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Original Article

Endurance exercise training during haemodialysis improves strength, power, fatigability and physical performance in maintenance haemodialysis patients

Thomas W. Storer[1,2], Richard Casaburi[2,3], Steven Sawelson[2] and Joel D. Kopple[2–4]

[1]El Camino College, Torrance, [2]David Geffen School of Medicine at UCLA, Los Angeles, [3]Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center, Torrance and [4]UCLA School of Public Health, Los Angeles, CA, USA

Abstract

Background. Endurance training improves cardiopulmonary fitness in maintenance haemodialysis (MHD). Because many MHD patients are profoundly deconditioned and exhibit significant muscle weakness, endurance training may also improve muscle strength and physical performance in these patients. This study assessed this possibility.

Methods. Twelve MHD patients performed incremental and constant work rate cycle exercise tests to determine peak work rate, VO_2peak and endurance time (ET). Lower extremity strength, power and fatigability, stair-climbing time, 10 m walk time and a timed up-and-go were assessed before and after 8.6 ± 2.3 weeks of thrice weekly, progressive, semi-recumbent, leg-cycle training during haemodialysis. Initial training intensity and duration targets were set at 50% peak work rate (WR) and 20 min, respectively, with a goal of progressing to 40 min at the highest WR tolerable. Non-exercising MHD patients and healthy volunteers with similar age, gender and race/ethnicity served as comparison groups.

Results. None of the subjects tolerated the initial target intensity. Therefore, WR was reduced to 19 ± 9 watts (30% of peak WR) for 19.9 min/session. At end of training, subjects cycled at 29 ± 25 watts (46% initial peak WR; $P = 0.01$) for 38 ± 8 min ($P < 0.001$). VO_2peak and ET improved 22% ($P = 0.018$) and 144% ($P = 0.001$), respectively. Quadriceps strength, power and fatigability improved 16% ($P = 0.002$), 15% ($P = 0.115$) and 43% ($P = 0.029$), respectively. The three measures of physical performance improved by 14–17% ($P < 0.031$). Total work performed in training increased by 5.5 ± 21.1 kJ/week (17%); a 165% increase during the study period.

Conclusions. Nine weeks of leg-cycling during haemodialysis in MHD patients improves not only cardiopulmonary fitness and endurance but also muscle strength, power, fatigability and physical function. These data underscore the value of endurance training in MHD.

Keywords: exercise capacity; muscle function; renal failure; semi-recumbent leg-cycling; total work

Introduction

A common but vexing complaint among many maintenance haemodialysis (MHD) patients is malaise and intolerance of virtually any form of exercise apart from self-care. Studies of exercise capacity and training in MHD patients frequently report low exercise tolerance [1]. Indeed, many studies indicate that MHD patients are profoundly deconditioned and often weak [2,3]. The cause of weakness is not entirely understood, but muscle atrophy, myopathy, malnutrition and carnitine deficiency have been proposed as contributors [2–4]. Recently, Johansen *et al.* [3] demonstrated that dialysis patients have significantly greater contractile area atrophy compared with healthy controls, even when corrected for habitual activity level. They further demonstrated that this atrophy was proportional to muscle weakness and reduced physical performance as determined by gait speed. These authors point out that the weakness resulting from muscle atrophy is an important cause of reduced physical function

Correspondence and offprint requests to: Thomas W. Storer, PhD, Division of Health Sciences, El Camino College, 16007 Crenshaw Blvd, Torrance, CA 90506, USA. Email: tstorer@elcamino.edu.
R.C. holds the Grancell-Burns Chair in the Rehabilitative Sciences.

and that greater emphasis should be placed on strategies to increase muscle mass and strength in this population [3].

Endurance exercise training has been examined most frequently as a therapeutic measure to improve physical capacity. Typically, endurance training improves VO_2peak by ~16% in MHD patients receiving erythropoietin [1]. While some studies have examined the effects of exercise training on physical performance (i.e. performance of daily functional activities, such as stair climbing, walking, rising from a chair) [1,5,6], fewer studies have focused specifically on examining the effects of exercise training on muscle function (i.e. strength, power and fatigability). These studies have used a variety of training methods; progressive resistance exercise training alone [7,8]; progressive resistance training combined with endurance training [9,10]; or endurance training using a variety of aerobic activities, ball games plus light resistance training [4]. A short study using twice weekly sessions of cycle ergometer endurance exercise for 6 weeks resulted in no changes in leg extension peak torque [11]. Although the most common and, possibly, the most convenient form of exercise training of MHD patients appears to be endurance training, there are no studies that have comprehensively assessed the effect of this type of training on muscle function.

The present study was undertaken to examine the extent to which endurance exercise training yields improvement in measures of muscle strength as well as physical function in MHD patients. The hypotheses tested were that (A) in the erythropoietin era where target haemoglobin levels are 11–12 g/dl, MHD patients still suffer not only from substantially reduced endurance performance, but also from a marked decrease in muscle function and the ability to carry out routine physical activities; (B) because of their profound muscular weakness, endurance exercise training in MHD patients provides an adequate stimulus not only to improve cardiopulmonary fitness, but also muscle strength, power and fatigability as well physical performance; and (C) endurance training leads to rapid increases in the amount of work that could be tolerated during exercise training.

Subjects and methods

Subjects

Twelve adults (seven males) undergoing MHD participated in this exercise-training study; they are referred to as exercising MHD patients. None of these patients had been exercising regularly before commencing the study. No patient had diabetes mellitus. A comparison group, designated as non-exercising MHD patients, consisted of 12 individuals undergoing MHD who received no exercise training but participated in assessments for most outcome measures before and after an 18 week study period. Causes of renal failure and comorbidities for the MHD patients are shown in Table 1. A second comparison group, comprised of 12 healthy, sedentary volunteers, was assessed only at baseline for the purpose of establishing reference values. Subjects in the two comparison groups were selected to be similar to the exercising MHD patients with respect to age, gender and race/ethnicity. All MHD patients were receiving erythropoietin as needed to maintain haemoglobin concentrations at 11–12 g/dl and continued all their medications during the course of this study. These studies were approved by the Los Angeles Biomedical Research Institute at Harbor–UCLA Medical Center and all subjects gave informed consent. Physical and clinical characteristics of the three groups at baseline are shown in Table 2.

Study design

All subjects completed baseline studies of cardiopulmonary fitness and muscle function. In addition, the exercising MHD subjects completed a series of physical performance tests and participated in 10 weeks of thrice weekly exercise sessions on a cycle ergometer during haemodialysis.

Cardiopulmonary exercise testing

To assess peak aerobic capacity (VO_2peak) and to ascertain the safety of exercise training, each participant completed a maximal incremental cardiopulmonary exercise test with 12 lead electrocardiography (Cardiosoft; Marquette Hellige, Munzinger, Germany) and blood pressure monitoring using standard methodology. The MHD patients performed these tests the day after a dialysis treatment. All tests utilized a calibrated electrically braked cycle ergometer (Ergoline 800;

Table 1. Causes of kidney failure and comorbidities in the MHD patients

Causes of kidney failure	Exercising MHD patients	Non-exercising MHD patients	Comorbidities	Exercising MHD patients	Non-exercising MHD patients
Hypertensive nephrosclerosis	8	6	Hypertension	11	4
Glomerulonephritis	1	2	Congestive heart failure	2	1
Nephrotic syndrome (unknown aetiology)	1	1	Past kidney transplant	4	
Polycystic kidney disease	1	0	Bilateral nephrectomy	1	
Cis-platinum therapy	1	0	Urinary retention		1
Unknown aetiology		3	Hepatitis C	1	
			Recurrent pancreatitis		1
			History of endometrial cancer	1	
			Recurrent herpes simplex I	1	
			Total abdominal hysterectomy	1	

Table 2. Physical and clinical characteristics of 12 MHD patients undergoing endurance exercise training and two comparison groups: 12 MHD patients who did not exercise and 12 healthy adults of similar, age, gender and race/ethnicity who did not regularly exercise

	Exercising MHD patients			Non-exercising MHD patients			Healthy volunteers		
	Females ($n=5$)	Males ($n=7$)	Total ($n=12$)	Females ($n=4$)	Males ($n=8$)	Total ($n=12$)	Females ($n=5$)	Males ($n=7$)	Total ($n=12$)
Age (years)	43 (3)	45 (11)	44 (9)	37 (11)	41 (7)	39 (9)	48 (12)	43 (12)	44 (12)
Race/ethnicity[a]	2/2/1	6/1/0	9/3/0	2/2/0	4/3/1	6/5/1	2/2/0	3/4/1	5/6/1
Height (cm)	162 (11)	179 (7)	172 (12)	159 (11)	169 (6)	165 (9)	159 (9)	171 (8)	167 (10)
Weight (kg)	66 (11)	83 (6)	76 (12)	65 (21)	69 (11)	67 (15)	63 (10)	750 (11)	70 (12)
BMI (kg/m^2)	25 (2)	26 (3)	26 (3)	25 (6)	24 (3)	25 (5)	24 (2)	25 (3)	25 (2)
MHD duration (months)	52.2 (41.0)	102.6 (97.1)	81.6 (80.2)	29.3 (14.6)	74.0 (100)	59.1 (83.1)	–	–	–
Haemoglobin (g/dl)	11.4 (1.4)	12.3 (2.8)	11.9^{b} (2.3)	12.5 (1.1)	12.1 (1.6)	12.8 (1.3)	13.2 (6.1)	14.5 (1.0)	14.1^{b} (1.1)
Serum urea nitrogen (mg/dl)	54.0 (11.7)	57.8 (15.3)	56.3^{b,c} (13.4)	29.5 (9.3)	39.4 (13.4)	36.1^{b,c} (12.7)	10.5 (2.1)	8.4 (3.1)	9.1^{b} (2.9)
Serum creatinine (mg/dl)	10.5 (2.6)	13.8 (1.8)	12.5^{b} (3.5)	7.7 (1.0)	11.3 (3.0)	10.1^{c} (3.0)	0.75 (0.19)	0.94 (0.23)	0.88^{b,c} (0.23)

Values are expressed as means (±SD). BMI, body mass index.
[a]African-American/Hispanic/Caucasian.
[b,c]Group means with the same superscript letter are significantly different, $P<0.05$.

SensorMedics Corporation, Yorba Linda, CA, USA) with work rate increments of 5–10 watts, so as to provide test durations of ~8–12 min. Minute ventilation and gas exchange were measured breath-by-breath with an automated metabolic measurement system (Vmax 229; SensorMedics, Yorba Linda, CA, USA). The key outcome variables analysed from 20s averages included VO_2peak and peak work rate. The VO_2peak was taken as the highest 20 s average for VO_2 during exhausting work.

Forty-five minutes following completion of the maximal incremental exercise test, subjects performed a constant work rate test with the same instrumentation. Work rate was set at 80% of the peak work rate achieved during the pre-training incremental exercise test. The same absolute work rate was used in both baseline and post-intervention constant work rate tests. Subjects were instructed to continue cycling for as long as possible, although a priori we chose to delimit the test to 15 min. The test was terminated when the subject could no longer maintain 50 r.p.m. pedal frequency despite encouragement or after 15 min had elapsed. Exercise duration was recorded to the nearest second with a stopwatch. The absolute difference in the duration of the constant work rate tests before and after training was taken as a measure of change in endurance performance.

Assessment of muscle function

Muscle function may be described with three primary performance components: strength, power and local muscle endurance, i.e. fatigability. To reduce the risk of tendon rupture or bone fracture [12], quadriceps strength was evaluated using the 5 repetition maximum (5-RM) approach [13] with the seated leg-press exercise (Keiser Sport, Fresno, CA, USA). For this assessment, subjects warmed-up with leg-cycling or treadmill walking followed by progressive warm-up lifts leading to the 5-RM. The 5-RM is defined as the maximum amount of weight that could be lifted in succession five times only with subjects being unable to complete a sixth repetition in good form using that weight.

Knee and hip extension power was assessed with a validated leg-power instrument (University of Nottingham Medical College, Nottingham, UK). Subjects were first familiarized with the procedures and then completed a 5–10 min warm-up. The test was performed with the subject's right foot on a foot pedal and the right knee flexed to 90°. The seat position required to achieve the desired knee angle was recorded to the nearest 0.5 cm for subsequent testing. Subjects were instructed to push the foot pedal as hard and as fast as possible. The instrument's data acquisition and processing routines calculated peak power (watts) using the mass of the flywheel and its revolution frequency. Trials were continued until peak power scores reached a plateau; typically 5–15 trials were required to observe a plateau. As the duration of effort required for each trial was <1 s, ~30 s rest was provided between trials. The power score was taken as the highest value observed during these trials and reported in watts/kg body weight.

Fatigability, the ability to sustain a static muscle contraction or make repetitive submaximal dynamic contractions, was assessed with the same bilateral leg-press exercise used in strength testing. After appropriate warm-up, subjects performed as many repetitions as possible against a resistance set to 80% of their pre-intervention 5-RM values.

To ensure reliability, the fatigability, power and 5-RM scores were reassessed within 7 days, but not <2 days after the first evaluation. If duplicate scores were within 5%, the higher of the two values was accepted as the strength score. If the two tests differed by >5%, additional studies were conducted ≥2 days apart, but within 7 days, until the two highest scores were within 5%.

Measures of physical performance

Three measures of functional performance were used: stair climbing, the ability to rise from a chair and walk a distance ('timed up-and-go') and time to walk a measured course. The stair-climbing task required subjects to ascend a four-step staircase (0.625 m) as fast as possible. A foot switch and a pair of photoelectric cells were interfaced with timers to measure the time of ascent. After familiarization, three trials were performed with the best time taken as the stair-climb score. Power (watts) was calculated from the subject's body weight, total vertical ascent and ascent time. The timed up-and-go was used as an assessment of functional mobility. Subjects rose from a standard, armless, wooden chair to a full standing position, walked 10 m, turned around a marker and returned to the seated position, performing these manoeuvres as fast as possible. A pressure switch was placed on the seat so that when subjects rose from the chair, a timer started. Returning to the chair and sitting stopped the clock. Five trials were given with 1 min rest between trials; the fastest time was accepted for the get-up-and-go score. Walking speed was determined to the nearest 0.01 s using photoelectric cells and timers over the middle 6.1 m of a 10 m flat course. Subjects were instructed to walk the measured course as fast as possible; the fastest of three trials was used as the final score for the walk test.

Exercise training

All exercise training was conducted during the first 90 min of the subjects' thrice weekly dialysis sessions, always under the direct supervision of an experienced exercise trainer, using an electrically braked, semi-recumbent leg-cycle ergometer (Sci-Fit Pro, Tulsa, OK, USA). Shortly after the start of an individual haemodialysis treatment, the ergometer was positioned so that the subject was able to exercise comfortably in the dialysis chair. Measurements of knee angle and ergometer positioning were recorded for precise repositioning on all training days. Heart rate, blood pressure and ratings of perceived exertion (RPE) were monitored every 10 min throughout each training session.

Initially, the training prescription was set for 20 min at an intensity representing 50% of the peak work rate achieved during the incremental exercise test [14]. However, some subjects were unable to tolerate this combination of intensity and duration of exercise, thus, requiring reductions in work rate so they could complete 20 min of cycling. If work rate reductions still precluded completion of 20 min of continuous exercise, an interval-training approach was employed. This consisted of using a 4:1 work:rest ratio, which was repeated until 20 min of cycling was completed. The work:rest ratio was adjusted upwards as tolerated until subjects were able to cycle for 20 min continuously at their initial work rate prescription. When subjects were able to tolerate 20 min at their prescribed work rate for three consecutive training sessions, duration increased as tolerated up to 40 min, at which time the load was increased as tolerated. To evaluate the rate of change in exercise tolerance, we calculated total work performed each training session (kJ) as the product of duration and work rate. Subjects were not given opportunities to make up missed training days.

Data analysis and statistics

Data are presented as means ± SD. Significance of changes from baseline after training within each MHD group was determined by paired *t*-tests. Significance of change from baseline between MHD groups was analysed with independent *t*-tests. Differences for baseline attributes as well as differences in post-training scores among the training group and the two comparison groups were determined by one-way analysis of variance (ANOVA). If ANOVA was significant, a Tukey post-hoc analysis was performed. A Kruskal–Wallis analysis was used to compare non-parametric data among the groups. Changes in total work per week over 10 weeks were assessed in a linear random coefficients mixed model using restricted maximum likelihood estimation with unstructured correlation between the linear equation parameters and Satterthwaite's determination of degrees of freedom. Statistical significance was taken as $P < 0.05$.

Results

Subject characteristics

Baseline characteristics of the exercising MHD patients and the two comparison groups are shown in Table 2. Nine of the exercising MHD subjects were African-American and three (including two women) were Hispanic. Subjects had been receiving MHD therapy for an average of 6.8 years (range: 0.8–24 years); their haemodialysers had multiple reuses. There were no significant differences among the groups for age, gender, race/ethnicity or body mass index. Neither haemoglobin nor serum creatinine values were different between the two patient groups. Serum urea nitrogen was significantly higher in the exercising patients compared with the non-exercising patients (Table 2). These clinical measures, including body weight, haemoglobin and serum creatinine and urea, obtained the day after a dialysis treatment in the baseline and post-training periods, did not change significantly in either of the two MHD groups (data not shown).

The 12 exercising MHD patients completed 8.6 ± 2.3 weeks (range: 4–10 weeks) of training. Eight of the 12 subjects completed all 10 weeks of the study. Of the remaining four patients, three developed acute illnesses of limited duration early in the course of training and then returned to their exercise-training regimen. Delayed recruitment of the fourth patient into the study and a firm deadline for termination of the protocol prevented these four patients from completing all 10 weeks of training. Compliance was calculated as days trained divided by the product of weeks completed and the number of training days possible per week, times 100. Overall, subjects averaged 88 ± 15% compliance (range: 66–100%). The eight individuals completing all 10 weeks of the study averaged 27.4 ± 3.1 exercising days out of 30 possible training days (91%). The remaining four subjects completing 4, 6, 6 and 7 weeks of training averaged 14.0 ± 4.7 days of training out of an average 17.3 ± 3.8 possible training days (81%).

Exercise training

Training intensity. The intensity of exercise during the first week of training averaged 19 (± 9) watts, corresponding to 32% (± 8%) of the subjects' pre-training peak work rate and 66% (± 24%) of the initial training intensity target. Despite this low work rate, the exercising MHD patients gave a subjective RPE of 'very hard' (6.8 ± 2.1) using the Borg 0–10 category-ratio scale. At the termination of their last week of training, patients were exercising at 29 ± 25 watts, representing a 46% increase (range: −28% to +233%) from their first week of training, but still were only at 88% of the initial target intensity. This work intensity corresponded to a subjective rating of effort of 'hard' (RPE: 5.2 ± 2.3), but was significantly lower than their RPE during the initial week of training ($P = 0.016$).

Training duration. Even with reduced training work rates, four patients were unable to complete the prescribed 20 min of continuous exercise during the first week of training, thus, requiring use of the interval training approach described in 'Subjects and methods'. On average, subjects completed a total of 19.9 (± 1.3) min of cycling per training session during the first week of training. Mean training duration in the last week of training was 37.9 ± 6.5 min per exercise session, a 90% (± 38%) increase from week 1.

Total work. Mean total work per week of training over subjects observed at each week and the numbers of subjects at each week are displayed in Figure 1. A mixed model was used to account for varying length of observation among subjects and to fit linear trends separately for each subject, thus, providing the summary regression line in Figure 1. The model predicts an increase of 5.5 KJ/week (95% confidence interval: 1.9–9.2 KJ/week; $P = 0.007$).

Cardiopulmonary exercise performance

Incremental exercise test

(i) VO_2peak. Average VO_2peak increased 22% ($P = 0.018$) in the exercising MHD patients (Table 3). Before training, subjects' VO_2peak averaged 57% of that for the healthy comparison group ($P < 0.001$). Training increased that average to 69% of VO_2peak observed in the healthy comparison subjects, a difference that remained significant ($P = 0.003$). Peak VO_2 did not change in the non-exercising MHD comparison group over their 18 week observation period (Table 3).
(ii) Peak work rate. As shown in Table 3, peak work rate in the exercising MHD group increased significantly following training ($P = 0.011$) with no change in the non-exercising MHD group. Peak work rate in the exercising MHD group averaged 43% ($P < 0.001$) of that for the healthy comparison group before training and increased to 60% of this value by the end of training ($P = 0.005$). No changes were noted for peak work rate in the non-exercising MHD comparison subjects.

Constant work rate test

(a) Endurance time. After training, the exercising MHD patients demonstrated a 144% increase in endurance time (5.5 ± 2 to 13.2 ± 3 min; $P < 0.001$) while the non-exercising MHD patients' endurance time decreased by 15% ($P > 0.05$). Half of the exercising MHD patients achieved

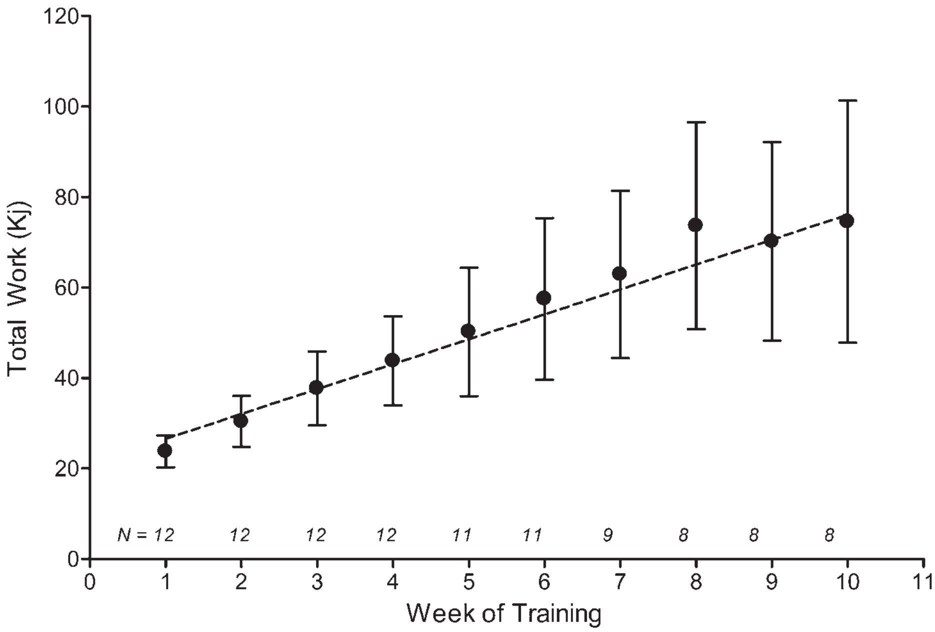

Fig. 1. Weekly mean (± SD) total work among subjects performing three leg-cycle training sessions per week. The dashed line gives the expected work according to weeks trained, calculated from random coefficients linear regression that accounts for varying weeks of training among subjects. *n*, number of subjects completing each training week. Total work was calculated from work rate and cycling duration each session and averaged over each week of training for each subject.

Table 3. Changes in endurance exercise performance in 12 MHD patients completing 8.6 weeks of progressive leg-cycle exercise training, 12 MHD patients who did not exercise and 12 healthy, sedentary volunteers

	Exercising MHD patients				Non-exercising MHD patients				Healthy volunteers
	Baseline	Post	Change (%)	P-value[a]	Baseline	Post	Change (%)	P-value[a]	Baseline
VO_2peak (ml/kg/min)	14.8[b] (4.2)	17.9 (6.1)	22[c] (20)	0.018	17.9[b] (6.2)	16.8[b] (7.0)	−6 (18)	0.238	25.8 (5.7)
Peak work rate (watts)	66[b,d] (32)	91 (48)	37[c] (31)	0.007	96 (37)	94 (38)	−9 (61)	0.806	152 (51)
Endurance time (min)	5.5 (2.0)	13.4 (2.6)	144[c] (170)	0.0001	7.8 (3.4)	6.7 (4.3)	−15 (30)	0.232	7.9 (2.6)
CWR test total work (kJ)	20.1[b] (14.2)	45.0 (22.6)	197[c] (194)	0.0009	31.1[b] (23.3)	19.0[b] (12.2)	−24 (17)	0.241	62.9 (50.0)

Values are expressed as means (±SD).
[a]Statistical significance of change from baseline.
[b]Significantly different from healthy comparison group, $P < 0.05$.
[c]Significantly different from change in non-exercising MHD patients, $P < 0.05$.
[d]Significantly different from baseline non-exercising MHD patients, $P < 0.05$.
CWR = Constant work rate

the pre-established ceiling of 15 min during post-testing. Consequently, improvements in endurance time for the exercising MHD group may have been underestimated.

(b) Total work. After training, the exercising MHD patients more than doubled total work output in the constant work rate test from 20.1 to 45.0 kJ ($P = 0.0009$). While still only 71% of the total work output in the healthy comparison group, the post-training values for these two groups were not statistically different (Table 3).

Muscle function

(I) Strength. Maximal voluntary muscle strength increased significantly in the exercising MHD group after 8.6 weeks of leg-cycling (16%; $P = 0.003$) (Table 4). This change was significantly greater ($P = 0.002$) than the non-significant 0.4% increase in the non-exercising MHD patients. After training, the initial 29% difference in 5-RM scores between the exercising MHD patients and the healthy comparison subjects was reduced by half and was not statistically different ($P = 0.391$).

(II) Power. At baseline, no differences in leg power (watts/kg) were observed among the three groups ($P = 0.217$) (Table 4). Training resulted in a non-significant 29% improvement in the exercising MHD group ($P = 0.115$) and a 7% decrease in the non-exercising patients.

(III) Fatigability. Repetitions to failure at 80% of the pre-training 5-RM improved significantly from 20 to 28 repetitions ($P = 0.029$) in the exercising MHD patients; the improved score was not significantly different from the fatigability score in the healthy comparison group (Table 4). The non-exercising MHD comparison group exhibited a non-significant decrease in leg-press fatigability.

(IV) Physical performance. All three measures of physical performance improved significantly after the leg-cycle exercise-training programme (Table 4). Stair-climb performance, expressed as time to ascend a total rise of 0.625 m as well as stair-climbing power (watts), increased by 14% ($P = 0.031$) and 22% ($P = 0.007$), respectively. Time to walk the middle 6.1 m of a 10 m walk course (expressed as velocity) improved from 164 to 194 cm/s, a 19% improvement ($P = 0.003$). Time to complete the timed-up-and-go test improved significantly 12% from 7.7 to 5.5 s ($P = 0.012$).

Discussion

The results from a number of endurance exercise-training studies in MHD patients indicate that these individuals can improve their exercise capacity. These studies focused primarily on the cardiopulmonary responses to endurance exercise training. The results of the present study underscore three key findings that may not be as well recognized in MHD patients undergoing endurance exercise training during haemodialysis. The first and principal finding is that MHD patients who complete a short-term progressive, low work rate, semi-recumbent leg-cycle endurance exercise training during haemodialysis can make substantial improvements not only in cardiopulmonary function, but also in muscle function and physical performance. The second key finding is that the ability to persist in relatively high work rate exercise can be improved significantly in MHD patients completing just 9 weeks of cycle exercise training. The third major finding is that tolerance of exercise training increases rapidly in MHD patients and that the rate of change in exercise tolerance can be sustained throughout an average of 8.6 weeks of training. Although this may be recognized

Table 4. Changes in muscle performance and physical function in 12 MHD patients completing 8 weeks of progressive leg-cycle exercise training, 12 MHD patients who did not exercise and 12 healthy, sedentary controls

Muscle function	Exercising MHD patients				Non-exercising MHD patients				Healthy volunteers
	Baseline	Post	Change (%)	*P*-value[a]	Baseline	Post	Change (%)	*P*-value[a]	Baseline
Leg-press strength, 5-RM (kg)	191[b] (62)	218 (77)	16[c] (10)	0.002	197[b] (52)	197[b] (48)	0.43 (4.9)	0.855	243 (56)
Leg extension power (watts/kg)	1.63 (1.05)	1.88 (0.71)	29[c] (41)	0.115	1.60 (0.66)	1.42 (0.44)	−7 (18)	0.195	2.11 (0.47)
Leg-press fatigability (repetitions)	19.7 (7.2)	28.3 (12.2)	53[c] (68)	0.029	24.7 (8.7)	19.7 (8.0)	−16 (26)	0.082	23.5 (8.7)
Physical performance									
Stair-climb time (s)	2.24 (0.46)	1.91 (0.53)	15 (18)	0.030					
Stair-climb power (watts)	222.0 (69.5)	270.3 (103.9)	22 (25)	0.007					
10 m walk (cm/s)	163.9 (57.4)	194.2 (72.8)	19 (16)	0.003					
Timed up-and-go (s)	7.56 (2.43)	6.50 (1.73)	12 (12)	0.012					

Values are expressed as means (± SD).
[a]Statistical significance of change from baseline.
[b]Significantly different from healthy comparison group, $P < 0.05$.
[c]Significantly different from non-exercising MHD patients, $P < 0.05$.

generally, experimental data in MHD patients are lacking, particularly the week to week changes in exercise tolerance.

Changes in cardiorespiratory function, muscle function and physical performance

Cardiorespiratory function. The 22% improvement in VO_2peak demonstrated in this study is similar to improvements reported in most previous studies conducted in the erythropoietin era [14]. Despite this improvement, the exercising MHD subjects in the present study remained 30% below the mean VO_2peak for the healthy comparison group (Table 3). It is possible that the short time course of training, the low absolute training intensity, the uraemic condition, including possibly a uraemic myopathy, and/or patients' comorbid conditions contributed to the failure to restore aerobic function to the level seen in the healthy population. However, periods of endurance exercise training as long as 6 months do not restore VO_2peak to normal values in MHD patients [4], suggesting that duration of training in itself cannot fully account for the inability of these individuals to attain normal endurance exercise capacity.

Muscle function. We believe that this is the first study to demonstrate in MHD patients significant improvements in measures of muscle strength, muscle power and fatigability consequent to endurance exercise training. Consistent with previous reports [1], muscle function was impaired in our exercising MHD patients. The baseline measures of muscle function averaged 20% below those seen in the healthy comparison group. However, all three measures of muscle function employed in this study showed significant improvement after short-term endurance exercise training. These improvements in muscle function include significant increases in leg-press strength (16%; $P = 0.002$) and fatigability (53%; $P = 0.029$) and a trend for improved leg extension power (29%; $P = 0.115$) (Table 3).

Typically, training goals for improvement in muscle strength and power are best achieved through task-specific resistance training [15]. Specificity of training suggests that in healthy individuals, endurance training has little effect on development of muscle strength or power [16]. The current findings that muscle function and physical performance improved with endurance training might be explained by the marked muscle weakness of MHD patients. Individuals in deconditioned states are regarded to exhibit the greatest initial gains in muscle function as a result of training because of a large adaptation potential [17]. Thus, endurance exercise training, even at lower intensities, may provide adequate resistance to improve muscle function in MHD patients. Our group has observed that in these same exercising MHD patients, mRNA levels for growth factors in skeletal muscle that promote hypertrophy tend to increase after training [insulin-like growth factor-I receptor (IGF-IR) 41%, $P = 0.013$; insulin-like IGF-I, 35%, $P = 0.107$]. Myostatin mRNA, which inhibits skeletal muscle hypertrophy, fell by 51% [18]. These data suggest that 9 weeks of endurance exercise training induce a cellular pattern of change in mRNA levels that may result in changes in synthesis of skeletal muscle protein that might promote the increased muscle performance observed in these patients.

The significant 16% improvement in leg-press strength observed in the present study using endurance exercise training alone is modest compared with the large improvements reported in the exercise-training regimens that combined resistance and endurance exercise in MHD patients or in pre-dialysis patients. One study that used resistance training alone in patients with chronic renal insufficiency not receiving dialysis [8] demonstrated a 32% overall increase in muscle strength. Surprisingly, however, the 16% increase shown with endurance exercise training in the present study was higher than the 12.7% improvement found after 12 weeks in a study using resistance training alone [7].

Several points should be considered when interpreting these findings. First is the difficulty in comparing results from different assessment methods and movement patterns. The small 12.7% increase in strength observed by Headley *et al.* [7] may have been compromised for two reasons. First, training was conducted on equipment that elicited a different type of muscle action (isoinertial) than that used for testing (isokinetic). Second, only 2 days of supervised isoinertial training was provided while a third day was performed using elastic resistance without supervision. Both reasons go against precepts of specificity of training and may have blunted measurement of the actual training effect.

We used 5-RM as our measure of strength in order to reduce the potential for injury [12]. It is possible that the 5-RM estimate of strength rather than the standard 1-RM method may have been more responsive to endurance training, since as repetitions-maximum increase above 1-RM the measurement becomes less a strength assessment and more an endurance assessment. Alternatively, studies that have assessed leg-press strength using the 5-RM and 1-RM methods in the same healthy individuals indicate that the 5-RM score is ~90% of the 1-RM and, thus, appears to be a reasonable surrogate strength measure [13].

Physical function. Every measure of physical function improved significantly in this study, supporting similar observations after endurance training in MHD and pre-dialysis patients [5,6,19,20]. Baseline 10 m walk velocity improved 19% from 164 ± 57 to 194.2 cm/s after training in the exercising MHD group. These velocities represent 73% and 86% of reference values and are somewhat higher both in speed and percentage improvement than those reported by Painter *et al.* in an older group of MHD patients [5]. The ability to improve walk speed has important functional significance in activities such as negotiating pedestrian crossings.

In the present study, stair-climbing time and power improved significantly, exhibiting increases of $15 \pm 18\%$ and $22 \pm 25\%$, respectively. Stair-climbing power is a function of time to ascend the stairs, total stair rise and body weight. Since body weight did not change significantly (data not shown), the increase in stair-climbing power may be attributed to muscle strengthening consequent to the endurance exercise training, thus, allowing a faster ascent. A similar observation was made by Mercer *et al.* [20], who noted a 22% improvement in the stair-climbing ascent segment of their WALK test. Improved stair-climbing speed and power noted in the exercising MHD patients may be helpful in negotiating stairways at home and in the community as well as in rising from a seated position.

Functional mobility, as determined by the timed up-and-go, improved $12 \pm 12\%$ in the exercising MHD patients. This finding induced by endurance exercise training is nearly identical to that of Heiwe *et al.* [19], who demonstrated an improvement of 13% after 12 weeks of dynamic and static quadriceps resistance exercise training in pre-dialysis patients. The observation that endurance exercise training was as effective as resistance training in improving functional mobility further emphasizes the low physical functioning of the MHD patient and the value of both endurance and resistance exercise training to improve physical function and perhaps quality of life.

Tolerance of exercise training. While it is expected that physical condition will improve in both healthy individuals and patients alike with a well-designed exercise-training programme, we are unaware of published studies examining the rate of change in exercise tolerance due to physical training in MHD patients. Significant improvements in endurance performance, muscle function and physical performance occurred within an average of 8.6 weeks of endurance training. Perhaps the most striking evidence for the improvement seen in the present study is that the average total work performed during each week of training began to increase almost immediately after the onset of exercise training. This improvement was apparent as early as the first week after training commenced (Figure 1). These observations suggest that MHD patients respond quickly to endurance exercise training and can make significant progress rapidly. Such quickly attained achievements may be motivating and help to maintain the commitment to exercise.

Limitations. The subjects used in this study were younger than the majority of patients who undergo MHD. In addition, small sample sizes and non-contemporaneous comparison groups may limit generalizability of the results. Subjects comprising the two patient groups were, however, drawn from the same dialysis units, followed similar dialysis practices and performed the same cardiopulmonary and muscle function tests using the same instrumentation as the exercising MHD patients. Subjects in both comparison groups were similar to the exercising MHD group with respect to age, gender and race/ethnicity. While not ideal, these characteristics offer some measure of control. The study may also limited by four of the 12 exercising MHD patients who did not complete all 10 weeks of training. We do not know if the significant improvements observed in the 12 subjects comprising the training group would have been further improved had they all completed 10 weeks of training.

In summary, significant improvements have been demonstrated in measures of muscle function and physical performance consequent to low work rate endurance training in MHD patients. These results are particularly noteworthy as they underscore the profound muscular weakness of MHD patients and emphasize the value of even modest, regular endurance exercise in stimulating significant improvements in muscle strength and physical function. Thus, lower intensity endurance training may provide appropriate preliminary conditioning and readiness for resistance exercise training that specifically targets improvement in measures of muscle function. In the event that resistance exercise training is not available or feasible, endurance training, as was employed in the present study, may provide good initial improvements. The observation that use of low work rate endurance exercise training can result in rapidly achieved and significant improvements in not only endurance performance, but also measures of muscle function and physical performance should be encouraging to both clinicians and patients.

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