**Cardiac dysfunction in dialysing adults with end-stage kidney disease is associated with exercise intolerance: a pilot observational study**

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**Running title:** Exercise dysfunction in adults with kidney failure (44/50 characters)

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**KEY WORDS**

Aerobic fitness, Cardiorespiratory, Chronic disease, Exercise, Physiology.

**ABSTRACT**

People with end-stage kidney disease (ESKD) often exhibit impaired cardiac structure and function, which may contribute to poor exercise capacity. This study used multimodal exercise testing to investigate the central and peripheral mechanisms of exercise limitation in adults with ESKD, also comparing in-centre haemodialysis (ICHD) to home haemodialysis (HHD). Seventeen adults (55.5±14.5 years; *n*=14 male; *n*=12 HHD participated. Resting cardiac examinations, followed by submaximal cycling cardiopulmonary exercise testing (CPET) and functional exercise testing, revealed cardiac structural abnormalities (increased left ventricular mass) and cardiac injury. Aerobic fitness in adults with ESKD was low, with pulmonary oxygen uptake (V̇O2)at the gas exchange threshold (GET) at 39 ± 8% predicted V̇O2peak. O2 pulse, an estimate of stroke volume (SV), was higher in HHD at rest (*p* = 0.05, *ES*=0.58) and during unloaded cycling (*p* = 0.05, *ES*=0.58) compared to ICHD. However, thoracic bioreactance derived SV at the GET was significantly higher in adults receiving ICHD versus HHD (*p*=0.01, *ES*=0.74). In adults with ESKD, cardiac output was positively associated with V̇O2 at the GET (*r*=0.61, *p*=0.04). This study highlights prevalent exercise dysfunction in adults with ESKD undergoing dialysis, with potential distinct differences between in-centre and home haemodialysis, mechanistically linked to underlying cardiac abnormalities.

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**INTRODUCTION**

Cardiovascular disease (CVD) is a risk factor, cause- and consequence of progressive kidney disease (1). In adults with end-stage kidney disease (ESKD), CVD manifests as increased left ventricular (LV) load, systolic dysfunction, and vascular calcification (1). Cardiac dysfunction, including chronotropic incompetence (2), reduced cardiovascular reserve (3), and cardiac injury (measured by [Troponin]) (4), has been implicated as a primary cause of exercise intolerance in this population, however this requires further investigation.

While changes in cardiovascular structure and function are a characteristic of ESKD (5), the pathogenesis of exercise (dys)function is multi-factorial (2,3,6). Sarcopenia is prevalent (7) and is associated with reduced peak oxygen uptake (V̇O2peak) (8) and increased mortality risk (9) in adults with ESKD. There is a need to comprehensively characterise the physiological mechanism(s) underpinning exercise limitations in dialysing adults with ESKD using new techniques available, particularly comparing different treatment modalities. Home haemodialysis (HHD), with its shorter and more frequent sessions, is expected to reduce physiological burden and subsequent dysfunction, potentially leading to better maintained fitness, compared to more traditional in-centre provision.

Cardiopulmonary exercise testing (CPET) provides comprehensive insight into exercise (dys)function and its underlying physiological mechanism(s) (10), but it is underutilised in people with ESKD. In earlier stages of chronic kidney disease (CKD) (3,11,12), reduced V̇O2peak, a prognostically useful variable (13) in this population, and submaximal aerobic fitness (the gas exchange threshold [GET]) (3,11), have been reported, with the GET associated with poor echocardiography-derived cardiac function at rest in adults with ESKD (14). Thoracic bioreactance, a non-invasive cardiac output monitoring method, combined with pulmonary gas analysis and near-infrared spectroscopy (NIRS), can further elucidate the dynamic balance between O2 delivery and utilisation during exercise (6), however, to date have been underused.

CPET provides limited information about other key fitness components, such as muscle function, gait, and balance, which are linked to falls risk, independence (20), and can independently predict all-cause mortality in adults with ESKD (22). Functional exercise tests, such as the short physical performance battery (SPPB; 16), 1-minute sit-to-stand test (1-minute STS; 17), gait speed (18), and peripheral muscle strength tests (19) including handgrip dynamometry, offer complementary insights into overall fitness and the ability to perform activities of daily living (15).

This study aimed to characterise exercise (dys)function in adults with ESKD on maintenance haemodialysis (HHD or ICHD), and provide mechanistic insights into exercise capacity in this cohort using multimodal exercise testing and measures of cardiac structure and function. We hypothesised that cardiac structure and function would be negatively associated with aerobic and functional exercise capacity in adults with ESKD, with better fitness and physiological function expected in those who dialyse at home more frequently.

**METHODS**

Fully informed written consent was obtained prior to enrolment into this single site, observational, cross-sectional study in adults with ESKD. All in-person visits were undertaken at the Wessex Kidney Centre. Participants attended a single visit (~4-hours) on a non-dialysis day, during which all testing was performed. Venous blood samples were obtained pre- and post-haemodialysis sessions, which preceded the research visit for both those receiving ICHD or HHD. Ethics approval was provided by the South Central – Oxford B Research Ethics Committee (REC reference: 18/SC/0684) and Health Research Authority and the study was pre-registered on ClinicalTrials.gov (NCT03925454).

**Participants**

Dialysing adults with ESKD, receiving HHD or ICHD under the clinical care of the Wessex Kidney Centre, participated. Participants continued usual care and dialysis regimens throughout . Body mass (Marsden®, Rotherham, UK) and stature were measured to the nearest 0.01 kg and 0.01 m, respectively. Body mass index (BMI) was calculated as mass (kg) / height (m)2 and body surface area (BSA) estimated (23). Body composition and hydration status were assessed using multifrequency bioelectrical impedance analysis (BIA; Fresenius Medical Care, Bad Homburg, Germany). Disease severity and the clinical profile of each individual was determined by their nephrology consultant, using recent medical records. Sarcopenia and cachexia were characterised using the European consensus guidelines (24), based upon muscle quantity, performance and muscle strength.

**Transthoracic echocardiography**

Transthoracic echocardiography (Vivid E9, GE Healthcare, Chicago, United States) was performed at rest in accordance with standardised clinical guidelines (25) and interpreted by an experienced cardiac physiologist (EL). *Q̇* represents the cardiac index (CI), which was calculated as cardiac output (L·min-1) / body surface area (m2), and SV represents the SV index (SVI; (mL·m-2) calculated as stroke volume (mL) / body surface area (m2). The Simpson’s biplane method of discs (26) was used to estimate systolic function and LV volumes, subsequently used to calculate the left ventricular ejection fraction (LVEF).

LV volume in systole and diastole were subsequently expressed relative to BSA. Linear measurements of LV dimensions were also taken in the parasternal long axis in accordance with British Society of Echocardiography guidelines (26). LV mass was calculated using these measurements and further indexed for BSA. The LV was imaged in all 3 apical windows (apical four chambers, two chambers and three chambers) and the myocardium divided using the 17-segment model for qualitative analysis. Speckle tracking was used for assessment of longitudinal deformation in systole in echocardiographic window giving a negative value for each segment. These were further averaged to derive the global longitudinal strain (GLS), a parameter used for assessment of LV systolic dysfunction and early subclinical markers of LV systolic dysfunction (27).

**Cardiac biomarkers**

In-centre phlebotomy was undertaken by a trained renal nurse, with all samples taken pre- and post-dialysis (using a 5008S CorDiax, Fresenius, Bad Homburg, Germany) from the individual’s dialysis vascular access site. For individuals dialysing at home (using a NxStage System One, Fresenius, Bad Homburg, Germany), samples were drawn either by the participant, or the individual in charge of their care (e.g. partner or family member).

Serum biomarkers of cardiac damage ([NTproBNP], [Troponin I] and dialysis clearance ([Beta-2-microglobullin] ([B2M])) in adults with ESKD were assessed pre- and post-haemodialysis. For those dialysis at home, 10 mL of blood was collected within serum separator tubes (SST; BD Vacutainer, BD Plymouth, United Kingdom), stored in their residential refrigerator for ≤ 6-hours, then returned to the hospital biochemistry department. Samples used for [Troponin I] analysis were spun at 3,500 rpm for 10-minutes at 4°C (Rotanta 460 centrifuge, Hettich, Tuttlingen, Germany). Samples used for [B2M] and [NTproBNP] were spun for at 3,000 rpm for 5-minutes within the Rotanta centrifuge and a further 4-minutes at the same speed within an automated track (Power express, Beckman Coulter, California, USA) at 4°C. Samples were analysed within 4-hours for [NT-proBNP] and [B2M] and within 7-hours for [TnI]. Analysis for [NT-ProBNP] was performed using enzyme-linked fluorescent assays ( on a Biomerieux® Vidas (Vidas, Basingstoke, UK; CV 5.02%) and for [Troponin I] and [B2M] using enzyme-linked immunosorbent assays on a DxI analyser (Beckman Coulter, California, USA; CV 4.80%) and a Beckman Coulter AU680 instrument (Beckman Coulter, California, USA; CV 4.10%), respectively.

**CPET**

A submaximal ramp incremental cycling protocol on an electronically braked cycle ergometer (Corival CPET, Lode, Groningen, The Netherlands) was used. Following 3-minutes of seated rest and 3-minutes unloaded cycling, resistance was increased incrementally using a continuous ramp protocol by a predetermined rate (5-10 W·min-1), based on sex, age and PA profile. Participants were instructed to maintain a cadence between 60-80 revs∙min-1 throughout exercise, with the test terminated when ratings of perceived exertion (RPE) (28) exceeded 15 (“hard”). Three-minutes of unloaded cycling and 10-minutes seated, monitored recovery concluded CPET.

Throughout rest and exercise, breath-by-breath changes in pulmonary gas exchange and ventilation were measured via a face mask and turbine system (Metalyzer 3B, Cortex, Leipzig, Germany). Prior to each test, gas analysers were calibrated using gases of known concentrations and the turbine volume transducer using a 3 L calibration syringe (Hans Rudolph, Kansas City, MO). Fingertip transcutaneous arterial O2 saturation (SpO2) ) was measured throughout using pulse oximetry (NONIN, Minnesota, USA) on a beat-by-beat basis, with exercise terminated if values dropped ≤ 85% or the nadir exceeded 4%. Beat-to-beat heart rate (HR) was measured by telemetry (H7, Polar, Kempele, Finland) and thoracic bioreactance (Cheetah Medical, Wilmington, Delaware, USA; see further details below) measured every 30-seconds. NIRS (Artinis®, Portamon system, The Netherlands; see further details below) was also utilised to measure peripheral muscle oxygenation. Appropriate normative reference values were used for interpretation of CPET parameters (29).

**Thoracic bioreactance cardiography**

Throughout rest and exercise, non-invasive thoracic bioreactance cardiography (Cheetah Medical, Wilmington, Delaware, USA), previously described and used in adults with ESKD by McGuire *et al.,* (30), was measured.

**Near-infrared Spectroscopy**

NIRS measurements were obtained using a commercially available continuous-wave portable system (Artinis®, Portamon system, The Netherlands), placed on the *m. vastus lateralis*, midway between the greater trochanter and the lateral epicondyle of the femur of the dominant limb leg. This system has been described by ﻿Theodorakopoulou *et al.,* (31). Plastic film and dark elastic bandages (3M®, Bracknell, United Kingdom) were used to minimise interference from extraneous light and moisture. During the pre-exercise rest phase, the leg was standardised in the downward phase.

**Functional tests of physical function**

Balance, sit-to-stand ability and gait speed were assessed using the short physical performance battery (SPPB), a well-recognised battery of tests which can assess physical function in adults with kidney disease (16). The SPPB includes three different standing balance tests with different foot positions (feet together, semi-tandem, and tandem); the sit-to-stand-5 (STS5), which requires participants to complete five movements from seated to a standing position as fast as possible; and gait speed testing, measuring the time to walk 2.44 m as quickly as possible. Handgrip strength, a useful measure of nutritional and functional status in kidney disease (21), was also measured. Participants completed repeated maximal handgrip strength tests, using their non-fistula arm, with adequate rest between repetitions, until 3 measurements were within 5% (mean: 3.5 ± 0.7 repetitions).

Following this, the 1-minute STS test was performed using a standardised protocol on a conventional chair with no arm rests (32). Participants were asked to stand up and sit down as often as possible as fast as possible for 1-minute and the number of repetitions performed recorded. Finally, hand dexterity of the non-fistula arm side was assessed using the Moberg’s picking up test (33), a marker of fine motor ability, both with eyes open and closed.

**Data analysis**

HR, V̇O2, breathing frequency (*f*R) carbon dioxide production (V̇CO2), minute ventilation (V̇E), and respiratory exchange ratio (RER) data were interpolated to 10-second averages, with peak exercise values taken as the highest achieved during the incremental test. The GET was determined using the V-slope method (34) and verified through visual inspection of the ventilatory equivalents (V̇E/V̇O2 and V̇E/V̇CO2) against time and end-tidal partial pressure for O2 and carbon dioxide. The arteriovenous O2 content difference [C(a-v)O2] was estimated via the rearrangement of the Fick equation [C(a-v)O2 = V̇O2/*Q̇*]. NIRS data were interpolated to 10-second intervals and expressed as the change, in arbitrary units and percentage change, from baseline to end-exercise.

**Statistical analysis**

Statistical analyses were conducted using the Statistical Package for the Social Sciences (IBM SPSS Statistics, version 27.0), with significance set *a priori* at *p* < 0.05 and a statistical trend toward significance set at ≤ 0.10. All data are expressed as mean ± standard deviation (SD) unless otherwise stated. Due to the low sample size, non-parametric testing was undertaken; the Spearman’s rank correlation coefficient was used to assess relationships between mechanistic physiological variables in the whole group and a subsequent Mann-Whitney U-test was used to perform sub-group analyses and compare means between those receiving HHD and ICHD. The effect size (*ES*; *r* [Rosenthal’s r]) was then calculated as ‘*r* = Z/√N’, with 0.1, 0.3 and 0.5 classified as a small, moderate and large effect, respectively (35). Figures were created within Python (V3.10.2) using the matplotlib package (V3.5.1).

**RESULTS**

In total, 17 adults with ESKD (age: 55.5 ± 14.5 years; *n* = 14 male) participated, of which 12 were receiving HHD and 5 receiving ICHD, respectively. Participant characteristics and clinical profiles are presented in Table 1. In accordance with the revised European consensus on sarcopenia (24), 3/17 (*n* = 2 ICHD) were classified as low strength, and 8/17 (*n* = 4 ICHD) as low performance. None were classified as low muscle quantity, when assessing skeletal muscle mass through BIA. No serious adverse events occurred during this study.

**Baseline cardiovascular structure and function**

Resting parameters of cardiac structure and function from transthoracic echocardiography are presented in Table 2. In the total group, LVEF was lower (in 7/17 participants) and *Q̇* (in 9/17 participants) and LVmass (in 11/17 participants) were increased when compared to British Society of Echocardiography normative reference values for healthy adults (25). Resting left ventricular end-diastolic diameter (LVEDD; Figure 1) was significantly greater (*p* = 0.03, *ES* = 0.53) in adults receiving HHD compared to those receiving ICHD. No significant between groups differences were evident in *Q̇* (*p* = 0.15, *ES* = 0.43) or SV (*p* = 0.41, *ES* = 0.25) at rest between the HHD and ICHD subgroups. Both serum [NTproBNP] and [TnI] were outside the normal ranges (36) post-haemodialysis in adults with ESKD, however no differences were present between adults receiving HHD or ICHD (*p* = 0.70 and 0.82 for [NTproBNP] and [TnI], respectively).

**Exercise testing**

*CPET*

Resting and exercise parameters from submaximal cycling CPET are presented in Tables 3 and 4. Of the 17 participants, 11 (*n* = 3 ICHD) completed CPET; six were considered medically contraindicated for exercise testing. V̇O2 at the GET was 0.88 ± 0.22 L·min-1, equivalent to 39 ± 8% predicted V̇O2peak. The mean V̇O2 at end-exercise (RPE 15) was 1.07 ± 0.3 L·min-1,equivalent to 53 ± 11 % predicted V̇O2peak. The mean ramp duration in the total group of dialysing adults was 635 ± 187 seconds. Resting V̇CO2 was significantly higher in the ICHD subgroup (0.48 ± 0.09 L·min-1) compared to HHD (0.34 ± 0.09 L·min-1, *p* = 0.02, *ES* = 0.68). All participants terminated exercise upon reaching an RPE of 15 on the Borg scale (28).

Non-invasively measured SV was significantly lower in adults receiving HHD (141.4 ± 13.8 mL·beat-1) versus ICHD (108.7 ± 17.6 mL·beat-1, *p* = 0.01, *ES* = 0.74) at the GET and end-exercise (156.8 ± 23.5 mL·beat-1 vs. 112.1 ± 18.4 mL·beat-1, *p* = 0.01, *ES* = 0.74). A large *ES* was evident for the difference between ICHD and HHD for estimated SV (O2 pulse) during unloaded cycling (*p* = 0.05, *ES* = 0.58) and end-exercise (*p* = 0.05, *ES* = 0.58).

*Functional tests*

Functional test parameters, relative to appropriate normative references values (33,37–39), are in Table 5. Of 17 participants, 16 (*n* = 5 ICHD) completed all functional field tests, with all achieving scores below normative reference values for the STS5 and 1-minute STS. No significant differences were evident between the HHD and ICHD subgroups for any functional test outcome.

**Muscle oxygenation**

Peripheral muscle oxygenation parameters, at rest and at the GET, are in Table 6. No significant differences were found in any markers of peripheral muscle oxygenation between groups or between baseline and GET.

**Mechanistic associations between cardiac structure and function and measures of physical fitness**

Within the total cohort, a statistically significant, moderate, positive association between the *Q̇* and relative V̇O2 (*r* = 0.61, *p* = 0.04; Figure 2) at the GET, was found, with associations trending toward significance between resting LV mass index and VE at the GET, and handgrip strength (Table 7). No other significant associations existed between aerobic fitness and mechanistically important variables of cardiac structure and function, nor mechanistic associations between body composition and peripheral muscular strength (Figure 3).

**DISCUSSION**

This study uniquely combined laboratory and field exercise tests with echocardiography, cardiac biomarkers, thoracic bioreactance, and NIRS to investigate central and peripheral mechanisms of exercise (dys)function in adults with ESKD receiving in-centre and home-based dialysis. Key findings revealed impaired ventricular function and LVH in adults with ESKD, which were mechanistically linked to the severely reduced exercise capacity. Additionally, adults with ESKD showed an inability to adequately raise tissue oxygenation and O2 utilisation during exercise. Both aerobic capacity and muscular function were below normative values in this population, with similar dysfunction observed in both ICHD and HHD patients.

LVH, commonly reported in ESKD, results partly from increased cardiac afterload and pulse wave velocity, associated with the increased *Q̇* and BP typically characterising adults with ESKD (1). Echocardiography in the present study identified reduced EF, *Q̇* and evidence of LVH compared to established norms. This is important, given known negative associations between cardiac parameters and adverse cardiovascular outcomes (LVEF is associated with increased CV events [hazard ratio 2.01]) in adults with ESKD (40)). These abnormalities were present in most participants, regardless of dialysis type, although LVEDD was significantly larger in adults receiving HHD, suggesting ventricular insufficiency in ICHD patients (41). Further to this, a trend towards a significant association between resting LV mass index and VE at the GET, as well as resting LV mass index and handgrip strength support a mechanistic link between cardiac dysfunction and compromised physical fitness in this population. These findings were contrary to previous evidence suggesting improvements in cardiac structure and function, in particular LVH and LV mass index, following a switch from conventional to more frequent haemodialysis (42). Abnormal [Troponin] and [NTproBNP] further characterised abnormal cardiac function in the present study cohort, highlighting the need for prospective evaluations comparing ICHD and HHD over time.

Using CPET to characterise physiological (dys)function in kidney disease has been relatively scarce. This study used non-invasive thoracic bio-reactance during CPET, revealing poor cardiac function that is mechanically linked to reduced exercising aerobic capacity. CPET was terminated prior to exhaustion, due to cardiac risk, however the reduced GET (39% predicted V̇O2peak) (43), still supports previous findings of exercise limitations in ESKD (3) and was still reduced compared to non-matched reference values of between 50-60% (44). Given that both peak and submaximal aerobic fitness appear to be associated with mortality in this population (45), the reduced cardiorespiratory fitness reported herein is of clinical importance. CPET was terminated before exhaustion due to cardiac risk, but the reduced GET (39% predicted V̇O2) still supports previous findings of exercise limitations in ESKD.

The present study also supports earlier reports of chronotropic incompetence in adults with ESKD during exercise (2), with a mean HR of 89 ± 17 beats·min-1 at the GET. In a large sample of healthy individuals (46), a peak *Q̇* comparable to our findings at GET (13.2 ± 3.5 L·min-1 vs. 11.16 ± 2.44 L·min-1 respectively) was achieved at a V̇O2 of 95% predicted, compared to our 39%. Our findings support a cardiovascular limitation during exercise in individuals with ESKD, with lower SV and *Q̇*, hindering O2 delivery to the muscles, in line with prior evidence (2). Adults receiving HHD had greater LVEDD compared to those on ICHD, however ICHD recipients exhibited significantly higher SV at both the GET and end-exercise, indicating increased chronotropic incompetence in the ICHD group.

Exercise capacity is not only determined by the ability to uptake O2 centrally,but also to extract and utilise locally within the muscle. Reduced diffusion of O2 from the capillary to mitochondria (47), and a diminished ability to increase peripheral muscle oxygenation during submaximal exercise (48), have previously been reported in ESKD. In the present study, NIRS indicated a blunted TSI% response, suggesting impaired muscle oxygenation and O2 utilisation during exercise. This supports previous research suggesting an impaired microvascular hyperaemic response in adults with kidney disease (31). The lack of any significant differences in TSI between baseline and GET in this study suggest a reduced ability to increase O2 utilisation in response to exercise. In addition to this, a recorded V̇O2 equal to 53% predicted V̇O2peak within this study, at 15/20 on the Borg scale suggests that whilst individuals may have been able to continue exercising, impaired O2 extraction within the working muscles led to increased lactate production, supported by a RER of 1.01 ± 0.05 at test termination. Previously, Wilkinson *et al.,* (6)used NIRS to explore skeletal muscle O2 saturation in individuals with CKD finding that, compared to healthy controls, adults with CKD demonstrated a greater deoxygenation rate, fatiguing sooner than controls, and taking significantly longer (83.1 ± 13.5 seconds vs. 36.8 ± 33.0 seconds, respectively, *p* = 0.01) to recover from their exercise. Findings from this study, and previous research suggest that adults with CKD, in particular ESKD, have a reduced ability to adequately raise TSI and O2 utilisation in response to exercise, which may further contribute to exercise tolerance.

Functional exercise tests, such as the SPPB, 1-minute STS, gait speed, and handgrip dynamometry, offer complementary insights into fitness and ADL capability (15, 16). Adults receiving ICHD in the present study showed abnormal SPPB scores, indicating greater risk of physical deterioration. Typically, an abnormal SPPB score is defined as ≤ 9 points (49), therefore the mean score in this study for HHD is normal. However, the mean of the ICHD sub-group was abnormal, demonstrating greater risk of deteriorating physical ability (50). Moreover, both HHD and ICHD patients had lower handgrip strength and STS results, reflecting reduced aerobic capacity and muscular strength, consistent with previous findings in individuals with CKD (22). Findings from this study suggest limited differences between HHD and ICHD, although caution is warranted given the moderate effects found in the balance test and STS5, respectively. Importantly, these impairments to functional ability have the potential to increase falls risk, reduce independence, quality of life and impair activities of daily living.

The findings of the present study must be considered in the context of a number of methodological limitations. Firstly, although some significant differences and large effects were found and the individuals receiving ICHD and HHD were closely matched, when accounting for the excess fluid carried by those receiving ICHD, the small, relatively heterogeneous and unbalanced groups limit the ability to generalise the results and does not allow for firm inter-group conclusions to be made. Therefore, larger studies utilising multimodal exercising testing are needed to confirm findings from this study, in particular focusing on defining the minimum clinically important difference for these tests between different dialysis modalities. Secondly, this study did not recruit and compare to any matched controls in characteristics which are known to influence physical performance, such as age or sex, and the low sample size prohibited the comparison with normative reference values and therefore future research needs to compare to matched controls to confirm these findings. Finally, whilst this study demonstrates the value of a number of non-invasive techniques, the low sample size and gender imbalance present within this study limits the generalisability of the findings and their applicability to the wider ESKD population, as well as potentially introducing bias which may affect the interpretability of the results. We performed a post-hoc power calculation based upon the differences in LVEDD. For 90% power and an α-level set at *p* = 0.05 (two tailed), with an effect size of 0.53, 36 individuals would be needed. Future trials should therefore aim to recruit at least 40 participants to account for loss to follow-up.

In conclusion, this study used multimodal exercise testing to examine impairments in aerobic fitness, peripheral muscle function, and fine motor ability in adults with ESKD, with limited differences found between those receiving ICHD vs. HHD. Submaximal fitness (GET) was reduced, with cardiac limitations caused by ventricular insufficiency and cardiac damage, and impaired O2 utilisation at the muscle, contributing to multi-factorial exercise dysfunction in adults with ESKD. These findings provide novel insights into the challenges faced by adults with ESKD.

**DATA AVAILABILITY**

The data that support the findings of this study are available on reasonable request from the corresponding author

**FUNDING**

This study was funded by NxStage Medical Inc.

**CONFLICT OF INTEREST**

This study was funded by NxStage Medical Inc.

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**TABLES**

**Table 1.** Participant characteristics and clinical profile.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Total** | **ICHD** | **HHD** | ***p*-value** | ***ES*** |
| **Age (years)** | 55.5 ± 14.5 | 55.0 ± 13.1 | 55.8 ± 15.6 | 0.79 | 0.06 |
| **Gender, *n* (male/female)** | 14/3 | 4/1 | 10/2 | - | - |
| **Weight (kg)** | 85.7 ± 20.4 | 97.0 ± 15.5 | 81.0 ± 20.9 | 0.14 | 0.36 |
| **Height (cm)** | 174.0 ± 8.0 | 173.0 ± 6.0 | 174.0 ± 9.0 | 0.53 | 0.15 |
| **BMI (kg·m-²)** | 28.4 ± 7.2 | 32.4 ± 5.0 | 26.7 ± 7.4 | **0.04\*** | **0.51\*** |
| **BSA (m2)** | 2.02 ± 0.25 | 2.15 ± 0.19 | 1.97 ± 0.26 | 0.17 | 0.33 |
| ***Body composition and hydration*** |  |  |  |  |  |
| **Saliva flow rate (mL·min-1)** | 0.30 – 0.40 | 0.04 ± 0.03 | 0.13 ± 0.20 | 0.69 | 0.11 |
| **Overhydration (L)** | 3.1 ± 4.2 | 8.5 ± 5.9 | 1.3 ± 1.6 | 0.43 | 0.18 |
| **Total body water (kg)** | 43.2 ± 5.6 | 42.7 ± 4.7 | 43.4 ± 6.2 | 0.87 | 0.05 |
| **Extracellular water (kg)** | 18.7 ± 3.0 | 18.6 ± 1.6 | 18.8 ± 3.6 | 0.69 | 0.11 |
| **Intracellular water (kg)** | 24.0 ± 6.1 | 22.8 ± 2.8 | 24.6 ± 7.2 | 0.96 | 0.02 |
| **LTM (kg)** | 43.2 ± 8.4 | 42.4 ± 8.9 | 43.6 ± 8.6 | 0.75 | 0.12 |
| **Haemodialysis vintage (months)** | 45.9 ± 43.5 | 53.6 ± 43.5 | 42.7 ± 44.9 | 0.34 | 0.23 |
| **Vascular access type (*n*)** | - | - | - | - | - |
| **Central venous catheter** | 3 | 0 | 3 | - | - |
| **Graft** | 3 | 1 | 2 | - | - |
| **Arteriovenous fistula** | 11 | 4 | 7 | - | - |
| ***Comorbidities (n)*** |  |  |  |  |  |
| **Hypertension** | 7 | 2 | 5 | - | - |
| **Diabetes** | 3 | 3 | 0 | - | - |
| **COPD** | 1 | 0 | 1 | - | - |
| **Cancer** | 5 | 0 | 5 | - | - |
| **Cardiac** | 6 | 4 | 2 | - | - |

N.B. BSA, body surface area; BMI, body mass index; COPD, chronic obstructive pulmonary disease; HHD, home haemodialysis; ICHD, in-centre haemodialysis; LTM, lean tissue mass. \* denotes statistical significance between HHD and ICHD.

**Table 2.** Cardiac structure and function in adults with end-stage kidney disease (ESKD) receiving either home- or in-centre haemodialysis.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | End-stage kidney disease | | Treatment | | | |
|  | Total group (*n* outside of normative range) | Norm. values\*\* | ICHD | HHD | *p-*value | *ES* |
| ***Echocardiography*** |  |  |  |  |  |  |
| LVEF (%) | 52.5 ± 11.9 (7) | ≥ 55 | 51.3 ± 6.7 | 52.9 ± 13.4 | 0.35 | 0.23 |
| SV (mL) | 74.0 ± 20.4 (4) | 50 - 100 | 76.6 ± 15.4 | 72.8 ± 22.9 | 0.69 | 0.10 |
| *Q̇* (L·min-1·BSA-1) | 3.9 ± 1.1 (9) | 5 – 6 | 3.6 ± 0.9 | 4.0 ± 1.3 | 0.94 | 0.02 |
| LV mass (g) | 233.3 ± 80.0 (9) | 72 – 219 | 222.4 ± 29.8 | 236.9 ± 91.8 | 0.90 | 0.03 |
| LV mass/BSA (g·m2) | 124.1 ± 43.3 (11) | 40 – 110 | 109.6 ± 18.2 | 128.9 ± 48.7 | 0.33 | 0.24 |
| LVEDD (mm) | 41.6 ± 10.2 (1) | 37 – 56 | 30.5 ± 13.7 | 45.3 ± 5.6 | **0.03\*** | **0.53\*** |
| LVESD (mm) | 33.8 ± 7.0 (3) | 22 - 41 | 31.4 ± 6.4 | 34.8 ± 7.3 | 0.24 | 0.28 |
| LV systolic volume (mL) | 60.1 ± 44.4 (3) | 15 – 62 | 45.0 ± 8.7 | 65.1 ± 50.7 | 0.31 | 0.25 |
| LV diastolic volume (mL) | 122.0 ± 51.9 (2) | 53 – 156 | 100.3 ± 23.5 | 129.2 ± 57.7 | 0.31 | 0.25 |
| Mild LVH (*n*) | 11 | - | 4 | 7 | - | - |
| Moderate LVH (*n*) | 2 | - | 1 | 1 | - | - |
| Severe LVH (*n*) | 1 | - | 0 | 1 | - | - |
| GLS (%) | -13.2 ± 4.6 (0) | < 21 % | -14.9 ± 0.9 | -12.3 ± 5.6 | 0.40 | 0.20 |
| LA volume/BSA (mL·m-2) | 28.1 ± 15.6 (2) | < 34 | 55.8 ± 6.9 | 54.3 ± 39.2 | 0.33 | 0.24 |
| TAPSE (cm) | 1.9 ± 0.5 (9) | ≥ 1.7 | 2.14± 0.5 | 1.9 ± 0.5 | 0.17 | 0.33 |
| ***Cardiac biomarkers (post-HD)*** |  |  |  |  |  |  |
| Troponin I (ng·L-1) | 16.4 ± 11.7 (6) | < 16.0 | 14.4 ± 7.0 | 18.4 ± 13.2 | 0.82 | 0.06 |
| NTproBNP (pg·mL-1) | 6908 ± 8698 (14) | < 125 | 4,926 ± 2759 | 8,360 ± 8965 | 0.70 | 0.10 |
| B2M (mg·L-1) | 9.9 ± 5.3 (3) | 7.0 – 18.0 | 23.6 ± 8.7 | 19.3 ± 6.7 | 0.59 | 0.15 |

\*\*Normative biochemistry values for healthy adults obtained from Corteville *et al*., (36). Normative echocardiography values obtained from the British Society of Echocardiography (26). \* denotes statistical significance between the HHD and ICHD subgroups. N.B. B2M, beta-2 Microglobulin; NTproBNP, B-type natriuretic peptide; EF, ejection fraction; ES, effect size; GLS, global longitudinal strain; HHD, home haemodialysis; ICHD, in-centre haemodialysis; LA, left atrium; LV, left ventricle; LVEDD, left ventricular end-diastolic diameter; LVH, left ventricular hypertrophy; LVESD, left ventricular end systolic diameter; *Q̇*, cardiac output; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion.

**Table 3.** Cardiopulmonary responses at rest and during unloaded cycling exercise.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable | Total group | ICHD (*n* = 3) | HHD (*n* = 8) | *p-*value | *ES* |
| ***Rest***  V̇O2 (L·min-1) | 0.46 ± 0.14 | 0.57 ± 0.14 | 0.41 ± 0.12 | 0.15 | 0.43 |
| V̇CO2 (﻿L·min-1) | 0.38 ± 0.11 | 0.48 ± 0.09 | 0.34 ± 0.09 | **0.02\*** | **0.68\*** |
| RER | 0.84 ± 0.12 | 0.87 ± 0.14 | 0.82 ± 0.11 | 0.68 | 0.12 |
| *F*R (breaths·min-1) | 17 ± 2 | 17 ± 2 | 17 ± 2 | 1.00 | 0.00 |
| O2 pulse (mL·min-1·beat-1) | 5.7 ± 1.7 | 7.6 ± 0.5 | 4.9 ± 1.4 | **0.05+** | **0.58\*** |
| SV (mL·beat-1) | 87.7 ± 18.7 | 97.1 ± 19.9 | 84.2 ± 18.3 | 0.41 | 0.25 |
| *Q̇* (L·min-1) | 6.8 ± 0.9 | 7.1 ± 0.4 | 6.6 ± 1.1 | 0.15 | 0.43 |
| HR (beats·min-1) | 79 ± 12 | 74 ± 19 | 81 ± 10 | 0.41 | 0.25 |
| SBP (mmHg) | 117 ± 15 | 116 ± 20 | 117 ± 15 | 0.92 | 0.03 |
| DBP (mmHg) | 78 ± 12 | 72 ± 13 | 81 ± 12 | 0.36 | 0.28 |
| ***Unloaded cycling (10 watts)*** |  |  |  |  |  |
| V̇O2 (L·min-1) | 0.55 ± 0.15 | 0.70 ± 0.19 | 0.5 ± 0.1 | 0.15 | 0.43 |
| V̇CO2 (L·min-1) | 0.47 ± 0.13 | 0.59 ± 0.18 | 0.42 ± 0.08 | 0.18 | 0.40 |
| RPE | 7 ± 1 | 8 ± 1 | 7 ± 1 | **0.07+** | 0.54 |
| RER | 0.84 ± 0.08 | 0.84 ± 0.05 | 0.85 ± 0.09 | 0.68 | 0.12 |
| V̇E (L·min-1) | 18.1 ± 5.7 | 22.6 ± 6.9 | 16.4 ± 4.5 | 0.15 | 0.43 |
| *F*R (breaths·min-1) | 18 ± 2 | 18 ± 4 | 18 ± 2 | 0.84 | 0.06 |
| O2 pulse (mL·min-1·beat-1) | 7.1 ± 2.71 | 9.7 ± 3.6 | 5.9 ± 1.3 | **0.05+** | **0.58\*** |
| SV (mL·beat-1) | 87.6 ± 17.8 | 97.8 ± 22.4 | 83.8 ± 15.2 | 0.41 | 0.25 |
| *Q̇* (L·min-1) | 6.7 ± 0.9 | 7.2 ± 1.2 | 6.5 ± 0.7 | 0.41 | 0.24 |
| HR (beats·min-1) | 82 ± 13 | 75 ± 20 | 84 ± 9.26 | 0.54 | 0.18 |
| SBP (mmHg) | 125 ± 15 | 131 ± 9 | 123 ± 17 | 0.84 | 0.06 |
| DBP (mmHg) | 80 ± 10 | 80 ± 6 | 79 ± 11 | 0.79 | 0.08 |

N.B. DBP, diastolic blood pressure; *ES*, effect size; *f*R, breathing frequency; HHD, home haemodialysis; HR, heart rate; ICHD, in-centre haemodialysis; *Q̇*, cardiac output; RER, respiratory exchange ratio; RPE, subjective rating of perceived exertion; SBP, systolic blood pressure; SV, stroke volume; V̇CO2, rate of carbon dioxide production; V̇E, minute ventilation; V̇O2, rate of oxygen consumption; \* denotes statistical significance between HHD and ICHD; + denotes a trend toward statistical significance between HHD and ICHD.

**Table 4.** Submaximal exercise responses at the gas exchange threshold and end-exercise (RPE of 15 on the Borg scale).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CPET variable | Total group | ICHD (*n* = 3) | HHD (*n* = 8) | *p-*value | *ES* |
| ***Gas exchange threshold*** |  |  |  |  |  |
| V̇O2 (﻿L·min-1) | 0.88 ± 0.22 | 0.95 ± 0.34 | 0.93 ± 0.18 | 0.84 | 0.06 |
| V̇O2 (% predicted) | 39 ± 8 | 39 ± 8 | 38 ± 10 | 0.88 | 0.02 |
| V̇O2 (﻿mL·min-1̇·kg-1) | 11.41 ± 3.02 | 10.29 ± 2.62 | 11.83 ± 3.21 | 0.61 | 0.14 |
| V̇CO2 (﻿L.min-1) | 0.74 ± 0.15 | 0.79 ± 0.19 | 0.79 ± 0.15 | 0.92 | 0.03 |
| WR (W) | 50 ± 17 | 54 ± 22 | 52 ± 17 | 0.84 | 0.06 |
| RER | 0.80 ± 0.08 | 0.87 ± 0.13 | 0.86 ± 0.06 | 0.91 | 0.03 |
| V̇E (L·min-1) | 26.7 ± 7.0 | 29.2 ± 7.6 | 27.9 ± 7.3 | 0.68 | 0.12 |
| *F*R (breaths·min-1) | 22 ± 9 | 33 ± 15 | 20 ± 5 | 0.22 | 0.37 |
| V̇E/V̇CO2 slope | 28.18 ± 10.23 | 21.93 ± 4.09 | 30.54 ± 11.03 | 0.09 | 0.48 |
| O2 pulse (mL·min-1·beat-1) | 8.7 ± 1.8 | 10.7 ± 1.6 | 8.8 ± 1.7 | 0.15 | 0.43 |
| SpO2 (%) | 97 ± 1 | 96 ± 1 | 97 ± 1 | 0.92 | 0.07 |
| SV (mL·beat-1) | 117.7 ± 22.1 | 141.4 ± 13.8 | 108.7 ± 17.6 | **0.01\*** | **0.74\*** |
| *Q̇* (L·min-1) | 11.2 ± 2.4 | 12.6 ± 3.7 | 10.6 ± 1.8 | 0.31 | 0.31 |
| HR (beats·min-1) | 89 ± 17 | 86 ± 23 | 99 ± 15 | 0.31 | 0.31 |
| SBP (mmHg) | 129 ± 27 | 118.0 ± 24.5 | 145.50 ± 25.17 | 0.15 | 0.43 |
| DBP (mmHg) | 80 ± 14 | 75.67 ± 14.74 | 89.38 ± 12.18 | 0.31 | 0.31 |
| ***End exercise*** |  |  |  |  |  |
| V̇O2 (﻿L·min-1) | 1.07 ± 0.3 | 1.23 ± 0.47 | 1.01 ± 0.23 | 0.36 | 0.28 |
| V̇O2 (% predicted) | 53 ± 11 | 54 ± 12 | 53 ± 12 | 0.91 | 0.01 |
| V̇O2 (﻿mL·min-1̇·kg-1) | 13.81 ± 4.56 | 15.35 ± 5.30 | 13.23 ± 4.50 | 0.31 | 0.30 |
| V̇CO2 (﻿L·min-1) | 1.08 ± 0.29 | 1.27 ± 0.4 | 1.00 ± 0.23 | 0.18 | 0.40 |
| WR (W) | 80 ± 30 | 95 ± 40 | 75 ± 26 | 0.36 | 0.28 |
| ΔVO2/ΔWR (mL·min-1·W-1) | 7.15 ± 3.77 | 4.88 ± 5.46 | 8.01 ± 2.94 | 0.24 | 0.40 |
| Exercise duration (s) | 635 ± 187 | 642 ± 209 | 616 ± 145 | 0.27 | 0.34 |
| RER | 1.01 ± 0.05 | 1.05 ± 0.07 | 1.00 ± 0.05 | 0.26 | 0.38 |
| V̇E (L·min-1) | 37.7 ± 7.6 | 41.2 ± 10.1 | 36.6 ± 6.9 | 0.41 | 0.25 |
| *F*R (breaths·min-1) | 25 ± 6 | 24 ± 1 | 25 ± 7 | 0.84 | 0.06 |
| HR (beats·min-1) | 112 ± 20 | 108 ± 27 | 114 ± 19 | 0.76 | 0.09 |
| O2 pulse (mL·min-1·beat-1) | 10.8 ± 2.6 | 13.3 ± 2.6 | 9.8 ± 1.9 | **0.05+** | **0.58\*** |
| SV (mL·beat-1) | 124.3 ± 27.9 | 156.8 ± 23.5 | 112.1 ± 18.4 | **0.01\*** | **0.74\*** |
| *Q̇* (L·min-1) | 12.6 ± 3.1 | 14.4 ± 5.0 | 11.9 ± 2.1 | 0.41 | 0.25 |
| SBP (mmHg) | 146 ± 24 | 142 ± 1 | 146 ± 25 | 0.15 | 0.43 |
| DBP (mmHg) | 88 ± 12 | 81 ± 1.5 | 89 ± 12 | 0.79 | 0.08 |

N.B. ICHD, in-centre haemodialysis; HHD, home haemodialysis; *ES*, effect size; V̇O2, rate of pulmonary oxygen uptake; V̇CO2, rate of carbon dioxide production; RER, respiratory exchange ratio; *f*R, breathing frequency; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; *Q̇*, cardiac output normalised to body surface area (BSA), CI; SV, stroke volume normalised to BSA, SVI; arterial O2 saturation, SpO2; RPE, subjective rating of perceived exertion; V̇E, minute ventilation; WR, work rate. \* denotes statistical significance (*p* < 0.05) between the HHD and ICHD subgroups. + denotes a trend towards statistical significance (*p* < 0.07) between HHD and ICHD.

**Table 5.** Functional exercise capacity of adults receiving ICHD or HHD compared to normative values.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Normative reference values \* | Total group (*n* outside of normative range) | ICHD (*n* = 5) | HHD (*n* = 11) | *p*-value | *ES* |
| SPPB |  |  |  |  |  |  |
| STS 5 (s) | 1.1 – 3.3 | 9.7 ± 4.9 (16) | 6.3 ± 7.0 | 11.3 ± 2.9 | 0.13 | 0.41 |
| Balance test (points) | 2.8 – 4.4 | 3.4 ± 1.3 (3) | 2.6 ± 1.9 | 3.8 ± 0.6 | 0.11 | 0.42 |
| Gait speed test (s) | 1.4 – 2.4 | 1.82 ± 0.65 (3) | 1.63 ± 0.96 | 1.92 ± 0.49 | 0.96 | 0.02 |
| Total (points) | 7.2 – 11.2 | 10 ± 3 (7) | 8 ± 5 | 11 ± 2 | 0.25 | 0.31 |
| Sit-to-stand 5 power (W·kg-1)  Moberg’s picking up test |  | 3.1 ± 1.6 | 4.2 ± 3.4 | 2.8 ± 0.6 | 0.18 | 0.37 |
| Eyes open (s) | 15.4 – 18.0 | 13.7 ± 6.6 (2) | 17.8 ± 11.1 | 11.8 ± 2.5 | 0.69 | 0.11 |
| Eyes closed (s) | 27.8 – 31.5 | 35.6 ± 30.7 (5) | 49.97 ± 52.65 | 29.14 ± 12.43 | 0.96 | 0.02 |
| Handgrip strength (kg) | 35 - 45 | 33.1 ± 7.9 (8) | 31.8 ± 10.5 | 36.2 ± 6.0 | 0.50 | 0.13 |
| 1-minute STS (reps) | 61 - 63 | 22 ± 14 (16) | 17 ± 17 | 25 ± 12 | 0.49 | 0.13 |

N.B. *ES*, effect size; HHD, home haemodialysis; ICHD, in-centre haemodialysis; reps, repetitions; STS, sit-to-stand; SPPB, short physical performance battery. \* Normative reference values obtained from Ramirez-Velez et al., (37), Amirjani et al., (33), Wang et al., (38), and Strassman et al., (51)

**Table 6.** Peripheral muscle oxygenation of the *m. vastus lateralis* at baseline and gas exchange threshold in adults receiving ICHD or HHD.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CPET variable | Total group | ICHD (*n* = 3) | HHD (*n* = 8) | *p* value | *ES* |
| ***Baseline*** |  |  |  |  |  |
| [O2Hb] (a.u.) | 10.11 ± 14.73 | 0.92 ± 3.61 | 13.56 ± 16.02 | 0.11 | 0.32 |
| [HHb] (a.u.) | 9.68 ± 15.54 | 0.14 ± 3.59 | 13.26 ± 16.97 | 0.11 | 0.32 |
| [tHb] (a.u.) | 19.79 ± 29.91 | 1.06 ± 1.64 | 26.81 ± 32.72 | 0.07 | 0.46 |
| TSI (%) | 75.99 ± 12.41 | 88.13 ± 14.39 | 71.44 ± 6.59 | 0.17 | 0.46 |
| V̇O2 (L·min-1) | 0.52 ± 0.08 | 0.56 ± 0.12 | 0.50 ± 0.07 | 0.51 | 0.15 |
| WR (W) | 0.30 ± 0.38 | 0.78 ± 0.39 | 0.13 ± 0.17 | 0.09 | 0.43 |
| ***Gas exchange threshold*** |  |  |  |  |  |
| [O2Hb] (a.u.) | 11.17 ± 15.94 | 3.04 ± 6.87 | 14.21 ± 17.49 | 0.16 | 0.36 |
| [HHb] (a.u.) | 9.46 ± 15.89 | 1.09 ± 3.80 | 12.61 ± 17.75 | 0.12 | 0.29 |
| [tHb] (a.u.) | 20.63 ± 31.31 | 4.12 ± 6.77 | 26.82 ± 35.03 | 0.20 | 0.35 |
| TSI (%) | 77.43 ± 13.56 | 88.44 ± 14.21 | 73.29 ± 11.56 | 0.12 | 0.29 |
| V̇O2 (L·min-1) | 0.80 ± 0.20 | 0.87 ± 0.23 | 0.78 ± 0.20 | 0.56 | 0.13 |
| WR (W) | 42.09 ± 16.24 | 41.67 ± 19.66 | 42.25 ± 16.32 | 0.97 | 0.04 |
| %HHb/%V̇O2 | 4.75 ± 5.88 | 4.23 ± 10.67 | 4.95 ± 4.08 | 0.92 | 0.08 |

N.B. a.u. , arbitrary units; L, Litres; O2Hb, oxy-haemoglobin, HHb, deoxy-haemoglobin, tHb, total haemoglobin, TSI, tissue saturation index; V̇O2, rate of oxygen consumption; WR, work rate.

**Table 7.** Correlations between fitness and mechanistic outcomes in adults with kidney failure receiving either HHD or ICHD.

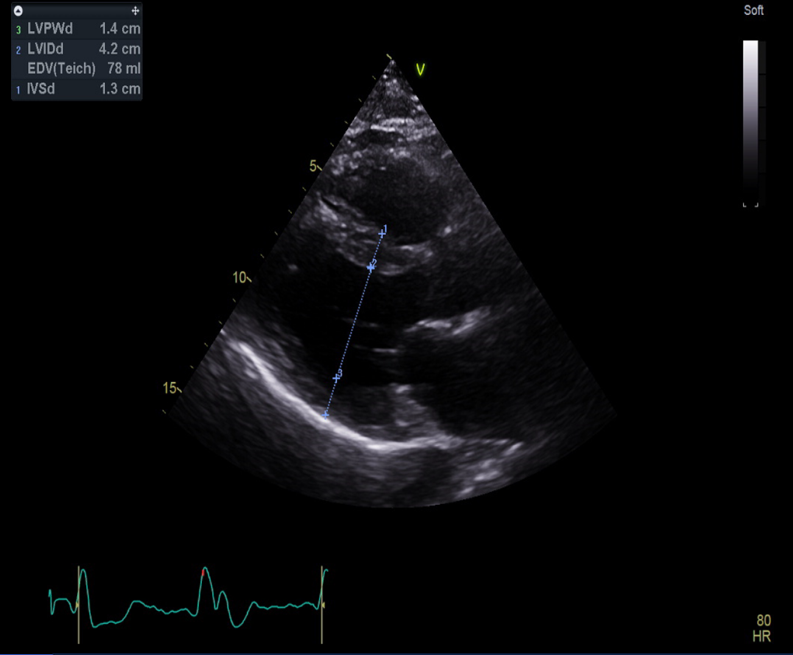
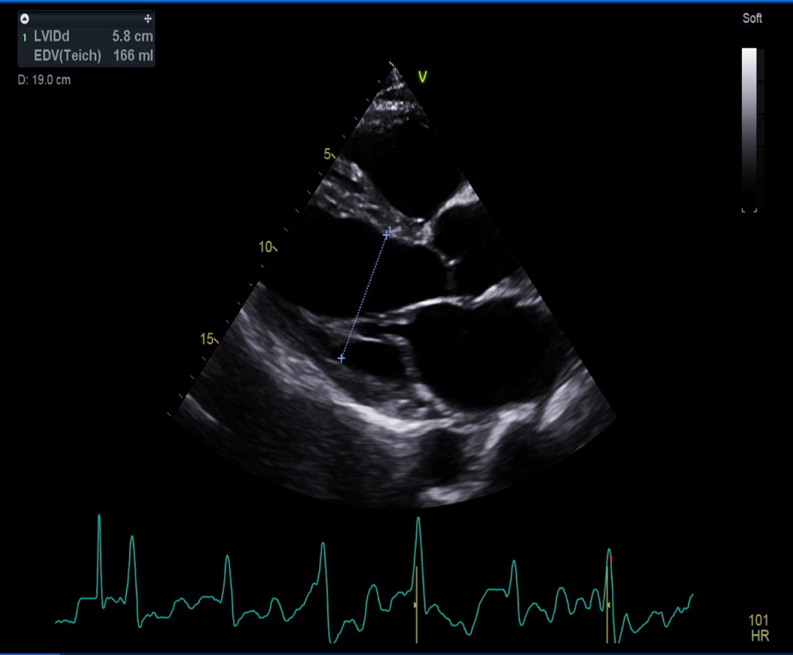
|  |  |  |
| --- | --- | --- |
| Variables | Correlation (*r*) | *p* value |
| Resting LV mass/BSA vs. V̇O2 at GET | -0.38 | 0.25 |
| Resting LV mass/BSA vs. V́E at GET | -0.58 | **0.06+** |
| Resting LV mass/BSA vs. WR at GET | 0.31 | 0.37 |
| Resting LV mass/BSA vs. handgrip strength | -0.54 | **0.08+** |
| Cardiac index at GET vs V̇O2 at GET | 0.61 | **0.04\*** |
| Resting EF vs. V̇O2 at GET | 0.55 | 0.10 |
| Resting EF vs. CI at GET | 0.03 | 0.93 |
| Resting LVEDD vs. V̇O2 at GET | 0.03 | 0.93 |

**\***Statistical significance at the *p* ≤ 0.05 level

+Statistical trend toward significance (i.e., *p* = 0.05–0.1)

**FIGURES**

**Figure 1.** Linear measurements of left ventricular (LV) dimensions in systole and diastole, assessed through the use of transthoracic echocardiography in an adult with end-stage kidney disease (ESKD) who was receiving home haemodialysis (HHD) (Plot A) and an adult with ESKD who was receiving in-centre haemodialysis (ICHD) (Plot B). A significantly larger (*p* = 0.03) LV end diastolic diameter can be seen in the adult receiving HHD.



**A**

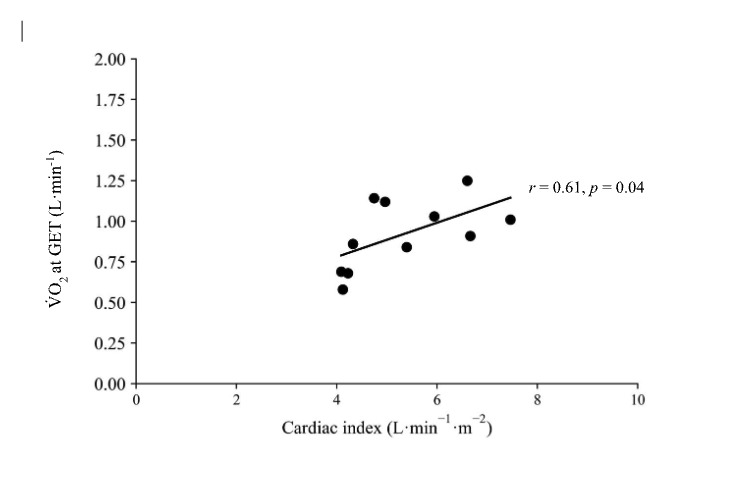
**B**

LVEDD

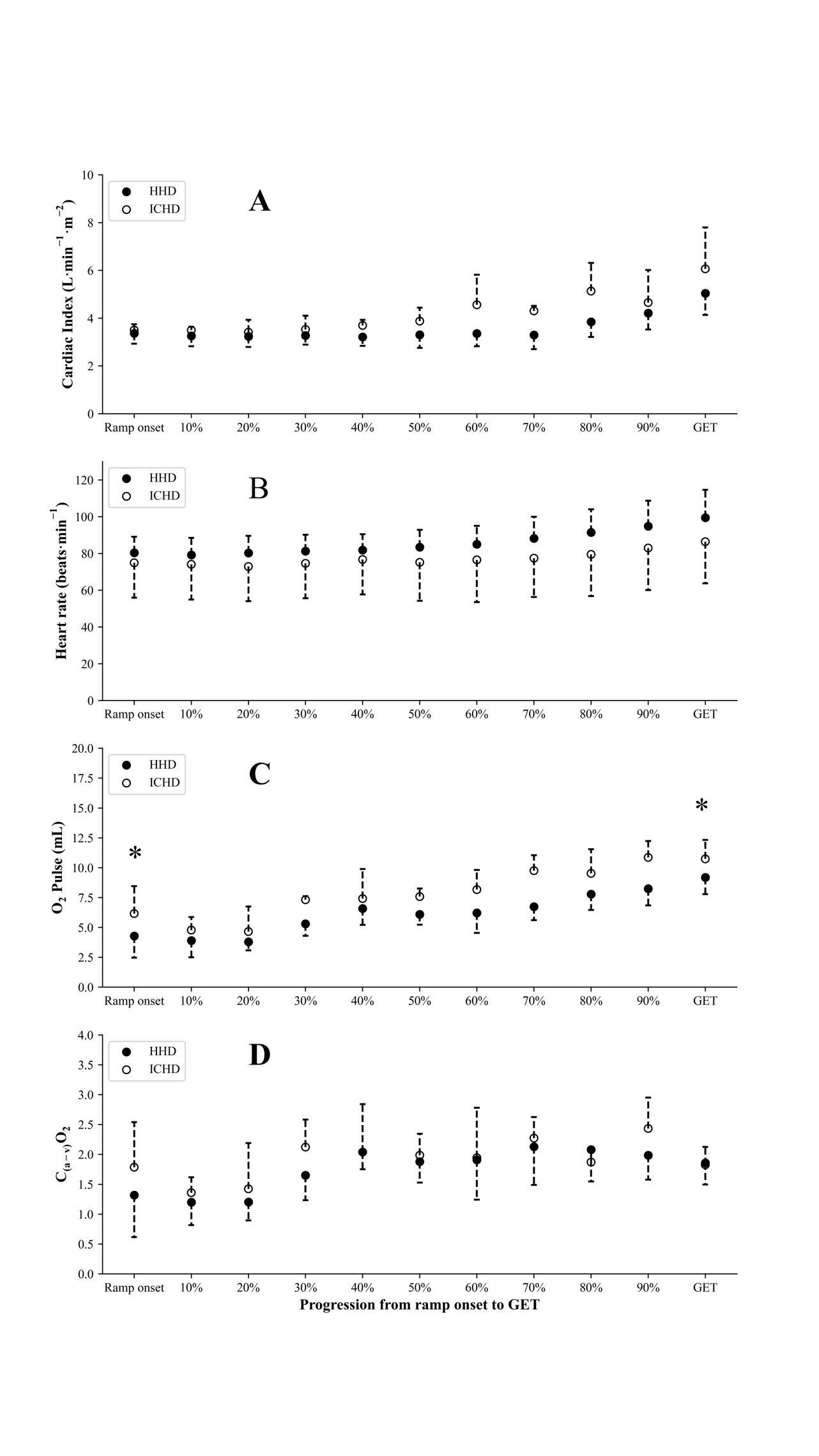
LVEDD

HHD

ICHD

****

**Figure 2.** Mechanistic association between cardiac index and pulmonary oxygen uptake (V̇O2) at the gas exchange threshold in chronically dialysing adults (in-centre and home-haemodialysis) living with end-stage kidney disease (ESKD).



**Figure 3.** A) Cardiac index in adults receiving in-centre haemodialysis (ICHD) or home haemodialysis (HHD) from baseline to the gas exchange threshold (GET) during submaximal ramp incremental cycling exercise; B) heart rate response of adults receiving ICHD or HHD from baseline to the GET during ramp incremental cycling; C) O2 pulse response of adults receiving ICHD or HHD from baseline to the GET during ramp incremental cycling exercise; D) normalised arteriovenous O2 content difference [C(a-v)O2] during ramp incremental cycling exercise to the GET. \**p* *<* 0.05, significant mean difference between adults receiving ICHD or HHD.