Improvement in exercise duration and capacity after conversion to nocturnal home haemodialysis

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Abstract

Background. Patients with end-stage renal disease (ESRD) have a reduced exercise capacity as assessed by peak oxygen uptake (VO2peak). Nocturnal haemodialysis (NHD) augments uraemic clearance and vascular responsiveness to nitric oxide and lowers blood pressure (BP) and peripheral resistance.

Methods. To assess the impact of NHD on exercise duration and capacity, 13 consecutive ESRD patients [age: 41 ± 3; (mean ± SEM)] and healthy normal subjects (n = 14) matched for age and body mass index exercised to peak effort (VO2peak) as determined by open-circuit spirometry during a graded cycle ergometer test with a ramp increase in work rate (by 17 watts/min).

Results. Exercise was performed before, 2 and 3–6 months after conversion from conventional haemodialysis (CHD) (3 sessions per week; 4 h per session) to NHD (5–6 sessions per week; 6–8 h per session). Exercise duration increased progressively [from 617 ± 50 (CHD) to 634 ± 47 (NHD 2 months) to 682 ± 55 (NHD 3–6 months), P = 0.03] as did exercise capacity, expressed as percent of predicted (based on age, sex and body size) VO2peak, [from 66 ± 8 (CHD) to 72 ± 6 (NHD 2 months) to 75 ± 6% (NHD 3–6 months), P < 0.05].

Conclusion. Enhanced uraemia control by NHD improved both exercise duration and capacity. When coupled with augmented uraemia management, an increase in physical activity, perhaps due to more effective oxygen delivery or improved muscle metabolism, has the potential to improve the quality of life of patients with ESRD.

Keywords: end-stage renal failure; exercise capacity; muscle; nocturnal home haemodialysis; uraemia

Introduction

Despite significant advances in the technical and medical aspects of renal replacement therapy, most end-stage renal disease (ESRD) patients receiving conventional haemodialysis (CHD) eschew exercise [1–3]. Exercise capacity, as assessed by peak oxygen uptake (VO2peak), is reduced by 40% compared with healthy individuals and becomes an independent predictor of mortality [4]. Pathology related to uraemia or CHD or to a ‘detraining effect’ that might compromise exercise capacity in this vulnerable population include anaemia [5], abnormal potassium regulation [6], impaired muscle perfusion and enhanced catabolic activity [7], reduced muscle mass, comorbid illness (e.g. congestive heart failure), abnormal muscle metabolism and an uraemic myopathy [3]. Importantly, if uraemia is corrected by renal transplantation, exercise capacity can improve [8].

Nocturnal haemodialysis (NHD) provides more frequent and intense haemodialysis (8–10 h during sleep, 5–7 nights per week) than CHD (3 sessions per week; 4 h per session) [9] and has been found, in both short- and long-term studies, to reverse several important risk factors or markers of adverse cardiovascular outcomes [10]. Anecdotal reports of increased levels of physical activity following this type of renal replacement therapy suggests that it may increase functional capacity, although objective measures of peak exercise capacity have not been reported [11].

The primary objective of this study was to document changes in exercise duration and exercise capacity (VO2peak) before and after conversion to NHD, and compare these with values obtained in normal control subjects matched for age and body size. We hypothesized that measured total exercise time and peak oxygen uptake would be increased and the general level of physical activity improved after 2 months or more of NHD.
Methods

This protocol was approved by the Research Ethics Board of the Toronto General Hospital—University Health Network. Consecutive ESRD patients ($n = 13$; 11 men; mean age: $41 \pm 3$ years) were recruited from patients at our centre undergoing training prior to conversion from CHD to NHD. Healthy normal subjects ($n = 14$; 12 men; mean age: $43 \pm 3$ years) matched for age and body mass index were recruited as controls. None had any acute or chronic illness. Written informed consent was obtained from each patient. ESRD patients were studied while on CHD, 2 months after NHD and 3–6 months after NHD. Normal subjects were studied once. All dialysis-related blood tests were obtained prior to dialysis at home for 8–10 h, 5–6 nights per week. Blood flow rates of 500–750 ml/min. NHD treatment consisted of haemodialysis at home for 8–10 h, 5–6 nights per week. Blood flow rates of 100–300 ml/min and F80 polysulphone dialyzers (Fresenius Medical care, Lexington, MA, USA) or Polyflux (polyamide) dialyzers (Gambro Inc., Hechingen Germany) were used. A dialysate flow rate of 350 ml/min was used during NHD. The same dialysers were used for CHD and NHD treatments.

Dialysis dose per treatment was estimated by equilibrated $\text{Kt/V}$ ($e\text{Kt/V}$) as described by Daugirdas and colleagues [17] where

$$e\text{Kt/V} = \text{spKt/V} - 0.6(\text{spKt/V})^t + 0.03 \quad (\text{spKt/V} - \text{single-pool Kt/V}, K = \text{delivered clearance, } t = \text{dialysis time and } V = \text{urea distribution volume})$$

$e\text{Kt/V}$ was determined using the blood urea reduction ratio [18].

Statistical analysis

Data are presented as mean ± SE. An unpaired $t$-test was used for between-group comparisons for normally distributed variables. Repeated measures analysis of variance was used to evaluate changes in variables over time with post hoc Student–Newman–Keuls test applied to assess differences between groups. A two-tailed $P$-value <0.05 (SPSS–11, SPSS Inc., Chicago, IL, USA) was required for significance. Linear regression analysis was performed to describe associations between selected variables.

Results

Baseline values

Thirteen ESRD patients (11 men; mean age: $41 \pm 3$ years) were studied (Table 1). At rest, CHD patients and normal subjects had similar heart rates and blood pressures (Table 2). While on CHD, the ESRD patients exercised for $617 \pm 50$ s, reaching a $\text{VO}_2\text{peak}$ of $1.83 \pm 0.21/\text{min}$, which represents $66 \pm 8\%$ of the peak predicted by their age, sex, body weight and height. In contrast, normal subjects matched for age and body mass index had longer exercise duration ($722 \pm 53$ s, $P < 0.001$ vs CHD) plus a higher $\text{VO}_2\text{peak}$ of $2.52 \pm 0.21/\text{min}$ ($P = 0.02$ vs CHD), which represents $90 \pm 4\%$ ($P = 0.01$ vs CHD) of their predicted peak.

At maximal exercise effort, the peak heart rate was less in the CHD group than in the healthy control subjects ($153 \pm 6$ vs $172 \pm 5$ beats per minute, $P = 0.02$), likely due in part to the prescription of $\beta$-blockers in four CHD patients. Peak systolic and diastolic blood pressures at maximal exercise effort were similar in the two groups (Table 2).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>$41 \pm 3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Gender (M: F)</td>
<td>11: 2</td>
</tr>
<tr>
<td>Aetiology of ESRD</td>
<td>Glomerulonephritis: 4</td>
</tr>
<tr>
<td></td>
<td>Adult polycystic kidney disease: 5</td>
</tr>
<tr>
<td></td>
<td>Type II diabetes mellitus: 2</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td>Congenital: 2</td>
</tr>
<tr>
<td></td>
<td>Severe secondary hyperparathyroidism: 2</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure: 1</td>
</tr>
<tr>
<td></td>
<td>Hypertension: 13</td>
</tr>
</tbody>
</table>
Nocturnal haemodialysis—2 months

In addition to doubling the frequency of dialysis, NHD delivered a significantly higher sessional $Kt/V$ than CHD (increasing this from 1.28 ± 0.1 (CHD) to 2.36 ± 0.3 (NHD), $P = 0.01$). Two months after the start of NHD, plasma phosphate levels decreased (1.44 ± 0.17 to 1.23 ± 0.10 mmol/l, $P = 0.01$) as did parathyroid hormone levels (51.7 ± 9.7 to 16.2 ± 4.7 pmol/l, $P < 0.05$). Haemoglobin concentration tended to increase [106 ± 4 (CHD) vs 112 ± 3 g/l (NHD), $P = 0.2$] without any change in erythropoietin administered (from 6500 ± 1760 to 5333 ± 1333 units per week, $P = 0.28$). Plasma albumin and bicarbonate did not change (Table 3).

After 2 months of NHD, there tended to be a fall in resting blood pressure, compared with CHD ($P > 0.05$), despite withdrawal of antihypertensive therapy (from 1.54 ± 0.3 to 0.5 ± 0.3 medications per patient, $P = 0.01$) and heart rate tended to increase, probably due to withdrawal of β-adrenoreceptor antagonists, in two patients, and diltiazem in one. In those patients, resting heart rate tended to increase (from 85 ± 6 to 97 ± 12/min, $P = NS$) (Table 3).

Peak exercise heart rate tended to increase after 2 months of NHD whereas peak systolic blood pressure, exercise duration and VO$_{2peak}$ were unchanged from CHD values (Table 2).

Nocturnal haemodialysis—3–6 months

After 3–6 months of NHD, biochemical variables continued to reflect enhanced uraemia clearance and were similar to values achieved after 2 months of NHD (Table 3).

Resting blood pressure and peak systolic blood pressure tended to be lower than after 2 months of NHD. Compared with CHD, exercise duration and VO$_{2peak}$ increased significantly to 682 ± 55 s ($P = 0.02$) and 75 ± 6% of predicted value ($P = 0.04$), respectively (Figures 1 and 2).

Beta-blockers were withdrawn in two subjects after conversion to NHD. As expected, their resting heart rates were higher after withdrawal of their cardiac-acting medications. Importantly, improvements in exercise duration and peak VO$_{2peak}$ in these particular

### Table 2. Exercise capacity, haemodynamics and total daily energy expenditures in ESRD patients and normal subjects

<table>
<thead>
<tr>
<th>Variables</th>
<th>Normal subjects</th>
<th>CHD</th>
<th>NHD 2 months</th>
<th>NHD 3–6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO$_{2peak}$ (ml/min)</td>
<td>2.52 ± 0.20</td>
<td>1.83 ± 0.2*</td>
<td>1.96 ± 0.2*</td>
<td>2.03 ± 0.2*</td>
</tr>
<tr>
<td>VO$_{2peak}$ (% predicted)</td>
<td>90 ± 4</td>
<td>66 ± 8*</td>
<td>72 ± 6*</td>
<td>75 ± 6*</td>
</tr>
<tr>
<td>Exercise duration (s)</td>
<td>722 ± 53</td>
<td>617 ± 50*</td>
<td>634 ± 47</td>
<td>682 ± 55*</td>
</tr>
<tr>
<td>Resting heart rate (per min)</td>
<td>79 ± 3</td>
<td>86 ± 4</td>
<td>96 ± 6*</td>
<td>94 ± 6*</td>
</tr>
<tr>
<td>Resting systolic blood pressure (mmHg)</td>
<td>116 ± 4</td>
<td>117 ± 3</td>
<td>108 ± 5</td>
<td>109 ± 5</td>
</tr>
<tr>
<td>Resting diastolic blood pressure (mmHg)</td>
<td>77 ± 3</td>
<td>72 ± 2</td>
<td>67 ± 3*</td>
<td>66 ± 2*</td>
</tr>
<tr>
<td>Peak heart rate (per min)</td>
<td>175 ± 2</td>
<td>153 ± 6*</td>
<td>169 ± 6</td>
<td>168 ± 6</td>
</tr>
<tr>
<td>peak systolic blood pressure (mmHg)</td>
<td>193 ± 6</td>
<td>176 ± 8</td>
<td>175 ± 8</td>
<td>169 ± 10*</td>
</tr>
<tr>
<td>peak diastolic blood pressure (mmHg)</td>
<td>84 ± 4</td>
<td>77 ± 3</td>
<td>77 ± 3</td>
<td>78 ± 3</td>
</tr>
<tr>
<td>TDEE (kcal/day)</td>
<td>NA</td>
<td>2952 ± 287</td>
<td>3005 ± 190</td>
<td>3245 ± 208</td>
</tr>
</tbody>
</table>

* $P < 0.05$ compared with normal subjects.

### Table 3. Effects of NHD variables modified by dialysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>CHD</th>
<th>NHD 2 months</th>
<th>NHD 3–6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Kt/V$</td>
<td>1.3 ± 0.3</td>
<td>2.4 ± 0.3*</td>
<td>2.1 ± 0.2*</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>106 ± 4</td>
<td>112 ± 3</td>
<td>111 ± 4</td>
</tr>
<tr>
<td>Pre-dialysis potassium (mmol/l)</td>
<td>4.8 ± 0.2</td>
<td>4.3 ± 0.1</td>
<td>4.5 ± 0.2</td>
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<tr>
<td>Pre-dialysis bicarbonate (mmol/l)</td>
<td>24 ± 0.6</td>
<td>24 ± 1.2</td>
<td>23 ± 0.9</td>
</tr>
<tr>
<td>Pre-dialysis phosphate (mmol/l)</td>
<td>1.44 ± 0.2</td>
<td>1.23 ± 0.1*</td>
<td>1.17 ± 0.1*</td>
</tr>
<tr>
<td>Pre-dialysis calcium (mmol/l)</td>
<td>2.37 ± 0.04</td>
<td>2.37 ± 0.08</td>
<td>2.33 ± 0.07</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>39 ± 0.8</td>
<td>40 ± 0.9</td>
<td>39 ± 0.5</td>
</tr>
<tr>
<td>Antihypertensive requirements (per patient)</td>
<td>1.54 ± 0.3</td>
<td>0.5 ± 0.3*</td>
<td>0.5 ± 0.2*</td>
</tr>
<tr>
<td>Classes of medications</td>
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<td></td>
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<tr>
<td>ACEI/ARB</td>
<td>8</td>
<td>3</td>
<td>3</td>
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<tr>
<td>BB</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diuretic</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* $P < 0.05$ compared with CHD.

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BB, β-Blocker; CHD: conventional haemodialysis; NHD, nocturnal haemodialysis.
subjects after conversion to NHD did not differ from those of the entire cohort.

No biochemical or haemodynamic factors, with the exception of haemoglobin, correlated directly with VO2peak ($r = 0.3$, $P < 0.05$) in the ESRD patients.

**Discussion**

Several strategies to improve the limited exercise capacity of individuals with ESRD [3] have been implemented, but for many such patients these have been difficult to adopt and maintain [1]. Once uraemia is corrected by kidney transplantation, exercise capacity improves after a lag time of about 8 weeks [8]. The present findings represent the first demonstration that more sustained and frequent dialysis can also augment exercise performance.

Uraemia alters skeletal muscle perfusion, oxygen delivery, mitochondrial function and metabolism [7,19]. Each of these abnormalities could cause patients with ESRD to fatigue quickly when exercising. If these maladaptations can be reversed by NHD, exercise capacity might improve.

Microscopic findings consistent with impaired microvascular perfusion in patients with ESRD include a decrease in capillary vascularity and atrophy of locomotor muscle fibres [19,20]. An important cause of such hypoperfusion is the stimulation, by uraemia of afferent renal nerves that elicit reflexively a marked and chronic increase in sympathetic vasoconstrictor traffic, directed at resistance vessels in skeletal muscle [21]. Total peripheral resistance is also increased [22]. One method of lowering efferent sympathetic nerve traffic, total peripheral resistance and blood pressure in this population is to explant the failing kidneys [21]. Another is to convert such patients to NHD; in a larger series, total peripheral resistance, blood pressure and plasma norepinephrine were reduced significantly after 2 months [23]. However, in the present investigation, significant increases in exercise duration and predicted VO2peak were not detected until NHD had been administered for 3–6 months. This temporal discordance indicates that reductions in peripheral resistance alone are insufficient to reverse immediately the exercise intolerance of ESRD. A similar dissociation between the time course of improvements in systemic haemodynamics and exercise capacity has been documented in the heart failure population, after both the introduction of vasodilator therapy [24,25] and after cardiac transplantation [26].

Engagement of the sympathetic nervous system optimizes exercise performance by increasing heart rate and stroke volume, and distributing cardiac output preferentially to working muscle. In health, sympathetically mediated vasoconstriction in exercising muscle is countered through a nitric oxide-mediated mechanism termed functional local 'sympatholysis' [27,28]. Although not formally tested in the present experiment, several lines of evidence would argue for an important reduction in the magnitude of local sympatholysis in the dialysis population, as compared with subjects with intact renal function. Muscle sympathetic nerve activity, which is increased markedly in ESRD [21] will increase even further during physical exercise [29]. At the same time, endogenous vascular nitric oxide bioavailability [30],

**Energy expenditure**

We did not observe any significant difference in total daily energy expenditure between CHD and NHD values at either time point. Thus, the improvements in exercise duration and exercise capacity that occurred after conversion to NHD cannot be attributed to a training effect resulting from increased physical activity (Table 2).

![Exercise duration in healthy age-matched control subjects (N), ESRD patients during CHD and in the same patients retested 2 months and 3–6 months after conversion to NHD. Note significant improvement in exercise duration after 3–6 months of NHD compared with CHD ($P = 0.02$).](#)

![Exercise capacity expressed as percent predicted VO2peak in healthy age-matched control subjects (N), ESRD patients during CHD and in the same patients retested 2 months and 3–6 months after conversion to NHD. Note significant improvement in exercise capacity after 3–6 months of NHD compared with CHD ($P = 0.04$).](#)
and responsiveness to exogenous nitrates [31] are greatly attenuated in this population. A reduction in such exercise-induced sympatholysis has been demonstrated recently in post-menopausal women, a state characterized by more modest disturbances in these microcirculatory regulatory systems [32]. The more substantive alteration in the balance between local vasoconstrictor and vasodilator mechanisms in exercising muscle in ESRD has even greater capacity to foreshorten exercise in this population. Conversely, conversion to NHD is accompanied by an increase in flow-mediated dilation, and in arterial vasodilator responsiveness to exogenous nitrates [23]. By improving blood flow and oxygen delivery to the capillary beds of active muscle, an increase in local nitric oxide bioavailability after conversion to NHD could contribute to the augmentation of exercise duration observed in these subjects.

Several groups have identified a net loss of muscle protein in uraemic individuals as a result of increased degradation or decreased synthesis [33]. Other groups have documented an up-regulation in muscle-specific ligase, which will induce muscle breakdown and atrophy [34]. In animal models, metabolic acidosis resulting from uraemia has been shown to activate the ubiquitin–proteasome system in skeletal muscle, also promoting its breakdown [35]. Additionally, there is growing literature indicating the inability of uraemic skeletal muscle to utilize substrates such as amino acids and carnitine [36]. Although some authors have attributed this abnormality in amino acid homoeostasis to the dietary restrictions imposed on such patients, others have documented a decreased anabolic response to amino acid supplementation in uraemic patients [37]. In sum, uraemic muscle is characterized by a catabolic state coupled with a deficiency in substrate bioavailability.

An emerging body of evidence suggests that augmentation of uraemic clearance by NHD may render such patients anabolic. Patients on NHD achieve normal plasma phosphate levels without dietary restriction [38]. A favourable impact on intracellular phosphate could reverse the direct negative effect of phosphate on muscle contractility, perhaps improving muscle fatigability during exercise [39,40]. This hypothesis requires additional investigation. Raj and colleagues [41] have reported an improvement in the blood amino acid profile and recently, our group has documented improvements in carnitine metabolism and utilization after conversion to NHD [42]. If NHD enhances metabolic substrate availability and decreases muscle breakdown thereby reducing muscle fatigue, exercise capacity would be expected to improve.

To date, most ESRD patients remain exercise intolerant [43] and their reduced aerobic capacity has been linked to an increased risk of cardiovascular mortality [4]. Expressing peak oxygen uptake in relation to exercise capacity on the basis of age and body size (i.e. the ‘norm’ of 100%) accounts for the dependence of peak oxygen uptake on age and muscle mass [13,44], and thus is a more useful and clinically relevant measure of the degree of exercise intolerance. Although the present findings demonstrate that NHD is associated with an improvement in exercise duration under standardized conditions, total daily energy expenditure was unchanged indicating that these ESRD patients did not alter their sedentary lifestyle. Therefore, in addition to intensive renal replacement therapy, physical activity should be encouraged.

Our study is limited by its observational nature and relatively small sample size, due in part to the novelty of this NHD treatment modality. Consequently, we cannot exclude the possibility that there was an innate selection bias within our patient population that may have predisposed to an increase in exercise performance. Future studies of this question, in larger populations, would benefit from the addition of a control group receiving CHD. Another limitation to our study is the change in medication profile after conversion to NHD. Although the influence of different antihypertensive medications on exercise capacity has not been examined in this specific patient population, the withdrawal of β-blockade did not cause a different response in exercise capacity in these particular subjects as compared with the entire cohort. Importantly, previous investigators have not noted a significant effect of withdrawing β-blockade or non-dihydropyridine calcium channel blockers on exercise capacity after renal transplantation [8]. Finally, there was a non-significant trend to higher haemoglobin concentrations after conversion to NHD; this may have a modest positive impact on oxygen delivery to exercising muscle [45].

In summary, conversion from CHD to NHD is accompanied, after a 3–6 month lag, by a significant improvement in exercise duration and capacity. It should be appreciated that the present reported increase in exercise duration is similar in magnitude to that observed in other clinically relevant therapeutics (e.g. the use of continuous positive airway pressure in heart failure patients [46]) which significantly improve quality of life. Further research is required in the ESRD population to delineate the relationship between the changes in uraemia clearance, muscle metabolism and its clinical consequences.

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Conflict of interest statement. None declared.

References

3291


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