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ORIGINAL ARTICLE

Cardiac stunning during haemodialysis: the therapeutic effect of intra-dialytic exercise

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ABSTRACT

Background. Cardiovascular risk is elevated in end-stage renal disease. Left ventricular (LV) dysfunction is linked to repetitive transient ischaemia occurring during haemodialysis (HD). Cardiomyocyte ischaemia results in 'cardiac stunning', evidenced by regional wall motion abnormalities (RWMAs). Ischaemic RWMA have been documented during HD resulting in maladaptive cardiac remodelling and increased risk of heart failure. Intra-dialytic exercise is well tolerated and can improve quality of life and functional capacity. It may also attenuate HD-induced cardiac stunning.

Methods. This exploratory study aimed to assess the effect of intra-dialytic cycle ergometry on cardiac stunning. Twenty exercise-naïve participants on maintenance HD (mean ± SD, 59 ± 11 years) underwent resting echocardiography and maximal cardiopulmonary exercise testing. Subsequently, cardiac stunning was assessed with myocardial strain-derived RWMAs at four time points during (i) standard HD and (ii) HD with 30 min of sub-maximal intra-dialytic cycle ergometry at a workload equivalent to 90% oxygen uptake at the anaerobic threshold (VO_2AT). Central haemodynamics and cardiac troponin I were also assessed.

Results. Compared with HD alone, HD with intra-dialytic exercise significantly reduced RWMAs after 2.5 h of HD (total 110 ± 4, mean 7 ± 4 segments versus total 77 ± 3, mean 5 ± 3, respectively; P = 0.008). Global cardiac function, intra-dialytic haemodynamics and LV volumetric parameters were not significantly altered with exercise.

Conclusions. Intra-dialytic exercise reduced cardiac stunning. Thirty minutes of sub-maximal exercise at 90% VO_2AT was sufficient to elicit acute cardio-protection. These data potentially demonstrate a novel therapeutic effect of intra-dialytic exercise.

Keywords: end-stage renal disease, global longitudinal strain, regional wall motion abnormality

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INTRODUCTION

Cardiovascular risk is increased in end-stage renal disease (ESRD) [1, 2]. In addition to the direct effects of chronic kidney disease (CKD), renal replacement therapy, such as maintenance haemodialysis (HD), precipitates ischaemic myocardial injury through altered cardiovascular haemodynamics [3, 4]. The resultant maladaptive cardiac remodelling and left ventricular (LV) dysfunction contribute to increased mortality, while compromising physical function and quality of life [1, 3, 5–10].

Cardiovascular haemodynamics are acutely depressed during HD. Rapid change in fluid volume reduces venous return and myocardial preload, thus contractile force and cardiac output are impaired [1, 11, 12]. The latter can decrease by as much as 1.5 L/min, increasing the risk of intra-dialytic hypotension [20 mmHg decrease in systolic blood pressure (SBP) and/or 10 mmHg decrease in mean arterial pressure], which occurs in 20–30% of HD treatments [13, 14]. This haemodynamic instability and systemic hypoperfusion can lead to ischaemic injury of gastrointestinal, cerebral and myocardial tissues [1, 9, 15].

Acute sub-clinical myocardial ischaemia during HD, or 'cardiac stunning', has been confirmed with magnetic resonance imaging and echocardiographic myocardial strain imaging through the identification of regional wall motion abnormalities (RWMAs) [1]. Myocardial ischaemia during HD has both acute and chronic consequences; ultimately, recurrent ischaemic injury, indicated by increased RWMA or cardiac troponin, promotes fibrotic cardiac remodelling and eventual heart failure [1, 11]. Medical interventions may include ultrafiltration profiling, haemodiafiltration and cooled dialysate [16]. Despite these, haemodynamic instability and cardiac stunning during HD are common and problematic, thus alternative therapeutic options must be explored [16].

When undertaken regularly, intra-dialytic exercise training, such as cycle ergometry, can improve aerobic capacity, quality of life and dialysis efficacy [17–21]. It may also confer immediate cardio-protection by increasing myocardial perfusion [16]. Acutely, exercise elevates cardiac output and increases O_2 delivery to active tissue [22]. This physiological state may promote haemodynamic stability during HD, thus sustaining coronary perfusion and preventing ischaemic cardiac stunning. Alternatively, ischaemic preconditioning may occur, whereby repetitive, sub-clinical ischaemia during intra-dialytic exercise may ultimately increase cardiomyocyte resistance to hypoxia [21]. There is limited research investigating the acute effects of intra-dialytic exercise on cardiac stunning.

Ischaemic cardiac stunning is an unfortunate consequence of essential HD treatment. The acute haemodynamic response to intra-dialytic exercise may attenuate or prevent cardiac stunning through increased myocardial perfusion or ischaemic preconditioning. Intra-dialytic exercise may prove to be a viable therapeutic strategy to reduce the considerable cardiovascular burden associated with CKD and its treatment. Consequently, this exploratory study aimed to assess the acute effect of intra-dialytic exercise on cardiac stunning. We hypothesized that cardiac stunning would be acutely reduced during maintenance HD with intra-dialytic exercise.

MATERIALS AND METHODS

In this exploratory prospective cohort study, 20 participants with ESRD were recruited from University Hospital Coventry and Warwickshire NHS Trust, between May 2017 and December 2018. After cardiopulmonary exercise testing (CPET) and resting transthoracic echocardiography on a non-dialysis day, participants were assessed under two different conditions: (i) a standard HD session (HD) and (ii) 30 min of objectively prescribed intra-dialytic constant load exercise (HD + CLE). Echocardiography and blood pressure (BP) monitoring were performed at four time points: (i) immediately before HD (pre-HD); (ii) after 1 h of HD had elapsed (1 h-HD); (iii) after 1.5 h of HD (1.5 h-HD); and (iv) after 2.5 h of HD (2.5 h-HD) (Figure 1).

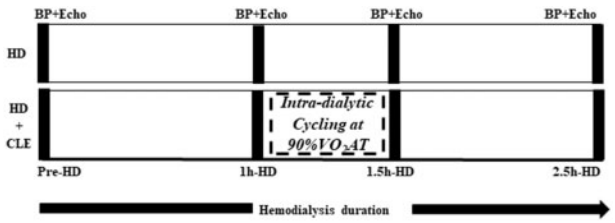


FIGURE 1: Schematic for HD and HD + CLE tests. Black bars indicate data collection time points: (i) pre-HD; (ii) 1 h-HD (pre-exercise); (iii) 1.5 h-HD (post-exercise); and (iv) 2.5 h-HD (1 h post-exercise). Dashed box indicates cycle ergometry during HD + CLE. Echo, echocardiogram.

Participants

Untrained adults with HD vintage >3 months, undergoing three times weekly HD, with a urea reduction rate of at least 65%, and able to cycle during HD, were included. Exclusion criteria included clinically significant valvular insufficiency or dysrhythmia, intra-dialytic BP > 180 systolic or >95 diastolic, >3 L fluid accumulation between HD sessions, haemoglobin <9.0 g/dL, ischaemic cardiac event (<1 month) or planned kidney transplant during the study. This study was approved by the Health Research Ethics Committee (17/LO/0368) and registered with ClinicalTrials.gov (NCT03064555). Written informed consent was obtained from all participants.

Echocardiogram

To assess global longitudinal strain (GLS) and RWMAs, echocardiography (Vivid IQ, GE Medical Systems) was performed by a trained researcher. Acquisition of apical two, three and four-chamber images (Figure 2), over three cardiac cycles, allowed quantification of GLS using automated function imaging. Endocardial wall motion was semi-automatically tracked with speckle tracking software (Echo-pack version 7.0, GE Medical Systems) and strain calculated as:

$$\varepsilon(t) = \frac{L(t) - L(t_0)}{L(t_0)}$$

where $L(t)$ is the length at the time instance t and $L(t_0)$ indicates baseline length. Instantaneous deformation was expressed relative to initial length [23], with lower negative values indicating greater LV deformation (i.e. −20% indicates greater deformation than −10%). A 17-segment model ('bullseye', Figure 3) was used to identify RWMAs, with a 20% relative reduction in strain from baseline, for each myocardial segment, indicating a RWMA [1]. Two- and four-chamber views also allowed measurement of LV volumetric parameters with Simpson's biplane method [23]. Heart rate (HR) was determined via ECG.

Data collection

For consistency, and to limit the haemodynamic effects of 2-day fluid accumulation, both testing sessions were performed

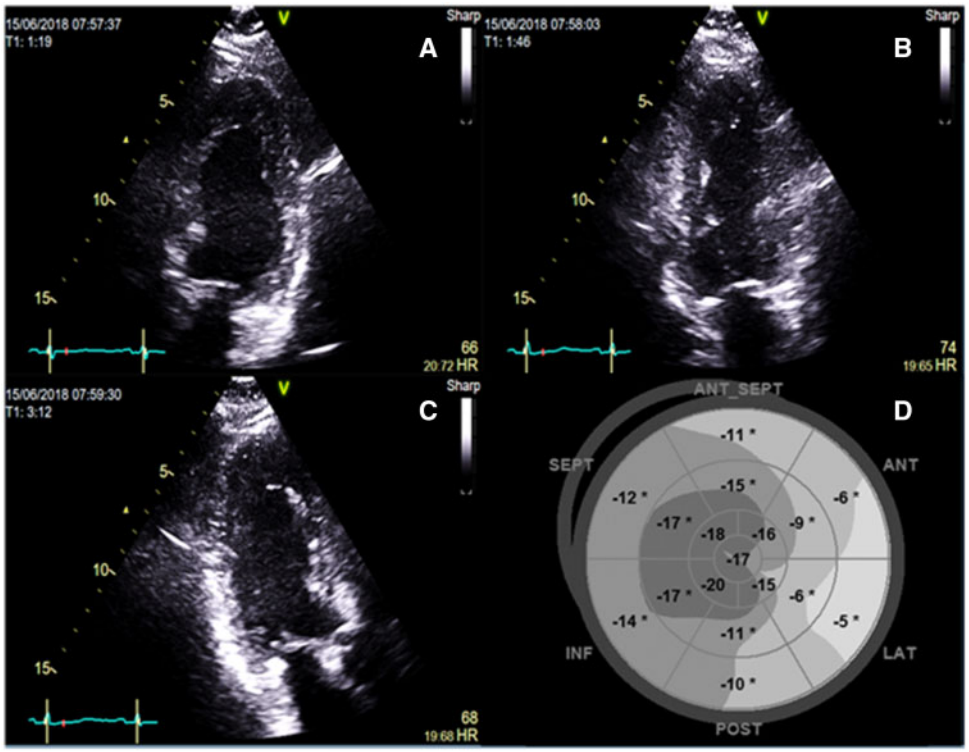
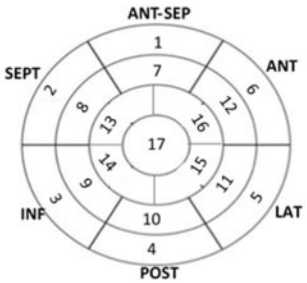


FIGURE 2: Typical echocardiogram assessment during HD. (**A**) Apical four-chamber view, (**B**) apical two-chamber view, (**C**) apical three-chamber view. Images A and B were used to calculate LV stroke volume, cardiac output, ejection fraction and end-diastolic and -systolic volumes with the Simpson's biplane method. Images A–C were used for GLS and RWMA assessment, and subsequently, a bullseye plot was produced (**D**). Dark grey indicates higher longitudinal strain with light grey and white indicating progressively lower longitudinal strain (hypokinesia). A score of 0 (white) indicates myocardial segment akinesia.



1. Basal anterior
2. Basal anteroseptal
3. Basal inferoseptal
4. Basal inferior
5. Basal inferolateral
6. Basal anterolateral
7. Mid anterior
8. Mid anteroseptal
9. Mid inferolateral
10. Mid inferior
11. Mid inferolateral
12. Mid anterolateral
13. Apical anterior
14. Apical septal
15. Apical inferior
16. Apical lateral
17. Apex

FIGURE 3: Regional bullseye plot of the left ventricle for identification of longitudinal strain and RWMAs. Each segment represents local myocardial function. ANT, anterior; LAT, lateral; POST, posterior; INF, inferior; SEPT, septal; ANT-SEP, anterior septal.

after a single non-dialysis day. During HD, and subsequently during HD + CLE test, LV function and central haemodynamics were assessed with transthoracic echocardiography and automated BP on the upper, non-fistula arm (Cheetah Medical, Maidenhead, UK), respectively, at four time points: (i) pre-HD; (ii) after 1 h-HD had elapsed; (iii) after 1.5 h-HD; and (iv) after 2.5 h-HD (Figure 1).

CPET

Maximal CPET was undertaken 1 week prior to data collection using an electronically braked cycle ergometer (Ergoline, Love Medical, Manchester, UK). A standard ramp protocol was employed with incremental load adjustment of 5, 10, 15 or 20 W/min to ensure optimal duration of 9–12 min. Participants were encouraged to maintain a cadence of 70 r.p.m. until voluntary exhaustion, indicated by a respiratory exchange ratio >1.15 [24]. Breath by breath analysis was carried out using a respiratory gas analysis system (Ergospirometer, Ergostik, Geratherm Respiratory, Bad Kissingen, Germany), whereby measurements of oxygen uptake (VO_2) and carbon dioxide production (VCO_2) were recorded, allowing identification of oxygen uptake at the anaerobic threshold (VO_2AT) with the V-Slope method [22, 25]. Data from CPET were used to accurately determine exercise intensity for the subsequent HD + CLE test.

HD

All participants were dialysing three times weekly for 4–5 h per session. Ultrafiltration rate was determined clinically, dependent on fluid accumulation between dialysis sessions. To limit differences in LV preload and cardiac output between tests, thereby allowing standardized comparison of haemodynamic responses, participants were encouraged to maintain fluid intake within clinically prescribed thresholds. HD filtration rates were the same for HD and HD + CLE tests, unless otherwise clinically directed.

Intra-dialytic CLE (HD + CLE) test

CLE was performed in the semi-recumbent position on an electronically braked cycle ergometer (Lower body bi-directional ergometer, Hudson Fitness, Dallas, TX, USA). Workload was adjusted with pedal resistance and cadence. After a 5-min warm-

up at 10 r.p.m. below testing r.p.m., 30 min of exercise was completed at a workload (Watts) equivalent to 90% VO_2AT, pre-determined from CPET. On completion, participants 'cooled down' with 3 min of unloaded pedalling at 50 r.p.m.

Cardiac troponin I

One plasma vacutainer (3 mL) was collected at 1 h-HD, 1.5 h-HD and 2.5 h-HD during both the HD and HD + CLE conditions. Pre-HD samples were not possible due to patient preparation for dialysis. Samples were centrifuged at 3000 r.p.m. at 21°C (Sigma 3-18 k Scientific Laboratory Supplies) and frozen at −80°C for subsequent analysis. Troponin I was assessed with commercially available sandwich enzyme-linked immunoassay kits (Abbexa, Cambridge, UK; abx252868; biotin conjugated antibody; sensitivity 9.38 pg/mL). Serial dilutions were performed ranging from 15.63 to 1000 pg/mL. Absorbance was measured at 450 nm wavelength. Sample concentration was determined using linear regression from pre-determined standard concentrations.

Sample size

Due to the exploratory nature of the study, an *a priori* power calculation was not possible. Therefore, 20 participants were recruited. Retrospective analysis of effect size for RWMAs was determined using Cohen's d.

Statistical analysis

Data were analysed with a two-way ANOVA within subjects for condition (HD and HD + CLE) and time (pre-HD, 1 h-HD, 1.5 h-HD and 2.5 h-HD). Where a main effect effect was identified, *post hoc* analysis was undertaken with a paired sample *t*-test. All data were expressed as mean ± SD. To correct violations of sphericity, degrees of freedom were adjusted using Greenhouse–Geisser (<0.75) or Huynh–Feldt (>0.75) where appropriate. Statistical significance was indicated by $P < 0.05$.

RESULTS

From May 2017 to December 2018, 70 patients were screened, of which 40 were eligible and 20 agreed to participate. Due to poor visualization of the lateral endocardial border, preventing accurate speckle tracking in two echocardiography assessments, 18 participants were included in the final analysis. Participants acted as their own controls by undertaking HD and HD + CLE testing separated by 1 week. HD and intra-dialytic exercise were well tolerated; one participant experienced peripheral fatigue, stopping twice during HD + CLE for 2 min, and two participants felt 'light headed' during the post-exercise period. Unplanned medical intervention was not required during or after any of the tests. All participants completed 30 min of cycling at 90% VO_2AT (mean workload 35 ± 10 W) after 1 h of HD had elapsed. Medication was not altered for the duration that each participant was enrolled in this study.

Baseline characteristics

Baseline characteristics are presented in Table 1. The mean age was 59 ± 11 years with females constituting 27% of participants. Mean dry weight was 72 ± 11 kg, and body mass index (BMI) was 24.4 ± 3.2 kg/m^2. HD vintage was 36 ± 40 months, with the most common CKD aetiologies being diabetic nephropathy (22%) and glomerular nephritis (22%).

HD parameters

There were no significant differences between tests for HD duration, post-HD weight or symptoms (Table 2). HD filtration volume (2422 ± 697 versus 2028 ± 799 mL), filtration rate (589 ± 139 versus 469 ± 209 mL) and pre-weight (74.4 ± 13.5 versus 73.4 ± 13.5 kg) varied slightly between HD and HD + CLE (Table 2).

Cardiac function

GLS progressively declined ($P = 0.012$) in all 18 participants during both HD (−14 ± 2 pre-HD to −13 ± 3% at 2.5 h-HD) and HD + CLE (−14 ± 4 pre-HD to −13 ± 4% at 2.5 h-HD) indicating decreased myocardial function. There was no difference between HD and HD + CLE in the reduction in GLS ($P = 0.489$; Figure 4).

RWMAs were identified in all 18 participants during HD and HD + CLE (Figure 4). The total number of RWMAs identified increased during HD to a maximum of 110 ± 4 segments at 2.5 h-HD. During HD + CLE, the total number of RWMAs identified increased to a maximum of 106 ± 3 segments at 1.5 h-HD. At the 2.5 h-HD timepoint, there were significantly fewer RMWAs during HD + CLE compared with HD (total 77 ± 3, mean 5 ± 3 versus total 110 ± 4, mean 7 ± 4 segments, respectively; $P = 0.008$). The greatest number of RWMAs occurred in the mid inferolateral and basolateral segments for HD and HD + CLE (Figure 5).

Cardiac output decreased ($P < 0.001$) by 21% during HD (4.6 ± 1.6 L/min pre-HD to 3.6 ± 1.7 L/min at 2.5 h-HD) and by 20% during HD + CLE (4.5 ± 1.5 L/min pre-HD to 3.6 ± 1.3 L/min at 2.5 h-HD). There was no difference ($P = 0.645$) in the reduction in cardiac output between HD and HD + CLE (Figure 4).

HR increased during HD + CLE (77 ± 10 b.p.m. pre-HD to 87 ± 15 b.p.m. at 1.5 h-HD; $P = 0.022$). There was a significant difference ($P = 0.024$) in HR between HD and HD + CLE at the 1.5 h-HD time point (Figure 4).

LV end-diastolic volume decreased ($P = 0.014$) by 17% during HD (135 ± 54 mL pre-HD to 112 ± 50 mL at 2.5 h-HD), and by 10% during HD + CLE (118 ± 46 mL pre-HD to 106 ± 51 mL at 2.5 h-HD). There was no difference ($P = 0.289$) between HD and HD + CLE in terms of the reduction in LV end-diastolic volume (Figure 4).

LV end-systolic volume ($P = 0.53$), ejection fraction ($P = 0.125$) and stroke volume ($P = 0.206$) did not change during HD or HD + CLE, nor were there any differences between the HD and HD + CLE conditions.

Troponin I

Cardiac troponin I did not differ over time ($P = 0.172$) during HD or HD + CLE, nor was there any difference between HD and HD + CLE ($P = 0.139$; Figure 4).

Haemodynamics

There were no statistically significant changes in SBP ($P = 0.262$), DBP ($P = 0.092$) or mean arterial pressure (MAP) ($P = 0.651$) over the duration of HD and HD + CLE, and there were no differences between the HD and HD + CLE conditions (Figure 6). However, there was a trend towards a difference in MAP between HD + CLE and HD ($P = 0.052$).

Effect size analysis

Retrospective analysis identified a moderate effect size (0.57) for RWMAs in 18 participants at the 2.5 h-HD time point [26] with a mean of 5 ± 3 segments for HD + CLE and 7 ± 4 segments for HD.

Table 1. Participant characteristics

Participant characteristics	ESRD ($n = 18$)
Age, years	59 ± 11
Weight, kg	72 ± 11
Height, cm	172 ± 11
BMI, kg/m^2	24.4 ± 3.2
Gender, *n* (male/female)	13/5
Smoking status, *n* (current/former/never)	4/4/10
Ethnicity, *n*	
Black	5
Caucasian	11
Asian	2
Haemodialysis vintage, months	41 ± 39
Comorbidities, *n* (%)	
Diabetes	4 (22)
Hypertension	10 (56)
Stroke	3 (17)
Coronary artery disease	6 (33)
Claudication	1 (6)
Heart failure	2 (11)
Hyperparathyroidism	5 (28)
CKD aetiology, *n* (%)	
Congenital	1 (6)
Chronic ureteric obstruction	1 (6)
Atypical haemolytic uraemic syndrome	1 (6)
Glomerular nephritis	4 (22)
Tubular necrosis	1 (6)
Good pasture syndrome	1 (6)
Renal carcinoma	1 (6)
Polycystic kidney disease	1 (6)
Diabetic nephropathy	4 (22)
Hypertensive nephropathy	1 (6)
Immunoglobulin A nephropathy	2 (11)
Medication, *n* (%)	
ACE inhibitors	5 (28)
Antiplatelet	3 (17)
Anticoagulants	6 (33)
Nitrates	3 (17)
Statins	7 (39)
Diuretics	5 (28)
Anti-arrhythmic	1 (6)
Calcium channel blockers	11 (61)
β-blockers	10 (56)
Hypoglycaemic agents	5 (27)
Erythropoietin	9 (50)
Corticosteroids	1 (6)
Thyroxine	1 (6)

Values expressed as mean ± SD where appropriate. An independent *t*-test was used to identify differences between groups. eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme.

Table 2. HD parameters

HD parameters	HD ($n = 18$)	HD + CLE ($n = 18$)	P-value
Weight, kg			
Pre-HD	74.4 ± 13.5[a]	73.4 ± 13.5[a]	0.013[a]
Post-HD	72.1 ± 13.8	71.6 ± 13.8	0.152
Duration, h:min	04:00 ± 00:39	04:00 ± 00:38	0.331
Filtration volume, mL	2422 ± 697[a]	2028 ± 799[a]	0.001[a]
Filtration rate, mL/h	589 ± 139[a]	469 ± 209[a]	0.001[a]
Symptoms, *n* (%)	–	–	0.163
Dizziness	2 (11)	2 (11)	–
Muscle cramps	0	1 (6)	–
Fatigue	0	1 (6)	–

Values are expressed as mean ± SD.
[a]Significant difference between HD and HD + CLE.

DISCUSSION

This exploratory study assessed the acute effect of cycle ergometry performed during maintenance HD. We report a significant reduction in cardiac stunning with intra-dialytic exercise, compared with HD without exercise. These data extend previous findings by objectively quantifying a duration and intensity of exercise (30 min at a workload equivalent to 90% VO_2AT) sufficient to provoke a reduction in cardiac stunning in exercise- naïve HD patients.

HD

Data from this study indicate that HD elicited a physiological and haemodynamic response consistent with previous reports [1, 9]. GLS, cardiac output and LV end-diastolic volume decreased significantly throughout HD. Simultaneously, the number of RWMAs increased, particularly between the 1.5 and 2.5 h-HD timepoints. Although not statistically significant, other LV volumetric and haemodynamic parameters appeared to decline throughout HD. Overall, this haemodynamic profile is typical of HD, relating to a steady decline in plasma volume during filtration, thus reduced LV preload and contractility [31].

With HD treatment, cardiovascular function deteriorates [1]; as cardiac output declines, so too does coronary blood flow [9], with resultant myocardial ischaemia. We observed an increase in RWMAs during HD, likely resulting from reduced coronary blood flow and cardiomyocyte hypoxia [1]. Predominantly, RWMAs during HD are indicative of myocardial ischaemia and are considered to be a key driver of heart failure [27], and thus increased mortality. Chronic, repetitive myocardial ischaemia can eventually lead to increased cardiomyocyte apoptosis and necrosis, a key determinant of myocardial fibrosis [1]. Acute stunning of myocardial segments also impairs haemodynamic stability, potentially reducing HD efficacy. Cardiac function is inevitably affected, manifesting as chronic LV systolic and diastolic impairment [1]. Previous work showed that 12 months of HD in patients with observable RWMAs resulted in an 8.6% decrease in LV ejection fraction [1], and in the longer term is associated with heart failure, and decreased survival and quality of life [1, 6, 9]. Preserving cardiac function and reducing the cardiovascular risks associated with HD are paramount.

Intra-dialytic exercise

GLS gradually declined during both experimental conditions in our study, corresponding with an increase in RWMAs. However, intra-dialytic exercise was associated with a significant reduction in RWMAs at 2.5 h-HD compared with HD without exercise. This is a key finding, illustrating the potential for intra-dialytic exercise to attenuate cardiac stunning. In a previous study, Penny *et al.* [21] also reported reduced RWMAs with intra-dialytic exercise in an HD cohort regularly undertaking intra-dialytic cycle ergometry as part of a clinical service. Our study extends these findings to an untrained HD population in which maximal exercise capacity was directly measured with CPET and subsequently used to individually prescribe exercise at a workload equivalent to 90% VO_2AT.

It is notable that, despite reduced RWMA during HD + CLE, a progressive and comparable decline in GLS was evident during both conditions. Therefore, global LV function was not visibly

improved, despite reduced RWMAs. This may suggest a greater contribution to GLS of previously hypokinetic segments during HD + CLE and, similarly, a lesser contribution of previously hyperkinetic segments. Thus, LV function was acutely maintained but with a more uniform distribution of myocardial work.

It is also notable that filtration rates and volumes were higher during the HD condition, compared with HD + CLE, both of which are associated with a greater prevalence of RWMAs [13]. However, this difference did not correspond to greater RWMAs at the 1 h-HD and 1.5 h-HD time points, rather, RMWAs occurred equally during both HD + CLE and HD. Additionally, almost identical haemodynamic and cardiac responses were observed at these time points during the HD + CLE and HD conditions. Only HR at 1.5 h-HD and RWMAs at 2.5 h-HD were different between conditions. Therefore, the higher filtration volume and rate in the HD group were not associated with greater impairment in cardiac function and, as such, were unlikely to have contributed to the finding of lower RWMAs at the 2.5-HD time point. Our data also agree with previous findings of reduced RWMAs with intra-dialytic exercise during HD [21].

To assess the potential for myocardial injury with intra-dialytic exercise, we measured cardiac troponin I. In agreement with previous findings [28], we did not observe any significant increase in cardiac troponin I with intra-dialytic exercise. However, the clinical significance of these findings is unclear. Meaningful assessment of cardiac troponin I was hindered by the small sample, large intra-individual variability and limited post-exercise measurement time points.

Ischaemic preconditioning

Intra-dialytic exercise reduced cardiac stunning at the 2.5 h-HD time point as evidenced by a reduction in RWMAs. We previously speculated that acutely augmenting venous return, LV preload and catecholamine-mediated redistribution of blood flow with intra-dialytic exercise may improve haemodynamic stability and coronary perfusion [16]. However, the observed reduction in RWMAs was not accompanied by greater haemodynamic stability measured with BP and LV volumetric parameters. There were no differences in any of these variables

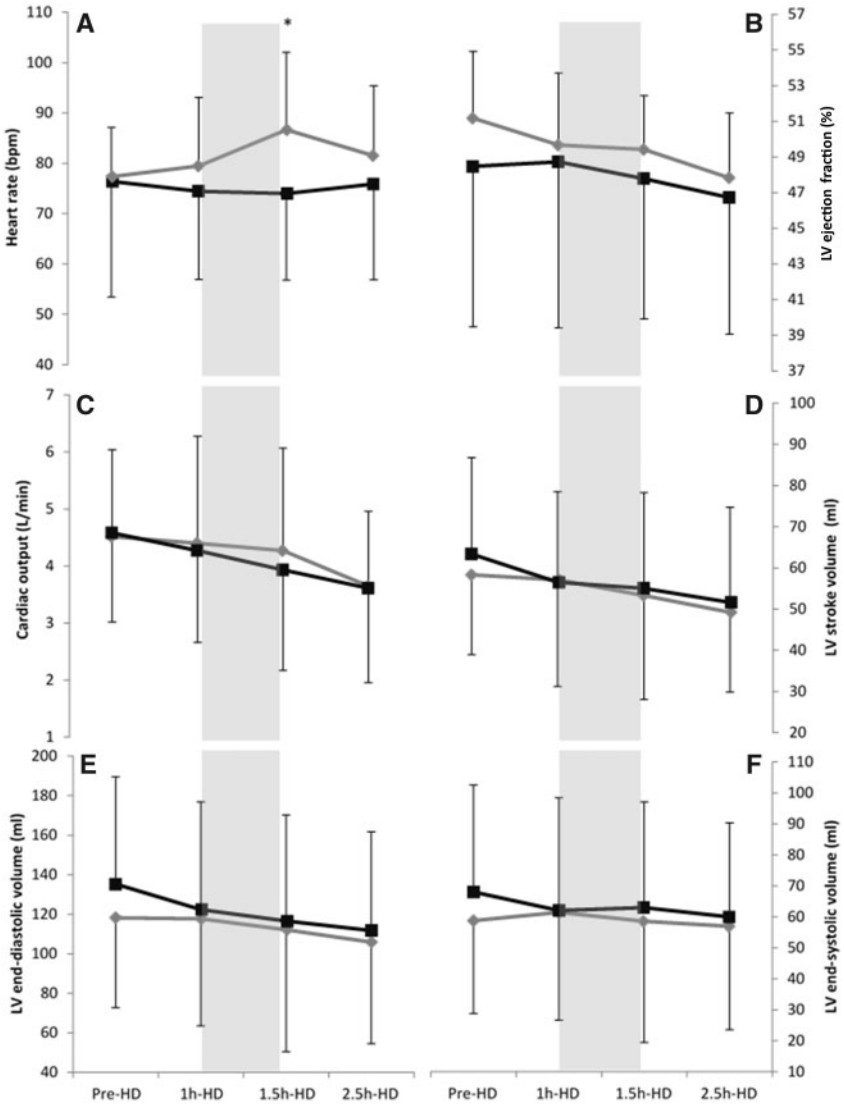


FIGURE 4: Cardiac function and troponin I during HD and HD + CLE conditions. Filled diamond indicates HD + CLE condition; filled square indicates HD condition. **(A)** HR, **(B)** ejection fraction, **(C)** cardiac output, **(D)** stroke volume, **(E)** LV end-diastolic volume, **(F)** LV end-systolic volume, **(G)** mean RWMAs, **(H)** GLS and **(I)** cardiac troponin I. Grey boxes indicate 30-min exercise period for HD + CLE. *Significant difference between HD + CLE and HD conditions.

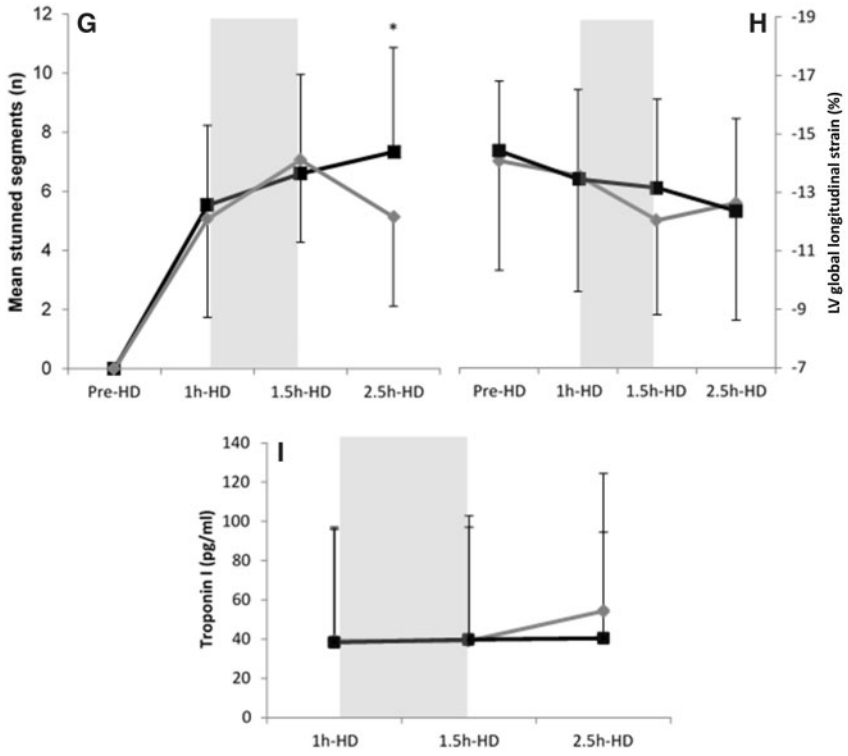


FIGURE 4: Continued

between conditions, indicating no obvious effect of exercise on the intra-dialytic haemodynamic profile. This corroborates the findings of Penny *et al.* [21], which showed no acute effect of intra-dialytic exercise on global cardiac function or BP. We cannot completely rule out enhanced coronary perfusion as a mechanism for decreased RMWAs in our study, as we did not perform any direct measures. However, given the lack of any difference in haemodynamic profiles between conditions, it is more likely that other mechanisms were responsible.

Recently, an ischaemic preconditioning effect was proposed with intra-dialytic exercise [21]. Data from our study closely reflect this work, thus the reduction in RWMA we observed with exercise may be a result of this phenomenon. Acute bouts of exercise-induced hypoxia can elicit a cardio-protective effect for up to 5 days [29]. This has been demonstrated in rat models, whereby exercise preconditioning reduced myocardial infarction size by increasing cardiomyocyte resistance to hypoxia. The molecular cascade eliciting this cardio-protective effect is poorly understood. However, proposed mechanisms include accelerated recovery of myocardial oxygenation, sustained upregulation of cardiac endothelial nitric oxide synthase, altered glycogen synthase kinase-3β, epidermal growth factor expression, improved contractile performance during reperfusion and heat shock protein expression [29]. The effects of ischaemic preconditioning are likely multifaceted. Identifying the molecular pathway responsible for this cardio-protective effect may be critical to understanding the mechanism of reduced cardiac stunning with intra-dialytic exercise.

Limitations

A number of limitations should be addressed. First, the study was exploratory to demonstrate proof of concept in a small predominantly male cohort; data should be interpreted in this context. However, by objectively assessing and prescribing exercise intensity, we were able to control for important confounding factors. Secondly, despite identification of a moderate effect size for RWMAs, it is unlikely that all variables were powered to detect change with $n = 18$ participants. Nevertheless, similar work proposed a sample size of 10 as sufficient to detect a 20% change in RWMAs [21], our primary variable of interest. Finally, we acknowledge the difference in filtration rates between conditions. However, it is very unlikely that this was responsible for the difference in RWMAs witnessed at 2.5 h-HD as there was no difference observed at the 1 h-HD and 1.5 h-HD time points. Regulation of filtration volume would avoid this limitation but this was not feasible on ethical grounds; patient care was at the discretion of the medical team.

CONCLUSION

Thirty minutes of intra-dialytic cycle ergometry, at an individually prescribed workload equivalent to 90% VO_2AT, significantly reduced cardiac stunning in a cohort of untrained participants undergoing maintenance HD. Our exploratory study is the first to identify the intensity and duration of exercise sufficient to elicit this acute cardio-protective response. These data further confirm the importance and clinical relevance of intra-dialytic exercise. To inform intra-dialytic exercise prescription guidelines, future work should endeavour to investigate the optimum tolerable intensity, timing and duration of exercise to induce the greatest magnitude of RWMA reduction. Clinical trials are required to assess the long-term effects of reduced cardiac stunning during HD, not only in relation to hard clinical endpoints, but also in relation to patient-reported outcomes. Our data suggest that intra-dialytic exercise may be acutely cardio-protective and, accordingly, should be routinely prescribed.

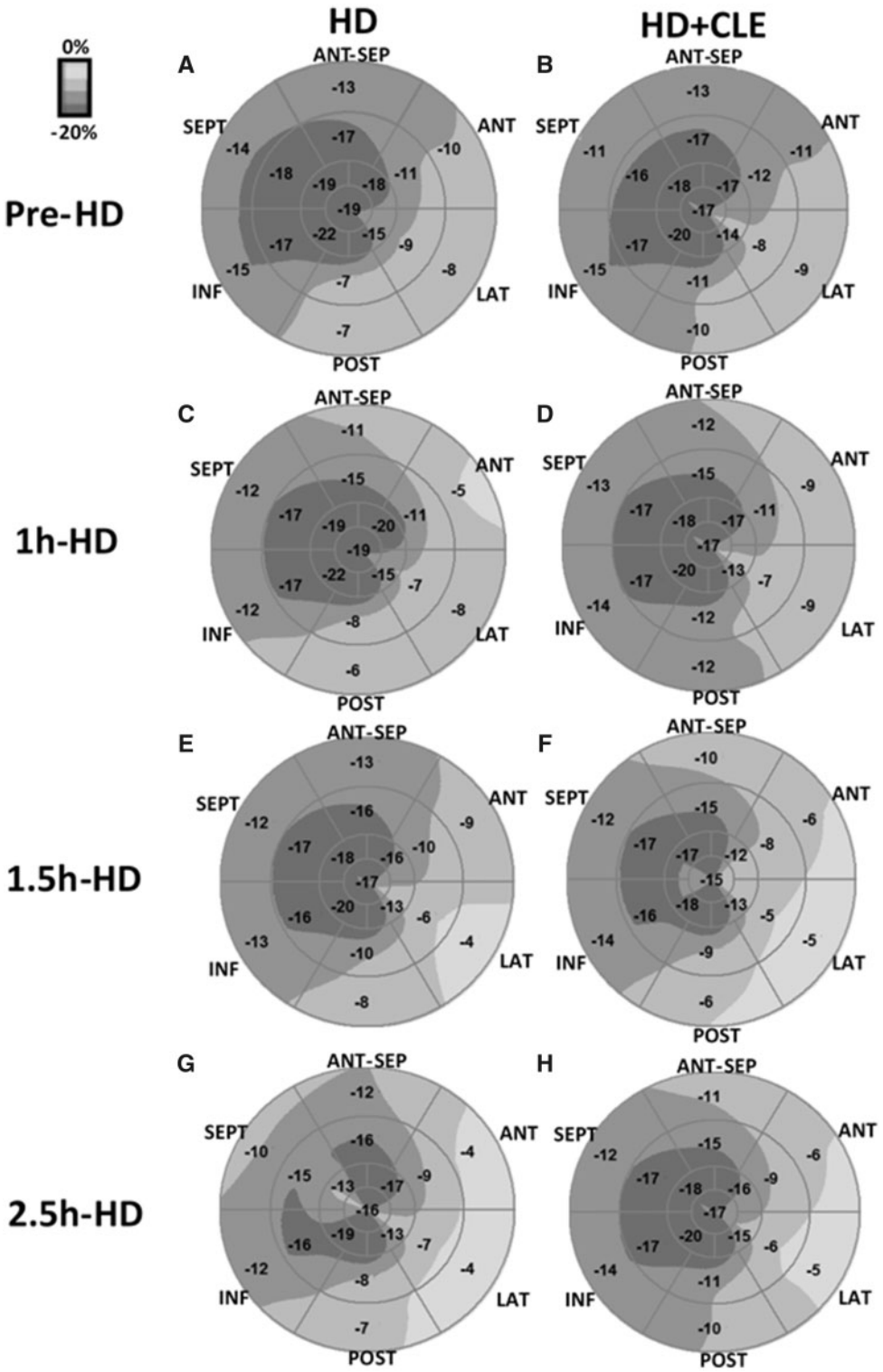


FIGURE 5: Mean regional longitudinal strain of the LV demonstrated using bullseye plots during pre-HD (**A** and **B**), 1 h-HD (**C** and **D**), 1.5 h-HD (**E** and **F**) and 2.5 h-HD (**G** and **H**) for HD (left column) and HD + CLE (right column). Dark grey indicates higher longitudinal strain, light grey indicates lower longitudinal strain (hypokinesia). For a detailed explanation of each segment and its myocardial representation, see Figure 3.

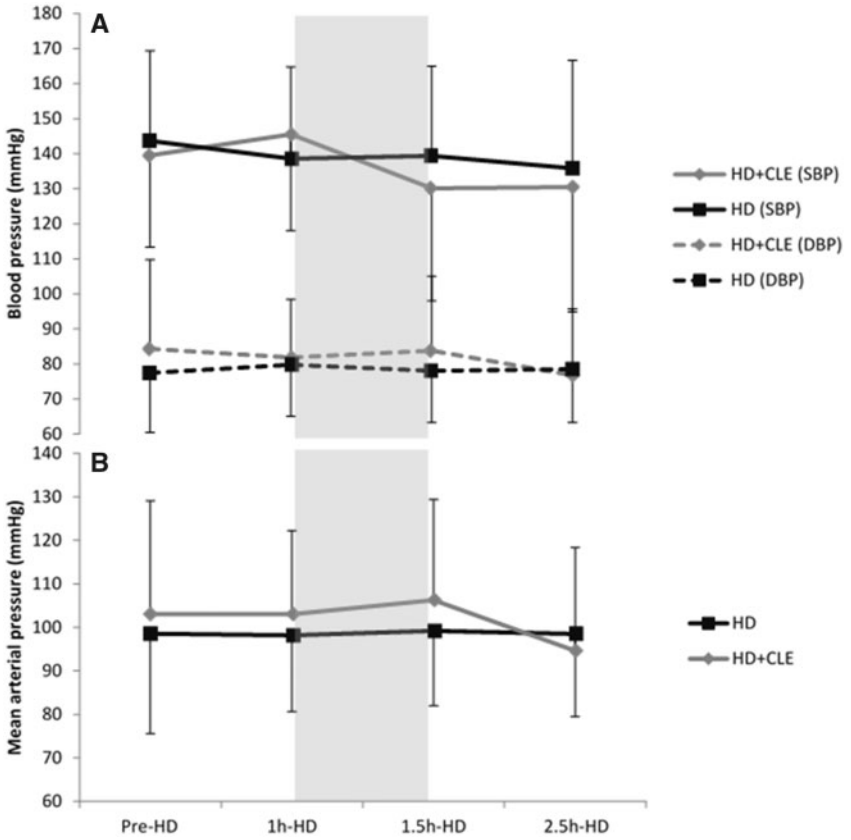


FIGURE 6: Intra-dialytic haemodynamics as SBP and DBP (**A**) and MAP (**B**). Grey boxes indicate the 30-min exercise period for HD + CLE.

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AUTHORS' CONTRIBUTIONS

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

CONFLICT OF INTEREST STATEMENT

None declared.

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