage of MVC. Fatigue was defined as inability to maintain percentage of MVC during exercise.

Statistical analysis. The [PCr] to [P_i] ratio was expressed as [PCr]/([PCr] + [P_i]), which normalizes the ratio and facilitates grouping of patient data. Data analysis was performed by repeated measures analysis of variance, with the Tukey post hoc test. All 9 control subjects successfully completed both static and rhythmic exercise, but not all patients successfully completed both protocols. 8 of 11 hemodialysis patients completed static exercise, but 10 completed rhythmic exercise. 9 of 11 transplant patients completed static exercise, but all 11 completed rhythmic exercise. Statistical P values of < 0.1 are reported.

Results

There were no differences between groups in muscle energy metabolism during recovery from static or rhythmic hand-grip exercise. For all three groups, recovery curves of pH and [PCr]/([PCr] + [P_i]) were similar (Figs. 1 and 2). During rhythmic exercise, hemodialysis patients depleted PCr more rapidly than renal transplant recipients or normal controls (Fig. 2). Both dialysis patients and transplant recipients had lower pH, or greater intracellular acidosis, than normal controls (Fig. 2). Dialysis patients experienced more fatigue and maintained only 71±2% of their MVC, while transplant recipients maintained 78±1%, and controls maintained 81±1% of their respective MVC's ($P < 0.05$ vs both groups). Thus, dialysis patients more rapidly depleted phosphocreatine and generated greater intracellular acidosis at lower relative exercise intensity. The overall exercise response of transplant recipients was between that of dialysis patients and normal controls: they depleted phosphocreatine less than dialysis patients, but were more acidotic than controls.

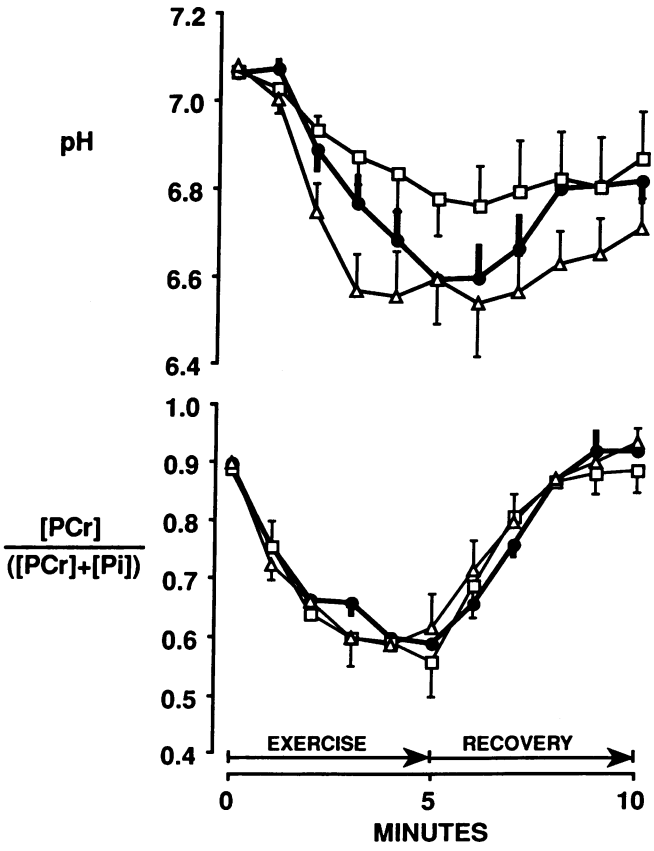

Figure 1. Intracellular pH and phosphocreatine stores ([PCr]/[PCr] + [P_i]) during and after 5 min of static exercise; initial force was 40% of MVC. Curves show similar recovery kinetics, minutes 6–10. □ HD patients, $n = 8$; △ RTX patients, $n = 9$; ● NC, $n = 9$; mean±SEM.

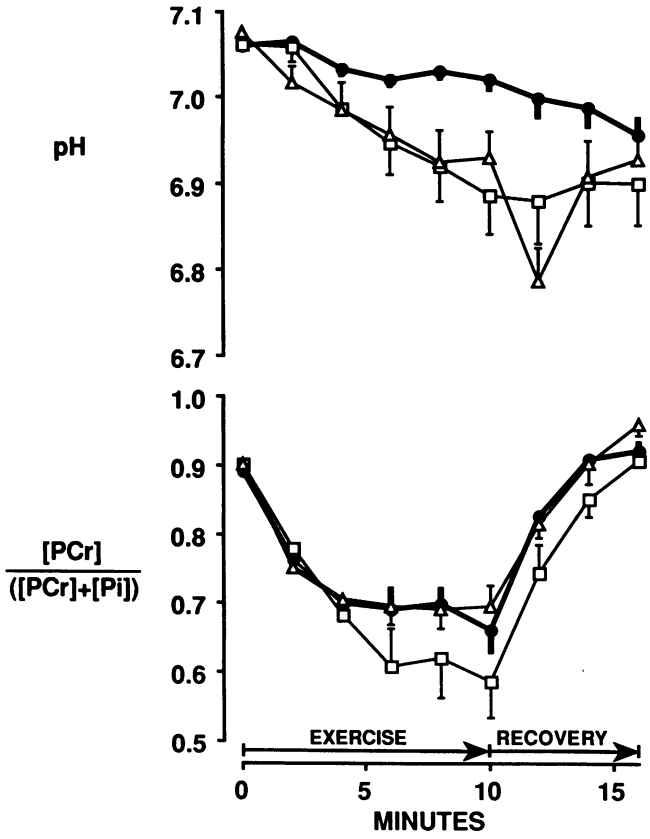

Figure 2. Intracellular pH and phosphocreatine stores ([PCr]/[PCr] + [P_i]) during and after 10 min of dynamic exercise, one MVC every 10 s. Controls had higher pH than dialysis patients ($P < 0.01$) or transplant recipients ($P < 0.01$). pH deviation in minute 12 of transplant recipients probably represents movement artifact. Dialysis patients had lower ([PCr]/[PCr] + [P_i]) than transplant recipients ($P < 0.05$) and normal controls ($P < 0.09$). Curves show similar recovery kinetics, minutes 10–16. □ HD patients, $n = 10$; △ RTX patients, $n = 11$; ● NC, $n = 9$; mean±SEM.

Discussion

The design of this experiment compares skeletal muscle metabolic responses to static and rhythmic exercise in three groups: hemodialysis patients, renal transplant recipients, and normal controls. The principle conclusions we draw from the results are: (*a*) that oxidative energy metabolism is subnormal in skeletal muscle of hemodialysis patients; (*b*) intrinsic ability to generate ATP is not the cause of this abnormality; and (*c*) that renal transplantation improves, but does not normalize, subnormal oxidative energy metabolism in exercising skeletal muscle.

One distinguishing feature of the present study was the use of both static and dynamic hand-grip exercise. Based on the reported differences in ^{31}P-MRS-determined pH, [P_i], and [PCr] during exercise with and without vascular occlusion (19), it is probable that static hand-grip is completely ischemic by nature. This observation is supported by the hydrostatic principle that when contractile force exceeds systolic blood pressure, blood flow through capillaries is prevented. The classic example is myocardial blood flow in the left ventricle, which occurs almost exclusively during diastole (20). Dynamic hand-grip is hyperemic by nature, local metabolic factors cause arteriolar vasodilation, the muscle contraction actively squeezes blood out of the capillaries, and blood flow is increased. Thus, static hand-grip ability is determined by the intrinsic metabolic capacity of the muscle, whereas rhythmic hand-grip ability is determined by the coupling of this intrinsic metabolic capacity to the oxygen delivery capacity of blood circulation to muscle.

Although ATP is produced by substrate level phosphorylation (glycolytic pathway), which is an oxygen-independent mechanism, the predominant source of ATP during muscular exercise is through the tricarboxylic acid cycle and oxidative phosphorylation, which are oxygen dependent mechanisms. Local ischemia during static hand-grip prevents ATP production by these oxygen dependent mechanisms, causing pyruvate to accumulate and be converted to lactate and hydrogen ions. Since only the glycolytic pathway produces pyruvate, intracellular pH roughly reflects glycolytic flux. Our use of pH to mark glycolytic flux was based on several previous findings. Most importantly, lactic acidosis is generally regarded as the dominant contributor to the decline in muscle pH (21–23). Furthermore, in the absence of robust glycolysis, even heavy exercise does not change muscle pH. Well-known examples are McArdle's disease, or myophosphorylase deficiency (24, 25), and glycogen depletion from endurance exercise (26–28). In McArdle's disease, lactic acidosis does not occur even during exercise with exogenous glucose administration, indicating that glucose uptake and oxidation are not adequate to cause muscle cell acidosis (29).

There are other causes of metabolic acidosis, but during exercise, these are likely to be small in comparison to lactic acidosis. For example, aerobic ATP generation causes CO_2 production. However, the reaction stoichiometry (30, 31) and inherent buffering capacity of skeletal muscle (32) cause CO_2 contribution to acidosis to be small. Residual oxygen, bound to myoglobin, could add to this oxidative source of acidosis, but intramyocyte P_{O_2} is only a few Torr during intense exercise (33), so this reserve and its effects are probably quite limited.

In addition to pH, the balance between energy supply (ATP) and demand (force maintained) is reflected by the fraction of PCr hydrolyzed to Cr and P_i. Therefore, we focused on intracellular pH and [PCr]/([PCr] + [P_i]) as indices that best describe the metabolic consequences of exercise, and are least sensitive to variance in voluntary effort, exercise intensity, or category of patient.

Based on these principles, the present data show subnormal oxidative energy metabolism in dialysis patients and renal transplant recipients. During static hand-grip exercise, pH and [PCr]/([PCr] + [P_i]) curves were similar for all groups. During rhythmic hand-grip, hemodialysis patients more rapidly developed intracellular acidosis and phosphocreatine depletion than transplant recipients, who were between hemodialysis patients and normal controls. These findings suggest hemodialysis patients have reduced oxidative generation of ATP, while transplant recipients have improved, but subnormal, oxidative ATP metabolism. In contrast, both hemodialysis patients and transplant recipients had normal postexercise recovery to baseline energy status, which is an oxygen dependent process. The recovery findings are inconsistent with reduced oxidative metabolism, and present a paradox with three possible explanations: (*a*) the patients had increased percentage, or recruitment, of type II fibers; (*b*) renal failure patients had increased use of ATP for noncontractile functions during exercise; or

(*c*) they had decreased oxygen flux from blood to muscle during exercise.

Numerous hemodialysis patient studies document myopathic changes, several of which could decrease oxygen-dependent metabolism. Deltoid, gastrocnemius, rectus femoris, and quadriceps femoris muscles have shown reduced oxidative enzyme activity, increased type II fiber percentage, fiber atrophy, low capillary density, mitochondrial inclusions, and low carnitine content (34–44); also, pallor of rectus femoris biopsy specimens implies low myoglobin content (personal observation of G. E. Moore). Each of these abnormalities would favor oxygen-independent energy metabolism (45–48).

The renal failure patients may have had different metabolic or biophysical efficiency than the controls, and required more ATP for a similar work output. Based on preliminary results from studies on hemodialysis patients, it has been suggested that exercise training may increase aerobic efficiency (4). One might reasonably speculate that hemodialysis patients require a greater fractional energy expenditure for noncontractile ATP-dependent processes, such as ion pumping. However, if this were a myopathic effect of uremia, we cannot explain why this would not persist during postexercise recovery.

There is good evidence for capillary-myofiber dissociation, i.e., myofibers without a capillary supply (4), which may have the most profound effect of all. The capillary-myofiber association is critical because this interface creates the greatest impedance to oxygen transfer from red cell to myocyte (49). Intramyocyte P_{O_2} is two or three Torr at peak exercise, some 20- to 50-fold less than arterial P_{O_2}. This enormous gradient occurs because the region comprised of the red cell wall, capillary, interstitial space, and sarcolemma has no carrier molecule, so transfer of poorly soluble oxygen depends on diffusion. This transfer is facilitated by acidosis, as the Bohr effect promotes release of oxygen from hemoglobin. Capillary-myofiber dissociation reduces capillary density and has two adverse effects: (*a*) the surface area for oxygen conductance is decreased, and (*b*) red cell transit time through capillaries is decreased. Since lower capillary density augments the greatest impediment to oxygen flux from blood to myocyte, we believe reduced oxygen flux is caused by decreased oxygen conductance. This hypothesis would provide a mechanistic basis for the observation that maximal oxygen extraction is attenuated in hemodialysis patients (50), and explain the disproportionality between hemoglobin and peak oxygen uptake after erythropoietin.

The present study preceded FDA approval of recombinant erythropoietin, anemia was not controlled, and low oxygen delivery might explain the present findings (51). ^{31}P-MRS muscle energy metabolism studies of EPO-treated hemodialysis patients are conflicting, one study showed improvement while the other did not (52, 53). However, previous EPO studies documenting very weak correlation between improved anemia and aerobic capacity suggest the major problem is oxygen extraction, not oxygen delivery.

What is the appropriate use of EPO if increased oxygen delivery alone does not benefit oxygen uptake? The present findings, exercise training data, and several EPO studies all suggest oxygen uptake is peripherally limited, so EPO therapy based on hemoglobin/hematocrit may not be functionally meaningful. Exercise training improves subnormal energy metabolism in congestive heart failure patients (54); maybe exercise training should be combined with EPO therapy in hemodialysis patients. It may well be worth the additional cost to combine exercise training with EPO therapy, to maximize benefit in functional capacity.

Acknowledgments

We gratefully thank Dr. Karl Brinker and the staff of Dallas Nephrology Associates.

This project was supported by a grant from the American Heart Association, Texas Affiliate, and National Institutes of Health grant RR-02584. L.A. Bertocci was supported by National Institutes of Health grant HL-07360.

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