ORIGINAL ARTICLE

Exercise Training During Hemodialysis Improves Dialysis Efficacy and Physical Performance

Trisha L. Parsons, PhD, Edwin B. Toffelmire, MD, Cheryl E. King-VanVlack, PhD

ABSTRACT. Parsons TL, Toffelmire EB, King-VanVlack CE. Exercise training during hemodialysis improves dialysis efficacy and physical performance. Arch Phys Med Rehabil 2006;87:680-7.

Objective: To determine the impact of a 20-week intradialytic exercise program, consisting of 60 minutes of cumulative duration, low-intensity exercise during the first 2 hours of dialysis, on dialysis efficacy, physical performance, and quality of life in self-care hemodialysis (HD) patients.

Design: One-group repeated measures.

Setting: Satellite HD units affiliated with a Canadian teaching hospital.

Participants: A convenience sample of 13 self-care HD patients who were stable on dialysis for a minimum of 6 months and were medically screened for significant cardiac, pulmonary, and/or musculoskeletal pathology that would preclude exercise.

Intervention: A 5-month intradialytic exercise program in which subjects exercised 3 times a week (cycle ergometer, mini-stepper) for 30 minutes in each of the first 2 hours of HD.

Main Outcome Measures: Dialysis efficacy (in single-pool model of urea kinetics [spKt/V]) was assessed prior to and at the end of each month of the exercise program. Physical function (6-minute walk test [6MWT]), and quality of life. (Kidney Disease Quality of Life–Short Form [KDQOL]) were determined at baseline and at weeks 10 and 20 of the exercise program.

Results: SpKt/V increased 11% at the end of the first month of the program ($P<.05$) and remained elevated for the duration of the program (18%–19%). Distance walked on the 6MWT increased by 14% at both weeks 10 and 20 ($P<.05$). No changes were noted in KDQOL scores.

Conclusions: A low-intensity intradialytic exercise program is a viable adjunctive therapy, which improves HD efficacy and physical function in HD patients.

Key Words: Exercise; Hemodialysis; Quality of life; Rehabilitation; Urea.

END-STAGE RENAL DISEASE (ESRD) is the point in kidney failure when approximately 90% of renal function has been lost, rendering the body incapable of maintaining proper fluid and electrolyte balance, adequate waste removal, and normal hormonal function.[1] To survive, people with ESRD must undergo some form of renal replacement therapy, namely, a kidney transplant, peritoneal dialysis, or hemodialysis (HD). In 2000, approximately 45% of the 25,000 Canadians with ESRD underwent HD, the fastest growing subpopulation of ESRD patients, and the focus population of this investigation.[2]

Despite regular HD treatments to replace some of the lost kidney function, HD patients suffer from a constellation of symptoms characterized by the "uremic" syndrome. These are typically manifested as (1) autonomic and/or motor neuropathies, (2) cardiac and/or skeletal muscle myopathies, (3) peripheral vascular changes (increased total peripheral resistance, impaired oxygen delivery), (4) anemia (loss of erythropoeitin production), (5) dysfunction of bone metabolism, (6) immunologic compromise, and (7) assorted physiologic complaints (nausea, vomiting, insomnia, fatigue, depression, anxiety).[3] Common ramifications of the uremic syndrome include (1) reduced physical work capacity to approximately 50% of that in healthy age- and sex-matched persons, (2) decreased health-related quality of life (HRQOL), and (3) cardiovascular disease including left ventricular hypertrophy, congestive heart failure, coronary artery disease, and hypertension.[4-6]

Exercise training in ESRD has lessened the impact of these ramifications by the attenuation of uremic neuropathies and myopathies, improved cardiac function, reduced blood pressure, increased physical work capacity, and overall enhancement in HRQOL.[7-10] Although most exercise programs have been instituted between dialysis sessions, recent investigations have promoted the concept of intradialytic exercise as a convenient intervention to improve compliance, provide motivation in a structured environment, and facilitate the medical monitoring of the exercising patient.[9,11]

We, however, approached intradialytic exercise from a physiologic perspective with the hypothesis that the increased muscle blood flow and greater amount of open capillary surface area in working muscles will result in a greater flux of urea and associated toxins from the tissue to the vascular compartment for subsequent removal at the dialyser. Few studies have measured the acute or long-term effects of intradialytic exercise on urea removal and dialysis efficacy in vivo. In response to a single bout of exercise, dialysis efficacy has been shown to increase between 15% and 25%.[12,13] This enhancement appears to be dependent on the total duration of intradialytic exercise, as those programs containing 30 minutes or less of cumulative exercise duration did not find improvements in dialysis efficacy with either an acute exercise bout[14] or training program.[15,16] However, total urea removal, measured in dialysate fluid, was significantly greater in subjects performing intradialytic exercise ($n=6$) as

From the School of Rehabilitation Therapy, Queen's University, Kingston, ON (Parsons, King-VanVlack); and Division of Nephrology, Kingston General Hospital, Kingston, ON (Toffelmire), Canada.

Presented in part to the Canadian Society of Nephrology, May 27–31, 2004, Toronto, ON, Canada; the Canadian Society of Nephrology, May 23–26, 2003, St. John's, NL, Canada; the McGill Rehabilitation Graduate Student Research Colloquium, April 25, 2003, Montreal, QC, Canada; and the Centre for Studies in Primary Care, Queen's University, February 27, 2003, Kingston, ON, Canada.

Supported by the Kidney Foundation of Canada (Allied Health Doctoral Fellowship); Garfield Kelly Research and Development Fund, Queen's University; and Bedal Foundation, Kingston General Hospital.

No commercial party having a direct financial interest in the results of the research supporting this article has or will confer a benefit upon the author(s) or upon any organization with which the author(s) is/are associated.

Correspondence to Cheryl E. King-VanVlack, PhD, School of Rehabilitation Therapy, Louise D. Acton Bldg, Queen's University, Kingston, ON K7L 3N6, Canada, e-mail: *kingce@post.queensu.ca.* Reprints are not available from the author.

0003-9993/06/8705-10267$32.00/0
doi:10.1016/j.apmr.2005.12.044

compared with nonexercising controls (n=7).[17] Zaluska et al[16] reported a 16% improvement in dialysis efficacy in 10 HD patients who cycled for 30 minutes during the first hour of dialysis over 6 months; however, some of this improvement may have been related to a significant increase in protein catabolic rate, which would augment urea clearance. To date, no study has definitively demonstrated that an intradialytic exercise program can result in improved serum urea clearance, the current clinical standard for the determination of dialysis efficacy.

The purpose of the current study was to determine the impact of a 20-week intradialytic exercise program, consisting of 60 minutes of cumulative duration, low-intensity exercise during the first 2 hours of dialysis, on dialysis efficacy, physical performance, and quality of life (QOL) in self-care HD patients. It is our hypothesis that intradialytic exercise will increase dialysis efficacy, which will in turn, be significantly correlated with improvements in physical performance and QOL.

METHODS

Participants

Self-care HD patients were recruited from the Kingston General Hospital Burr Wing and Belleville Satellite Dialysis Units. Subjects were recruited from the afternoon and evening sessions on the Monday-Wednesday-Friday rotation resulting in a total recruitment pool of approximately 50 subjects. People had to be on HD a minimum of 6 months, over the age of 18, and willing to sign an informed consent form approved by the Research Ethics Board at Queen's University prior to their inclusion in the study. Those subjects with significant cardiovascular, neurologic, and/or orthopedic complications, as determined by the attending nephrologists, were excluded from the study.

Exercise Program

A schematic representation of the study protocol is shown in figure 1. The exercise program was 20 weeks in duration. Subjects exercised, under the supervision of a physiotherapist, 3 times a week corresponding with their thrice-weekly dialysis schedule. The prescribed exercise duration was 60 minutes, performed as two 30-minute exercise bouts with a 30-minute recovery period between bouts during the first 2 hours of a 4-hour dialysis session. This exercise protocol was chosen for 2 reasons. First, previous investigations showed that three 15-minute bouts of exercise during HD were insufficient to cause a detectable increase in serum urea removal and that two 30-minute bouts of exercise substantially elevated the amount of urea removed in dialysate fluid.[17] Second, many HD patients were unable to exercise during the third hour of dialysis due to hypotension; a common cardiovascular event later in dialysis.[17-19] Exercise was performed using either a weighted cycle ergometer[a] or a mini-stepper,[b] which provided resistance by hydraulic resistance. These 2 modalities were chosen because they elicit substantive increases in urea removal as measured in dialysate fluid[17] and the machines could be readily positioned on the floor directly in front of the dialysis recliner for subject use. Subjects selected their own exercise intensity (pace, load) in which they could comfortably complete 30 minutes of exercise in a given bout. Regardless of the self-selected exercise intensity, heart rate increased on average 20 beats per minute across all subjects. Blood pressure and heart rate were recorded at rest, at 15 and 30 minutes of exercise, and at 15 minutes of recovery.

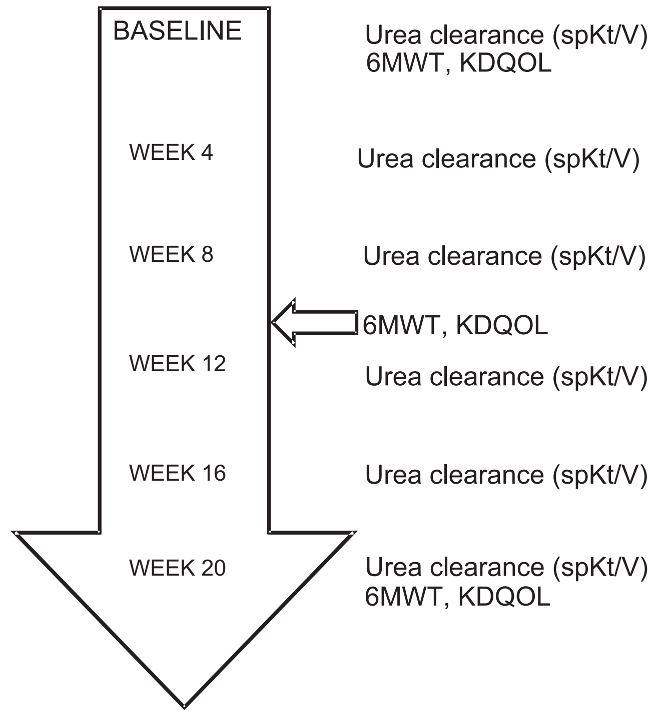

Fig 1. Schematic of study protocol. Baseline measures (spKt/V, 6MWT, KDQOL) were obtained prior to the start of the 20-week intradialytic exercise program. spKt/V was measured every 4 weeks of the exercise program while 6MWT and KDQOL were measured at weeks 10 and 20 of the exercise program. Abbreviations: KDQOL, Kidney Disease Quality of Life–Short Form; 6MWT, six minute walk test; spKt/V, single-pool model of urea kinetics.

Outcome Measures

Serum urea clearance. Urea is a middle molecular weight molecule that readily crosses the dialysis membrane and the clearance of this molecule from the blood during dialysis is the standard measure of dialysis efficacy. A number of bedside equations are available to estimate urea clearance, the most common being the single pool model as defined by Jindal et al.[20] Therefore, urea clearance was determined at baseline and on a monthly basis during the exercise program. Pre- and postdialysis (immediately at the end of dialysis) blood samples were drawn (nephrology nursing staff) to obtain respective serum urea concentrations, in order to calculate a single-pool model of urea kinetics (spKt/V), according to the formula:

$$spKt/V = .04\ (C_o - C_t/C_o)(100) - 1.2$$

where C_o and C_t are the initial and end dialysis serum urea concentrations (in mmol/L), respectively.[20] SpKt/V is a dimensionless value representing fractional urea clearance and reflects the exchange of urea across 1 interface (1 pool); the vascular compartment and the dialyser.[21] The minimum target dose (in spKt/V) recommended by the Kidney Disease Quality Outcomes Initiative is 1.2.[22] However, the Jindal equation loses predictive accuracy when the percentage reduction of urea (PRU) is less than 45 and greater than 75. PRU is defined as:

$$PRU = \frac{(\text{pre SUN} - \text{post SUN})}{\text{pre SUN}}$$

where SUN is serum urea nitrogen.

Higher PRU, mathematically equivalent to the urea reduction ratio (URR), is associated with smaller body mass, female sex, or high-efficiency dialysis.[23] In this circumstance, spKt/V can be calculated using the second-generation logarithmic equation established by Daugirdas is recommended.[22]

$$spKt/V=(-1n[R-0.008\times t]+4-3.5\times R)\times UF/W$$

where R is the post-pre SUN ratio, t is session length (in hours), UF is the volume of fluid removed during dialysis (in liters), and W is postdialysis body weight (in kilograms).

Six-minute walk test. The 6-minute walk test (6MWT) was performed at baseline, at week 10 (mid), and at week 20 (post) of the exercise program according to the procedure recommended by the American Thoracic Society.[24] Subjects walked a premeasured, indoor circuit (43m), attempting to cover as much distance as they could in 6 minutes, with the measured distance in meters as the outcome. Blood pressure and heart rate were determined at rest, 6 minutes (peak exercise), and 5 minutes of recovery. The 6MWT has been shown to be a reliable indicator of functional performance in the ESRD population[25-27] and has previously been used as an outcome measure with intradialytic exercise training programs.[9,10,27-30]

Kidney Disease Quality of Life Questionnaire. The Kidney Disease Quality of Life–Short Form (KDQOL) was developed from the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and assesses QOL on 8 generic (physical function, role limitations due to physical problems, bodily pain, general health, social function, role limitations due to social problems, energy and fatigue, mental health) and 12 disease-specific subscales (effects of kidney disease, symptom list, work status, burden of kidney disease, cognitive function, sexual function, quality of social interaction, sleep, social support, dialysis staff encouragement, overall health, patient satisfaction).[31] Each subscale is scored out of 100, with higher scores indicating greater perceived health. Subjects completed the questionnaire independently, with assistance available from the investigators as required. The subscales were quantified using a software package obtained from the KDQOL authors. The KDQOL was administered at baseline, at 10 (mid), and at 20 weeks (post) of the exercise program.

Other blood work analyses. Serum concentrations for hemoglobin (in g/L), creatinine (in μmol/L), and potassium (in mmol/L) were determined from blood samples drawn at baseline and during each of the 5 months of training in order to monitor changes in oxygen carrying capacity, kidney function, and electrolyte balance, respectively.

Data Analysis

All data are reported as mean ± standard deviation (SD). One-way repeated-measures analysis of variance was used for comparison of study measures with multiple means comparisons performed using the Bonferroni post hoc test. Significance was accepted at P less than .05. Correlational analyses between spKt/V (urea clearance) and the 6MWT and QOL outcome measures were performed using the Spearman rank correlation.

RESULTS

Subject demographic data are summarized in table 1. Of 20 self-care HD patients that were recruited from the Kingston General Hospital Burr Wing and Belleville Satellite Dialysis units, complete data from 13 subjects were obtained. One subject was withdrawn from the study by the investigators after the baseline 6MWT, which revealed previously unrecognized exercise-induced angina. Two additional subjects withdrew due to orthopedic complications related to hyperparathyroidism and preexisting osteoarthritis limiting performance of the prescribed exercise program, respectively. Four other subjects withdrew due to either (1) a preexisting pulmonary condition that prevented regular participation in the exercise program (n=1), (2) an irregular dialysis schedule which precluded accuracy of the dialysis efficacy indices (n=1), (3) travel out of province for greater than 1 month (n=1), or (4) preexisting dialysis hypotension that prevented exercise on more than 80% of the dialysis sessions (n=1). Twelve of the 13 subjects received erythropoietin in order to correct anemia. The most common conditions that led to renal failure were polycystic kidney disease (n=3) and hypertensive nephrosclerosis (n=3). Two subjects were diagnosed with diabetes, 6 with hypertension, and 2 with osteoarthritis. Four subjects had documented cardiovascular disease. Ten subjects were receiving at least 1 antihypertensive agent: β-blockers (n=5), angiotensin-converting enzyme inhibitors (n=5), calcium channel blockers (n=6), and α-blockers (n=2). Dialysis prescription was set by the medical team, and monitored on a monthly basis. Four different dialysers were prescribed: Fresenius F80 (n=5), Fresenius F80S (n=1), Fresenius F80A (n=1), and Fresenius Optiflux 160 (n=6).

The values for predialysis hemoglobin (in g/L), serum urea (in mmol/L), serum creatinine (in μmol/L), serum albumin (in

Table 1: Demographic Profile of the Study Group (N=13)

Characteristics	Values
Age (y)	53±18
Protein catabolic rate ($g\cdot kg^{-1}\cdot d^{-1}$)	1.57±0.29
Dry weight (kg)	76.8±14.2
No. of women	5
Dialysis vintage (mo)	46±25
Primary diagnosis (n)	
Diabetic nephropathy	2
Hypertensive nephrosclerosis	3
Infectious glomerulonephritis	1
Polycystic kidney disease	3
Goodpasture's syndrome	1
Wegener's granulomatosis	1
Focal segmental glomerulonephritis	1
Uretic obstruction	1
Comorbidities (n)	
Diabetes mellitus	2
Cardiac history	4
Hypertension	6
Osteoarthritis	2
Medications (n)	
Erythropoeitin	12
β-blockers	5
Angiotensin-converting enzyme inhibitors	5
Ca^{++} channel blockers	6
α-blockers	2
Dialysis prescription	
Frequency (d/wk)	3×/wk
Duration (min)	243±5
Blood flow rate (mL/min)	386±42
Dialysate flow rate (mL/min)	539±110
Dialyser	OP 160 (n=6); F80 (n=5); F80S (n=1); F80A (n=1)

NOTE. Values are mean ± SD or as otherwise indicated.
Abbreviation: OP, Fresenius Optiflux.

Table 2: Predialysis Serum Chemistry Values (N=13)

Variable	Baseline*	Week 4	Week 8	Week 12	Week 16	Week 20
Hemoglobin (g/L)	119±8	120±8	118±8	118±7	115±4	117±5
Serum creatinine (μmol/L)	858±191	843±182	847±182	835±186	833±181	832±197
Serum potassium (mmol/L)	4.7±0.5	4.8±0.6	4.6±0.7	4.5±0.3	4.8±0.3	4.7±0.6
Serum urea (mmol/L)	21.2±4.3	22.2±5.7	21.6±4.9	21.1±4.1	21.9±4.5	21.2±2.9
Serum albumin (g/L)	41±3	41±3	40±4	39±4	39±5	40±4

NOTE. Values are mean ± SD.
*Baseline values obtained prior to the start of the intradialytic exercise program.

g/L), and serum potassium (in mmol/L) are listed in table 2. No significant differences were observed in these blood values across the 20-week exercise program.

The mean values ± SD for spKt/V using both the Jindal and second-generation Daugirdas equations and for PRU are listed in table 3. SpKt/V was determined on a monthly basis; however, there were a number of missing data points in months 2 and 3 of the training program, due to laboratory misplacement of data or last-minute alterations in patient's HD scheduling which led to skewing of serum urea data. Therefore, the data presented at baseline, and at weeks 4, 16, and 20 of the exercise program, represented complete data from all 13 subjects. Serum urea clearance (in spKt/V) was determined using the Jindal equation, which estimates dialysis efficacy from the PRU.[20] SpKt/V (Jindal) increased 15% by the end of week 16 of the training program and remained elevated at that level at week 20.

The Jindal equation provides a valid prediction of spKt/V when the PRU falls within the range of 45% to 75%, which was the case for all subjects at the beginning of the study. PRU increased significantly by the end of the first month of the exercise program and fell outside of the valid prediction range in 7 of the 13 subjects (see table 3). Due to this unforeseen occurrence, spKt/V was recalculated using the second-generation logarithmic equation described by Daugirdas because it is accurate across a wider range of PRU.[22] SpKt/V (Daugirdas) increased 11% by the end of 4 weeks of the exercise program and remained elevated at week 16 (19%) and at week 20 (18%). The values for spKt/V using the Jindal equation were significantly greater than those determined by the Daugirdas equation ($P<.01$).

The mean values ± SD for the distance walked on the 6MWT are shown in figure 2. Initially, subjects walked an average of 520±101m, which increased significantly to 572±95m and 593±108m at the end of 10 and 20 weeks of the exercise program, respectively; however, the values for 6MWT distance between weeks 10 and 12 did not differ significantly. This translated into an approximate 14% improvement in functional performance at the end of a 20-week intradialytic exercise program. A weak correlation ($r=.32$, $P<.06$) was found between the distance walked on the 6MWT and the spKt/V (Daugirdas).

Table 3: Serum Urea Clearance (in spKt/V)

Variable	Baseline*	Week 4	Week 16	Week 20
spKt/V (Jindal)	1.56±0.25	1.70±0.24	1.79±0.23†	1.75±0.24†
PRU (%)	68.9±6.1	72.6±6.0†	74.6±6.0†	73.8±6.0†
spKt/V (Daugirdas)	1.42±0.25	1.58±0.27†‡	1.69±0.30*‡	1.64±0.30†‡

NOTE. Values are mean ± SD.
*Baseline values obtained prior to the start of the intradialytic exercise program.
†Significant difference as compared with the respective control value at $P<.05$.
‡Significant difference as compared with Jindal value at the same time point at $P<.05$.

The baseline values for the KDQOL and the SF-36 questionnaire are listed in tables 4 and 5, respectively. No significant differences in either the generic or disease-specific subscales occurred as a result of the training program suggesting that there was no change in self-reported QOL. No significant correlations were observed between change in scores on the subscales on the KDQOL or SF-36 with the change in urea clearance using the Daugirdas equation (in spKt/V).

DISCUSSION

The primary findings of the current study were (1) an overall 11% increase in serum urea clearance and (2) a 14% improvement in functional performance using the 6MWT after a 20-week intradialytic exercise program. The intradialytic exercise program resulted in a substantive increase in dialysis efficacy; the consequence of which may be related to the observed improvements in functional capacity. It was hypothesized that with exercise during dialysis, the increase in muscle blood flow and open capillary surface area would increase the flux of urea from the tissue to the vascular compartment resulting in increases in serum urea clearance and hence improvement in dialysis efficacy. Serum urea clearance increased 11% after the first month of a 5-month training program using the second-generation Daugirdas equation and remained elevated at months 4

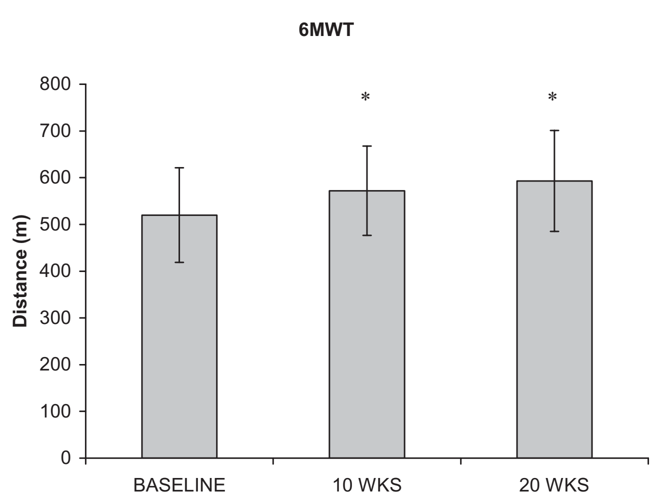

Fig 2. Functional physical performance as measured by the distance walked in meters during the 6MWT. Measures were obtained prior to baseline and at 10 and 20 weeks (WKS) of an intradialytic exercise program. Values are mean ± SD. *Significant difference from baseline value at $P<.05$.

Table 4: Comparison of Disease-Specific KDQOL Subscales: Current Study Versus Normative Data From a Hemodialysis Population in the United States

Subscale	Current Study Baseline Values (N=13)	U.S. HD Population[31] (N=165)
Symptom/problem list	82±14	72±16
Effects of kidney disease	68±19	59±23
Burden of kidney disease	49±17	50±30
Work status	69±25	23±36
Cognitive function	92±7	79±19
Quality of social interaction	81±16	80±17
Sexual function	95±7 (n=5)	69±34
Sleep	65±17	59±22
Social support	77±24	68±23
Dialysis staff encouragement	84±23	67±22
Overall health	64±15	59±20
Patient satisfaction	83±14	73±20

NOTE. Values are mean ± SD. Before the start of the exercise program (baseline values), subjects in the current study reported higher scores on all but one (burden of kidney disease) of the KDQOL subscales as compared with the U.S. HD population.[31]

(19%) and 5 (18%) of the training program. The Jindal equation was initially used to determine spKt/V but the PRU was increased with the intradialytic exercise program well beyond its valid prediction range for spKt/V (.45–.75). Using this less accurate prediction equation, significant changes in spKt/V were only observed toward the end of the exercise program. In contrast, the second-generation Daugirdas equation, which incorporates the ultrafiltration volume, postdialysis weight, and dialysis duration, provides a truer estimate of spKt/V across a wider range of PRU. Accordingly, with the Daugirdas equation, significant improvements in urea clearance were observed as early as the first month of the exercise program. These findings clearly indicate that exercise can be used as an adjunctive therapy to enhance dialysis efficacy. However, caution must be used when selecting the most appropriate modeling equation to assess dialysis efficacy with intradialytic exercise programs.

This is the first study to definitively demonstrate that a structured, low-intensity, 60-minute cumulative duration exercise program during dialysis will improve dialysis efficacy. Few studies to date have measured the acute or long-term effects of intradialytic exercise on urea removal and dialysis efficacy in vivo. Three studies have examined Kt/V responses to an acute exercise bout during 1 dialysis session[12,13] or over 3 dialysis sessions in 1 week.[14] Kong et al[12] found, using a double-pool model of urea kinetics (dpKt/V), that dpKt/V increased from 1.00 to 1.15, urea rebound decreased from 12.4% to 10.9%, and the URR increased from .63 to .68 in 11 HD patients who cycled for a cumulative duration of 60 minutes by performing 5 to 20 minutes of exercise interspersed with 10-minute rest intervals in a single dialysis session. In another study, 10 patients served as controls while 10 exercised throughout the dialysis session with 5 to 10 minutes of rest when necessary, using an adapted cycle ergometer.[13] Single and equilibrated pool (on-line dialysate monitor) Kt/V were significantly enhanced (≈25%), URR increased (≈10%), and urea rebound was reduced in the exercising as compared with control patients, in the face of a constant protein catabolic rate.[13] In contrast, no changes in equilibrated Kt/V (online urea monitor) (1.3±0.2 to 1.3±0.3) or URR (71.9±9.1 to 73.9±7.6, P=.08) were found in 12 HD patients who performed cycle exercise on average of 69±16min/wk or about 13min/dialysis session.[14] These findings suggest that exercise of a duration of 60 minutes or more performed during HD may enhance urea removal and therefore improve dialysis efficacy. However, little information was provided by the above studies with respect to the timing of the exercise during the dialysis session and the exercise intensity, making it difficult to interpret these results in terms of a standardized exercise protocol.

Three studies to date have examined the effect of an intradialytic exercise program over the course of several weeks on urea removal. Cappy et al[15] used a self-paced intra- or interdialytic exercise program in which subjects gradually worked up to 20 to 40 minutes of exercise per dialysis session over the course of a year. No significant changes in spKt/V from initial values of 1.38±0.32 occurred at 3 months (n=16), 6 months (n=6), or 12 months (n=4) of exercise training; however, the data for both intra- and interdialytic exercise subjects were pooled making it difficult to interpret the findings with respect to the effect of intradialytic exercise alone on spKt/V.[15] In another study,[17] HD patients (n=6) exercised for 15 minutes in each of the first 3 hours of dialysis at 40% to 50% of their maximum work capacity for 8 weeks. No changes in spKt/V or dpKt/V were noted across the exercise program between the exercise group (n=6) and the control group that did not perform intradialytic exercise (n=7). However, total urea removal as measured in the dialysate fluid over the first 2 hours of dialysis was significantly greater in the exercise group at 8 weeks of the exercise program as compared with the control group. These data suggested that exercise increased the rate of urea removal but the magnitude was insufficient to alter serum urea levels. In this study, approximately one third of the exercise bouts could not be performed in the third hour of dialysis due to vascular instability (hypotension); therefore, the average exercise duration was only 30 minutes per session and may have been insufficient to elicit changes in serum urea values.[17] In contrast, another study,[16] in which 10 HD patients cycled for 30 minutes during the first hour of dialysis over a period of 6 months, noted a 16.5% improvement in spKt/V (1.03±0.27 to 1.20±0.28, P=.026). Some of this improvement, however,

Table 5: Comparison of Generic QOL Subscales (SF-36)

Subscale	Current Study Baseline (N=13)	Painter et al[9] (N=180)	Oh-Park et al[30] (N=18)
Physical function	**74±21**	**48±28***	NR
Role–physical	**69±38**	**40±40***	NR
Pain	**80±24**	**61±28***	NR
General health	56±16	45±22	NR
Emotional well-being	86±11	72±19	NR
Role–emotional	92±28	64±42	NR
Social function	88±15	67±28	NR
Energy and fatigue	53±27	47±23	NR
Physical component summary	**45±8**	**35±11***	**36±9***
Mental component summary	**54±8**	**48±11**	**49±10***

NOTE. Values are mean ± SD. Baseline, pre-exercise program values in the current study. Pre-exercise intervention in 2 other investigations.[9,30]
Abbreviation: NR, not reported.
*Significant improvement (P<.05) occurred in this subscore value on completion of the respective exercise program. Physical function, role–physical, pain, physical component summary, and mental component summary subscales were higher in the current study as compared with the other 2 investigations (indicated by boldface).

may have been associated with a concurrent increase in protein catabolic rate because increased urea production will increase urea clearance. Therefore, the current investigation is the first to demonstrate a significant improvement in urea clearance (spKt/V) with about 60 minutes of low-intensity intradialytic exercise at a constant protein catabolic rate.

The intradialytic exercise program also resulted in enhanced physical performance (6MWT). Distance walked on the 6MWT increased approximately 14% in response to the 5-month exercise program, indicating a significant improvement in physical function in the exercising subjects. We had initially hypothesized that the enhanced dialysis efficacy would be associated with improved outcomes on the 6MWT. A causal relationship could have been established if a control group that exercised off-dialysis had been included in the study. Given that we started with 20 subjects and with the attrition rate we experienced, had we differentiated the subjects into 2 exercise groups (intradialytic, extradialytic), then the number of subjects per group would have been 6 or 7 which would have substantively limited the statistical power of the study. With the anticipated attrition rate, we chose to employ a 1 group within-subject repeated-measures design that allowed for a moderate degree of control, reduced the intersubject variability and increased group number. Despite this, the relationship between the distance walked on the 6MWT (in meters) and spKt/V (Daugirdas) demonstrated a weak correlation (r=.32, P<.06), most likely due to the small number of subjects and low statistical power of the linear correlation (.48).

The 6MWT has been used as an outcome measure of physical function in a number of exercise training programs in the ESRD population. Our findings are in agreement with those of Ridley et al[29] in which a 14% increase in the distance walked on the 6MWT was found in 18 HD patients who underwent a 12-week exercise program in which cycle exercise was performed during HD for about 60 minutes a session at an intensity that patients reported feeling as "slightly winded." However, other studies, which have used extradialytic programs, demonstrated lesser or no change in 6MWT performance in HD subjects. Painter et al[9] found an 8% increase in the distance walked on the 6MWT in 44 patients who participated in an 8-week home program and an 8-week intradialytic exercise program as compared to their baseline distance of 517±190m. Further, no significant changes in 6MWT distance were found in 20 HD patients who cycled for a shorter duration (20min) during dialysis (somewhat strong intensity on the Borg rating of perceived exertion scale) in combination with strength training before or after dialysis (50% of 5 repetition maximum) for 12 weeks.[28] Finally, Headley et al[27] reported a 5% increase in distance walked on the 6MWT (522±49m to 546±54m, P<.05) after 12 weeks of off-dialysis resistance training. Our program and that of Ridley,[29] which employed intradialytic exercise, resulted in similar improvements in 6MWT that were greater than those obtained using either a combination of intra- and extradialytic or purely extradialytic exercise. Two important points can be made from these comparisons. First, the 2 studies that employed strictly intradialytic exercise of 60 minutes in duration reported the greatest improvements in 6MWT as compared with combined intra- and extradialytic programs or purely extradialytic programs. This greater performance may be a consequence of the greater dialysis efficacy that we have demonstrated with intradialytic exercise. The 14% improvement in 6MWT performance is even more striking in our study, given the preexisting high level of function (baseline 6MWT, 520±101m) and the low intensity of the exercise program, because larger improvements are expected when starting from a greater level of deconditioning and/or using a higher intensity of exercise training.[32]

The 14% increase in 6MWT performance is most likely not due to a learning effect for 2 reasons. First, learning effects with the 6MWT have been primarily shown with repeat measures within the same day. In the current study, each subject performed the test only once at baselines and at 10 and at 20 weeks. It is highly unlikely that a learning effect persists for 10 weeks and no data have been published regarding repeatability greater than 4 weeks; however, it is assumed that this effect wears off after several weeks.[24] Further, we have conducted other pilot studies in which 15 HD patients performed the 6MWT prior to dialysis 3 weeks apart. We found that the mean difference in 6MWT distances between the 2 trials was less than 1% (546.6±148.8m vs 549.6±153.6m, P=.330). Our findings concur with those of Headley[27] who performed pre-intervention measures twice, 6 weeks apart in 10 HD patients on nondialysis days. The 6MWT distance averaged 522.1±46.2m in the first trial and 521.9±48.5m in the second trial, which were separated by 6 weeks. We are therefore confident that the increase in 6MWT distance was the result of the intradialytic exercise program and not due to a learning effect.

Physical work capacity is generally reduced in HD patients due to myopathies (cardiac and skeletal muscle), neuropathies (heart, blood vessels), and peripheral vascular pathology.[6] Given that these pathologies are associated with uremic toxins, we hypothesized that the increased clearance of toxins with intradialytic exercise would minimize the effect of these toxins on various physiologic systems, thereby enhancing cardiovascular and skeletal muscle performance. It is notable that the improved outcomes in urea clearance and physical function in the current study were the result of a low rather than a high intensity (60%–70% maximum heart rate) program normally recommended by more traditional exercise rehabilitation guidelines to improve endurance performance. Patients with ESRD represent a clinical population, which has severe functional limitations and for the practical implementation of a long-term adjunctive rehabilitation program during HD, patients are more likely to participate when the workload is not unduly taxing. Accordingly, offering a low-intensity intradialytic program, which is time efficient for the patient, improves dialysis efficacy, and increases physical function, can maximize patient participation.

Finally, the noted improvement in dialysis efficacy was not associated with improvements in self-reported QOL, as assessed by the KDQOL-36, which includes both disease-specific and generic subscales. Previously, we also found no change in generic QOL as assessed by the SF-36 after an 8-week intradialytic training program in 6 HD patients.[17] Other studies that have evaluated the impact of supervised exercise training have demonstrated stronger results with respect to changes in generic QOL in the HD population. Painter[9] reported a significant increase in the physical function (48±28 to 52±28, P<.05), role–physical (40±40 to 54±42, P<.001), bodily pain (61±28 to 70±26, P<.05), and physical component summary (PCS) subscores (35±11 to 38±10, P<.001) of the SF-36 in HD patients after a 16-week training program that consisted of an 8-week home program and an 8-week intradialytic cycling regime as compared with a nonexercising control group. Finally, Oh-Park et al[30] reported significant improvements in the mental component summary (MCS) (49±10 to 55±8, P<.004) and PCS (36±9 to 45±8, P<.003) subscale scores of the SF-36 in 18 HD patients after a 3-month intradialytic training program (2–3 times/wk; lower-extremity strength training and 30-min cycle ergometry). In both studies, the baseline values for the associated subscales were much lower than those in the present study (see table 5). Accordingly, the fact that these 2 studies found significant improvements may have been due to the fact that their patient population entered the exercise program at a lower HRQOL.

Therefore, other studies that have evaluated the impact of either mixed intra- and extradialytic or purely intradialytic exercise training have demonstrated improvements in generic QOL. Our inability to show significant changes in QOL in the current study may have been in part due to the preexisting high level of perceived well-being of the patients, and thus, a ceiling effect of the selected instrument. Manns et al[33] reported that patients with spKt/V levels greater than or equal to 1.3 had better QOL as measured by significantly higher scores ($P<.05$) in 4 of 11 kidney-disease targeted domains and 6 of 8 generic domains. In the current study, baseline spKt/V was 1.42±0.25 (Daugirdas), greater than the proposed threshold level of 1.3. In this respect, the relatively high scores of our subjects were not to be fully unexpected. However, it was surprising that our HD patient scores on the generic QOL subscales (SF-36) were similar to those reported for the healthy Canadian population[34] and the disease-specific subscale scores were greater on 11 of 12 subscales than those reported for an HD population in the United States (see table 4).[31] Painter et al[10] reported that HD patients with PCS scores less than 34 on the SF-36 showed significant improvement with exercise training while those with PCS scores greater than 34 did not. The 2 studies that demonstrated improvements in subscale scores of the SF-36 reported baseline PCS scores of 35±11[9] and 36±9,[31] respectively, almost 10 points below that reported in the current study (45±8) (see table 5). On the MCS, subjects in the current study reported an average score of 54±8, which was greater than the mean score reported in the general Canadian population (52±9),[34] suggesting a preexisting high level of mental, social, and emotional functioning. A number of our patients reported changes in their energy level, improved ability to perform daily activities, and a greater sense of accomplishment, which were not reflected by the results of the selected QOL instruments. Because this anecdotal information suggested there were QOL benefits associated without intradialytic exercise program, a qualitative investigation using a phenomenologic approach may better capture the QOL perceptions of HD patients undergoing an exercise rehabilitation program.

CONCLUSIONS

The primary findings of the current study were that a low-intensity, intradialytic exercise program resulted in a significant improvement in urea clearance perhaps due to the acute increases in blood flow to working muscle. Further, the long-term (20wk) low-intensity intradialytic exercise program resulted in physiologic adaptations that improved physical function (distance walked on the 6MWT). No significant changes were found in generic or disease-specific QOL after the 5-month exercise program, which was perhaps related to a ceiling effect on the selected instruments (KDQOL, SF-36). Further investigations are required to identify the mechanisms underlying the improvements in urea clearance with an intradialytic exercise program so that it may be effectively used as an adjunctive therapy to HD. The current study was unable to determine a causal relationship between enhanced dialysis efficacy with intradialytic exercise and improved performance on the 6MWT, due to the lack of an adequate control group that underwent an extradialytic exercise program and potentially due to low statistical power (low number of subjects). Clearly, this is the next issue to be addressed in future investigations. The consequences of improved dialysis efficacy with intradialytic physiologic manifestations of the uremic syndrome (ie, uremic myopathy, uremic neuropathy) have yet to be identified.

Acknowledgments: We thank Cherry Miranda and Jeffery Hawn for their assistance with data collection. And we thank the nursing staff both in the Burr Wing Dialysis Unit at Kingston General Hospital and the Belleville Satellite Dialysis Unit for their support and guidance during the exercise study. Special recognition goes to Margo McMurray, Diane Carty, Susan Pine, and Debbie Young for their enthusiastic support of the project.

References

1. Zawada ET. Initiation of dialysis. In: Daugirdas JT, Blake PG, Ing TS, editors. Handbook of dialysis. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p 3-11.
2. (CORR) Canadian Organ Replacement Register. Preliminary report for dialysis and transplantation 2002. Ottawa: Canadian Institutes of Health Information; 2002. Available at: http://secure.cihi.ca/cihiweb/dispPage.jsp?cw_page=reports_corr2002prelim_e. Accessed December 27, 2005.
3. Man NK, Zingraff J, Jungers P. Long-term hemodialysis. Boston: Kluwer Academic; 1995.
4. Diaz-Buxo J, Lowrie E, Lew N, Zhang H, Lazarus J. Quality-of-life evaluation using Short Form 36: comparison in hemodialysis and peritoneal dialysis patients. Am J Kidney Dis 2000;35:293-300.
5. Horl MP, Horl WH. Hemodialysis-associated hypertension: pathophysiology and therapy. Am J Kidney Dis 2002;39:227-44.
6. Johansen KL. Physical functioning and exercise capacity in patients on dialysis. Adv Renal Replace Ther 1999;6:141-8.
7. Koufaki P, Nash PF, Mercer TH. Assessing the efficacy of exercise training in patients with chronic disease. Med Sci Sports Exerc 2002;34:1234-41.
8. Deligiannis A, Kouidi E, Tassoulas E, Gigis P, Tourkantonis A, Coats A. Cardiac effects of exercise rehabilitation in hemodialysis patients. Int J Cardiol 1999;70:253-66.
9. Painter P, Carlson L, Carey S, Paul SM, Myll J. Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. Am J Kidney Dis 2000;35:482-92.
10. Painter P, Carlson L, Carey S, Paul SM, Myll J. Low-functioning hemodialysis patients improve with exercise training. Am J Kidney Dis 2000;36:600-8.
11. Cheema BS, Smith BC, Singh MA. A rationale for intradialytic exercise training as standard clinical practice in ESRD. Am J Kidney Dis 2005;45:912-6.
12. Kong CH, Tattersall JE, Greenwood RN, Farrington K. The effect of exercise during haemodialysis on solute removal. Nephrol Dial Transplant 1999;14:2927-31.
13. Sun Y, Chen B, Jia Q, Wang J. [The effect of exercise during hemodialysis on adequacy of dialysis] [Chinese]. Zhonghua Nei Ke Za Z 2002;41:79-81.
14. Vaithilingam I, Polkinghorne MB, Atkins R, Kerr PG. Time and exercise improve phosphate removal in hemodialysis patients. Am J Kidney Dis 2004;43:85-9.
15. Cappy CS, Jablonka J, Schroeder ET. The effects of exercise during hemodialysis on physical performance and nutrition assessment. J Renal Nutr 1999;9:63-70.
16. Zaluska A, Zaluska WT, Bednarek-Skublewska A, Ksiazek A. Nutrition and hydration status improve with exercise training using stationary cycling during hemodialysis (HD) in patients with end-stage renal disease (ESRD). Ann Univ Mariae Curie Sklodowska [Med] 2002;57:342-6.
17. Parsons TL, Toffelmire EB, King-Van Vlack CE. The effect of an exercise program during hemodialysis on dialysis efficacy, blood pressure, and quality of life in end-stage renal disease patients. Clin Nephrol 2004;61:261-74.
18. Moore GE, Painter PL, Brinker KR, Stray-Gundersen J, Mitchell JH. Cardiovascular response to submaximal stationary cycling during hemodialysis. Am J Kidney Dis 1998;31:631-7.

19. Bregman H. Complications during hemodialysis. In: Daugirdas J, Blake PG, Ing TS, editors. Handbook of dialysis. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p 148-68.
20. Jindal KK, Manuel A, Goldstein MB. Percent reduction in blood urea concentration during hemodialysis (PRU). A simple and accurate method to estimate Kt/V urea. ASAIO J 1987;33:286-8.
21. O'Connor AS, Leon JB, Sehgal AR. The relative predictive ability of four different measures of hemodialysis dose. Am J Kidney Dis 2002;40:1289-94.
22. National Kidney Foundation. Kidney Dialysis Outcome Quality Initiative (K/DOQI). Clinical practice guidelines for hemodialysis adequacy: update 2000. Available at: http://www.kidney.org/professionals/kdoqi/guidelines_updates/doqi_uptoc.html#hd. Accessed December 27, 2005.
23. Frankenfield DL, McClellan WM, Helgerson SD, Lowrie EG, Rocco MV, Owen WF Jr. Relationship between urea reduction ratio, demographic characteristics, and body weight for patients in the 1996 National ESRD Core Indicators Project. Am J Kidney Dis 1999;33:584-91.
24. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
25. Fitts SS, Guthrie MR. Six-minute walk by people with chronic renal failure. Am J Phys Med Rehabil 1995;74:54-8.
26. Holub C, Lamont M, Lombardo A, et al. The reliability of the six-minute walk test in patients with end-stage renal disease. Acute Care Perspect 2002;11:8-11.
27. Headley S, Germain M, Mailloux P, et al. Resistance training improves strength and functional measures in patients with end-stage renal disease. Am J Kidney Dis 2002;40:355-64.
28. DePaul V, Moreland J, Eager T, Clase CM. The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: a randomized controlled trial. Am J Kidney Dis 2002;40:1219-29.
29. Ridley J, Hoey K, Ballagh-Howes N. The exercise-during-hemodialysis program: report on a pilot study. CANNT J 1999; 9(3):20-6.
30. Oh-Park M, Fast A, Gopal S, et al. Exercise for the dialyzed: Aerobic and strength training during hemodialysis. Am J Phys Med Rehabil 2002;81:814-21.
31. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL) instrument. Qual Life Res 1994;3:329-38.
32. Painter P, Moore G, Carlson L, et al. Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. Am J Kidney Dis 2002;39:257-65.
33. Manns BJ, Johnson JA, Taub K, Mortis G, Ghali WA, Donaldson C. Dialysis adequacy and health related quality of life in hemodialysis patients. ASAIO J 2002;48:565-9.
34. Hopman W, Towheed T, Anastassiades T, et al. Canadian normative data for the SF-36 health survey. Canadian Multicentre Osteoporosis Study Research Group. CMAJ 2000;163:265-71.

Suppliers

a. Monark Rehab Trainer Ergometer 881E; BHM Medical, 5155 Spectrum Way, Unit 33, Mississauga, ON l4W 5A1, Canada.
b. Avon Canada Inc, 5500 Trans-Canada Hwy, Pointe-Claire, QC H9R 1B6, Canada.