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Cardiopulmonary and metabolic physiology during hemodialysis and inter-/intra-dialytic exercise

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Abstract

Background: Hemodialysis is associated with numerous symptoms and side effects which, in part, may be due to sub-clinical hypoxia. However, acute cardio-pulmonary and metabolic physiology during hemodialysis is not well defined. Intra-dialytic and inter-dialytic exercise appear to be beneficial and may alleviate these side effects. To better understand these potential benefits, the acute physiological response to exercise should be evaluated. The aim of this study was to compare and characterise the acute physiological response during hemodialysis, intra-dialytic and inter-dialytic exercise.

Methods: Cardiopulmonary physiology was evaluated during three conditions; 1) hemodialysis without exercise (HD), 2) intra-dialytic exercise (IDEx), and 3) inter-dialytic exercise (Ex). Exercise consisted of 30 minutes constant load cycle ergometry at 90% $\dot{V}O_2$ AT (anaerobic threshold). Central hemodynamics (via non-invasive bio-reactance) and ventilatory gas exchange were recorded during each experimental condition.

Results: Twenty participants (59 ± 12 yrs, 16/20 male) completed the protocol. Cardiac output (Δ = -0.7 L/min), O_2 uptake (Δ = -1.4 ml/kg/min) and arterial-venous O_2 difference (Δ = -2.0 ml/O_2/100ml) decreased significantly during HD. Respiratory exchange ratio exceeded 1.0 throughout HD and IDEx. Minute ventilation was lower ($p = 0.001$) during IDEx (16.5 ± 1.1 L/min) compared to Ex (19.8 ± 1.0 L/min). Arterial-venous O_2 difference was partially restored further to IDEx (4.6 ± 1.9 ml/O_2/100ml) compared to HD (3.5 ± 1.2 ml/O_2/100ml).

Conclusion: Hemodialysis altered cardiopulmonary and metabolic physiology, suggestive of hypoxia. This dysregulated physiology contributed to a greater physiological demand during intra-dialytic compared to inter-dialytic exercise. Despite this, intra-dialytic exercise partly normalised cardiopulmonary physiology during treatment which may translate to a reduction in the symptoms and side effects of hemodialysis.

New & Noteworthy statement

This study is the first to directly compare cardiopulmonary and metabolic physiology during hemodialysis, intra-dialytic exercise and inter-dialytic exercise. Hemodialysis was associated with increased respiratory exchange ratio, blunted minute ventilation, and impaired O_2 uptake and extraction. We also identified a reduced ventilatory response during intra-dialytic exercise compared to inter-dialytic exercise. Impaired arterial-venous O_2 difference during hemodialysis was partly restored by intra-dialytic exercise. Despite dysregulated cardiopulmonary and metabolic physiology during hemodialysis, intra-dialytic exercise was well tolerated.

Key words

NICOM, non-invasive cardiac output monitor; VE, minute ventilation; (a-v) O_2 difference, arterial-venous O_2 difference; CPEX, cardiopulmonary exercise test; IDEx, constant load exercise during hemodialysis.

Key learning points

What is already known about this subject:

- Hypoxia during hemodialysis poses unique risks to patients, most notably, ischemic myocardial, gastrointestinal and cerebral injury. Multiple debilitating symptoms and side effects result.
- Intra-dialytic exercise is well tolerated and provides a range of potential benefits.
- It is important to better understand cardiopulmonary and metabolic physiology during hemodialysis and intra-dialytic exercise to inform treatment strategies for the debilitating symptoms and side effects associated with hemodialysis.

What this study adds:

- This is the first study to comprehensively characterise cardiopulmonary and hemodynamic responses during hemodialysis, intra-dialytic exercise and inter-dialytic exercise.
- Minute ventilation and O_2 extraction are acutely dysregulated with hemodialysis.
- Intra-dialytic exercise may partially restore O_2 extraction.

What impact this may have on practice or policy:

- Evidence now exists for systemically dysregulated cardiopulmonary physiology during hemodialysis, potentially driven by acute changes in pH. This better understanding of the causes of hemodialysis-induced hypoxia is likely to aid development of novel treatments.
- By understanding the acute physiological response to inter-dialytic and intra-dialytic exercise, health and exercise practitioners are better informed to prescribe evidence-based exercise.

Introduction

Maintenance hemodialysis is associated with an incrementally worse prognosis over and above the effects of chronic kidney disease (CKD) (5,8,12). Altered cardiopulmonary and metabolic physiology during hemodialysis treatment appears to be partly responsible (2,5,12). In addition to the long-term clinical implications, quality of life is negatively affected, and patients are severely burdened due to unpleasant side-effects such as syncope, muscle cramps, dyspnea and fatigue (32).

Acutely, hemodialysis alters physiology, most notably impairing cardiovascular hemodynamics (2). These physiological perturbations can cause intra-dialytic hypotension (33), with the resultant hypoxia leading to ischemic injury (7,8,23). Decreased plasma volume, cardiac output and O_2 uptake efficiency are believed to be key drivers of hemodialysis-induced hypoxia (8,12). This may be exaggerated by common CKD complications such as anemia and chronotropic incompetence. Despite these documented risks, cardiopulmonary and metabolic physiology during hemodialysis is not well understood, limiting the ability to adequately manage debilitating symptoms and long-term consequences.

Exercise rehabilitation provides a range of potential benefits in CKD. A program of intra-dialytic exercise can improve aerobic capacity, cardiovascular function and inflammation (16,22,25). Exercise during hemodialysis may also improve solute removal, and stabilise cardiovascular hemodynamics (28). Exploratory studies of intra-dialytic cycle ergometry, have recently reported improved O_2 saturation, partial pressure of O_2 (PaO_2), and reduced myocardial regional wall motion abnormalities, indicative of attenuated cardiac stunning (6,24,27). As such, this form of exercise may help to reduce the side effects and risks associated with hemodialysis.

Exercise rehabilitation for CKD can also be performed between dialysis sessions, referred to as inter-dialytic exercise. Inter-dialytic exercise can improve aerobic capacity and cardiovascular function (19), but poor adherence may limit benefit (29,34). Conversely, intra-dialytic exercise has the advantage of making use of sedentary time which may lead to better compliance (14,28). Despite the proposed benefits of both exercise training modalities, there is limited understanding of the acute physiological response to exercise under the different conditions. To date, no study has directly compared the acute physiology of intra-dialytic and inter-dialytic exercise. By doing so, not only will the potential influence of exercise on the negative consequences of hemodialysis be better understood, but exercise prescription for CKD can be optimised.

A greater knowledge of cardiopulmonary and metabolic physiology during hemodialysis may inform clinical decision making and treatment strategies. Equally, understanding the differences in acute physiology between intra-dialytic and inter-dialytic exercise will contribute to safe and effective evidence-based exercise prescription in CKD patients undergoing hemodialysis. The aim of this experimental study was to evaluate and compare cardiopulmonary and metabolic physiology during hemodialysis, intra-dialytic exercise and inter-dialytic exercise.

Materials and methods

The study was approved by the U.K. Health Research Ethics Committee (17/LO/0368), registered with Clinicaltrials.gov (NCT03064555), and conducted in accordance with the declaration of Helsinki. Informed consent was obtained from all participants.

Study procedures

Patients receiving maintenance hemodialysis at University Hospital Coventry and Warwickshire NHS trust were enrolled. After completion of a maximal cardiopulmonary exercise test (CPEX) on a non-dialysis day, data were collected from each participant during three experimental conditions, the order of which was determined with a randomised cross-over design to control for carry-over effect; 1) hemodialysis without exercise (HD), 2) intra-dialytic exercise (IDEx; exercise performed during haemodialysis), and 3) inter-dialytic exercise (Ex; exercise performed between hemodialysis treatments). Each consecutively recruited patient was assigned to a testing sequence according to predetermined blocks (sequence 1: Ex, IDEx & HD; sequence 2: IDEx, HD & Ex; sequence 3: HD, IDEx & Ex). Inter-dialytic exercise was undertaken on a non-dialysis day, and to limit the potential effect of fluid accumulation on cardiovascular hemodynamics, the HD and IDEx conditions took place after a single non-dialysis day. Each condition took place on the same day, separated by one week. Ventilatory gas exchange and cardiovascular hemodynamics were recorded during all experimental conditions.

Participants

Untrained adults with hemodialysis vintage greater than three months, undergoing three times weekly treatment and able to cycle, were recruited. Exclusion criteria included clinically significant valvular insufficiency or dysrhythmia, intra-dialytic blood pressure >180 systolic or >95 diastolic, >3 litres fluid accumulation between hemodialysis sessions, hemoglobin <9.0 g/dL, ischemic cardiac event (<1 month), or planned kidney transplant during the study.

Cardiopulmonary exercise test

Cardiopulmonary exercise testing was conducted on an electronically braked cycle ergometer (Ergoline, Love medical, Manchester) using a ramp protocol until exhaustion (4). To limit early test termination, all participants were made aware of the sensations typically associated with the test (e.g. leg fatigue, breathlessness). After three minutes rest, unloaded pedaling was performed for three minutes. Subsequently, load was increased (5-20 Watts per minute) whilst maintaining a cadence of 70 rpm. Electrocardiogram was continuously monitored and blood pressure measured at two-minute intervals. Peak oxygen uptake ($\dot{V}O_2$ peak) was identified as the mean $\dot{V}O_2$ during the final 20 seconds of exercise. $\dot{V}O_2$ at the ventilatory anaerobic threshold ($\dot{V}O_2AT$) was determined via the V-slope method and confirmed with ventilatory equivalents (4).

Hemodialysis

Hemodialysis duration ranged from 4-5 hours, and ultrafiltration rate from 450-800 ml/min, dependent on fluid accumulation between non-dialysis days. Filtration rates during the HD and IDEx conditions were the same unless otherwise advised by the clinical team. Three patients were prescribed ultrafiltration profiling. Dialysate composition comprised of sodium 138 mmol/L, potassium 1-3 mmol/L, magnesium 0.5 mmol/L, calcium 1.0-1.8

mmol/L, chloride 108-110 mmol/L, acetate 3mmol/L and bicarbonate 38 mmol/L. Dialysate temperature ranged from 36.2-36.5 °C.

Inter- and intra-dialytic exercise

Both exercise modalities were completed on the same electronically braked cycle ergometer (lower body bi-directional ergometer, Hudson Fitness, Dallas, Texas) in a semi-recumbent position. Participants started with a five-minute warm-up at a speed of 10 rpm below testing RPM, after which exercise commenced at a workload equivalent to 90% $\dot{V}O_2AT$ for 30 minutes. This intensity was selected as the highest theoretical intensity at which participants could sustain aerobic exercise. During the IDEx and Ex conditions, exercise intensity was regulated with pedal resistance and cadence to maintain a workload (Watts) equivalent to that achieved at 90% $\dot{V}O_2AT$ during CPEX. On completion, a three-minute cool down was performed. Intra-dialytic exercise was commenced after one hour of hemodialysis had elapsed.

Outcome measures

Non-invasive cardiac output monitor

A non-invasive cardiac output monitor (Cheetah Medical, Wilmington, Delaware) recorded heart rate and stroke volume continuously, and blood pressure at five-minute intervals, for the first 2.5 hours of the HD and IDEx conditions. For the Ex condition, these parameters were measured throughout exercise and only once post-exercise to avoid lengthy appointments on non-dialysis days. Four dual sensor electrodes were placed on the posterior flanks (superior to the iliac crest) and scapula to limit artefact during exercise. Each electrode passed a high-frequency current across the thorax. Each signal was processed separately and digitally averaged over 30 seconds. The signal processing unit determined the relative phase shift ($\Delta\varphi$) of the input signal, relative to the output signal. $\Delta\varphi$ represented changes in blood flow through the aorta with stroke volume (SV) estimated using $SV = C \cdot VET \cdot \Delta\varphi/\Delta t_{max}$; where C was a constant of proportionality and VET was ventricular ejection time determined using ECG signals to identify aortic valve opening and closure. The relative bioreactance phase shift from the injected and measured currents after traversing the thorax was indicated by $\Delta\varphi/\Delta t_{max.}$ Cardiac output was subsequently calculated using SV x heart rate. For the measurement of hemodynamics, thoracic bioreactance demonstrates good test-retest reliability (ICC: 0.95; $p < 0.001$) and validity ($R = 0.82$; Slope = 0.82) in healthy participants during exercise (17) and cardiac surgery patients (31) respectively. Further, it has been shown to provide consistent minute-by-minute cardiac output monitoring during hemodialysis (20).

Ventilatory gas exchange

For the HD and IDEx conditions, breath by breath measurements were recorded during the exercise period (or corresponding period of HD) and at 10-minute intervals for one hour after exercise. During the Ex condition, breath by breath analysis was performed throughout exercise and for 10 minutes thereafter (figure 1). Ventilatory gas exchange could not be collected prior to at the initiation of hemodialysis due to patient set-up. Oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and minute ventilation (VE) were recorded. The Fick equation was rearranged to derive arterial-venous O_2 difference as follows: $\dot{V}$

$$\dot{V}O2 = CO\ x\ (Ca - Cv)$$

Rearranged:

$$\frac{\dot{V}O2}{CO} = Ca - Cv$$

Where Ca denotes arterial O_2 content, and Cv denotes venous O_2 content.

Statistical analysis

Data were assessed for normality using the Kolmogorov-Smirnov test, and analyzed with a two-way within subjects ANOVA for condition (HD, IDEx and Ex) and time. Post-hoc analysis was performed at each time point where a main effect was identified, and corrected using Bonferroni adjustments. In addition, data points collected at five-minute intervals during the 30-minute exercise period (or equivalent period during HD) were pooled for each condition. Group means were then compared using a within subjects ANOVA with post-hoc-analysis corrected using Bonferroni adjustments. This allowed us to explore overall differences between conditions during the exercise period (or equivalent period during HD). To address violations of sphericity, degrees of freedom were corrected using Greenhouse-Geisser (<

0.75) or Huynh-Feldt (> 0.75) where appropriate (3). All data were expressed as mean ± SD. < 0.05 indicated statistical significance; $p = 0.000$ was corrected to $p < 0.001$ (18).

Results

Recruitment and participants

Of 71 patients screened, 29 were eligible and 20 agreed to take part (figure 2). Patient demographics are presented in table 1. Hemodialysis duration did not differ between the HD and IDEx conditions. Resting measurements were similar between all three conditions apart from respiratory exchange ratio (RER) which was elevated during HD and IDEx conditions compared to the Ex condition (Table 2). Further, pre-hemodialysis weight, filtration rate and filtration volume differed between the HD and IDEx conditions.

Table 1: Participant characteristics

Age (yrs)	59 ± 12
Weight (kg)	74 ± 15
Height (cm)	171 ± 10
BMI (kg/m^2)	25 ± 4
Body surface area (m^2)	1.85 ± 0.21
$\dot{V}O_2$ peak (ml/kg/min)	13.28 ± 2.69
Workload at $\dot{V}O_2$ peak (W)	70 ± 17
$\dot{V}O_2$ AT (ml/kg/min)	9.15 ± 2.58
Workload at VAT (W)	39 ± 14
Sex, n (male/female)	14/6
Smoking status n, (current/former/never)	3/3/14
Ethnicity	
Black	5
Caucasian	13
Asian	2
eGFR (ml/min/1.73m^2)	9.5 ± 3.1
Hemodialysis vintage (months)	41 ± 39
Comorbidities (n, %)	
Diabetes	4 (20)
Hypertension	12 (60)
Stroke	3 (15)
Coronary artery disease	7 (35)
Claudication	1 (5)
Heart failure	
I	2 (10)
II	0

III	0
IV	0
Carcinoma	3 (15)
Asthma	0
COPD	1 (5)
Ulcerative colitis	2 (10)
Hyperparathyroidism	5 (25)
CKD aetiology (n, %)	
Congenital	1 (5)
Chronic ureteric obstruction	1 (5)
Atypical haemolytic uremic syndrome	1 (5)
Glomerular nephritis	4 (20)
Tubular necrosis	1 (5)
Good pasture syndrome	1 (5)
Renal carcinoma	1 (5)
Polycystic kidney disease	1 (5)
Diabetic nephropathy	5 (25)
Hypertensive nephropathy	1 (5)
IgA nephropathy	3 (15)
Medication (n, %)	
ACE inhibitors	5 (25)
Antiplatelet	3 (15)
Anticoagulants	8 (40)
Nitrates	3 (15)
Statins	8 (40)
Diuretics	5 (25)
Anti-Arrhythmic	1 (5)
Calcium channel blockers	11 (55)
Beta-blockers	11 (55)
Hypoglycemic agents	5 (5)
Erythropoietin	10 (50)
Corticosteroids	1 (5)
Thyroxine	1 (5)

Data as mean ± SD or n (%). BMI, body mass index; $\dot{V}O_2$, oxygen uptake; VAT, ventilatory anaerobic threshold; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ACE, angiotensin converting enzyme.

Table 2: Resting cardiopulmonary and hemodynamic measurements.

	HD (n = 20)	IDEx (n = 20)	Ex (n = 20)	*P* value
VE (L/min)	9.3 ± 3.5	9.7 ± 3.0	10.0 ± 4.1	0.589
$\dot{V}O_2$ (ml/kg/min)	3.7 ± 1.1	4.0 ± 0.7	4.3 ± 1.2	0.091
$\dot{V}CO_2$ (ml/kg/min)	3.8 ± 1.3	4.1 ± 1.0	3.5 ± 1.3	0.193
RER	1.04 ± 0.14*	1.00 ± 0.1*	0.86 ± 0.01	<0.001
(a-v) O_2 difference (ml/O_2/100ml)	5.6 ± 1.7	5.8 ± 1.5	6.0 ± 2.9	0.269

CO (L/min)	5.1 ± 1.2	5.1 ± 1.1	5.6 ± 1.1	0.312
SV (ml)	69 ± 17	71 ± 20	79 ± 19	0.050
HR (bpm)	75 ± 8	79 ± 14	73 ± 8	0.062
MAP (mmHg)	99 ± 18	103 ± 26	106 ± 21	0.061
SBP (mmHg)	144 ± 26	146 ± 27	148 ± 26	0.076

Data as mean ± SD. *significant difference ($p < 0.05$) compared to the Ex condition (ANOVA). VE, minute ventilation; RER, respiratory exchange ratio; (a-v) O_2 difference, arterial venous O_2 difference; CO, cardiac output; SV, stroke volume; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

Participant symptoms during experimental conditions

Data collection and exercise were well tolerated. One participant experienced peripheral fatigue accompanied by paroxysmal atrial fibrillation and, as such, stopped twice during both the IDEx and Ex conditions for approximately two minutes. Two participants experienced pre-syncope during the HD and after the IDEx conditions. Symptoms did not differ between the HD and IDEx conditions (table 3).

Table 3: Hemodialysis parameters

	HD (n = 20)	IDEx (n = 20)	*P* value
Weight (kg)			
Pre HD	75.3 ± 15.7	74.8 ± 15.0	0.009*
Post HD	72.8 ± 14.7	72.8 ± 15.1	0.152
Duration (h:min)	4.00 ± 00.20	4.00 ± 00.22	0.330
Filtration volume (ml)	2500 ± 702	2000 ± 894	0.003*
Filtration rate (ml/h)	610 ± 147	494 ± 214	0.009*
Symptoms (n, %)			0.163
Pre-syncope	2 (11)	2 (11)	
Muscle cramps	0	1 (5)	
Fatigue	0	1 (5)	
Atrial fibrillation	1 (5)	1 (5)	

Data as mean ± SD or n (%). *significant difference ($p < 0.05$) between the HD and IDEx conditions (t-test). HD, haemodialysis.

Ventilatory gas exchange

$\dot{V}O_2$ and $\dot{V}CO_2$ decreased significantly over the course of the HD (Δ = -1.4 and -1.5 ml/kg/min respectively) and IDEx conditions, (Δ = -1.2 and -1.3 ml/kg/min respectively) (figure 3). $\dot{V}O_2$ and $\dot{V}CO_2$ were significantly higher during the exercise period for both the Ex (6.2 ± 0.3 ml/kg/min) and IDEx (7.0 ± 0.35 ml/kg/min) conditions, compared to the HD condition (6.0 ±

0.28 ml/kg/min). $\dot{V}CO_2$ remained elevated for 10 minutes after the exercise period during the Ex (7.5 ± 0.54 ml/kg/min) and IDEx (8.2 ± 0.46 ml/kg/min) conditions compared to the HD condition (3.4 ± 0.14 ml/kg/min). RER significantly increased from rest during the exercise period of the Ex (Δ = +0.14) and IDEx (Δ = +0.10) conditions.

VE increased significantly during the exercise period of the IDEx (Δ = 9.0 L/min) and Ex (Δ = 15.0 L/min), conditions (figure 3). However, overall mean VE during the exercise period for the IDEx condition (16.5 ± 1.1 L/min) was significantly lower than the Ex condition (19.8 ± 1.0 L/min).

During the exercise period, and for 10 mins thereafter, (a-v) O_2 difference was significantly higher during the IDEx (5.8 ± 0.4 ml/O_2/100ml) and Ex (6.0 ± 0.5 ml/O_2/100ml) conditions compared to the HD condition (5.5 ± 0.4 ml/O_2/100ml) (figure 3). Further, (a-v) O_2 difference decreased significantly from before to after the exercise period during the IDEx condition (Δ = -1.4 ml/O_2/100ml), and over the corresponding time period of the HD condition (Δ = -2.0 ml/O_2/100ml).

Cardiac

Heart rate was significantly higher during the exercise period for the Ex (90 ± 3 bpm) and IDEx (95 ± 4 bpm) conditions compared to the HD condition (75 ± 2 bpm) (figure 4). For 20 minutes after the exercise period during the IDEx condition, heart rate remained elevated (87 ± 15 bpm) compared to before the exercise period (79 ± 14 bpm). Stroke volume and cardiac output significantly increased during the exercise period for the Ex (Δ = 6.4 L/min) and IDEx (Δ = 8.0 L/min) conditions. Further, cardiac output decreased significantly after the exercise period, compared to before exercise, during the IDEx condition (Δ = -0.8 L/min), and during the corresponding time period of the HD condition (Δ = -0.7 L/min).

Hemodynamic analysis

Systolic blood pressure was significantly greater during the exercise period of the Ex condition (158 ± 6 mmHg) compared to the HD condition (140 ± 7 mmHg) and for 10 minutes thereafter (figure 5). There was no difference between conditions for diastolic blood pressure. During the exercise period of the IDEx condition, systolic blood pressure was significantly greater (152 ± 7 mmHg) during the first 15 minutes of exercise compared to the HD condition (141 ± 28 mmHg). Systolic blood pressure was not significantly different after the exercise period during the IDEx condition (130 ± 32 mmHg) compared to before exercise (140 ± 26 mmHg), and over the corresponding time period of the HD condition (139 ± 26 vs. 144 ± 26 mmHg). Mean arterial pressure was significantly higher during the first 15 minutes of the IDEx condition (113 ± 23 mmHg) compared to the corresponding time-period of the HD condition (98 ± 19 mmHg).

Exercise period (Ex and IDEx conditions) and corresponding time period (HD condition)

Pooled means during the exercise period for the Ex and IDEx conditions and during the corresponding time period of the HD condition showed that there was a significant difference between the two exercise conditions and the HD condition for all measures. In addition, RER was significantly lower during the Ex condition compared to the HD and IDEx conditions (table 4).

Table 4: Mean values for the exercise period

	HD (n = 20)	IDEx (n = 20)	Ex (n = 20)	*P* value
VE (L/min)	8.8 ± 3.3	16.8 ± 4.5*	20.2 ± 4.3*#	<0.001
$\dot{V}O_2$ (ml/kg/min)	3.4 ± 0.6	7.7 ± 1.6*	8.1 ± 1.8*	<0.001
$\dot{V}CO_2$ (ml/kg/min)	3.4 ± 0.7	8.2 ± 2.1*	7.6 ± 1.7*#	<0.001
RER	1.03 ± 0.08	1.03 ± 0.08	0.95 ± 0.07*#	0.016
(a-v) O_2 difference ($ml/O_2/100ml$)	5.0 ± 0.8	6.0 ± 2.1*	6.2 ± 2.1*	0.005
CO (L/min)	5.1 ± 1.2	11.1 ± 4.3*	9.9 ± 3.0*	<0.001
SV (ml)	70 ± 17	115 ± 47*	110 ± 35*	<0.001
HR (bpm)	74 ± 9	95 ± 16*	90 ± 14*	<0.001
MAP (mmHg)	98 ± 18	108 ± 21*	111 ± 19*	<0.001
SBP (mmHg)	139 ± 27	153 ± 28*	158 ± 25*	<0.001

Data as mean ± SD. * significant difference to HD (ANOVA). # significant difference to IDEx (ANOVA). VE, minute ventilation; RER, respiratory exchange ratio; (a-v) O_2 difference, arterial-venous O_2 difference; CO, cardiac output; SV, stroke volume; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

Discussion

Our data show that acutely, maintenance hemodialysis has a considerable impact on cardiopulmonary and metabolic physiology, as evidenced by reduced VE, elevated RER, and a progressive reduction in O_2 uptake during treatment. By comparing exercise modalities, we have also identified that intra-dialytic exercise represents a significantly greater physiological challenge than inter-dialytic exercise.

Hemodialysis

In the present experimental study, $\dot{V}O_2$ and $\dot{V}CO_2$ progressively declined over the duration of a single hemodialysis treatment. Simultaneously, (a-v) O_2 difference decreased by 36% and RER was consistently greater than 1.0, suggesting a greater reliance on anaerobic metabolism (figure 3). Collectively these findings indicate impaired oxygen uptake during hemodialysis mediated by a systemic reduction in both O_2 delivery and extraction, potentially resulting in hypoxia. These data are supported by previous studies reporting hypoxemia (decreased PaO_2 and sO_2) (6), and decreased VE (15,35). This response may partly explain increased hypoxic injury with hemodialysis treatment. Hypoventilation during hemodialysis, caused by acute alkalosis, is thought to be a key driver of hypoxia (6). Bicarbonate in dialysate, whilst intended to buffer hydrogen ion accumulation, may inadvertently impair respiratory drive (11). This mechanism may explain the decreasing $\dot{V}O_2$ and $\dot{V}CO_2$ throughout the HD condition in our study. Whilst initially compensatory, a reduction in VE may ultimately decrease O_2 availability. Additionally, CO_2 buffering may cause a leftward shift in the oxyhemoglobin dissociation curve (Bohr effect), potentially impairing O_2 delivery to tissue, explaining decreasing (a-v) O_2 difference with hemodialysis. Hypoxia during hemodialysis, therefore, is likely multifactorial with both hemodialysis dependent and pathological (e.g. anemia, capillary rarefaction, pulmonary edema and cardiomyopathy) drivers (26).

We also observed a decline in cardiac output during the HD condition. This has been documented previously associated with a reduction in plasma volume during filtration (20) leading to decreased left ventricular pre-load and stroke volume. Decreasing cardiac output likely contributes to ischemic injury due to hypo-perfusion, most notably myocardial, cerebral and splanchnic (7,10,23). Likewise, pulmonary perfusion, a key determinant of gas exchange, is also dependent upon cardiac output and may equally be compromised, further contributing to hypoxia. Myocardial ischemia during hemodialysis has an acute detrimental effect on cardiac function (24). Left ventricular regional wall motion abnormalities, indicative of cardiomyocyte hypoxia, can cause systolic dysfunction, persistent heart failure and reduced survival (9,21). Overall, the evidence suggests that reduced cardiac output during hemodialysis has a repetitive, sub-clinical and multi-systemic effect leading to not only unpleasant symptoms during and after each hemodialysis treatment, but also chronic maladaptation and cardiovascular pathology.

Hemodialysis vs. intra-dialytic exercise

As with the HD condition, both $\dot{V}O_2$ and $\dot{V}CO_2$ decreased during the IDEx condition, demonstrating progressive reduction in ventilatory gas exchange. Despite (a-v) O_2 difference decreasing after intra-dialytic exercise, the change was considerably less (25%) compared to hemodialysis alone (36%), indicating that exercise may partially restore cellular O_2/CO_2 diffusion gradients. These findings agree with previous work which showed that intra-dialytic exercise reversed hypoxemia (6). Consequently, intra-dialytic exercise may acutely improve O_2 extraction and decrease hypoxemia, potentially helping to circumvent acute hemodialysis-induced hypoxia and the associated debilitating symptoms.

We did not observe a significant change in mean arterial or systolic blood pressure during intra-dialytic exercise, but a downward trend (~10 mmHg) was apparent during the hour after exercise (figure 5). Hypotension, in combination with greater myocardial demand during hemodialysis, may predispose patients to an increased risk of sub-clinical myocardial ischemia (13). However, cardiac injury markers troponin I, heart fatty acid binding protein and creatine kinase have not been shown to increase in response to intra-dialytic hypotension (13). Nevertheless, it would seem that there is an increased risk of intra-dialytic hypotension after exercise which may result in side effects. However, there were no reports of nausea, fatigue, dyspnea or syncope after exercise in our study, indicating the relative tolerability of intra-dialytic exercise.

Inter-dialytic vs. intra-dialytic exercise

By directly comparing inter-dialytic and intra-dialytic exercise, we were able to quantify the acute effect of hemodialysis on cardio-pulmonary and metabolic physiology. Minute ventilation was significantly lower during intra-dialytic exercise when compared to inter-dialytic exercise despite cycle ergometry being performed at the same external workload. Our data are strongly suggestive of impaired ventilatory drive due to buffering of CO_2. Under normal conditions, accumulation of CO_2 from increased metabolic work initiates an increase in VE (11). In contrast, bicarbonate buffering of CO_2 during hemodialysis may inhibit this mechanism during intra-dialytic exercise. This response may result in decreased arterial O_2 content contributing to ventilation-perfusion mismatching. In combination with an inadvertent loss in CO_2, it may also impair O_2 extraction at the tissue level, further supporting our observation of impaired (a-v) O_2 difference during hemodialysis.

Cardiac output appeared consistently greater during the intra-dialytic (~1 L/min) compared to inter-dialytic exercise period (figure 4). However, this difference was not statistically significant. Nevertheless, this may indicate greater hemodynamic demand during hemodialysis. Decreased O_2 uptake resulting from reduced ventilation, in combination with sub-optimal tissue O_2 extraction, may result in greater dependency on an increased blood flow achieved by an augmented cardiac output (30). This is supported by the elevated stroke volume and heart rate we witnessed (albeit not statistically significant) throughout intra-dialytic exercise compared to inter-dialytic exercise.

During the IDEx condition, the RER was above 1.0 at all-time points, significantly higher than during the Ex condition. As the external workload was matched between conditions, our data suggest a greater reliance on anaerobic metabolism during intra-dialytic exercise. This should be considered when prescribing this form of exercise, as intensities above the ventilatory anaerobic threshold may be unsustainable and peripheral fatigue more likely (1). Despite this, participants were able to complete 30 minutes of intra-dialytic cycle ergometry at the same external workload as inter-dialytic exercise, thus an elevated RER does not appear to limit exercise tolerance.

Limitations

Using a randomised cross-over design, we aimed to describe acute cardiopulmonary and metabolic physiology during three different experimental conditions. Whilst participants were clinically representative of the hemodialysis population, the study was relatively small, thus likely underpowered to detect change in some measures. Although the same participants were studied for all three experimental conditions, there were inevitable differences between the HD and IDEx conditions for filtration rate and volume. Matching filtration rates and volumes between these two conditions was not possible as prescription was dictated by the clinical team. These differences may have had an impact on our observations although stroke volume appeared unaffected pre-exercise, with no difference between the HD and IDEx conditions. Additionally, both IDEx and HD conditions were performed after one hour of hemodialysis and thus changes in plasma volume were likely small at this point. Several other issues should be mentioned. A large proportion of those screened were not eligible based on our exclusion criteria and thus the current data may not be applicable for all patients. The lack of a pre hemodialysis measure of O_2/CO_2 gas exchange does limit some observations. Finally, it should be noted that we did not measure (a-v) O_2 difference directly but instead determined it using the Fick equation.

Conclusion

Hemodialysis is associated with abnormal cardiopulmonary physiology, evidenced in our study by increased respiratory exchange ratio, blunted VE, and impaired O_2 uptake and extraction. Primarily, these responses suggest sub-clinical hypoxia during hemodialysis, potentially contributing to unpleasant symptoms and pathology. Addressing this abnormal physiology, with exercise or medical interventions, may help reduce the symptom burden of hemodialysis. These perturbations also contribute to the altered acute physiological response observed during intra-dialytic compared to inter-dialytic exercise. Nevertheless, participants completed 30 minutes of intra-dialytic cycle ergometry at an intensity above the ventilatory anaerobic threshold with no significant adverse events.

Author contributions

G. M., S. M. and E. J. H. designed the study; S. M. and K. C. was responsible for data collection; S. M. was responsible for data analysis; S. M. and G. M. drafted the paper; S. M., G. M., E. J. H., D. R., and N. K. revised the paper and approved the final manuscript.

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Conflicts of interest: None

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Figures

Figure 1: Schematic showing data collection during the three experimental conditions. Black bars indicate start/stop of inter-/intra-dialytic cycle ergometry or the corresponding period during the HD condition. NICOM, non-invasive cardiac output monitoring; BP, blood pressure; $\dot{V}O_2AT$, oxygen uptake at the anaerobic threshold; HD, hemodialysis condition; IDEx, intra-dialytic exercise condition; Ex, inter-dialytic exercise condition.

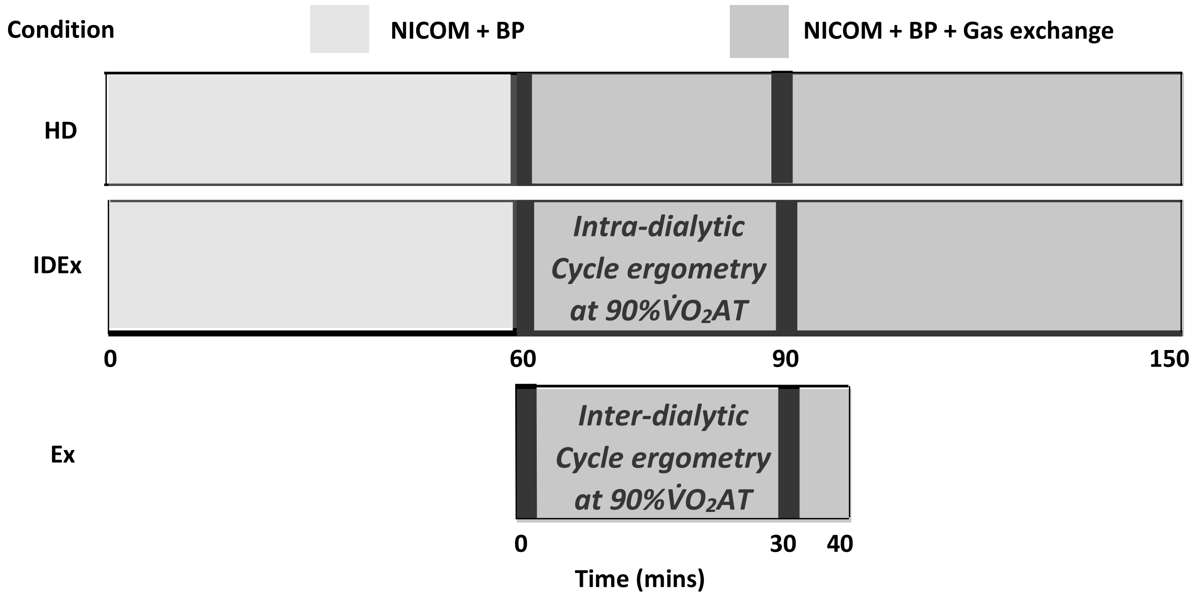
Figure 2: Participant screening, recruitment, exclusion and drop-out. AF, atrial fibrillation; BMI, body mass index; HD, hemodialysis without exercise; IDEx, intra-dialytic exercise; Ex, inter-dialytic exercise.

Figure 3: $\dot{V}O_2$ uptake (A), $\dot{V}CO_2$ production (B), RER (C), VE (D) and (a-v) O_2 difference (E) during the IDEx, Ex and HD conditions. Data as mean ± SD at each time point. 'Pre-exercise' data were recorded after 60 minutes of HD had elapsed for the IDEx and HD conditions. Grey boxes indicate the 30-minute exercise period for the IDEx and Ex conditions. 'Post-exercise' refers to the one-hour period after exercise for the IDEx condition and the corresponding period for the HD condition. Data were recorded for only 10 minutes post-exercise for the Ex condition. Analysis was performed with a two-way within subjects ANOVA for condition (HD, IDEx and Ex) and time. [#] significant difference between pre-exercise and the indicated time point. * significant difference between HD and Ex or IDEx conditions. [†] significant difference between the Ex and IDEx conditions.

Figure 4: Cardiac output (A), stroke volume (B) and heart rate (C) during the HD, Ex and IDEx conditions. Data as mean ± SD at each time point. 'Pre-exercise' data were recorded after 60 minutes of HD had elapsed for the IDEx and HD conditions. Grey boxes indicate the 30-minute exercise period for the IDEx and Ex conditions. 'Post-exercise' refers to the one-hour period after exercise for the IDEx condition and the corresponding period for the HD condition. Data were recorded for only 10 minutes post-exercise for the Ex condition. Analysis was performed with a two-way within subjects ANOVA for condition (HD, IDEx and Ex) and time. * significant difference between HD and Ex or IDEx conditions. # significant difference between pre-exercise and the indicated time point. [a] significant difference between pre-HD and the indicated time point.

Figure 5: Systolic blood pressure (A) and mean arterial pressure (B) during IDEx, Ex and HD conditions. Data as mean ± SD at each time point. 'Pre-exercise' data were recorded after 60 minutes of HD had elapsed for the IDEx and HD conditions. Grey boxes indicate the 30-minute exercise period for the IDEx and Ex conditions. 'Post-exercise' refers to the one-hour

period after exercise for the IDEx condition and the corresponding period for the HD condition. Data were recorded for only 10 minutes post-exercise for the Ex condition. Analysis was performed with a two-way within subjects ANOVA for condition (HD, IDEx and Ex) and time. * significant difference between HD and Ex condition. † significant difference between IDEx and HD condition. # significant difference between pre-exercise and indicated time point.



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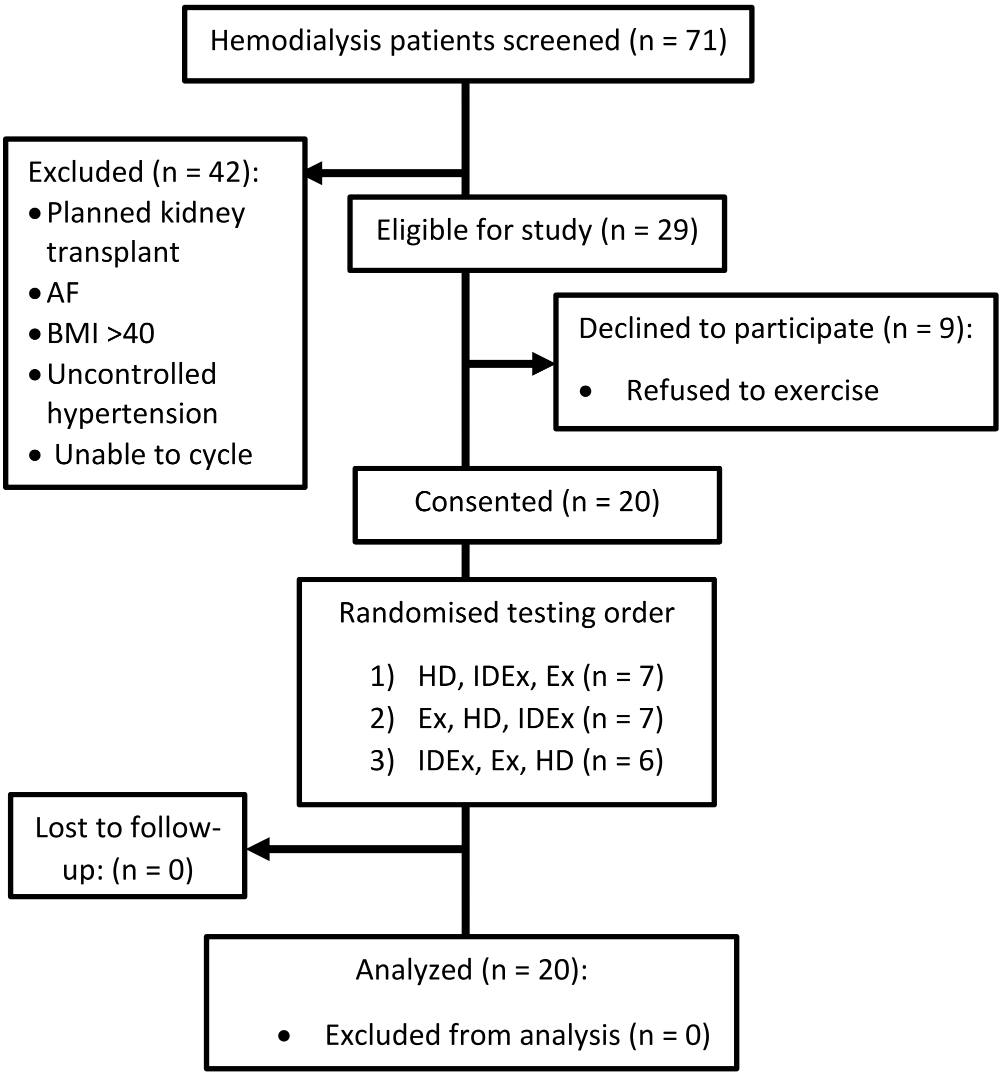
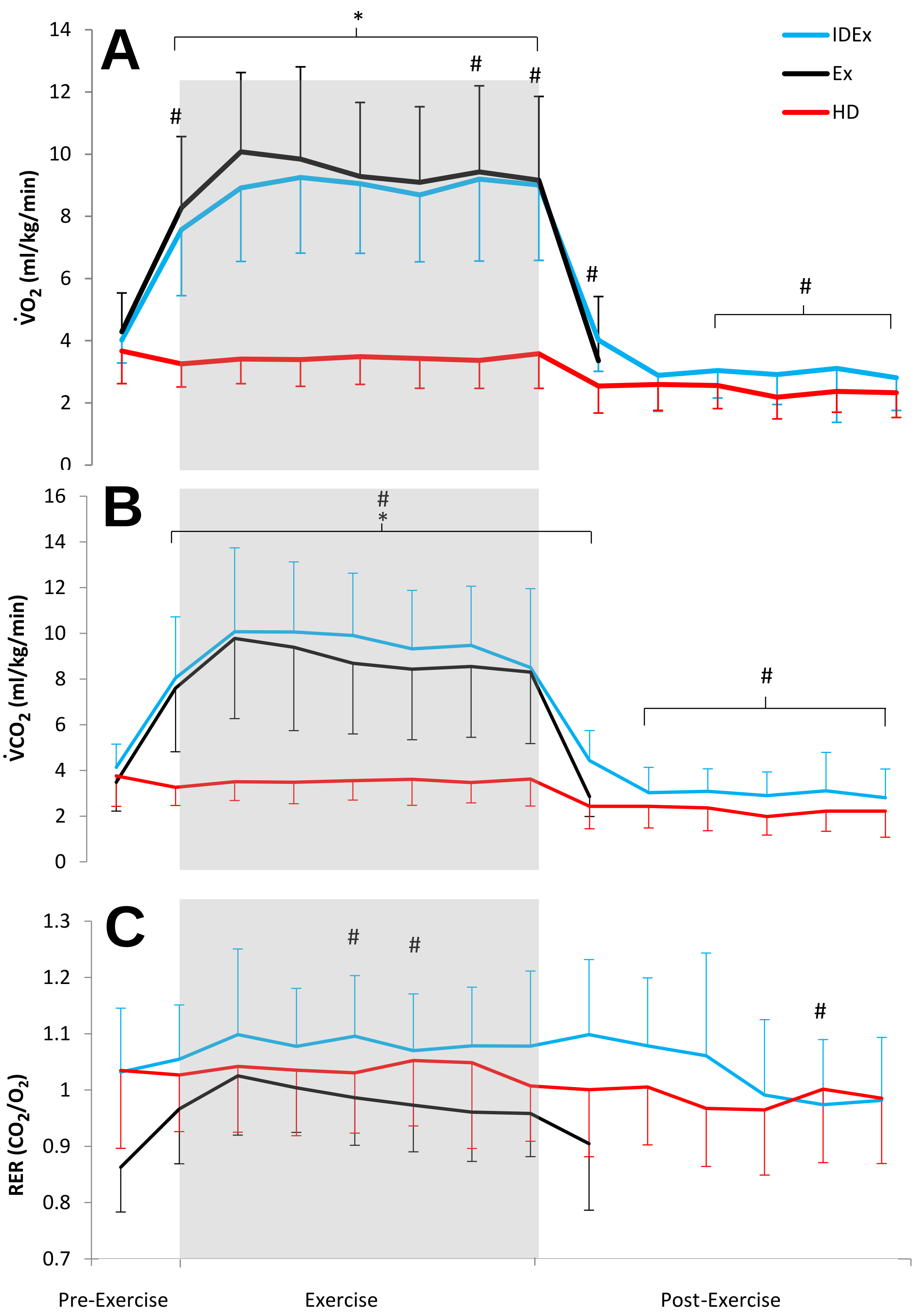


Figure 2: Participant screening, recruitment, exclusion and drop-out. AF, atrial fibrillation; BMI, body mass index; HD, hemodialysis without exercise; IDEx, intra-dialytic exercise; Ex, inter-dialytic exercise.


A
B
C
IDEx
Ex
HD
V̇O2 (ml/kg/min)
V̇CO2 (ml/kg/min)
RER (CO2/O2)
Pre-Exercise
Exercise
Post-Exercise
*
#
0
2
4
6
8
10
12
14
16
0.7
0.8
0.9
1
1.1
1.2
1.3

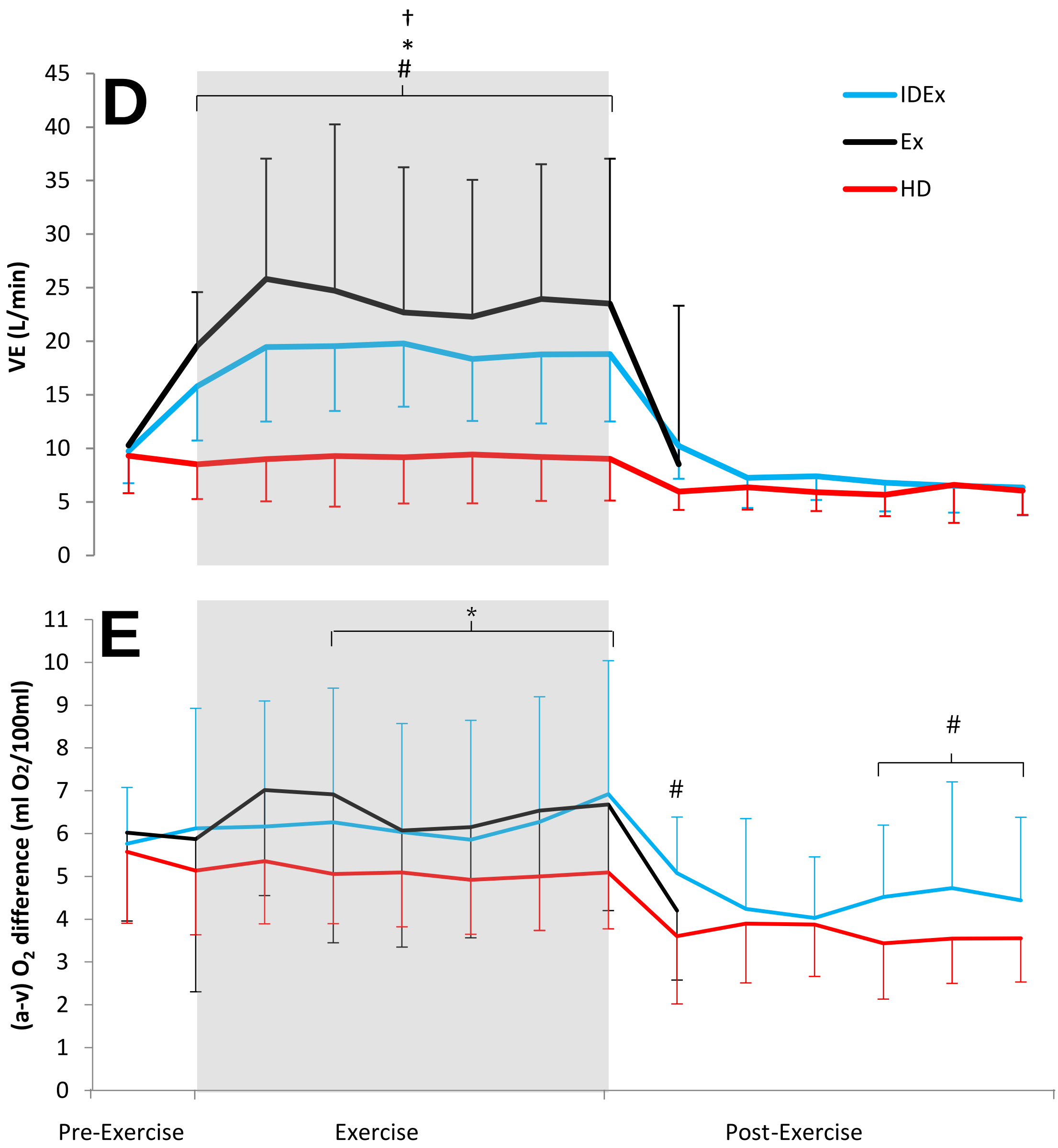


Figure 3: $\dot{V}O_2$ uptake (A), $\dot{V}CO_2$ production (B), RER (C), VE (D) and (a-v) O_2 difference (E) during the IDEx, Ex and HD conditions. Data as mean ± SD at each time point. 'Pre-exercise' data were recorded after 60 minutes of HD had elapsed for the IDEx and HD conditions. Grey boxes indicate the 30-minute exercise period for the IDEx and Ex conditions. 'Post-exercise' refers to the one-hour period after exercise for the IDEx condition and the corresponding period for the HD condition. Data were recorded for only 10 minutes post-exercise for the Ex condition. Analysis was performed with a two-way within subjects ANOVA for condition (HD, IDEx and Ex) and time. [#] significant difference between pre-exercise and the indicated time point. * significant difference between HD and Ex or IDEx conditions. [†] significant difference between the Ex and IDEx conditions.

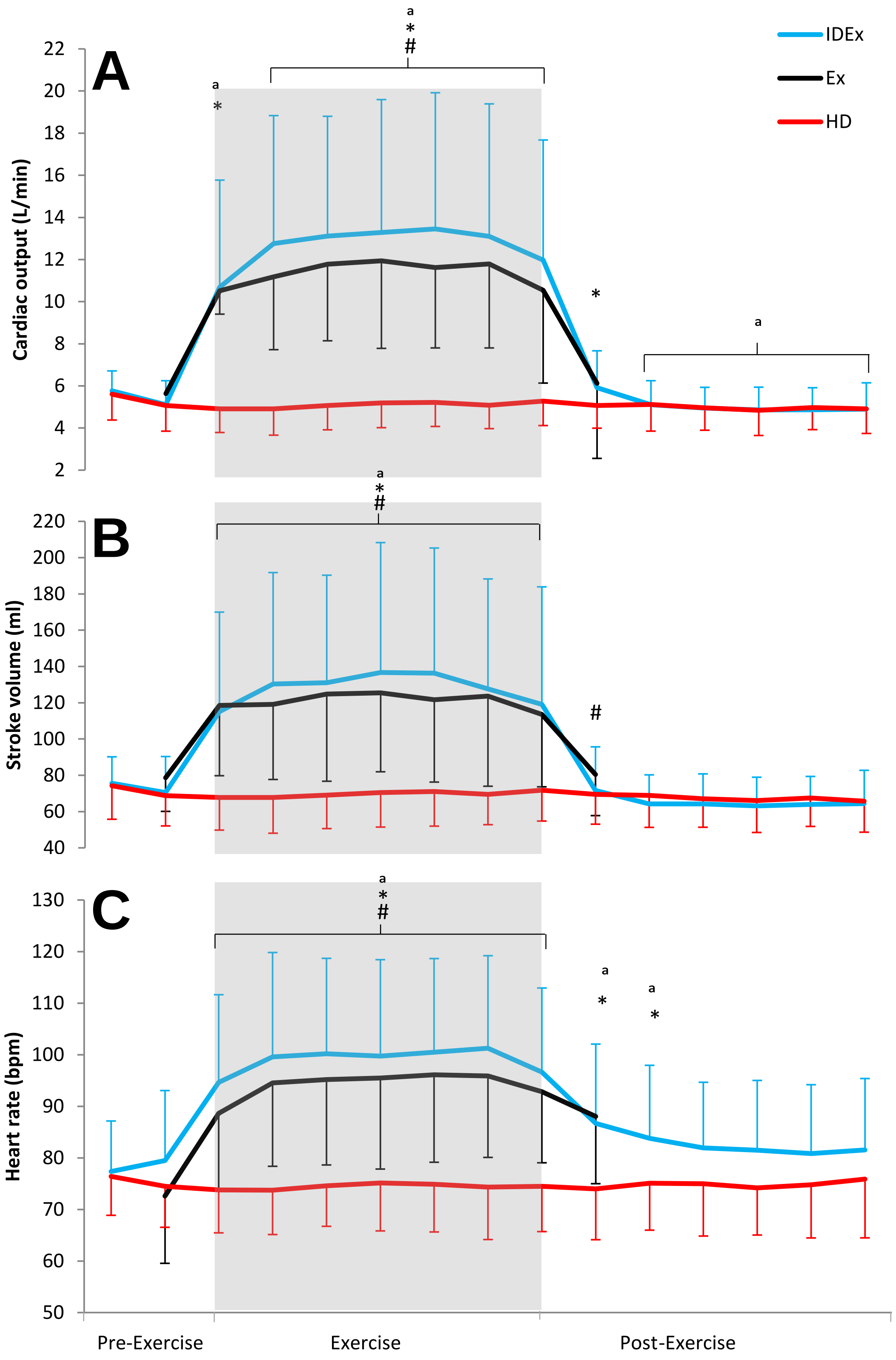

A
B
C
IDEx
Ex
HD
Cardiac output (L/min)
Stroke volume (ml)
Heart rate (bpm)
Pre-Exercise
Exercise
Post-Exercise

Figure 4: Cardiac output (A), stroke volume (B) and heart rate (C) during the HD, Ex and IDEx conditions. Data as mean ± SD at each time point. 'Pre-exercise' data were recorded after 60 minutes of HD had elapsed for the IDEx and HD conditions. Grey boxes indicate the 30-minute exercise period for the IDEx and Ex conditions. 'Post-exercise' refers to the one-hour period after exercise for the IDEx condition and the corresponding period for the HD condition. Data were recorded for only 10 minutes post-exercise for the Ex condition. Analysis was performed with a two-way within subjects ANOVA for condition (HD, IDEx and Ex) and time. * significant difference between HD and Ex or IDEx conditions. # significant difference between pre-exercise and the indicated time point. [a] significant difference between pre-HD and the indicated time point.

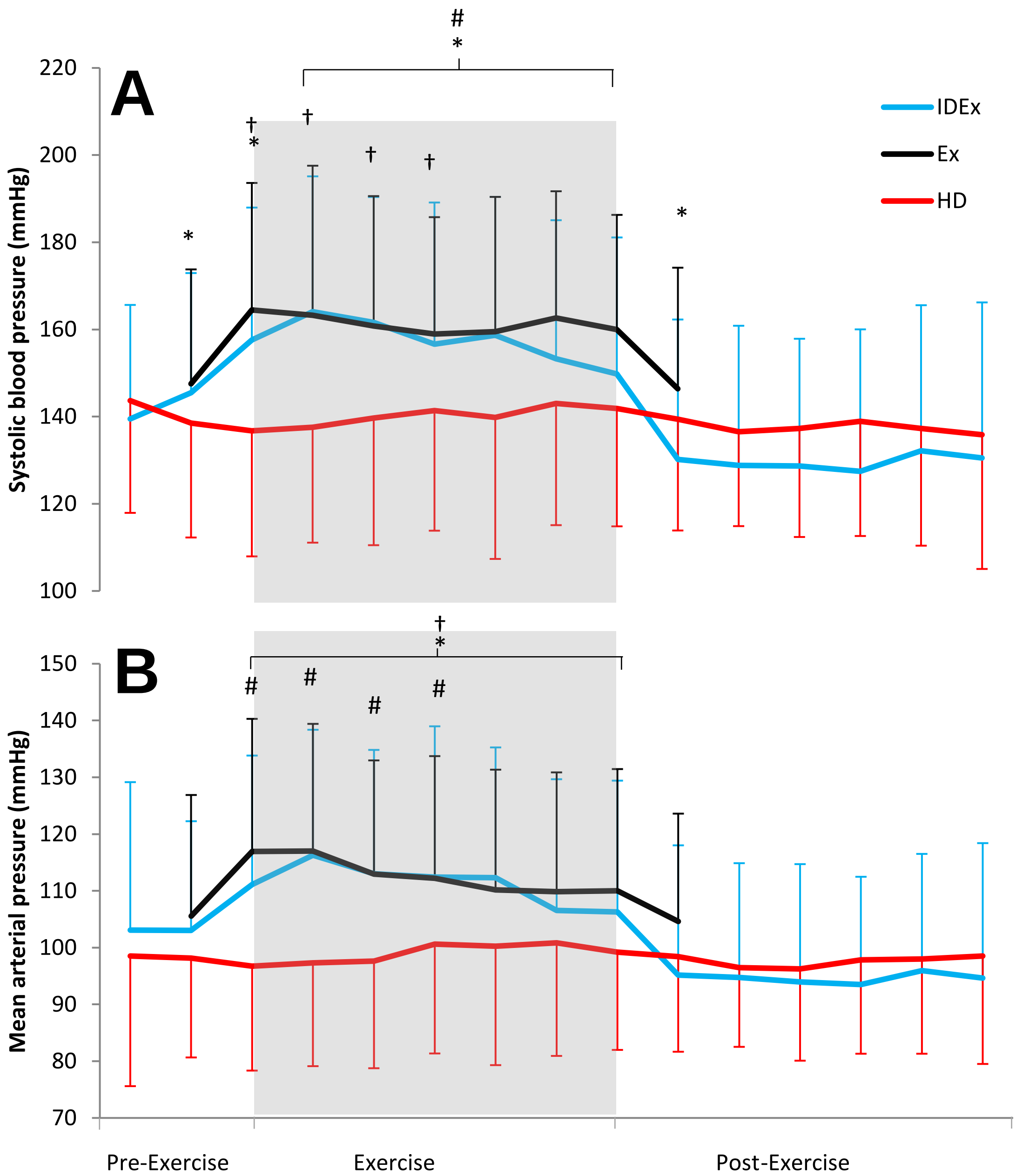


Figure 5: Systolic blood pressure (A) and mean arterial pressure (B) during IDEx, Ex and HD conditions. Data as mean ± SD at each time point. 'Pre-exercise' data were recorded after 60 minutes of HD had elapsed for the IDEx and HD conditions. Grey boxes indicate the 30-minute exercise period for the IDEx and Ex conditions. 'Post-exercise' refers to the one-hour period after exercise for the IDEx condition and the corresponding period for the HD condition. Data were recorded for only 10 minutes post-exercise for the Ex condition. Analysis was performed with a two-way within subjects ANOVA for condition (HD, IDEx and Ex) and time. * significant difference between HD and Ex condition. † significant difference between IDEx and HD condition. # significant difference between pre-exercise and indicated time point.

Table 1: Participant characteristics

Age (yrs)	59 ± 12
Weight (kg)	74 ± 15
Height (cm)	171 ± 10
BMI (kg/m^2)	25 ± 4
Body surface area (m^2)	1.85 ± 0.21
$\dot{V}O_2$ peak (ml/kg/min)	13.28 ± 2.69
Workload at $\dot{V}O_2$ peak (W)	70 ± 17
$\dot{V}O_2$ AT (ml/kg/min)	9.15 ± 2.58
Workload at VAT (W)	39 ± 14
Sex, n (male/female)	14/6
Smoking status n, (current/former/never)	3/3/14
Ethnicity	
Black	5
Caucasian	13
Asian	2
eGFR (ml/min/1.73m^2)	9.5 ± 3.1
Hemodialysis vintage (months)	41 ± 39
Comorbidities (n, %)	
Diabetes	4 (20)
Hypertension	12 (60)
Stroke	3 (15)
Coronary artery disease	7 (35)
Claudication	1 (5)
Heart failure	
I	2 (10)
II	0
III	0
IV	0
Carcinoma	3 (15)
Asthma	0
COPD	1 (5)
Ulcerative colitis	2 (10)
Hyperparathyroidism	5 (25)
CKD aetiology (n, %)	
Congenital	1 (5)
Chronic ureteric obstruction	1 (5)
Atypical haemolytic uremic syndrome	1 (5)
Glomerular nephritis	4 (20)
Tubular necrosis	1 (5)
Good pasture syndrome	1 (5)
Renal carcinoma	1 (5)
Polycystic kidney disease	1 (5)
Diabetic nephropathy	5 (25)
Hypertensive nephropathy	1 (5)

IgA nephropathy	3 (15)
Medication (n, %)	
ACE inhibitors	5 (25)
Antiplatelet	3 (15)
Anticoagulants	8 (40)
Nitrates	3 (15)
Statins	8 (40)
Diuretics	5 (25)
Anti-Arrhythmic	1 (5)
Calcium channel blockers	11 (55)
Beta-blockers	11 (55)
Hypoglycemic agents	5 (5)
Erythropoietin	10 (50)
Corticosteroids	1 (5)
Thyroxine	1 (5)

Data as mean ± SD or n (%). BMI, body mass index; $\dot{V}O_2$, oxygen uptake; VAT, ventilatory anaerobic threshold; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ACE, angiotensin converting enzyme.

Table 2: Resting cardiopulmonary and hemodynamic measurements.

	HD (n = 20)	IDEx (n = 20)	Ex (n = 20)	*P* value
VE (L/min)	9.3 ± 3.5	9.7 ± 3.0	10.0 ± 4.1	0.589
$\dot{V}O_2$ (ml/kg/min)	3.7 ± 1.1	4.0 ± 0.7	4.3 ± 1.2	0.091
$\dot{V}CO_2$ (ml/kg/min)	3.8 ± 1.3	4.1 ± 1.0	3.5 ± 1.3	0.193
RER	1.04 ± 0.14*	1.00 ± 0.1*	0.86 ± 0.01	<0.001
(a-v) O_2 difference ($ml/O_2/100ml$)	5.6 ± 1.7	5.8 ± 1.5	6.0 ± 2.9	0.269
CO (L/min)	5.1 ± 1.2	5.1 ± 1.1	5.6 ± 1.1	0.312
SV (ml)	69 ± 17	71 ± 20	79 ± 19	0.050
HR (bpm)	75 ± 8	79 ± 14	73 ± 8	0.062
MAP (mmHg)	99 ± 18	103 ± 26	106 ± 21	0.061
SBP (mmHg)	144 ± 26	146 ± 27	148 ± 26	0.076

Data as mean ± SD. *significant difference ($p < 0.05$) compared to the Ex condition (ANOVA). VE, minute ventilation; RER, respiratory exchange ratio; (a-v) O_2 difference, arterial venous O_2 difference; CO, cardiac output; SV, stroke volume; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

Table 3: Hemodialysis parameters

	HD (n = 20)	IDEx (n = 20)	*P* value
Weight (kg)			
Pre HD	75.3 ± 15.7	74.8 ± 15.0	0.009*
Post HD	72.8 ± 14.7	72.8 ± 15.1	0.152
Duration (h:min)	4.00 ± 00.20	4.00 ± 00.22	0.330
Filtration volume (ml)	2500 ± 702	2000 ± 894	0.003*
Filtration rate (ml/h)	610 ± 147	494 ± 214	0.009*
Symptoms (n, %)			0.163
Pre-syncope	2 (11)	2 (11)	
Muscle cramps	0	1 (5)	
Fatigue	0	1 (5)	
Atrial fibrillation	1 (5)	1 (5)	

Data as mean ± SD or n (%). *significant difference ($p < 0.05$) between the HD and IDEx conditions (t-test). HD, haemodialysis.

Table 4: Mean values for the exercise period

	HD (n = 20)	IDEx (n = 20)	Ex (n = 20)	*P* value
VE (L/min)	8.8 ± 3.3	16.8 ± 4.5*	20.2 ± 4.3*#	<0.001
$\dot{V}O_2$ (ml/kg/min)	3.4 ± 0.6	7.7 ± 1.6*	8.1 ± 1.8*	<0.001
$\dot{V}CO_2$ (ml/kg/min)	3.4 ± 0.7	8.2 ± 2.1*	7.6 ± 1.7*#	<0.001
RER	1.03 ± 0.08	1.03 ± 0.08	0.95 ± 0.07*#	0.016
(a-v) O_2 difference ($ml/O_2/100ml$)	5.0 ± 0.8	6.0 ± 2.1*	6.2 ± 2.1*	0.005
CO (L/min)	5.1 ± 1.2	11.1 ± 4.3*	9.9 ± 3.0*	<0.001
SV (ml)	70 ± 17	115 ± 47*	110 ± 35*	<0.001
HR (bpm)	74 ± 9	95 ± 16*	90 ± 14*	<0.001
MAP (mmHg)	98 ± 18	108 ± 21*	111 ± 19*	<0.001
SBP (mmHg)	139 ± 27	153 ± 28*	158 ± 25*	<0.001

Data as mean ± SD. * significant difference to HD (ANOVA). # significant difference to IDEx (ANOVA). VE, minute ventilation; RER, respiratory exchange ratio; (a-v) O_2 difference, arterial-venous O_2 difference; CO, cardiac output; SV, stroke volume; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.