The Impact of Exercising During Haemodialysis on Blood Pressure, Markers of Cardiac Injury and Systemic Inflammation – Preliminary Results of a Pilot Study

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Key Words
Blood pressure • Cardiovascular disease • Exercise • Haemodialysis • Inflammation

Abstract
Background/Aims: Patients requiring haemodialysis have cardiovascular and immune dysfunction. Little is known about the acute effects of exercise during haemodialysis. Exercise has numerous health benefits but in other populations has a profound impact upon blood pressure, inflammation and immune function; therefore having the potential to exacerbate cardiovascular and immune dysfunction in this vulnerable population. Methods: Fifteen patients took part in a randomised-crossover study investigating the effect of a 30-min bout of exercise during haemodialysis compared to resting haemodialysis. We assessed blood pressure, plasma markers of cardiac injury and systemic inflammation and neutrophil degranulation. Results: Exercise increased blood pressure immediately post-exercise; however, 1 hour after exercise blood pressure was lower than resting levels (106±22 vs. 117±25 mm Hg). No differences in h-FABP, cTnI, myoglobin or CKMB were observed between trial arms. Exercise did not alter circulating concentrations of IL-6, TNF-α or IL-1ra nor clearly suppress neutrophil function. Conclusions: This study demonstrates fluctuations in blood pressure during haemodialysis in response to exercise. However, since the fall in blood pressure occurred without evidence of cardiac injury, we regard it as a normal response to exercise superimposed onto the haemodynamic response to haemodialysis. Importantly, exercise did not exacerbate systemic inflammation or immune dysfunction; intradialytic exercise was well tolerated.

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**Introduction**

Patients with end-stage renal disease (ESRD) have a substantially increased incidence of cardiovascular events and mortality. Many 'traditional' risk factors influencing cardiovascular health are not pertinent for ESRD patients [1]; factors such as inflammation, malnutrition and intradialytic hypotension are more evidently associated with poor survival [2, 3].

Uraemia and haemodialysis (HD) provides increased opportunities for endotoxin influx, recurrent infections and immune activation leading to chronic systemic inflammation [4]. ESRD patients consequently have a dysfunctional immune system that is both chronically over-activated and anergic [5, 6]. In addition, HD is associated with myocardial demand ischaemia that leads to transient myocardial stunning, often with concomitant intradialytic hypotension [7]. Repeated bouts of myocardial stunning are associated with a reduced ejection fraction and increased likelihood of mortality. Both of these factors (immune and myocardial dysfunction) are crucial in the pathogenesis of cardiovascular mortality that is so common in ESRD patients.

ESRD patients are highly inactive and this is exacerbated on days when they have HD treatment [8, 9]; further, poor physical performance is associated with mortality and hospitalisation rates and poor arterial and heart function [10, 11]. As with most populations, regular exercise is reported to have numerous benefits for early CKD, HD and transplant patients. These include improved exercise capacity, quality of life and cardiovascular health [12-15].

Exercise during HD is feasible and compliance and drop-out rates are better compared to exercise programmes for HD patients away from dialysis [16, 17]. Intradialytic exercise occurs at a time when patients are otherwise completely sedentary and is an effective way to change the exercise culture and behaviour of HD patients [18, 19]. Exercise in healthy populations has been suggested as an effective means to reduce systemic inflammation [20]; however, an acute bout of exercise also has notable effects on blood pressure [21] and immune function [22]. Exercise, for example, can stimulate a muscular release of IL-6 into circulation; usually met by an anti-inflammatory response to restore resting levels [23]. ESRD patients are highly vulnerable and the dysfunctional immune and cardiovascular systems in these patients may not adequately respond to the profound transient effects on blood pressure, circulating markers of inflammation, and immune function that can occur with exercise. Little is known of the immediate impact of exercising during HD, a time when patients are at an even greater susceptibility to infection, inflammation and haemodynamic alterations.

The aims of this study were to analyse the immediate effects of a bout of physical exercise during HD on haemodynamic stability, circulating markers of inflammation and aspects of immune function compared to a usual-care HD session.

**Subjects and Methods**

**Participants**

A pragmatic sample of 15 HD patients who were regularly exercising during HD as part of a service development programme gave informed consent to participate in the study and all patients completed both study periods (Figure 1), their basic characteristics are described in Table 1.

Patients were recruited from a satellite haemodialysis unit in the University Hospitals of Leicester NHS trust. The study received approval from the NHS Research Ethics Committee (ref. 10/H0406/36). Patients were not eligible if they were under 18 years, had established contraindications to exercise [24], lower limb vascular access, recent clinically overt infection, prescribed immunosuppressive therapy, or an insufficient command of English to consent. All patients used polysulfone high-flux dialysers. The dialysate, dialyser, needle size and dialysis duration and prescriptions were unchanged between study days.
Dungey/Bishop/Young/Burton/Smith: Exercise During Haemodialysis

Outcomes

Blood pressure was taken using an electronic sphygmomanometer at the start of dialysis (0 min), and then at the same time as blood samples drawn directly from the HD lines pre-exercise (60 min), immediately post-exercise (100 min), 1 h post-exercise (160 min) and at the end of dialysis (240 min) and the equivalent times during the control HD session. Rate pressure product (RPP) was calculated as heart rate x SBP.

Haematology

Haematology and a differential white cell count were measured using an automated cell counter (Ac.T 5diff OV, Beckman Coulter; High Wycombe, UK). Outcome measures are adjusted for changes in plasma volume [26].

Circulating markers of systemic inflammation and cardiac injury

Plasma concentrations of IL-6, TNF-α, IL-1ra (R&D systems, Abingdon, UK) and CRP (IBL International

Study design

Patients participated in two trial arms during HD treatment usually separated by a week and carried out on the same day of the week. During the exercise arm patients performed a 5-min warm-up followed by a 30-min bout of intradialytic exercise using a specially-designed cycle ergometer (Letto series; Reck, Germany) 60 min into their HD session. Patients cycled at self-selected gears at a perceived exertion of ‘somewhat hard’ using the Rating of Perceived Exertion scale (RPE) [25]. RPE and power output were recorded every 5 min with participants encouraged to adjust the gear to match the required RPE. Patients were familiar with the cycle ergometer and RPE scale from routinely taking part in an exercise programme at the renal unit for at least 3 months. Exercise was not novel for these patients, but instead represents the usual effect of exercise during HD for patients that regularly take part in intradialytic exercise. During the control arm the patient rested throughout HD.

Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>57.9 ± 10.5</td>
</tr>
<tr>
<td>Sex (n)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>Ethnicity (n)</td>
<td></td>
</tr>
<tr>
<td>White British</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Indian</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 9</td>
</tr>
<tr>
<td>Dry weight (kg)</td>
<td>76.5 ± 20.0</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.4 ± 6.5</td>
</tr>
<tr>
<td>Haemodialysis vintage (y)</td>
<td>3.62 (1.77-3.82)</td>
</tr>
<tr>
<td>Primary disease (n)</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Cystic / Poly</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (13%)</td>
</tr>
</tbody>
</table>

n = 15. Data are mean ± standard deviation, median (interquartile range), or n (%)
GmbH, Hamburg, Germany) were measured using commercially available ELISA kits. Simultaneous detection of early (heart-type fatty acid-binding protein [h-FABP] and myoglobin) and late (cardiac troponin I [cTnI] and creatine kinase MB [CKMB]) markers of myocardial injury were assessed using a commercially available biochip assay and Evidence Investigator (Randox Ltd., Crumlin, UK).

**Monocyte phenotyping**

10 μL CD14-fluorescein isothiocyanate and 10 μL CD16-phycocerythrin (Becton Dickinson [BD] Biosciences, Oxford, UK) were added to 120 μL heparinised whole blood and incubated on ice in the dark for 20 min. Erythrocytes were lysed (FACS lysis buffer, BD Biosciences, Oxford, UK) and the cells washed through addition of chilled phosphate buffered saline (PBS) containing 0.5% bovine serum albumin and 2 mmol/L EDTA. After centrifugation the cells were resuspended in 400 μL chilled PBS solution and analysed by flow cytometry (FACSCalibur, BD Biosciences, Oxford, UK). 100,000 events were collected per analysis.

Monocyte populations were identified using CellQuest software (BD Biosciences, Oxford, UK). Neutrophils were eliminated using side-scatter vs. CD16. Monocytes identified on morphology were then grouped into three phenotypes; CD14+CD16- (classical), CD14+CD16+ (intermediate) and CD14+CD16++ (non-classical) [27]. CD14 CD16- were disregarded as non-monocytes.

**Neutrophil degranulation**

1 mL heparinised blood was added to 50 μL bacterial extract (10 mg/mL, Sigma-Aldrich, Gillingham, UK) and another 1 mL blood left unstimulated. Samples were incubated at 37 °C for 60 min with gentle inversion after 30 min. Samples were centrifuged at 13,000 x g for 2 min and the supernatant harvested. Plasma elastase was assessed in the bacterially-stimulated and unstimulated samples using a commercially available ELISA specific for polymorphonuclear cell elastase (BioVendor GmbH, Heidelberg, Germany).

**Omitted samples**

One patient did not provide consent for blood sample collection and data is only included for blood pressure. Sufficient blood volume for all outcome measures could not be obtained from two patients; the number of patients included for each outcome measure is described. One participant was excluded from cytokine data due to a difference of >5 mg/L in CRP between exercise and control study periods. Outliers were excluded from specific outcome measures if values were more than two orders of standard deviation different from the group mean, or if unstimulated plasma elastase >500 μg/L. Monocyte phenotypes could not be defined in one patient due to unclear fluorescence patterns and were excluded from this analysis.

Statistical analysis was repeated including omitted samples with no change to the results; likewise for completeness, analysis was repeated before adjustment for plasma volume changes without change to the results.

**Randomisation**

The trial was organised in a randomised-crossover design using a website designed specifically for research randomisation to determine order [28].

**Blinding**

The nature of the exercise intervention precluded blinding.

**Statistics**

Treatment conditions and baseline differences between arms were compared using paired t-tests or Wilcoxon signed-ranks tests where applicable. Two-factor repeated measures ANOVA was used to analyse data: trial arm (exercise vs. control) x time. Where data was non-normally distributed (Shapiro-Wilk) ANOVA was performed on the logarithmic transformation of the data and reported in original form. If the omnibus test found a significant effect post hoc paired t-tests and repeated contrasts were used and adjusted for multiple comparisons using the Holm-Bonferroni method [29]. Effect sizes (ES) were calculated using Cohen's D. Statistical analysis was performed on Statistical Package for Social Sciences (SPSS v.21, IBM, New York, USA). Data is presented as mean ± standard deviation or median (interquartile range) as described. Statistical significance was accepted at P<0.05.
Results

Exercise and Haemodialysis

All fifteen recruited patients successfully completed 30 min of cycling starting 60 min into HD, as well as the comparator HD period without exercise. The patients reported the exercise as “somewhat hard”; specifically, an RPE of 13±1. The mean power output was measured as 21.5±8.1 W.

Parameters of haemodialysis treatment were not different between the arms (Table 2). Prescribed medications, haemodialysis and ultrafiltration did not vary. No adverse events were reported.

Haemodynamic parameters

In both arms, systolic blood pressure (SBP) fell after initiation of HD (P≤0.007; ES≥0.84; Figure 2). SBP was significantly higher immediately after exercise compared to the control arm (125±18 vs. 112±20 mm Hg; P=0.03; ES=0.71). However, 1 h after completion of exercise SBP had fallen and was significantly lower than controls (106±22 vs. 117±25 mm Hg; P=0.04; ES=0.46), there were no differences at the end of HD. Heart rate was elevated post-exercise (P<0.001; ES=0.78; Table 3). Consequently, the rate pressure product (RPP) was significantly higher immediately post-exercise compared with the control arm (P<0.001; ES=1.15; Table 3), this fell subsequently with a trend for lower RPP 1 h post-exercise (P=0.08; ES=0.47) and significantly lower at the completion of HD (P=0.02; ES=0.15).

Haematology and monocyte phenotypes

Exercise had no significant effect on total or differentiated leukocyte counts (Table 4). The proportion of intermediate monocytes fell during HD in both arms (effect of time: P=0.002), the proportion was lower at the end of HD compared to the first sample (P=0.006; ES=0.80). Trends for an effect of exercise on intermediate and non-classical...
monocytes were observed (Table 4). The proportion of intermediate monocytes appeared to fall by a greater amount in the exercise arm (interaction: \( P = 0.09 \)) but post hoc tests were not statistically significant \((P>0.17)\). The proportion of non-classical monocytes appeared to increase immediately post-exercise (interaction: \( P = 0.08 \)), post hoc tests found no statistically significant differences \((P>0.14)\).

**Markers of systemic inflammation**

Exercise had no effect on circulating concentrations of IL-6, TNF-\( \alpha \) or IL-1ra (Table 4). Across both arms IL-6 appeared to increase during HD (effect of time: \( P = 0.03 \)) although post hoc tests were not statistically different \((P>0.17)\). Conversely, TNF-\( \alpha \) decreased during HD across both arms (effect of time: \( P = 0.004 \)), at the end of HD TNF-\( \alpha \) concentrations were significantly lower than the pre-exercise sample \((P=0.04, ES=0.68)\). CRP was measured at the 60-min time-point as a reference marker of systemic inflammation and concentrations were similar between trial arms (Table 4, \( P = 0.7 \)).

**Circulating markers of cardiac injury**

Exercise had no significant effects on h-FABP, myoglobin, CKMB or cTnI (Table 3). h-FABP and myoglobin significantly fell during both arms suggesting a clearance through HD (effect of time: both \( P < 0.001 \)); no anomalies or outliers were observed. Similarly, CKMB showed a trend for a reduction across both arms (effect of time: \( P = 0.06 \)). The majority of cTnI results were below the limits of detection, there was no pattern for increasing concentrations of cTnI.

**Neutrophil degranulation**

Unstimulated plasma elastase increased in both arms but with no effect of exercise (effect of time: \( P = 0.05 \); Table 4). Neither HD nor exercise had a significant effect on the total neutrophil response to bacterial stimulation. After adjustment to degranulation per neutrophil an effect of exercise was observed (Table 4); despite an apparent trend for suppressed responsiveness post-exercise post hoc paired t-tests and repeated contrasts found no significant differences between arms \((P>0.096)\).
Discussion

Exercise at an intensity that patients found achievable during HD was sufficient to cause a significant increase in SBP during exercise followed by notable post-exercise hypotension. These deviations in blood pressure occurred without increasing markers of myocardial damage. Further, intradialytic exercise did not exacerbate circulating markers of inflammation or immune dysfunction.

Other studies have also observed an increase in SBP during a bout of intradialytic exercise from as little as 10 min duration [30-32]. These studies concluded that exercise during HD is met with a stable haemodynamic response; the cardiovascular response to exercise is normal and superimposed onto the response to HD. However, if ultrafiltration volumes are high, exercise may be contraindicated later in HD treatment due to gradually decreasing blood pressure and cardiac output [33]. Normally, the maintenance of blood pressure during HD is crucial and exacerbation of intradialytic hypotension may be detrimental to...
health [34]. Exercise places an additional demand upon the heart (as seen by the RPP) at a time when it is at an increased susceptibility to demand ischaemia, potentially increasing the risk of myocardial stunning and left ventricular dysfunction [7]. The post-exercise hypotension witnessed therefore theoretically suggests an increased risk of myocardial injury. Reassuringly however, markers of cardiac injury were not different between arms and considering both cTnI and h-FABP have good sensitivity and specificity for detecting myocardial damage in the immediate aftermath of a cardiac event [35, 36].

The observed fall in blood pressure post-exercise is not exclusive to intradialytic exercise. Extensive reviews of ‘post-exercise hypotension’ in the general population show SBP is frequently decreased in the hours following exercise. The response in healthy individuals may be negligible but is marked in hypertensive populations [21]. ESRD patients typically present with hypertension [37]; moderate-intensity walking exercise in patients with earlier stage chronic kidney disease (CKD, stage 2-4) has been shown to significantly reduce SBP and DBP during the hour following exercise compared with controls (-6.5 mm Hg and -2.5 mm Hg) [38].

Despite the negative associations of intradialytic hypotension, there is no evidence, from this or other studies, to suggest exercise causes any subclinical myocardial injury. Elsewhere, no serious adverse events have been reported after around 28,000 h of intradialytic exercise [13]. Moreover, ESRD patients who regularly exercise during HD improve heart rate variability, left ventricular ejection fraction and risk rating of sudden cardiac death [39-41]. Further research is required to delineate myocardial and vascular function during and after intradialytic exercise and the long-term impact of regular training.

Intradialytic exercise had little effect on circulating cytokines or leukocyte counts. In the general population circulating concentrations of IL-6 increase after a bout of exercise [23]. Despite the potential for exacerbated circulating cytokine concentrations post-exercise (reported in other conditions; e.g. COPD [42] and cystic fibrosis [43]) intradialytic exercise had no effect. This may be because the exercise stimulus was insufficient, or that a minor release was not noticeable above the effects of HD or uraemia, or that uraemia per se inhibits the pathway for exercise-induced IL-6 secretion in the muscle as indicated by reduced muscle IL-6 mRNA in response to exercise seen in 5/6 nephrectomy rats [44]. Short duration exercise has been shown to exacerbate circulating TNF-α concentrations in COPD and heart failure patients [45, 46]; reassuringly, this study found no increase in plasma TNF-α after exercise. A recent systematic review highlighted a lack of understanding of the acute effects of exercise on inflammatory markers in chronic inflammatory diseases [47]. One recent paper reported an increase in IL-10 after HD including 20 min cycling with a similar absence of changes in IL-6 and TNF-α [48]. Another study found no immediate change in CRP after intradialytic resistance exercise despite a decrease in the antioxidant superoxide dismutase [49]. It is therefore reassuring that the present study found no exacerbation of inflammation. Long-term anti-inflammatory benefits of regular exercise have been observed at low-to-moderate intensity that is not associated with an acute release of IL-6 [50]. Whether regular exercise of this nature has beneficial anti-inflammatory properties in HD patients is currently unclear [51].

An observable trend for an increase in proportion of non-classical monocytes occurred post-exercise. In healthy populations a preferential mobilisation of CD16+ monocytes (specifically non-classical) is also observed after exercise [52] and similar results have been recently been reported in pre-dialysis CKD patients [53]. Greater expression of adhesion molecules on CD16+ monocytes result in a greater proportion of these phenotypes in the marginal pool, particularly during HD [54]; it appears exercise causes an enhanced demargination of these cells.

Both exercise and HD may stimulate a spontaneous elastase release [55, 56]. Importantly, intradialytic exercise did not appear to exacerbate spontaneous elastase secretion that increased during HD. Suppressed neutrophil degranulation is apparent after intense exercise in healthy individuals [55]; conversely, enhanced neutrophil responsiveness was
observed 1 h post-exercise in pre-dialysis CKD patients [57]. Neither a clear improvement nor deterioration was observed here after intradialytic exercise.

Overall it appears that intradialytic exercise at the intensity and duration that HD patients could manage in this trial did not exacerbate the circulating inflammatory factors measured. The power output, although low, appears comparable to other studies [58] but due to the different equipment and programmes used it is difficult to make meaningful comparisons. The effect of altering exercise intensity or duration warrants future research.

The UF goal of this cohort of patients is representative of local practice but may be lower than seen in other populations (e.g. higher in the US). Larger UF targets may exacerbate alterations in blood pressure. Previous studies have shown that exercise later in HD (after three hours) may be contraindicated for individuals with a high UF target [33]; therefore, it seems advisable to consider both these aspects when prescribing exercise. Exercise late in HD should be avoided for those susceptible to hypotension or having large fluid volumes removed.

There are some limitations to this study which should be acknowledged. This study represents a single mode, duration and intensity of exercise; other patterns of exercise may have differing effects. The present mode and intensity was chosen as part of a pragmatic approach on the basis of patient feedback. The patients in this study were accustomed to intradialytic exercise, when patients first start an exercise programme and exercise is novel a more exaggerated response may occur. Also, it should be noted that patients eligible to take part in exercise are healthier with a lower risk of complications [59].

The randomised-crossover design allows direct comparisons to be made between the two study periods and reduces the potential impact of confounding elements such as circadian rhythm. The sample size precludes definitive conclusions from being made. However, it does inform the design of further investigations examining post-exercise hypotension in HD patients, especially to investigate whether a single bout of exercise has prolonged effects on blood pressure and what impact other forms of exercise have.

Conclusion

In summary, exercise at an intensity that patients are able to complete during HD caused an increase in blood pressure during exercise followed by a significant post-exercise hypotension. In this instance, the intradialytic hypotension occurred in the absence of myocardial injury and likely represents a normal haemodynamic response to exercise superimposed onto the impact of HD. Intradialytic exercise did not exacerbate the pro-inflammatory environment or immune dysfunction associated with ESRD; therefore, from both perspectives, moderate-intensity cycling exercise during HD is well tolerated.

Disclosure Statement

Outside the submitted work Reck UK (manufacturers of the exercise bike) funded MD, HMLY and JOB to attend the 2012 BMJ Awards. There are no other financial conflicts of interest. The results presented in this paper have not been published previously in whole or part, except in abstract format. An abstract of preliminary data from this study was presented at the 2013 American Society of Nephrology annual conference.

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