Exercise Performance Falls over Time in Patients with Chronic Kidney Disease Despite Maintenance of Hemoglobin Concentration

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Physical function is limited in patients with kidney disease, although previous studies have been confounded by anemia. What is not clear is how physical performance changes over time as renal function deteriorates. A cohort of 12 patients (10 male, two female; mean ± SD age 49 ± 11 yr) who had stages 3 to 4 chronic kidney disease without previous anemia were examined, and nine were followed for a 2-yr period. Assessments were made of peak oxygen consumption (VO_{2peak}) by cycle ergometry, leg extension strength, and fatigue on an isokinetic dynamometer and thigh muscle cross-sectional area (TMCSA) by computed tomography. At baseline, creatinine clearance was 31 ± 13 ml/min and hemoglobin concentration ([Hb]) was 129 ± 9g/L. VO_{2peak} was low (1.88 L/min, 82% of predicted), and maximal isometric voluntary contraction was 188 ± 42 Nm, with a TMCSA of 144 ± 27 cm^2. VO_{2peak} correlated with creatinine clearance corrected for body surface area ($r = 0.613$, $P = 0.034$) but not to [Hb]. VO_{2peak} adjusted for patient weight correlated with leg fatigue ($r = -0.693$, $P = 0.012$). For those with follow-up tests, there were falls in renal function by 28% ($P = 0.007$) and VO_{2peak} by 9% ($P = 0.03$), whereas [Hb] did not change. Leg strength fell across a range of isokinetic speeds ($P = 0.04$), whereas no change in TMCSA was observed. In conclusion, exercise performance as measured by aerobic (VO_{2peak}) and leg strength tests were reduced in patients with stages 3 to 4 chronic kidney disease. As renal function declined over time, there was a corresponding decline in exercise performance even when [Hb] was maintained.

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It is well recognized that patients with chronic kidney disease (CKD) have limited physical function. This has been shown both subjectively in quality-of-life surveys (1) and objectively by measures of exercise such as walking times/distances (2), treadmill (3) and cycle ergometry tests (4–6), and measures of strength (3,6–8). A reduced ability to exercise has significance not only on quality of life but also on morbidity and mortality. Using the Short Form 36 (SF-36) quality-of-life questionnaire, low scores for self-reported physical function in patients who initiated dialysis are independently associated with a higher mortality risk (to a level similar to that of low albumin) (9).

Why exercise performance is limited remains unclear. In patients with CKD, there is an independent association with exercise performance across a wide range of renal function (5) that can be improved significantly after renal transplantation (10). However, despite good kidney function and exercise training programs, the level of exercise performance does not return to expected "normal" values up to 1 yr after transplantation (11). The most significant feature that confounds many of these studies is anemia, which, when treated in both patients with CKD (12) and hemodialysis patients (13–17), has resulted in improved exercise performance. Unfortunately, the absolute rise in hemoglobin (Hb) has not been matched by similar improvements in exercise.

We also previously found impaired potassium (K^+) regulation during exercise in hemodialysis patients compared with healthy control subjects (18). Because muscle K^+ disturbances are linked with muscle fatigue (19), this was suggested to contribute to reduced exercise capacity in hemodialysis patients (18). When Hb concentration ([Hb]) was corrected, the change in plasma [K^+] to work performed ($\Delta[K^+]$/work) ratio (as a marker of K^+ regulation during exercise) was inversely related to [Hb] (15). This has not been studied in patients who have CKD and are not on dialysis.

We therefore studied patients who have CKD and have not had a history of anemia to assess the relationships of aerobic exercise performance, muscular strength, and fatigability with renal function and muscle mass. We then followed the cohort for up to 2 yr to examine the relative impact of changes in kidney function and [Hb] with respect to exercise performance. In addition, we studied aerobic performance with respect to K^+ regulation.

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Materials and Methods

Patients with CKD were recruited from the Royal Melbourne and Western Hospitals (Victoria, Australia) and followed for 2 yr or until they commenced dialysis if renal function deteriorated. The research was carried out under the principles of the Declaration of Helsinki. All patients gave written informed consent after approval from the human research ethics committees of the Royal Melbourne Hospital and Victoria University (Melbourne, Australia).

Inclusion criteria were age between 18 and 70 yr, a calculated creatinine clearance (Cockcroft-Gault) between 15 and 50 ml/min, and [Hb] ≥120 g/L with satisfactory iron stores. Exclusion criteria were a history of [Hb] <120 g/L at any time, expected to commence dialysis within 12 mo, body mass index >40 kg/m^2, significant history of left ventricular failure or ischemic heart disease, peripheral vascular or cerebrovascular disease, uncontrolled hypertension, severe hyperparathyroidism, pregnancy, active malignancy, or renal transplant.

Data were collected on patients' age, gender, and body size. Hematology and biochemistry tests were performed at baseline and every 3 mo during the course of the study. Creatinine clearance was calculated as per Cockcroft and Gault (20). Medications and medical and social history were noted at each exercise test visit.

Tests

The following tests were performed at both baseline and end of study. Cycle ergometry and leg strength tests were performed on different days separated by a minimum of 48 h.

Cycle Ergometry and Peak Oxygen Consumption. All tests were performed on an electronically braked cycle ergometer (Lode Excalibur, Groningen, Netherlands) with seat and handlebar positions kept constant for each patient upon repeated testing. An incremental exercise test was performed according to a protocol of 2 min seated rest followed by cycling with a pedal cadence of 60 to 70 rpm. An initial resistance of 15 W was applied and increased by 15 W each minute until fatigue, defined as the inability to maintain pedal cadence >60 rpm. Expired air was collected *via* a two-way nonrebreathing valve (Hans-Rudolph Co., Kansas City, MO) and a 6-L mixing chamber. Expired volume was measured using a flow transducer (KL Engineering, Sunnydale, CA), and mixed expired oxygen and carbon dioxide were analyzed by rapid responding gas analyzers (model S-3A; Amtek, Pittsburgh, PA). Ventilatory gas data were calculated over 15 s, and VO_2 was calculated (TurboFit, Ventura, CA). Recordings were taken every 15 s, and the VO_{2peak} was taken as the highest recorded mean of two consecutive results. All patients had 12-lead cardiac telemetry monitoring during the test and for 30 min after fatigue. Predicted VO_{2peak} was calculated using the formula of Wasserman for sedentary, healthy individuals (21).

Blood Sampling. A 20-G intravenous cannula was inserted into a dorsal hand vein or distal forearm vein for blood sampling during the test. The venous blood was arterialized by placing the hand in a water bath (45°C) for 10 min before exercise testing and sustained until 10 min into recovery (22). Samples were taken at rest; at the end of each minute of exercise until fatigue; at fatigue; and then at 1, 2, 5, and 10 min into recovery. A 4-ml sample was collected in a plain tube. A 0.5-ml whole-blood aliquot was removed and stored on ice for duplicate measures of [Hb] and hematocrit (Sysmex, K-800, Kobe, Japan). The remaining portion was centrifuged for 3 min at 4500 rpm. The plasma then was analyzed in duplicate for [K^+] (Ciba Corning 865pH/Blood Gas Analyzer; Bayer, Norwood, MA). Fluid shifts were calculated according to changes in [Hb] and hematocrit (23). Change in plasma volume (ΔPV) from baseline allowed the calculation of net K^+ change at each time point.

Leg Strength and Fatigue Tests. Isometric and dynamic leg strengths were assessed on an isokinetic dynamometer (Cybex Norm 770; Henley HealthCare, Medway, MA). The patients were seated in a chair with the back set at 90 degrees. Straps secured the patient across the chest, hips, and dominant thigh and ankle, with the axis of rotation centered to the femoral condyles, allowing assessment of dominant leg extension. The dynamometer was calibrated before every testing session, and torque data were adjusted for gravity. After a warm-up of 1.5 min, gentle extension and flexion and isometric strength (maximal voluntary contraction [MVC]) was assessed at a 60-degree knee extension, in triplicate. Isokinetic leg strength was performed at speeds of 60, 120, 180, 240, 300, and 360 degrees/s in triplicate through a range of 0 to 90 degrees. Each patient had a familiarization test. Formal tests then were conducted on 3 separate days, with the mean of the three tests recorded.

Muscle fatigue also was assessed on the dynamometer for the dominant leg. The patient performed 30 maximal extensions at an isokinetic speed of 180 degrees/s at a frequency of 0.5 Hz. The fatigue index (FI) was calculated as the percentage of force drop over the 30 repetition using the following formula:

$$\text{FI}(\%) = \frac{(\text{mean of 3 highest values in initial 5}) - (\text{mean of 3 highest values in last 5})}{(\text{mean of 3 highest values in initial 5})} \times 100$$

Each patient had a familiarization test. Formal tests then were conducted on 3 separate days, with the mean of the three tests recorded.

Thigh Muscle Cross-Sectional Area. Thigh muscle cross-sectional area (TMCSA) was measured by computed tomography (CT) scan (16 Channel Scanner, GE Medical Systems, Waukesha, WI). An initial anterior–posterior scout film was taken of the thigh, and then a single transverse image was taken of the dominant leg 20 cm above the medial femoral condyle. Muscle area was calculated as the total area of the muscle compartment minus the femur area.

Statistical Analyses

All data are presented as mean ± SD unless specified. Pearson correlation coefficients are used for baseline data, and a backward stepwise regression analysis model was used for multiple variables where stated. Paired *t* test was used to compare baseline and end-of-study results. All tests were performed using Sigma Stat software (version 2.03; SPSS Inc., Chicago, IL) with significance taken as $\alpha < 0.05$.

Results

Patient Characteristics

Twelve patients were enrolled (10 male, two female). No patients were undertaking any form of regular exercise. Baseline characteristics, cause of renal failure, biochemistry, and hematology are shown in Table 1. Although all patients completed the baseline set of tests, three patients subsequently withdrew. One deteriorated quickly and commenced dialysis 3 mo after baseline testing. One was unable to do further tests because of knee pain, and one withdrew because of poor recovery after major surgery. Therefore, nine patients had follow-up tests, and seven completed a full 2 yr.

For those with follow-up, calculated creatinine clearance fell (35 ± 13 *versus* 25 ± 11 ml/min; $P = 0.007$). During the same period, [Hb] did not change (131 ± 10 *versus* 126 ± 11 g/L; $P = 0.21$). There were no other changes from baseline characteristics for patient size and blood biochemistry (data not shown).

Table 1. Patient characteristics at baseline[a]

Patient	Gender	Cause of Renal Failure	Age (yr)	Weight (kg)	BMI (kg/m^2)	[Hb] (g/L)	Creatinine (mmol/L)	Creatinine Clearance (ml/min)	Urea (mmol/L)	[K^+] (mmol/L)
1	M	TIN	66	85	30	149	0.20	39	13	4.8
2	M	PCKD	35	92	38	121	0.26	46	12	3.9
3	F	PCKD	41	86	31	136	0.31	29	18	5.4
4	M	FSHS	50	108	32	115	0.52	23	33	5.3
5	M	IgA	46	109	32	121	0.27	47	14	5.0
6	M	GN	44	69	22	121	0.64	13	27	5.0
7	M	RVD	48	76	30	138	0.20	43	11	4.6
8	M	RVD/CE	62	72	27	133	0.36	19	28	4.9
9	M	Lithium	55	110	37	134	0.25	46	16	5.0
10	M	Reflux/RVD/stones	61	75	26	132	0.31	23	22	5.1
11	F	Alport syndrome	27	92	33	125	0.83	13	20	5.3
12	M	Diabetes	50	47	18	127	0.18	29	21	5.5
Mean (SD)			49 (11)	85 (19)	30 (6)	129 (9)	0.36 (0.20)	31 (13)	20 (7)	5.0 (0.4)

[a]BMI, body mass index; CE, cholesterol embolism; FSHS, focal and segmental hyalinosis and sclerosis; GN, glomerulonephritis; [Hb], hemoglobin concentration; IgA, IgA glomerulonephritis; [K^+], plasma potassium concentration; PCKD, polycystic kidney disease; RVD, renovascular disease; TIN, tubulointerstitial nephritis. Blood tests were taken at rest.

Medications varied greatly between patients. β Blockers were used by four patients, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers were used by 11, calcium channel blockers were used by four, diuretics were used by six, vitamin D was used by four, and insulin was used by one. During the trial, β blocker therapy did not change; 6 patients had alterations in vitamin D therapy and phosphate binders.

Cycle Ergometry and VO_{2peak}

All patients cycled to volitional fatigue, eventually stopping as a result of leg weakness ($n = 8$), shortness of breath ($n = 1$), or both ($n = 3$). Satisfactory test performance was indicated by the mean respiratory exchange ratio (RER) of 1.14 ± 0.05 at peak exercise (Table 2). Heart rate at fatigue was 93 ± 9% of maximum predicted (220 − age bpm for those who were not on β blockers compared with 63 ± 11% for those who were treated with β blockers; $P < 0.001$). There were no adverse events and, in particular, no significant adverse electrocardiogram changes during the tests or in recovery.

Results for VO_{2peak} achieved and predicted, peak work rate, total work achieved, and heart rate for the baseline test are shown in Table 2. Only two patients were able to achieve a VO_{2peak} >100% of predicted. Other than maximum heart rate,

Table 2. Results for incremental cycle ergometry test to volitional exhaustion (baseline test)[a]

Patient	VO_{2peak} (L/min)	Predicted VO_{2peak} (L/min)	% of Predicted VO_{2peak}	VO_{2peak}/Weight (ml/min per kg)	Exercise Time (min)	Peak Work Rate (W)	Total Work (kJ)	Peak HR (beats/min)	% of Maximum HR	Peak RER
1	1.60	1.96	82	18.8	8.75	120	38.5	84	55	1.14
2	1.94	2.53	77	21.2	10	135	49.5	150	81	1.14
3	1.60	1.83	87	18.7	9	120	40.5	100	56	1.17
4	2.24	2.84	79	20.8	11.5	165	64.8	140	82	1.10
5	3.28	3.04	108	30.0	15	210	108.0	178	102	1.19
6	1.75	2.53	69	25.3	9.5	135	45.0	139	79	1.05
7	1.76	2.20	80	23.3	10	135	49.5	149	87	1.14
8	1.29	1.94	67	17.8	6.5	90	22.0	163	103	1.07
9	2.06	2.49	83	18.7	10	135	49.5	156	95	1.14
10	2.09	2.07	101	27.9	10	150	49.5	150	94	1.11
11	1.74	2.13	82	19.0	9	120	40.5	196	102	1.15
12	1.16	1.81	64	24.7	7	90	25.2	110	65	1.22
Mean (SD)	1.88 (0.54)	2.28 (0.40)	82 (13)	22.2 (4.03)	9.7 (2.2)	134 (32)	48.5 (21.9)	143 (32)	83 (17)	1.14 (0.05)

[a]VO_{2peak}, taken as maximum result during incremental cycle test (calculated as mean of two consecutive 15-s results); Predicted VO_{2peak}, calculated from the formula of Wasserman *et al.* (21); Exercise Time, time to volitional fatigue, excluding 2 min of rest. Result taken as last completed 15-s period; Total Work, total cumulative work performed; HR, heart rate; % of maximum HR, percentage of maximum heart rate where maximum heart rate is calculated as 220 − (age) beats/min; RER, respiratory exchange ratio.

treatment with a β blocker had no impact on exercise results. From rest to volitional fatigue, plasma volume fell by a mean of 11 ± 5%, and plasma [K^+] rose (4.97 ± 0.42 *versus* 6.21 ± 0.51 mmol/L). This represents a rise in plasma [K^+] of 1.09 ± 0.25 mmol/L when corrected for the change in plasma volume and a corresponding $\Delta[K^+]$/work ratio of 25.9 ± 10.7 μmol/L per J.

From a reduced baseline VO_{2peak}, there was a further decline in VO_{2peak} with follow-up testing over 2 yr, matched by a reduced time to fatigue and total cumulative work performed (Table 3, Figure 1). The tests were comparable in peak RER and heart rates. There were no differences between baseline and follow-up tests in the relative decline in plasma volume (−10.5 ± 3.3 *versus* −9.1 ± 4.5%; $P = 0.39$) or increase in [K^+] (1.08 ± 0.18 *versus* 1.00 ± 0.22 mmol/L; $P = 0.36$) during exercise.

Leg Strength and Fatigue Tests

MVC was 188 ± 42 Nm ($n = 12$) at baseline and for those with follow-up testing did not change over time (Table 3). Dynamic strengths are demonstrated in Figure 2. The follow-up tests found significantly lower peak torque ($P < 0.05$) for isokinetic speeds of 60, 120, 180, and 240 degrees/s. Across the entire torque-velocity curve, including MVC, there was a main effect for time, with baseline greater than follow-up values ($P = 0.04$). When torque is expressed relative to weight (Nm/kg), follow-up tests had a lower peak torque ($P < 0.05$) for isokinetic speeds of 120, 180, and 240 degrees/s. When torque was expressed relative to the TMCSA, there were no statistical differences between baseline and follow-up tests. The calculated FI was 22 ± 7% at baseline. For the nine patients with follow-up tests, it did not change (21 ± 6 *versus* 19 ± 6%; $P = 0.62$).

Table 3. Comparative baseline and follow-up tests ($n = 9$) for cycle ergometry, leg strength and fatigue index, and TMCSA[a]

	Baseline	Follow-Up
VO_{2peak} (L/min)	1.83 ± 0.61	1.66 ± 0.58[b]
VO_{2peak} (ml/min per kg)	22.1 ± 4.1	20.1 ± 4.7[b]
% Predicted VO_{2peak}	80 ± 13	73 ± 12
Time to fatigue (min)	11.5 ± 2.4	10.3 ± 2.6[b]
Total cumulative work (kJ)	47.5 ± 24.8	37.6 ± 23.9[b]
Peak HR (beats/min)	136 ± 32	127 ± 33
% Peak HR	80 ± 19	75 ± 18
RER at fatigue	1.14 ± 0.05	1.10 ± 0.10
Body weight (kg)	83 ± 20	84 ± 22
MVC (Nm)	178 ± 33	172 ± 31
Isokinetic strength (Nm; degrees/s)		
60	150 ± 34	135 ± 27[b]
120	124 ± 33	111 ± 24[b]
180	104 ± 28	92 ± 17[b]
240	85 ± 24	71 ± 14[b]
300	68 ± 21	61 ± 16
360	61 ± 17	54 ± 17
FI (%)	21 ± 6	19 ± 6
TMCSA (cm^2)	145 ± 30	146 ± 32

[a]Data are mean ± SD. FI, fatigue index; MVC, maximal voluntary contraction; TMCSA, thigh muscle cross-sectional area.
[b]$P < 0.05$.

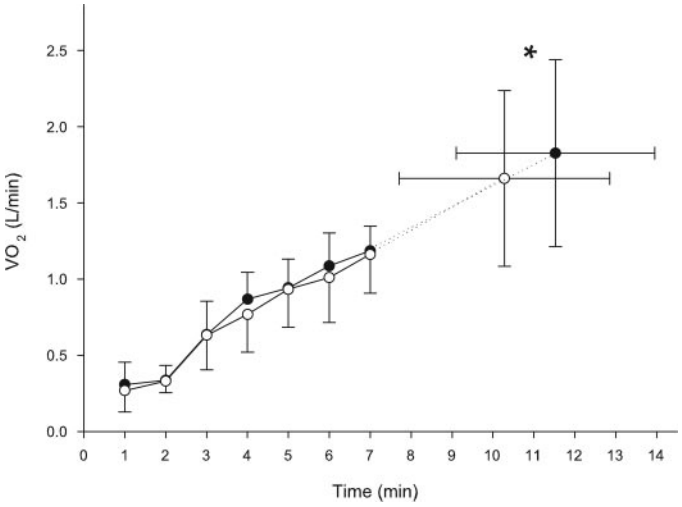

Figure 1. Mean (±SD) oxygen consumption (VO_2) during incremental cycle ergometry test to volitional exhaustion at Baseline (●) and end of study (○; $n = 9$). *Peak VO_2 (VO_{2peak}) was lower at fatigue for the end-of-study tests ($P = 0.03$), and the test duration was shorter ($P = 0.04$).

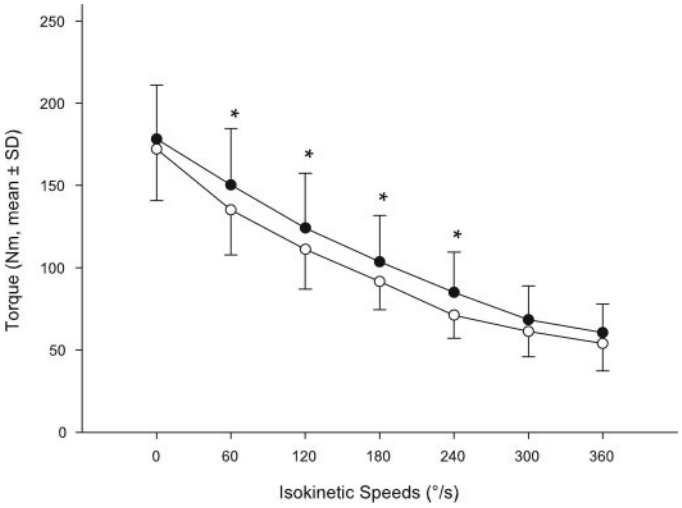

Figure 2. Mean (±SD) isometric and isokinetic peak muscle strengths at baseline (●) and end of study (○) measured on Cybex Norm 770 dynamometer ($n = 9$; *$P < 0.05$). ANOVA across speeds between groups ($P = 0.04$).

TMCSA

The TMCSA at baseline measured 144 ± 27 cm^2 ($n = 12$). For the nine patients who were followed for 2 yr, this did not change ($P = 0.66$; Table 3).

Correlations

As with the normal healthy population, a strong linear relationship was seen between VO_{2peak} and the total work per-

formed ($r = 0.98$, $P < 0.001$; Figure 3). Baseline VO_{2peak} had a number of correlates on univariate analysis (Table 4), including creatinine clearance when adjusted for BSA (Figure 4). There was no relationship between VO_{2peak} and [Hb]. The change in creatinine clearance and the change in VO_{2peak} during the study period did not correlate. VO_{2peak} adjusted for weight correlated inversely with the thigh muscle FI ($r = -0.693$, $P = 0.012$; Figure 5). Baseline MVC correlated with weight ($r = 0.668$, $P = 0.0176$) and height ($r = 0.827$, $P < 0.001$) but not TMCSA, [Hb], or renal function ($n = 12$).

Discussion

This study examined patients who had moderate to severe CKD (stages 3 to 4) yet have maintained a near-normal [Hb] without a history of anemia. We found that exercise performance that was measured by VO_{2peak} on a cycle ergometer was significantly below that predicted for healthy, sedentary individuals of the same age and gender (21) and inversely correlated to thigh muscle fatigue. We also found that despite the maintenance of [Hb], VO_{2peak} declined a further 9% as mean creatinine clearance fell by 28%. This was also associated with a decline in muscle strength, despite maintenance of muscle cross-sectional area.

Measured either by peak work rate or VO_2, numerous exercise studies have demonstrated that patients with CKD underperform compared with predicted performance capabilities (24) or with healthy control subjects (8); however, the relationship between renal function and exercise capacity usually is confounded by the associated anemia that occurs with CKD. Anemia *per se* is well established as a factor that limits exercise in the normal population (25,26), and a direct relationship between Hb and VO_2 also has been demonstrated in patients with CKD (5,6). Furthermore, when anemic patients with CKD are treated with erythropoietin to increase [Hb], exercise capacity (12) and VO_{2peak} (27) have been shown to improve, although only modestly compared with the increase in [Hb]. The patients in this study had not previously been anemic, and they maintained a near-normal [Hb] throughout; however, of note is that these patients already had a reduced VO_{2peak} at entry to the study despite the preserved [Hb]. During 2 yr of follow-up, we found a further 9% fall in VO_{2peak} without a change in [Hb], suggesting that, at least in this cohort of patients, factors other than a decline in oxygen-carrying capacity influence the deterioration in exercise performance.

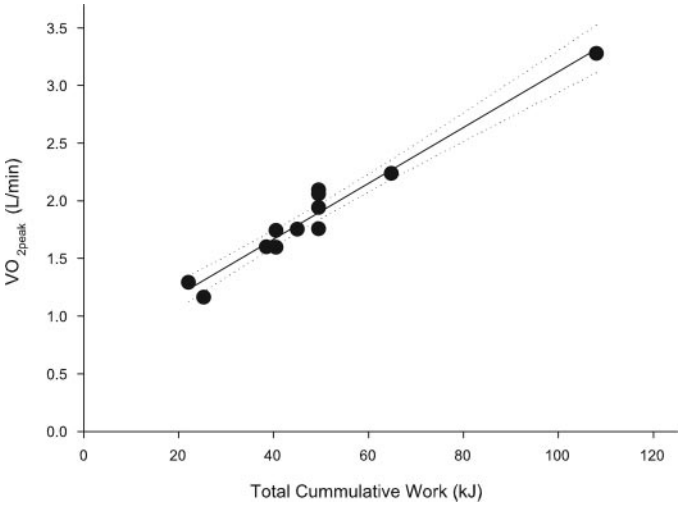

Figure 3. Correlation between VO_{2peak} for incremental cycle ergometry test and total cumulative work performed during the test for 12 patients at baseline. Regression line is shown with 95% confidence intervals (CI; $r = 0.98$, $P < 0.001$).

Table 4. Univariate correlations with VO_{2peak} at baseline tests ($n = 12$)

VO_{2peak} (L/min)	r	P
Creatinine clearance corrected for BSA (ml/min per 1.73 m^2)	0.613	0.034
Weight (kg)	0.730	0.007
Height (m)	0.719	0.008
MVC (N)	0.661	0.019
TMCSA (cm^2)	0.619	0.032
[Hb] (g/L)	−0.405	NS

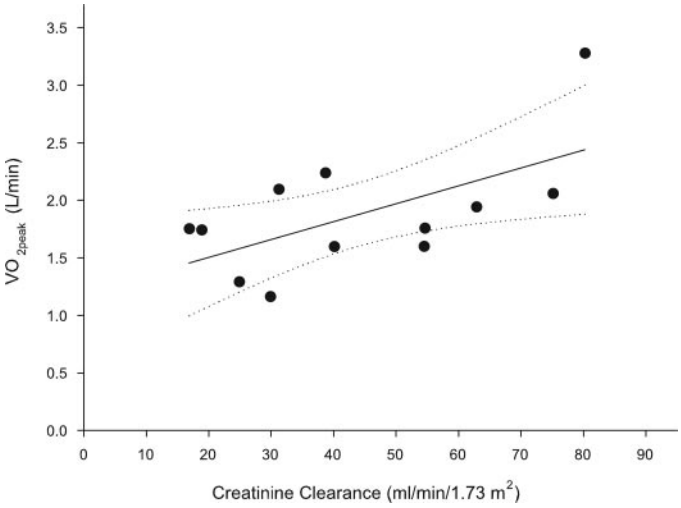

Figure 4. VO_{2peak} *versus* creatinine clearance (Cockcroft-Gault, corrected for BSA) for baseline tests. Regression line ± 95% CI ($r = 0.613$, $P = 0.034$; $n = 12$).

Our findings support a strong relationship between renal function and VO_{2peak} in those with moderate CKD even when [Hb] has been maintained. It seems that at least moderate renal dysfunction is required before this relationship is observed. Previously, Clyne *et al.* (5) demonstrated a correlation between reduced GFR (<30 ml/min) and maximal exercise capacity when controlled for Hb, and a *post hoc* analysis of the Heart and Estrogen/Progestin Replacement Study (HERS) found poor subjective physical function correlated with renal function beginning when the GFR fell below 60 ml/min (CKD stage 3) (28). This also is supported by a study of young adults with mild renal impairment (29) and another in the elderly (30), which had similar exercise performances to their control groups.

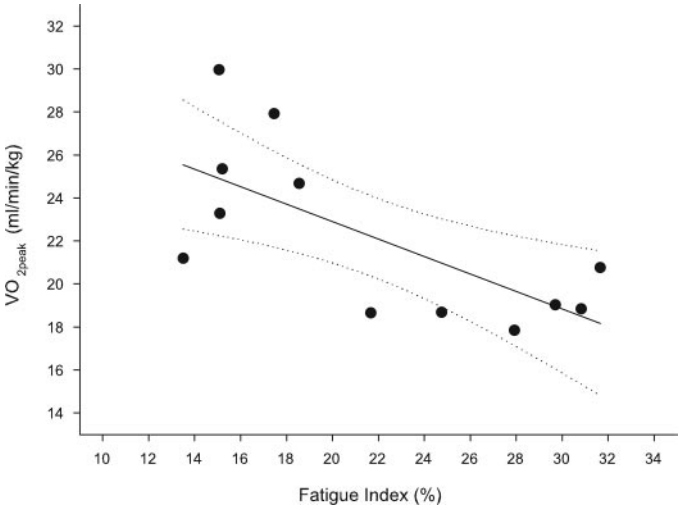

Figure 5. VO_{2peak} (adjusted for body weight) *versus* fatigue index (% force fall over 30 leg extensions performed at 0.5 Hz, 180 degrees/s; $n = 12$; $r = -0.693$, $P = 0.012$). Regression line ± 95% confidence interval.

One factor that is known to affect aerobic performance is muscular strength. For this cohort of patients, we found a relationship between VO_{2peak} and strength (MVC). This relationship has previously been noted by Diesel *et al.* (31), who found in hemodialysis patients that strength was a better predictor of exercise capacity than [Hb]. Kettner-Melsheimer *et al.* (6) earlier had found a marked reduction in isometric leg extension strength in patients with CKD, being only two thirds that of healthy control subjects in men and one quarter in women. The patients in this study exhibited a mean MVC of only 85% of a comparative sedentary control group from our laboratory (unpublished data), a similar reduction to that from the predicted VO_{2peak}. Corresponding with the decline in aerobic performance over 2 yr was a fall in muscle strength parameters across the dynamic range of isokinetic strength tests.

The parallel reductions in both VO_{2peak} and muscle strength without a change in [Hb] suggest that intrinsic muscle changes such as enzymatic defects or alterations in fiber type and structure contribute more to poor performances than do limitations in oxygen supply. Underscoring this is our finding that the short isokinetic fatigue test correlated inversely with the longer aerobic VO_{2peak} results. This relationship also is suggested by a study that showed that strength training alone can improve VO_{2peak} (7) even when thigh muscle area does not change (3).

One enzymatic abnormality that potentially could affect exercise performance relates to the regulation of muscle intracellular K^+ by the sodium-potassium ATPase. Intracellular K^+ is reduced in renal failure (32), and resting muscle membrane potential has been found to change linearly in association with renal function (33). Disturbances in muscle K^+ homeostasis also have been linked with muscular fatigue (19). Together with a more recent study demonstrating a relatively higher plasma K^+ rise with exercise in hemodialysis patients (18), this suggests that abnormalities in muscle K^+ regulation may be a factor that limits exercise performance. Although the patients in this study had a relatively high plasma $[K^+]$ before exercise testing (5.0 ± 0.4 mmol/L), we found that the ΔK^+/work performed ratio was similar to that in the control subjects reported by Sangkabutra *et al.* (18), which was significantly lower than that in hemodialysis patients. Between baseline and follow-up tests in this study, however, there was no difference in the $[K^+]$ rise with exercise. We also found no correlation between the change in plasma $[K^+]$ and renal function, [Hb], or VO_{2peak}, suggesting that, in this cohort at least, $[K^+]$ increases did not restrict muscle performance and thus incremental exercise. The normal ΔK^+/work ratio found here is consistent with findings of McMahon *et al.* (15) in hemodialysis patients, in whom [Hb] raised from 100 to 140 g/L resulted in a lower ΔK^+/work ratio.

Histologic muscle changes that are found in CKD also may influence muscle function. Grossly altered muscle fiber size and fiber type distribution are seen in both patients with CKD (34,35) and hemodialysis patients (36,37). It is interesting that these can be improved not only with exercise training (38,39) but also when [Hb] is increased with erythropoietin treatment (40). In addition to fiber changes, the amount of contractile tissue will have an impact on exercise performance. We used CT scanning for cross-sectional area as a measure of index of muscle size and therefore were unable to determine fat content of the muscle. CT scanning has been validated as a reliable indicator of nutrition in hemodialysis patients (41); however a magnetic resonance scan is more sensitive. Magnetic resonance scanning previously found that the proportion of muscle contractile tissue is reduced in hemodialysis patients compared with healthy control subjects despite similar muscle size (42).

There are limitations to this study. The small sample size highlights the difficulties of enrolling patients with CKD in studies that require a long follow-up and a number of assessments. This was compounded by the relative difficulty of finding nonanemic patients with CKD. Selection bias was an additional potential limitation because the enrolled patients were likely to be healthier and well motivated. This, however, only highlights the very limited exercise capacity of patients with CKD in general as others are likely to have an even poorer performance. Another factor with the potential to limit VO_{2peak} could be the multiple medications that are required by patients with CKD. The most significant is β blocker therapy. Fortunately, this was not translated into a reduced exercise performance in this study. Although the four patients in this study had significantly lower heart rates at fatigue, there was no difference in any other parameter measured either before exercise or at fatigue, including the RER, consistent with previous studies (5).

Conclusion

Exercise performance was reduced in CKD stages 3 to 4 even in the absence of anemia. Whether measured by oxygen consumption or leg strength, exercise performance progressively fell as renal function deteriorated. The likely causes are myriad, although, in this study, intrinsic muscle changes that result in reduced muscle strength and fatigue, and aerobic performance are likely to be dominant. To maintain the well-being and functional capacity of patients with CKD, therefore, attention

should be directed toward maintaining strength and aerobic fitness as well as focusing on renal function and anemia.

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