The haemodynamic response to submaximal exercise during isovolaemic haemodialysis

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Abstract

Introduction. Exercise during haemodialysis has potential benefits but may compromise cardiovascular stability. We studied its acute effects on relative blood volume (RBV) and other haemodynamic parameters.

Methods. Two groups of 10 patients were exercised submaximally using a stationary cycle during isovolaemic dialysis whilst RBV was monitored continuously. In study 1, patients exercised for two 10 min periods separated by 10 min rest. Cardiac output (CO), peripheral vascular resistance (PVR), central blood volume (CBV) and stroke volume were measured using ultrasound dilution immediately before and after each exercise session. In study 2, haemoglobin, serum total protein and albumin levels were measured before and immediately after the exercise session and at the nadir of the RBV trace.

Results. RBV fell immediately on exercise initiation, the maximum reduction being 2.0 ± 1.1% (after 5.9 ± 1.4 min of exercise 1: P < 0.001) and 2.0 ± 1.2% (after 4.7 ± 2.3 min of exercise 2: P < 0.001). CO increased significantly after both periods of exercise (4.5 ± 0.96 and 5.1 ± 1.1 to 7.2 ± 2.1 and 7.9 ± 2.4/min, P < 0.001 in both). Stroke volume increased significantly and PVR fell significantly during exercise. CBV increased in absolute terms but fell as a proportion of CO. Mean haemoglobin level at the RBV nadir was significantly higher than baseline (12.3 ± 1.8 vs 11.8 ± 1.7 g/dl: P < 0.05: mean change 4.4 ± 2.3%), as was mean total protein concentration (66.0 ± 6.9 vs 62.0 ± 8.1 g/l: P = 0.001: mean change 6.8 ± 5.9%) and mean serum albumin concentration (36.0 ± 3.9 vs 34.1 ± 3.9 g/l: P < 0.001: mean change 5.8 ± 3.5%).

Conclusion. The haemodynamic response to exercise during haemodialysis is comparable with that in normal individuals. The rapid reduction in RBV on exercise occurs in spite of a significant increase in CO, mainly as a consequence of fluid shifts from the microvasculature to the interstitium.

Keywords: cardiac output; exercise; haemodialysis; haemoglobin; relative blood volume; serum albumin

Introduction

Exercise during haemodialysis has many potential benefits, including increased peak oxygen uptake [1], improved self-reported physical functioning [1] and enhanced urea clearances [2]. It has been suggested that the cardiovascular response to exercise during haemodialysis is superimposed onto that of the dialysis process. The response has been shown to remain ‘adequately stable’ during the first 2 h of treatment, though thereafter cardiovascular decompensation may occur which could preclude further exercise [3]. In previous pilot studies, we observed a rapid fall in relative blood volume (RBV) immediately after commencement of exercise and before the onset of ultrafiltration (UF). This might have an important effect on the capacity of patients to tolerate exercise during haemodialysis.

Blood volume monitors (BVMs) infer RBV from ultrasonically measured changes in the density of blood, which are determined mainly by changes in haematocrit (Hct) and plasma protein concentration. A constant mass of red cells and plasma proteins, and uniform mixing throughout the circulation are assumed. A number of mechanisms may account for a fall in RBV during exercise on isovolaemic haemodialysis. Exercise-induced redistribution of blood volume from the central to the microcirculation would increase whole body Hct (interpreted by the BVM as a fall in RBV), since the prevailing Hct is less in the microcirculation [4]. If this were the sole effect of exercise, plasma protein concentrations would not change. Any increased fluid translocation from the microcirculation to the interstitium would cause comparable increases in whole body Hct, plasma total protein and albumin concentrations. Any loss of albumin-rich fluid from the microcirculation to the interstitium would abrogate the rise in serum albumin concentration.
We devised this study to quantify the fall in RBV which occurs immediately after commencement of exercise on isovolaemic haemodialysis and to investigate its possible causes.

Materials and methods

Patients

Two groups of 10 patients (exercise protocols 1 and 2) were recruited from our unit. Informed consent was obtained for the study, which was approved by the North Herts NHS Trust Ethics Committee. All had been treated by thrice-weekly maintenance haemodialysis for at least 3 months. Dialysis access was by arterio-venous fistula. None had recirculation demonstrable on ultrasound dilution (Transonic). None had current angina or any other clinically apparent condition likely to impair their capacity to perform stationary cycling.

Dialysis technique

Dialysis was carried out using a Fresenius Medical Care 4008H machine incorporating a BVM, blood temperature monitor and a blood pressure and pulse monitor. The BVM obtained estimates of relative blood volume by measuring the time taken for ultrasound pulses to travel through a precisely defined cuvette located in the arterial blood line. All patients were treated exclusively using high-flux synthetic membranes, predominantly polysulfone. Dialysers were reused with peracetic acid (Renalin, Minntec Inc., USA) as the main processing agent. Bicarbonate was used as buffer. Ultrapure water was used for all dialysis-related processes. Stringent bacteriological standards were maintained. Dialysis was prescribed and monitored using a two-pool kinetic model to ensure a Kt/V of 1.2. This was a composite of Kt/V (renal) and Kt/V (dialysis). Mean dialysis time was 180 min (range 140–225 min). The midweek dialysis session was chosen for the studies. Blood flow rates and dialysate flow rates were kept constant over the study period. Dialysis fluid temperature was maintained at 36°C throughout the procedures. No UF was performed during the study period.

Experimental protocols

Exercise protocol. Exercise was performed using a stationary cycle (Trailblazer) in the semi-recumbent position. This was placed in front of the patient so pedalling did not disturb the dialysis procedure or the posture of the patient, which did not change throughout the dialysis session. Exercise load was set to achieve a target heart rate at least 20% greater than the pre-dialysis baseline pulse rate. Exercise was initiated 15 min after the start of the dialysis session to allow for stabilization of the RBV trace and to minimize any posture-related changes to RBV. In protocol 1, 10 patients exercised for two 10 min periods separated by 10 min rest. In protocol 2, 10 patients exercised once for 10 min. In each protocol, after completion of the exercise session(s), the prescribed UF volume was removed in a linear fashion during the remainder of the dialysis session.

Experiment 1. Exercise protocol 1 was employed during which haemodynamic parameters were measured. The measurements undertaken were pulse, blood pressure and RBV, which were monitored continuously, and cardiac output (CO), peripheral vascular resistance (PVR), central blood volume (CBV) and stroke volume, which were measured using ultrasound dilution (Transonic Systems, Ithaca, NY) immediately before and after each exercise session (four times in all for each patient) [5]. In brief, this technique requires the administration of a 30 ml bolus of warm (body temperature) normal saline over 4–7 s into the venous line. After passage of the indicator saline through the heart and lungs, its passage through the arterial line is detected by an ultrasound sensor. CO is calculated from the concentration curve obtained with a reproducibility of 4.3±3.8%. CBV and PVR can be calculated from the CO measurement, with similar reproducibility, using previously described formulae and patient data [5].

Experiment 2. Exercise protocol 2 was employed. Pulse, blood pressure and RBV were monitored continuously. In addition, blood was drawn from the arterial port immediately before and immediately after the exercise session. Additional samples were taken at the nadir of the RBV trace. All samples were analysed for blood haemoglobin level (LP 20 miniphotometer, Dr Bruno Lange Gmbh Medical Division), total serum protein concentration (modified Biuret reaction, Dade Behring Clinical Chemistry System) and serum albumin (by an immunochemical reaction, Dade Behring Clinical Chemistry System).

Rationale for investigatory protocols

Two identical periods of exercise were performed in protocol 1 in order to allow determination of the reproducibility of the haemodynamic changes and to allow comparison of haemodynamic changes in the exercise period with those in an intervening control period with the patient in the same posture. The haemodynamic effects of exercise and its effect on blood haemoglobin, serum total protein and albumin levels were assessed on different dialysis sessions to avoid the dilutional effects on the concentration measurements of saline boluses used to measure cardiac output. These concentration measurements were performed during a single exercise session and recovery period to limit the volume of blood required.

Statistics

Analysis of variance for repeated measures was used to test the null hypothesis for differences between repeated values of parameters. In experiment 1, the values of RBV used were those pertaining to before both exercise periods, at the nadir of the RBV trace during both exercise periods and after both exercise periods. The values of all other parameters used in experiment 1 were those pertaining to before and after each exercise period. In experiment 2, the values of all parameters used were those pertaining to before the exercise period, at the nadir of the RBV trace during exercise, and at the end of exercise. In the event of rejection of the null hypothesis, post hoc tests were performed by the Bonferroni multiple comparison test to determine the significance of differences between mean values of individual parameters at these different time points.
Results

Study groups

The clinical characteristics of the two exercise protocol groups are shown in Table 1. There were no significant differences between the groups with respect to gender, mean weight, dialysis vintage, residual renal function, interdialytic weight gain, haemoglobin levels, dose of erythropoietin and pre-dialysis potassium levels. One patient in protocol group 2 was diabetic. One patient in protocol group 1 had a previous well-recovered cerebrovascular event, and one in protocol group 2 had undergone previous coronary artery bypass grafting. Ten patients, five in each group, took antihypertensive medication. Five patients in study group 1 and one in study group 2 took either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Three patients in study group 2 took low-dose $\beta$-blockers in contrast to none in study group 1.

Experiment 1

Haemodynamic stability was maintained throughout both periods of exercise. The pulse rate rose from 87±11 to 112±18 beats per min during the first period of exercise and from 87±14 to 112±18 beats per min during the second period ($P<0.001$ in both cases). Systolic blood pressure also increased during both periods of exercise [129±17 to 142±9 mmHg ($P<0.05$) and 123±14 to 141±11 mmHg ($P<0.001$)]. Diastolic blood pressure did not change significantly during either period of exercise (79±10 to 83±10 and 77±11 to 83±10 mmHg).

RBV fell rapidly and significantly immediately after the start of exercise (Figure 1). The maximum reduction of RBV was 2.0±1.1% at 5.9±1.4 min into exercise 1 ($P<0.001$ compared with onset of exercise 1) and 2.0±1.2% at 4.7±2.3 min into exercise 2 ($P<0.001$ compared with onset of exercise 2). Some recovery occurred during the remainder of the exercise such that the mean reduction in RBV was 1.3±1.3% ($P<0.05$) by the end of exercise 1 and 1.0±1.5% by the end of exercise 2 ($P=NS$). RBV recovery continued in the resting phase, increasing by 2.5±1.0% ($P<0.001$) between the end of exercise 1 and the onset of exercise 2.

CO increased significantly after both periods of exercise [4.5±0.96 and 5.1±1.1 to 7.2±2.1 and 7.9±2.4 l/min, $P<0.001$ in both (Figure 2)]. Stroke volume increased significantly with exercise from 54.3±19.6 and 58.6±15.3 to 88.3±37.7 and 92.1±34.9 ml ($P<0.001$ in both). CBV increased with exercise (0.69±0.24 and 0.76±0.26 to 0.93±0.43 and 0.96±0.40 l; $P<0.05$ in both). When expressed as a percentage of cardiac output, CBV fell significantly during exercise (14.5±2.1 and 14.4±2.7% to 11.7±2.2 and 11.5±2.6% post, $P<0.001$ in both). PVR fell significantly (22.4±4.5 and 19.9±4.1 to 14.4±4.0 and 13.5±4.4 mmHg/ml/min, $P<0.001$ in both).

Experiment 2

Haemodynamic stability was maintained throughout the period of exercise. RBV fell rapidly and significantly in the first 5 min to a nadir of 3.0±0.8% below baseline ($P<0.001$) before partial recovery by the end of the

Table 1. Clinical characteristics of patients in study groups

<table>
<thead>
<tr>
<th>Study group</th>
<th>Study group</th>
<th>$P$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37±12</td>
<td>47±24</td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>4:6</td>
<td>6:4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61±17</td>
<td>64±20</td>
</tr>
<tr>
<td>Dialysis vintage (months)</td>
<td>59±50</td>
<td>45±56</td>
</tr>
<tr>
<td>Residual urea clearance (ml/min)</td>
<td>1.1±1.4</td>
<td>1.2±1.5</td>
</tr>
<tr>
<td>Interdialytic weight gain (kg)</td>
<td>1.7±0.8</td>
<td>2.0±1.2</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>11.6±1.7</td>
<td>12.4±0.7</td>
</tr>
<tr>
<td>Pre-dialysis potassium (mmol/l)</td>
<td>5.3±0.5</td>
<td>5.1±0.8</td>
</tr>
<tr>
<td>No. of antihypertensive agents</td>
<td>0.6±0.7</td>
<td>0.8±1.2</td>
</tr>
</tbody>
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Values are mean±SD.
exercise session to a value 2.2 ± 1.5% less than baseline (P < 0.001). Haemoglobin levels increased during the period of exercise (Table 2). The mean haemoglobin level at the nadir of the RBV trace was significantly higher than baseline (11.8 ± 1.7 g/dl: P < 0.001: mean change 4.4 ± 2.3%). The mean level at the end of the exercise period remained higher than baseline (12.0 ± 1.8 g/dl) but not significantly so. Serum total protein levels also rose significantly during exercise. The mean total protein level was significantly higher at the nadir of the RBV trace than at baseline (66.0 ± 6.9 g/l: vs 62.0 ± 8.1 g/l: P = 0.001: mean change 6.8 ± 5.9%). The mean level at the end of the exercise remained significantly higher than at baseline (63.6 ± 5.2 g/l: P = 0.01). Serum albumin likewise increased during exercise. The mean serum albumin level at the RBV nadir was 36.0 ± 3.9 g/l vs 34.1 ± 3.9 g/l at baseline (P < 0.001: mean change 5.8 ± 3.5%). The mean level at the end of dialysis remained significantly higher than at baseline (35.5 ± 3.3 g/l: P = 0.001). There was no correlation between changes in haemoglobin levels, serum albumin concentrations and serum total protein concentrations.

Discussion

This study has demonstrated that a significant fall in RBV occurs immediately after the onset of submaximal exercise during isovolaemic haemodialysis. The mean magnitude of the change was 2–3% of blood volume. The effect may therefore contribute to haemodynamic instability on haemodialysis especially in the presence of concurrent UF. At the same time, there was a significant increase in CO, and a significant reduction in PVR. In absolute terms, there was a non-significant increase in CBV, but CBV as a proportion of CO fell. Haemoglobin, total plasma protein and albumin concentration rose abruptly and significantly.

Exercise in normal individuals, in addition to increasing cardiac output and reducing peripheral resistance, also induces a reduction in total blood volume and plasma volume up to 8.4 and 15.3, respectively, when the exercise is maximal [6]. This reflects fluid movement from vascular space to the interstitium of exercising muscles [7]. The changes are rapid, apparent by 1 min, maximal by ~5 min [8], dependent on posture and on the type of exercise carried out [9]. Splenic contraction and release of red cells has been demonstrated following maximal exercise, but has little effect on red cell volume measurements [10]. During recovery, there is increased protein movement from extravascular to intravascular compartments [11], such that plasma volume expansion of up to 10% can be seen within 24 h of intense exercise [12].

In haemodialysis patients, cardiac output increased and systemic vascular resistance decreased during the first 2 h of exercise [3]. However, during the following hour, there was a substantial change in these parameters, CO decreasing and systemic vascular resistance increasing, presumably due to a UF-induced reduction in blood volume, though this was not directly assessed. A small (1%) exercise-induced reduction in RBV has been observed in the absence of UF, which reversed at the end of exercise [13]. UF, in the absence of exercise, has been shown to reduce CO in haemodialysis patients without overt cardiac disease [14].

Our findings, interpreted in the light of these previous studies, suggest that during submaximal exercise, though CBV is maintained or increased in absolute terms with respect to resting values, a greater proportion of the increased CO is shifted from the central circulation to the microcirculation. Within the microcirculation, there is increased hydraulic permeability of the capillary bed resulting in fluid shifts into the interstitium. This fluid shift causes a reduced plasma volume reflected in the observed 6.8% increase in total protein concentration. The changes in serum albumin (5.8%) and haemoglobin (4.4%) were similar but not identical. While it is not possible to exclude some loss of albumin-rich fluid from the microcirculation to the interstitium, or an effect on RBV of haematocrit redistribution, we have not found any direct evidence for either of these processes. The changes we have described are maximal after ~5 min of submaximal exercise and tend to diminish as exercise continues. This presumably relates to an increase in the circulatory refilling from the interstitium as exercise continues.

There are a number of potential methodological drawbacks to this study. Changes in haemodynamic parameters and blood constituent concentrations were not measured simultaneously because the methodology used to measure haemodynamic parameters required repeated small volume saline injection which may have interfered with concentration measurements. Adoption of the supine position results in a fall in haematocrit
and serum albumin levels maximal in 15 min in normal individuals, but continuing for at least 30 min in haemodialysis patients [15]. The phenomenon has been attributed to mobilization of fluid from the interstitium into the circulation. We commenced our measurements after 15 min of haemodialysis in the semi-recumbent position. This was to allow stabilization of the RBV trace following the assumption of this posture at the commencement of the dialysis session. The same posture was maintained during the subsequent exercise period and during the intervening rest period in experiment 1. We are confident, therefore, that the haemodynamic and concentration changes observed during the study were related to the periods of exercise rather than to the initiation of haemodialysis or to changes in posture.

We have found that submaximal exercise induces haemodynamic changes similar to those seen in normal subjects. There is a significant increase in cardiac output in spite of a fall in plasma volume, which results from loss of fluid from the microvasculature to the interstitium. These findings have an important bearing on the tolerability of exercise during haemodialysis. Short periods of intermittent submaximal exercise are well tolerated, inducing a haemodynamic response similar to that in normal patients. These findings complement previous work, which has suggested that exercise during [3] and immediately after [16] or between [17–19] haemodialysis sessions is well tolerated and has many significant benefits. However, it should be noted that our patients were young compared with the dialysis population in general and had well corrected anaemia, that the exercise was brief and submaximal, and that it took place in the absence of UF. Our findings may not extrapolate to older patients, subjected to more prolonged or intense exercise in the context of high UF rates.

Conflict of interest statement. None declared.

References


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