

Exertional Fatigue in Patients With CKD

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Background: Fatigue is one of the most prevalent symptoms in chronic kidney disease (CKD). However, fatigue mechanisms are poorly understood due in part to nonspecific definitions. This study investigates exertional fatigue during simulated activities of daily living, focusing on oxygen delivery and utilization.

Study Design: “Explanatory” matched-cohort study.

Participants & Setting: 13 patients with CKD (stages 3b-4; mean age, 62 ± 13 [SD] years) and 13 healthy controls, mean matched for age, height, body mass and composition, and physical activity level. Participants completed an incremental cycle ergometer test to simulate energy expenditure of typical activities of daily living.

Factor: 4 exercise intensities: 1, 1.8, 2.4, and 3.1 metabolic equivalent tasks (METs).

Outcomes: The primary outcome was exertional fatigue by rating of perceived exertion (RPE) on a 6-20 scale.

Measurements: Other multidimensional measures of fatigue: UK Short Form Health Survey 36 (UK SF-36) Vitality and Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-Fatigue) subscales. Physiologic measures of the oxygen transport and utilization chain (expired gas analysis, cardiac output, and arterial oxygen content) and blood lactate.

Results: RPE was increased in patients compared with controls at 2.4 (10.5 [ie, light] ± 2.7 vs 8.7 [very light] ± 1.7 units) and 3.1 (12.5 [somewhat hard] ± 2.6 vs 10.2 [light] ± 1.7 units) METs (interaction $P = 0.03$), which was consistent with higher chronic fatigue in patients by both the UK SF-36 Vitality ($P = 0.01$) and FACIT-Fatigue ($P = 0.004$) subscales. Arterial oxygen content was decreased in patients ($P = 0.001$), but cardiac output and oxygen extraction ratio were unchanged, decreasing oxygen delivery ($P = 0.04$). Respiratory exchange ratio ($P = 0.004$) and blood lactate production ($P = 0.002$) were increased.

Limitations: Those inherent to a matched-cohort study.

Conclusions: Using a novel application of the outcome measure RPE, patients with non-dialysis-dependent CKD reported considerable exertional fatigue during simulated activities of daily living. Poor compensation for mild anemia contributed to this symptom. In addition to anemia, the entire oxygen transport chain needs to be targeted to treat fatigue in patients with CKD.

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INDEX WORDS: Activities of daily living; anemia; exercise capacity; hemoglobin; oxygen delivery; perceived exertion; quality of life.

In chronic kidney disease (CKD), fatigue is reported as the most prevalent and severe symptom experienced by patients.¹⁻³ Such fatigue has been identified as the principal factor influencing quality of life in this population,^{2,4,5} and fatigue also impacts on mortality.⁶ However, fatigue is poorly investigated, diagnosed, and treated in patients with CKD.

Scientific investigations in this area lack a precise definition of fatigue. Fatigue is recognized to be multidimensional in nature and consists of various subtypes, each of which may have distinct mechanisms.⁷ It has been advocated that explanatory studies of specific fatigue subtypes are needed to clarify pathophysiology in relation to phenomenology.⁷ One subtype of fatigue is exertional fatigue, defined as an increased sense of effort in relation to a task.⁸ This subtype can be measured easily during physical tasks using the extensively validated rating of perceived exertion (RPE) scale.⁹ By simulating normal activities of daily living and simultaneously obtaining measurements of RPE, it becomes possible to define and measure a specific construct of fatigue of particular relevance to quality of life.¹⁰

In addition to problems defining fatigue, the exact cause of fatigue in patients with CKD is unknown. One potential mechanism is an altered oxygen transport chain^{11,12}; oxygen delivery and/or oxygen utilization may be impaired in patients with CKD.¹³ In this

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regard, it increasingly is being recognized that oxygen utilization has a relatively minor role in CKD myopathy and fatigue, evidenced by elegant studies showing normal mitochondrial function.¹⁴⁻¹⁷

In contrast, oxygen convection (from the lung to the muscle capillary) and specifically anemia are commonly cited causes of general fatigue in patients with CKD.¹⁸ More recently, it has been advocated that anemia treatment be targeted by patient-reported fatigue, although the optimal hemoglobin target is unclear.¹⁹ Furthermore, the influence of mild anemia on exertional fatigue is ambiguous because when healthy persons are made anemic experimentally, they compensate to maintain oxygen delivery (eg, by elevating cardiac output), especially at lower exercise intensities, as typically experienced during activities of daily living.²⁰⁻²² Experimental evidence contradicting a primary role of mild anemia in fatigue also is provided by the surprisingly minor impact of erythropoietin therapy on this symptom.^{23,24} Thus, some authors have concluded that oxygen conductance (muscle capillary to mitochondria) is of greater importance than oxygen convection/anemia.²⁵

Still, previous studies must be interpreted cautiously. These studies often investigated maximal²⁶ and single-leg²⁷ exercise paradigms, but submaximal exercise and whole-body exercise better simulate activities of daily living. When submaximal comparisons have been made, exercise intensities relative to participants' maximal exercise capacity often have been used,²⁵ making interpretation of oxygen delivery and utilization variables difficult due to different absolute exercise intensities. Furthermore, most studies focus on hemodialysis patients, although this subgroup makes up only a small fraction of patients with CKD.²⁸ Whether fatigue also occurs in patients with moderate CKD is underinvestigated, and whether such patients with CKD adapt to reduced oxygen delivery is unknown, making guidelines for how to treat conditions such as exertional fatigue and anemia difficult to offer.²⁹

Therefore, the aim of this study was to determine whether exertional fatigue, assessed by RPE, is elevated in patients with CKD during simulated activities of daily living. A secondary aim was to determine the role of oxygen delivery and utilization in exertional fatigue, investigating whole-body, submaximal, and absolute exercise intensities to better represent activities of daily living. We hypothesized that exertional fatigue, assessed by RPE, would be increased in patients with CKD during submaximal exercise. Furthermore, we hypothesized that oxygen convection/anemia would be involved minimally in such elevated exertional fatigue due to cardiac compensation maintaining oxygen delivery, thus suggesting that other

factors (such as poor oxygen conductance from muscle capillary to mitochondria) are of greater importance to exertional fatigue in patients with CKD.

METHODS

Patients and Study Design

After ethical approval from the North West Wales Research Ethics Committee, a matched-cohort study was completed. Using a convenience sampling method, patients were approached during routine nephrology outpatient clinics at Gwynedd Hospital between October 2007 and January 2008. Control participants were approached by e-mails and letters to friends and relatives of patients, hospital staff, and the local community between October 2007 and June 2010. Inclusion criteria for patients were CKD stage 3b (estimated glomerular filtration rate [eGFR] of 30-44 mL/min/1.73 m²) or 4 (eGFR of 15-29 mL/min/1.73 m²), as defined by eGFR (calculated using the isotope-dilution mass spectrometry-traceable 4-variable MDRD [Modification of Diet in Renal Disease] Study equation)³⁰ from 2 serum samples at least 3 months apart. Exclusion criteria for controls were current CKD stages 1-5 and medications that elicit abnormal physiologic responses to exercise (eg, β -blockers). Exclusion criteria for both groups were age younger than 18 years, history of renal replacement therapy or acute kidney injury, any uncontrolled metabolic condition (eg, gross obesity or uncontrolled diabetes), pulmonary or neuromuscular disease, hemoglobin concentration <11 g/dL, and not being able to self-ambulate for 50 m.

After written informed consent, all participants presented at the School of Sport, Health and Exercise Sciences between January 2008 and July 2010 for testing procedures. All participants attended for testing on 2 occasions: visit 1 was to familiarize participants with the protocol and use of the RPE scale, and visit 2 was identical to visit 1 and was completed 7 days later. Data from visit 2 were used for analysis. Participants abstained from alcohol, caffeine, and strenuous exercise for 24 hours prior to appointments, then consumed a standard light meal and water 2 hours prior to arrival.

Assessment of Participant Characteristics and Psychological Outcomes

Height, body mass, and body composition were measured using a wall-mounted stadiometer and bioelectrical impedance analyzer (TBF300MA; Tanita, www.tanita.co.uk). Physical activity level was assessed by 7-day pedometer counts (Digi-Walker SW-200; Yamax, www.yamax.co.uk). Cause of CKD was classified as previously described.³¹ To provide a general overview of quality of life including fatigue, version 2 of the UK (English) Short Form Health Survey 36 (SF-36) was selected.³² This survey is a UK English translation of version 2 of the US (English) SF-36. The Vitality subscale was of particular interest and is presented herein. To provide a measure of chronic illness-associated fatigue, the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) subscale was selected due to good face validity to assess anemia-related fatigue.³³ To determine whether affect may have influenced these measures, the 20-item Positive and Negative Affect Schedule (PANAS) was used to assess positive (the degree to which the individual feels enthusiastic and alert) and negative affect (the degree to which the individual feels aversive mood states and general distress) during the preceding week.^{34,35} Participants then were familiarized with the 15-point 6-20 RPE scale⁹ using the provided standard written instructions and appropriate anchoring. Points 6, 13, and 20 equated to verbal descriptors of "no exertion at all," "somewhat hard," and "maximal exertion," respectively.

Box 1. Equations Used in Assessment of Physiologic Outcomes

$$\begin{aligned} \text{MAP} &= (0.66 \times \text{DBP}) + (0.33 \times \text{SBP}) \\ T_{sP_r} &= \text{MAP}/\dot{Q} \\ \text{CaO}_2 &= \text{Hb} \times 1.39 \times (\text{SpO}_2/100) \\ \text{DO}_2 &= \dot{Q} \times \text{Hb} \times 1.39 \times (\text{SpO}_2/100) \\ \text{o}_2\text{ER} &= (\text{VO}_2/\text{DO}_2) \times 100 \end{aligned}$$

Note: For MAP in mm Hg; T_{sP_r} , mm Hg/L/min; \dot{Q} , L/min; CaO_2 , mL/L; Hb, g/L; SpO_2 , %; DO_2 , L O_2 /min; o_2ER , %; and VO_2 , L/min.

Abbreviations and definitions: CaO_2 , blood oxygen-carrying capacity; DBP, diastolic blood pressure; DO_2 , whole-body oxygen delivery; Hb, hemoglobin; MAP, mean arterial pressure; o_2ER , whole-body oxygen extraction ratio; \dot{Q} , cardiac output; SBP, systolic blood pressure; SpO_2 , arterial oxygen saturation; T_{sP_r} , total systemic peripheral resistance; VO_2 , oxygen uptake.

Assessment of Physiologic Outcomes

Exercise testing consisted of submaximal cycle ergometer exercise (Corival; Lode, www.lode.nl) with progressively increasing intensity. After measurements at rest, participants cycled at 60 rpm and 0 W, then intensity was increased by 25 W every 3 minutes to a maximum of 150 W or heart rate of 75% of predicted maximum (calculated as $220 - \text{age}$). Only the 3 lowest exercise intensities were completed by all participants and hence their inclusion here. These intensities were selected to represent the energy expenditure of typical activities of daily living.³⁶ In this sample, intensities represented: at rest, 1.00 ± 0.33 metabolic equivalent tasks (METs; eg, sitting quietly); 0 W, 1.84 ± 0.55 METs (eg, ironing); 25 W, 2.38 ± 0.52 METs (eg, food shopping); and 50 W, 3.10 ± 0.68 METs (eg, putting away household items), in which 1 MET represents the ratio of work metabolic rate to the metabolic rate at rest or oxygen uptake of 3.5 mL/kg/min.³⁶

In the last 30 seconds at each intensity, RPE was recorded and outcome measurements were averaged and obtained. Minute ventilation, oxygen uptake (consumption), carbon dioxide production, and respiratory exchange ratio were measured/calculated by an automated gas analyzer (Metalyser 3B; Cortex, www.cortex-medical.de). Heart rate, stroke volume, cardiac output (\dot{Q}), blood pressure, and total peripheral resistance were obtained by integrating a thoracic bioimpedance analyzer (Physioflow; Manatec, www.physioflow.com) and an automated blood pressure monitor (Tango; SunTech Biomedical, www.suntechmed.com). The validity of \dot{Q} estimations using this thoracic bioimpedance analyzer has been shown against the direct Fick method during submaximal cycling exercise.³⁷ Arterial oxygen saturation (SpO_2) was determined by fingertip pulse oximetry (Onix 9500; Nonin, www.nonin.com). Blood outcome measurements were obtained from arterialized blood collected from the earlobe after topical application of a vasodilating agent (Finalgon cream; Boehringer Pharma, www.boehringer-ingenheim.co.uk). Blood lactate and hemoglobin concentrations were determined by handheld lactate analyzer (Lactate Pro LT1710; Akray, www.akray.co.jp) and desktop photometer (HemoCue Ltd, www.hemocue.com). Using the measures described, mean arterial blood pressure, total systemic peripheral resistance, blood oxygen-carrying capacity, whole-body oxygen delivery, and whole-body oxygen extraction ratio were calculated using the equations shown in Box 1.³⁸

Leg muscle deoxygenation was determined continuously by spatially resolved spectroscopy of the nondominant leg in the vastus lateralis. The deoxygenated hemoglobin signal is dependent on changes in oxygen extraction and generally is independent of blood perfusion.³⁹ After determination of subcutaneous fat depth, an adhesive probe of a continuous wave near-infrared spectroscopy instrument (Nimo; Nirox, www.nirox.it) was placed on the skin 15 cm above the proximal border of the patella and 5 cm

lateral to the midline of the thigh. The validity of this technique has been shown previously for patient populations,⁴⁰ whereas the reliability of this technique in our laboratory ranged from good (eg, coefficient of variation of deoxygenated hemoglobin is 4.8% at 100 W) to adequate (coefficient of variation of deoxygenated hemoglobin at rest is 10.2%), tested on 10 healthy people 1 week apart.

Statistical Analyses

All data are presented as mean \pm standard deviation. All statistical analyses were completed using SPSS, version 18 (IBM Corp, www.ibm.com) and statistical significance was accepted at $P \leq 0.05$. After checking and correcting for relevant assumptions,⁴¹ 2-tailed independent-sample *t* tests were used to compare demographic and psychological assessment data and also psychophysiological data obtained at rest. Analyses of variance were used to compare data obtained during the incremental test with a between factor of group (patient and control) and a repeated-measures factor of intensity (1.8, 2.4, and 3.1 METs). Significant main effects and interactions were followed up with Tukey tests or stepdown Holm-Bonferroni tests, as appropriate.^{41,42} For the main outcome measure of RPE, effect size (eta squared, η^2) also was used to describe the proportion of the total variability in RPE attributable to group allocation, where 0.01 is small, 0.06 is medium, and 0.14 is large effects.⁴³

This study was powered to test the hypothesis that exertional fatigue, assessed by RPE, would be increased in patients with CKD during submaximal exercise. During the incremental exercise test, a significant main effect of group (patient vs control) by analysis of variance would provide support for the hypothesis. Using the tables of Bausell and Li⁴⁴ (2002), 12 participants per group would result in an 80% chance of obtaining statistical significance through the main effect of group. Effect size was estimated to be 1.2, calculated from a study using a protocol similar to ours in patients with chronic fatigue syndrome, whereby reported RPE values were 0.16 per watt in patients and 0.10 per watt in controls (pooled SD = 0.05).¹⁰

RESULTS**Participant Characteristics**

Recruitment and participation are shown in Fig 1. Mean eGFR in the patient group was 29 ± 10 mL/min/1.73 m²; 5 patients were in stage 3b and 8 patients were in stage 4 CKD. Causes of CKD were arteriopathic ($n = 1$), diabetic ($n = 3$), infective/obstructive ($n = 1$), systemic ($n = 1$), and uncertain ($n = 7$). Mean values for all other clinical data and blood variables were within the ranges recommended by the Renal Association Standard (data not shown). Seven patients were prescribed an angiotensin-converting enzyme inhibitor; 1 patient, an angiotensin II receptor antagonist; 5 patients, β -blockers; 2 patients, an α -blocker; 4 patients, a calcium channel blocker; 5 patients, a lipid-lowering agent; 6 patients, a diuretic; and 5 patients, erythropoietin. Of the controls, 2 were hospital staff, 2 were friends of patients, and 9 were from local clubs and societies (eg, Rotary Club and Women's Institute). No participants were current smokers.

Matching of patients to controls was successful, with no significant differences between groups for

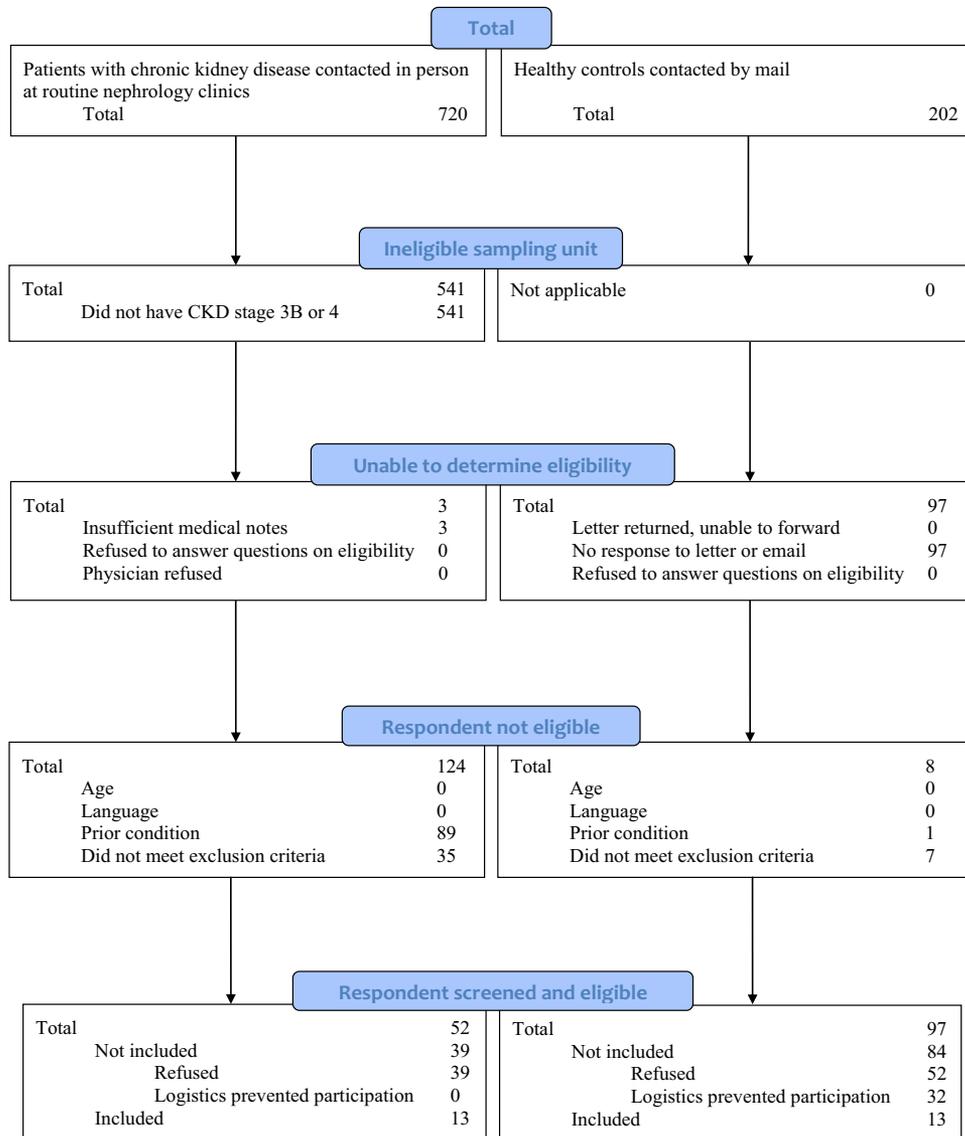


Figure 1. Recruitment and participation of patients with chronic kidney disease (CKD) and healthy controls.

sex, age, height, body mass and composition, and physical activity level (Table 1, top half). Psychological measurements of fatigue were significantly elevated in patients compared with controls (Table 1, bottom half). Patients also had significantly lower scores of positive affect, suggesting that patients were less enthusiastic and alert than controls.

Psychophysiological Outcomes

At rest (1 MET; Table 2), most psychophysiological outcomes were similar in patients and controls ($P = 0.1-0.9$ by t test). Exceptions included hemoglobin concentration ($P = 0.001$), arterial oxygen content ($P = 0.005$), and whole-body oxygen delivery (patients vs controls: 1,016 vs 1,249 mL/min of oxygen; $P = 0.05$), which were all decreased in patients

despite increased arterial oxygen saturation ($P = 0.002$).

During the incremental exercise test, the main outcome measure of RPE was greater in patients than in controls, being significantly elevated in patients at 1.8 METs by 1 scale point and at 2.4 and 3.1 METs by approximately 2 scale points (Fig 2). This elevation equated to a subjective descriptor increase in patients at 2.4 METs (eg, food shopping) from very light to light and at 3.1 METs (eg, putting away household items) from light to somewhat hard.

Significantly elevated blood lactate production at 2.4 and 3.1 METs (Fig 3) and significantly decreased oxygen uptake at 2.4 and 3.1 METs (Table 2), combined with a significantly increased respiratory exchange ratio throughout the incremental test (Table 2),

Table 1. Characteristics and Psychological Data of Chronic Kidney Disease Patients and Healthy Controls

| | Patients | Controls | <i>P</i> ^a |
|--|---------------|----------------|-----------------------|
| Sex | | | NA |
| Male | 8 | 8 | |
| Female | 5 | 5 | |
| Age (y) | 62 ± 13 | 63 ± 7 | 0.9 |
| Body mass (kg) | 78.5 ± 17.2 | 80.5 ± 11.6 | 0.7 |
| Height (cm) | 169 ± 10 | 174 ± 9 | 0.2 |
| Body fat (%) | 29.2 ± 8.5 | 28.9 ± 11.4 | 0.7 |
| Hemoglobin (g/dL) | 13.3 ± 1.5 | 15.4 ± 1.4 | <0.001 ^b |
| Systolic blood pressure (mm Hg) | 122 ± 28 | 120 ± 16 | 0.8 |
| Diastolic blood pressure (mm Hg) | 73 ± 12 | 79 ± 10 | 0.2 |
| Physical activity level (steps per wk) | 8,248 ± 3,321 | 10,163 ± 2,246 | 0.9 |
| UK SF-36 vitality ^c | 61.7 ± 19.0 | 78.3 ± 8.7 | 0.01 ^b |
| FACIT-Fatigue ^d | 35.7 ± 11.8 | 47.5 ± 3.6 | 0.004 ^b |
| PANAS positive affect ^e | 33.4 ± 5.7 | 38.0 ± 5.7 | 0.05 ^b |
| PANAS negative affect ^e | 16.0 ± 5.2 | 13.8 ± 4.6 | 0.3 |

Note: Except where indicated, data are given as mean ± standard deviation. Conversion factor for hemoglobin in mg/dL to mg/L, × 10.

Abbreviations: FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue; NA, not applicable; PANAS, Positive and Negative Affect Schedule; UK SF-36, UK Short Form Health Survey 36.

^aStatistical significance by independent-samples *t* test.

^b*P* ≤ 0.05.

^cVitality subscale, transformed into a 0-100 score in which lower score indicates reduced vitality.

^dFatigue subscale, scored out of 52, in which lower score indicates increased fatigue.

^eScored out of 50, in which lower score indicates decreased affect.

revealed a greater reliance on anaerobic glycolysis in patients compared with controls. Of the central physiologic factors that potentially could explain this phenomena, arterial oxygen content was significantly decreased in patients due to a significantly and substantially (~25%) decreased hemoglobin concentration (Table 2). This decrease outweighed a significant but minor (~2%) elevation in patients' SpO₂ (Table 2). Furthermore, similar heart rate, stroke volume, and consequently cardiac output response in patients (Table 2) resulted in significantly reduced whole-body oxygen delivery (Fig 4).

Further contributing to increased reliance on anaerobic glycolysis, at the periphery, patients did not increase oxygen extraction. This was confirmed by

both methods of determination: first at the whole-body level (oxygen extraction ratio, Table 2) and again in the vastus lateralis, evidenced by near-infrared spectroscopy. Specifically, the deoxygenated hemoglobin signal showed no difference in response between patients and controls (analysis of variance group effect, *P* = 0.8; interaction effect, *P* = 0.5), instead showing in both groups an expected transient decrease on initiation of exercise followed by a gradual increase as exercise intensity increased (combined group mean values at 1 MET, 18 ± 13 μM; at 1.8 METs, 14 ± 11 μM; at 2.4 METs, 15 ± 11 μM; and at 3.1 METs, 16 ± 12 μM).

DISCUSSION

This study shows that exertional fatigue is present in patients with moderate CKD. Specifically, patients with CKD stages 3b and 4 reported increased RPE during simulated activities of daily living. Patients with CKD had a greater contribution to energy production from anaerobic sources, consistent with a mechanism of altered oxygen delivery. However, contrary to our hypotheses, patients with CKD did not compensate for mild anemia by increasing cardiac output and did not increase oxygen extraction, suggesting that compensatory mechanisms in the oxygen transport chain failed to address decreased arterial oxygen content. Thus, these data are consistent with both an oxygen convective (lung to muscle capillary) and oxygen conductive (capillary to mitochondria) defect in CKD.

This study investigated exertional fatigue at exercise intensities designed to represent activities of daily living, such as ironing, food shopping, and putting away household items.³⁶ Similar study designs have been used in other diseases, including chronic fatigue syndrome.¹⁰ Consistent with these studies and with multidimensional measurements of fatigue obtained in patients with CKD,¹⁸ RPE successfully discriminated between fatigued patients with CKD and nonfatigued healthy controls. Thus, RPE seems to be a valid measure of exertional fatigue. Various potential physiologic parameters have been hypothesized to explain such increased fatigue in patients with CKD.¹⁸ Uniquely, RPE measurement allows the simultaneous assessment of these physiologic parameters and of the specific construct of exertional fatigue, enabling enhanced exploration of fatigue's underlying mechanisms.

The increased anaerobic metabolism shown in the present data set is consistent with previous reports⁴⁵ and theoretically could be due to poor oxygen utilization. However, oxygen utilization (mitochondrial function) has been shown to be normal in patients with CKD, especially after accounting for confounding

Table 2. Physiologic Data for Chronic Kidney Disease Patients and Healthy Controls During an Incremental Exercise Test

| Parameter | Group | At Rest (1 MET) | 0 W (1.8 METs) | 25 W (2.4 METs) | 50 W (3.1 METs) | P | |
|---|-------|--------------------|-------------------|--------------------|--------------------|--------------------------------|-------------------------|
| | | | | | | Group × Intensity ^a | Pt vs Ctrl ^b |
| VO ₂ (mL/min) | Pt | 0.24 ± 0.07 | 0.49 ± 0.18 | 0.61 ± 0.19 | 0.79 ± 0.21 | 0.03 ^c | 0.2 |
| | Ctrl | 0.30 ± 0.09 | 0.52 ± 0.12 | 0.71 ± 0.13 | 0.91 ± 0.16 | | |
| VCO ₂ (mL/min) | Pt | 0.21 ± 0.05 | 0.43 ± 0.16 | 0.56 ± 0.18 | 0.77 ± 0.20 | 0.7 | 0.8 |
| | Ctrl | 0.25 ± 0.08 | 0.43 ± 0.09 | 0.58 ± 0.10 | 0.79 ± 0.12 | | |
| Respiratory exchange ratio | Pt | 0.88 ± 0.06 | 0.88 ± 0.10 | 0.93 ± 0.07 | 0.97 ± 0.08 | 0.1 | 0.004 ^c |
| | Ctrl | 0.85 ± 0.06 | 0.83 ± 0.05 | 0.83 ± 0.06 | 0.87 ± 0.06 | | |
| V _E (L/min) | Pt | 9.8 ± 2.5 | 14.7 ± 3.7 | 19.6 ± 4.9 | 23.9 ± 6.1 | 0.2 | 0.8 |
| | Ctrl | 9.2 ± 3.1 | 16.0 ± 3.1 | 19.6 ± 2.5 | 25.2 ± 2.9 | | |
| Cardiac output (L/min) | Pt | 5.9 ± 1.4 | 7.6 ± 1.6 | 8.4 ± 1.5 | 9.5 ± 1.7 | 0.3 | 0.4 |
| | Ctrl | 6.5 ± 1.5 | 7.9 ± 1.4 | 8.8 ± 1.6 | 10.3 ± 2.0 | | |
| Heart rate (beats/min) | Pt | 77 ± 11 | 86 ± 7 | 90 ± 9 | 97 ± 11 | 0.3 | 0.6 |
| | Ctrl | 77 ± 13 | 82 ± 15 | 87 ± 17 | 97 ± 17 | | |
| Stroke volume (mL/beat) | Pt | 78 ± 15 | 91 ± 18 | 97 ± 18 | 101 ± 19 | 0.8 | 0.4 |
| | Ctrl | 85 ± 13 | 97 ± 13 | 102 ± 12 | 106 ± 14 | | |
| MAP (mm Hg) | Pt | 89 ± 16 | 92 ± 14 | 100 ± 23 | 96 ± 13 | 0.3 | 0.9 |
| | Ctrl | 92 ± 9 | 93 ± 7 | 95 ± 8 | 99 ± 10 | | |
| T _s P _r (mm Hg/L/min) | Pt | 15.9 ± 5.3 | 12.6 ± 3.1 | 12.1 ± 2.7 | 10.3 ± 1.9 | 0.7 | 0.4 |
| | Ctrl | 14.8 ± 3.2 | 12.0 ± 2.3 | 11.1 ± 2.2 | 9.9 ± 1.9 | | |
| Hb (g/dL) | Pt | 13.3 ± 1.5 | 13.1 ± 1.6 | 13.3 ± 1.3 | 13.1 ± 1.3 | 0.3 | <0.001 ^c |
| | Ctrl | 15.4 ± 1.4 | 15.5 ± 1.4 | 15.2 ± 1.3 | 15.2 ± 1.4 | | |
| SpO ₂ (%) | Pt | 98 ± 1 | 98 ± 1 | 98 ± 1 | 98 ± 1 | 0.8 | 0.002 ^c |
| | Ctrl | 96 ± 2 | 97 ± 1 | 96 ± 2 | 97 ± 2 | | |
| o ₂ ER (%) | Pt | 25 ± 9 | 35 ± 10 | 43 ± 10 | 48 ± 13 | 0.1 | 0.7 |
| | Ctrl | 26 ± 11 | 38 ± 13 | 42 ± 11 | 50 ± 12 | | |
| CaO ₂ (mL O ₂ /L) | Pt | 171 ± 19 | 169 ± 20 | 170 ± 16 | 169 ± 17 | 0.4 | 0.001 ^c |
| | Ctrl | 193 ± 18 | 196 ± 16 | 191 ± 16 | 192 ± 18 | | |

Note: Except where indicated, data are given as mean ± standard deviation. Conversion factor for hemoglobin in mg/dL to g/dL, ×10.

Abbreviations: CaO₂, arterial oxygen content; Ctrl, control; Hb, hemoglobin; MAP, mean arterial blood pressure; METs, metabolic equivalent tasks; o₂ER, whole-body oxygen extraction; Pt, patient; SpO₂, arterial oxygen saturation; T_sP_r, total systemic peripheral resistance; VCO₂, carbon dioxide production; V_E, minute ventilation; VO₂, oxygen uptake.

^aStatistical significance for interaction of group (patients vs controls) × intensity (1.8, 2.4, and 3.1 METs) by analysis of variance.

^bStatistical significance for main effect of group (patients vs controls) by analysis of variance.

^cP ≤ 0.05.

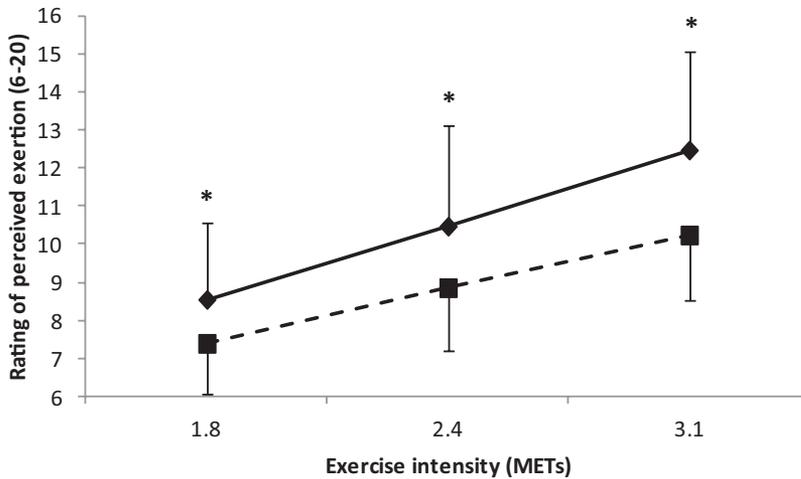


Figure 2. Rating of perceived exertion (RPE) of patients with chronic kidney disease (solid line) and healthy controls (dashed line) during an incremental exercise test. Data are mean \pm standard deviation. RPE was always greater in patients than in controls: analysis of variance significant main effect of group ($P = 0.03$) with a large effect size (0.18); no interaction effect ($P = 0.2$). *Patients significantly different from controls by follow-up test. Abbreviation: METs, metabolic equivalent tasks.

factors such as physical activity level and age.^{15-17,46} Therefore, the present data for increased lactate production and respiratory exchange ratio are more likely due to altered oxygen delivery.

A seminal study investigated oxygen delivery in patients with CKD using comprehensive invasive measures.²⁵ However, analysis of such data to establish the effect of anemia on oxygen delivery was hampered by the use of exercise intensities set relative to participants' maximal oxygen uptake, resulting in healthy controls exercising at much greater absolute power outputs than patients with CKD. Thus, any observed changes to oxygen delivery may have been due to different metabolic rates rather than a defect in the oxygen transport chain per se. Therefore, the present study provides important additional information concerning oxygen delivery. Even when exercising at the same absolute submaximal exercise intensity, as experienced during activities of daily living, whole-body oxygen delivery is decreased in patients with stages 3b and 4 CKD. If oxygen delivery is decreased, both leg and respiratory muscles will experience greater muscle fatigue,¹² which has been shown experimentally^{11,47} to increase RPE, as observed here.

This finding is in contrast to induced anemia in healthy people. Reduced hemoglobin concentration normally increases limb blood flow, venous return, and sympathetic tone, resulting in elevated heart rate and stroke volume.^{29,48-50} Such a cardiac output increase, combined with blood flow redistribution²⁹ and biochemical changes,^{29,51,52} maintains oxygen delivery sufficiently so that aerobic glycolysis is sustained and exertional effort (RPE) remains largely normal, at least during submaximal exercise intensities as observed during activities of daily living.^{20,21,50}

Whether chronically anemic patients with CKD adapt to decreased hemoglobin levels using similar mechanisms is poorly understood.²⁹ The present data suggest that patients with CKD adapt inadequately, with an insufficient increase in cardiac output that reduces oxygen convection, resulting in increased anaerobic glycolysis and ultimately increased exertional fatigue. In patients with CKD, cardiac control is altered^{53,54} and medications such as β -blockers blunt

As exercise intensity increased, blood lactate levels increased to a greater extent in patients than in controls: analysis of variance significant interaction effect ($P = 0.002$). *Patients significantly different from controls by follow-up test. Abbreviation: METs, metabolic equivalent tasks.

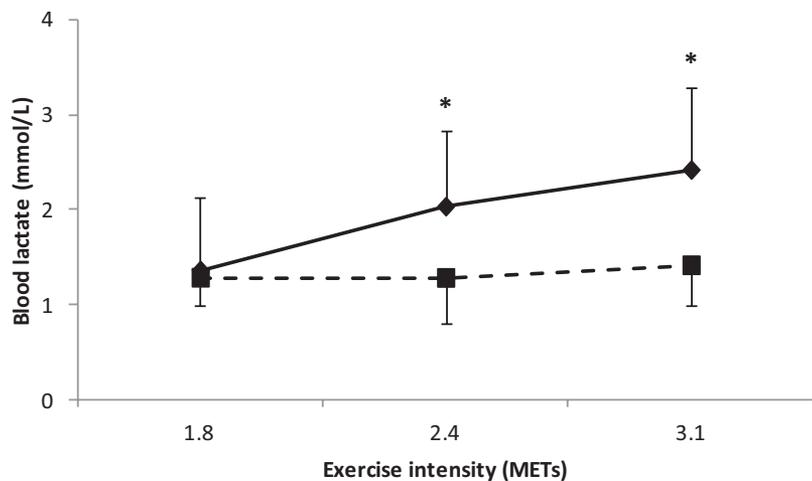


Figure 3. Blood lactate levels of patients with chronic kidney disease (solid line) and healthy controls (dashed line) during an incremental exercise test. Data are mean \pm standard deviation. As exercise intensity increased, blood lactate levels increased to a greater extent in patients than in controls: analysis of variance significant interaction effect ($P = 0.002$). *Patients significantly different from controls by follow-up test. Abbreviation: METs, metabolic equivalent tasks.

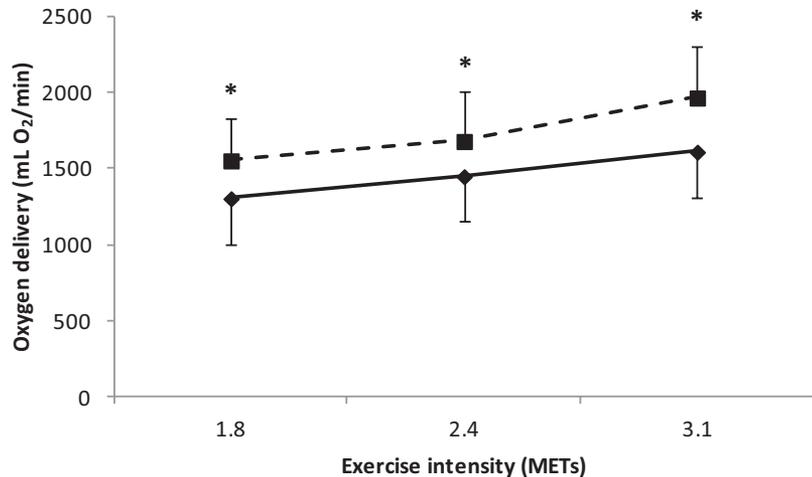


Figure 4. Whole-body oxygen delivery for patients with chronic kidney disease (solid line) and healthy controls (dashed line) during an incremental exercise test. Data are mean \pm standard deviation. Oxygen delivery was calculated as per Methods section. Oxygen delivery was always lower in patients than in controls: analysis of variance significant main effect of group ($P = 0.04$); interaction effect ($P = 0.1$). *Patients significantly different from controls by follow-up test. Abbreviation: METs, metabolic equivalent tasks.

sympathetic stimulation,²⁹ potentially explaining the observed lack of central compensation. Blood flow redistribution and biochemical changes at muscle level also may be inadequate and are worthy of further investigation.^{29,51,52}

Patients also could have compensated for anemia and reduced oxygen delivery by increasing oxygen extraction.^{50,52} However, 3 sources of evidence in the present study suggest that oxygen extraction remained inappropriately normal. First, blood lactate level and respiratory exchange ratio were increased, showing that patients relied on anaerobic glycolysis rather than increased oxygen extraction to sustain aerobic glycolysis. Second, whole-body oxygen extraction ratio, calculated from whole-body oxygen uptake and oxygen delivery, was similar between patients and controls. Third, near-infrared spectroscopy measurements of deoxygenated hemoglobin in the vastus lateralis did not increase in patients compared with controls, indicative of unchanged oxygen extraction when directly assessed in the muscle.³⁹ Although the mechanism for the lack of increase in oxygen extraction was not specifically investigated in the present study, the data are consistent with previous research suggesting oxygen conductance from capillary to mitochondria is altered in CKD.²⁵ In this regard, the increased oxygen saturation present in patients with CKD is consistent with a leftward-shifted oxygen hemoglobin disassociation curve that would hamper oxygen unloading at the tissues.⁵⁰ Additionally, muscle wasting typical of this population⁵⁵ may reduce mitochondrial mass, further limiting oxygen extraction.

However, muscle wasting was not specifically investigated in the present study. Other limitations include lack of detailed analysis of psychological effects on fatigue. Positive affect was reduced in patients with CKD. In this matched-cohort study, use of a convenience sampling method may have selected less fatigued patients, underestimating fatigue severity. Also,

the study did not include invasive assessments of cardiac output and limb metabolism, instead using techniques including RPE, impedance cardiac output assessment, and near-infrared spectroscopy. Nevertheless, these techniques have been validated in patient populations,^{10,37,40} and the study offers novel outcome measures that could facilitate future fatigue research in CKD. Other study strengths include holistic assessment of patients during protocols relevant to activities of daily living, a well-controlled study design using group-matched healthy controls for parameters such as physical activity level, a laboratory setting, and a specific definition of fatigue to investigate this multidimensional symptom.⁷

The present data fuel the debate on hemoglobin targets in CKD; although safety concerns may exist, the lack of compensation for anemia in the present study suggests that blood oxygen-carrying capacity could be increased to reduce exertional fatigue. To maximize benefits of increased hemoglobin levels, mechanisms resulting in a lack of compensation for anemia, which we speculate would include diminished cardiac function, reduced oxygen conductance, and muscle wasting, should be targeted. Exertional fatigue (RPE) also should be considered as an outcome measure in future fatigue intervention trials.

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