Recovery Time after Hemodialysis Is Inversely Associated with the Ultrafiltration Rate

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Keywords
Hemodialysis · Time of recovery · Ultrafiltration rate · Dialysate sodium · Dialysate temperature

Abstract
Introduction: The present study aimed to determine the variables that are associated with a longer dialysis recovery time (DRT) and to define the relationship that exists between DRT and the ultrafiltration rate (UFR) in prevalent chronic hemodialysis (CHD) patients. Methods: We studied 210 prevalent CHD of 5 hemodialysis units in Central Italy. Patients were invited to answer to the question: “How long does it take you to recover from a dialysis session?” Answers to this question were subsequently converted into minutes. Demographic, clinical and laboratory parameters were recorded for each patient as well as the UFR (mL/kg/h), the dialysate sodium concentration and temperature. Results: Median DRT was 180 min (60–420). Ninety five (45%) patients had a DRT ≥ the median value. Mean UFR was 9.2 ± 3.0 mL/kg/h.

Patients with a lower DRT had a less prevalent disability in the instrumental activities daily living, had a higher UFR, and a lower dialysate temperature, as compared with subjects with higher DRT. According to the logistic regression model, UFR was associated with a DRT below the median (i.e., 180) in the unadjusted model (OR 1.12; 95% CI 1.02–1.23; p = 0.019), after adjusting for age and sex (OR 1.11; 95% CI 1.01–1.22; p = 0.025), and in the fully adjusted model (OR 1.11; 95% CI 1.04–1.22; p = 0.040). UFR increase was associated with increasing probability of DRT below the median (p for trend = 0.035). The highest tertile of DRT was associated with UFR below the mean value (i.e., 9.2 mL/kg/h) in multinomial logistic regression having the lowest DRT tertile as reference. DRT was significantly lower in patients with UFR > 13 mL/kg/h than in patients with UFR 10–13 or < 10 mL/kg/h. Conclusion: DRT is inversely associated with UFR in CHD patients. Whether a high UFR should be recommended to reduce the DRT needs to be elucidated through an adequate prospective randomized study.

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Introduction

After a hemodialytic session, end-stage renal disease (ESRD) patients on chronic hemodialysis (CHD) frequently have the following complaints: a sensation of prostration, tiredness, weakness, exhaustion, weariness, or fatigue. Such sensations reduce the capacity to perform common and simple daily activities and impair the patients’ well-being [1–2].

Lindsay et al. [3] have recently shown in a group of ESRD patients treated by frequent HD that the response to a simple question “How long does it take you to recover from a dialysis session?”, that gives in minutes the time to recover from hemodialysis (dialysis recovery time [DRT]), was interpreted easily, was easy to which to respond, and had a statistically significant negative correlations with all but one of the Short Form 36 (SF36) Health Survey subscales [3].

A longer recovery time impairs the quality of life and increases the risk of mortality [4]. Little is known about the determinants of recovery time [5–7]. Recently, we have demonstrated that recovery time is significantly associated with post-dialysis fatigue and that the severity of post-dialysis fatigue was negatively and weakly associated with the ultrafiltration rate (UFR) [8]. The association between a longer recovery time and a higher UFR has been shown by some authors but not by others [4, 9].

The aim of the present study is to determine the variables that are associated with a longer recovery time and, in particular, to define the relationship that exists between recovery time and UFR in prevalent patients on CHD.

Patients and Methods

All prevalent ESRD patients receiving CHD at 5 hemodialysis units in Central Italy (Teaching Hospital “A Gemelli” of Rome, Hospital “Carlo Urbani” of Jesi, Hospital “Civile”of Senigallia, Hospital “Umberto Parini” of Aosta, and Hospital “SS. Annunziata” of Chieti) between January and December 2017 were eligible for inclusion in the study. Exclusion criteria were as follows: dialysis duration < 1 year, diagnosis of dementia based on Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, presence of acute infectious disease(s), and active cancer or active cancer treatment. The study was performed in adherence to the Declaration of Helsinki and the protocol was approved by the Ethics Committee of each of the participating centers. Written informed consent was obtained from all participants before enrollment in the study.

For each participant, the following parameters were recorded at the time of inclusion in the study: age, gender, underlying renal disease, weight, height, hemodialysis regimen, type and number of comorbid conditions, the Charlson comorbidity index [10], the mean of the last 5 values of the interdialytic weight gain and of the UFR (mL/kg/h; using the post-dialysis weight), the mean number of symptomatic intradialytic hypotensive events in the last 5 hemodialysis sessions (symptomatic hypotension was defined as a fall in the systolic BP below 100 mm Hg accompanied by at least one of the following symptoms: diaphoresis, nausea, vomiting, cramps, headache, or dizziness).

The recovery time after the hemodialysis session was calculated according to Lindsay et al. [3]. Patients were invited to answer to the following single open-ended question: “How long does it take you to recover from a dialysis session?” Responses were subsequently converted into the number of minutes [3].

Functional ability was estimated using the Katz’ activities of daily living (ADLs), and the Lawton and Brody scale for instrumental activities of daily living (IADLs) [11–12]. These scales are most commonly adopted for assessing functional independency for clinical and epidemiological purposes; disability in the ADLs was defined as need of assistance for performing 2 or more ADLs. The reason for not choosing a single-point decline is that impairment in 2 ADLs is less likely to capture physiological fluctuations in functional performance. Impairment in IADL function was identified by a score < 7; this higher cutoff level is generally adopted to avoid a “floor effect.” The ADL scale is based on 7 levels of self-performance including dressing, eating, toilet use, bathing, mobility in bed, locomotion, and transfer. Similarly, the IADL scale is based on 7 levels of self-performance including meal preparation, housework, managing finance, phone use, shopping, transportation, and managing medications. Insomnia and restless leg syndrome were assessed through the Dialysis Symptom Index [13]. Finally, the Kt/V was calculated according to a standard formula and used as an index of adequacy of the hemodialysis treatment. The mean number of symptomatic intradialytic hypotensive events in the last 5 hemodialysis sessions (symptomatic hypotension was defined as a fall in the systolic BP below 100 mm Hg accompanied by at least one of the following: diaphoresis, nausea, vomiting, cramps, headache, or dizziness).

All patients were receiving conventional 4-h bicarbonate hemodialysis, 3 times a week. The blood flow ranged from 250 to 300 mL/min with a dialysis rate flow of 500 mL/min. All patients were treated with high-permeability membranes.

Weight was measured to the nearest 0.1 kg using a high-precision mechanical scale and standing height to the nearest 0.1 cm based on wall measure with participants wearing light indoor clothes and no shoes. Body Mass Index was calculated as weight (kg) divided by height squared (m²).

Blood samples were obtained from HD patients directly through the arteriovenous fistula or the central venous catheter immediately before their scheduled HD session at the beginning of the week. The plasma was separated within 30 min, and samples were kept frozen at –70 °C if not analyzed immediately. Laboratory parameters were measured by routine methods at the Department of Laboratory Medicine, Catholic University of Rome.

The study was approved by the local Ethics Committee and written informed consent was obtained from all patients before enrollment in the study.

Statistical Analyses

Statistical analyses were performed using SPSS for Mac 20.0. Differences were considered significant at the \( p < 0.050 \) level. Data of continuous variables are presented as mean values ± SD. Medi-
ans and inter-quartile ranges were provided for non-normally distributed variables. Analysis of variance for normally distributed variables was performed according to a DRT equal and above or below the median value; otherwise, the nonparametric Mann-Whitney U test was adopted. The two-tailed Fisher’s exact test was used for dichotomous variables.

Multivariable logistic regression analysis was adopted to estimate the association of a recovery time equal and above the median with age, sex, and all those variables, which differed significantly (p < 0.050) in univariate analyses. Also, multivariable logistic regression was used to assess the association between a DRT above the median and increasing UFR tertiles.

To rule out any role of functional ability in the association between recovery time and UFR, the analysis of the interaction term “IADLs disability * UFR” was performed, using the multivariable logistic model. Eventually, the summary model was analyzed in multinomial logistic regression having increased DRT tertiles as the dependent variable.

### Results

Three hundred and ten patients were considered eligible. One hundred were excluded because of dialysis duration < 1 year (n = 56), diagnosis of dementia based on DSM-IV criteria (n = 5), presence of acute infectious disease (n = 24), active cancer or active cancer treatment (n = 15). Two hundred and ten patients were studied. The median DRT was 180 min (60–420), and 95 (45%) patients had a DRT ≥ the median value. The mean UFR was 9.2 ± 3.0 mL/kg/h. The characteristics of participants according to a DRT equal and above or below the median are depicted in Table 1. Specifically, patients with a lower DRT had a less prevalent disability in the IADLs, had a higher UFR, and a lower dialy-
sate temperature as compared with subjects with higher recovery time.

According to the logistic regression model, UFR was associated with a DRT below the median (i.e., 180) in the unadjusted model (OR 1.12; 95% CI 1.02–1.23; \( p = 0.019 \)), after adjusting for age and sex (OR 1.11; 95% CI 1.01–1.22; \( p = 0.025 \)), and in the fully adjusted model (OR 1.11; 95% CI 1.04–1.22; \( p = 0.040 \); Table 2), adjusted for those variables (disability IADLs, dialysate temperature), which showed significant differences in univariate analyses.

Also, analysis of the interaction term indicated that the association of DRT < median with UFR did not vary according to functional impairment in the IADLs (\( p = 0.591 \)). Interestingly, increasing UFR was associated with increasing probability of a DRT below the median (\( p \) for trend = 0.035); however, only the highest tertile was significantly associated with lower DRT. Eventually, only the highest tertile of the DRT was associated with a UFR below the mean value (i.e., 9.2 mL/kg/h) in multinomial logistic regression having the lowest DRT tertile as reference (Fig. 1).

Finally, patients were divided into 3 groups according to the UFR: (1) <10 mL/kg/h; (2) 10–13 mL/kg/h; (3) >13 mL/kg/h [14]. The demographic, clinical, and laboratory characteristics of these 3 groups are shown in the Table 3. However, DRT was significantly lower in patients with UFR >13 mL/kg/h (350 ± 100 min) than in patients with UFR <10 mL/kg/h (200 ± 90 min).

**Discussion**

The present study shows that the recovery time after the dialytic session is inversely related to the UFR, with the highest tertile of the recovery time being associated with a UFR below the mean value.

Data on the correlation between recovery time and UFR are few and conflicting [4, 9, 14, 15]. In the study of Rayner et al. [4], a longer recovery time was associated with greater intradialytic weight loss, longer dialysis session duration, and dialysate sodium concentration <140 mEq/L. In addition, a U-shaped association between recovery time and UFR was found, with both slow and fast UFR (<5 and >15 mL/min, respectively) being associated with a shorter recovery time compared with a UFR of 5–15 mL/min [4]. Conversely, Hussein et al. [9] have demonstrated that a higher UFR was associated with a longer recovery time. Finally, in the study of Harford et al. [15], any correlation between recovery time and UFR was found.

Which are the underlying mechanisms of the inverse association between recovery time and UFR found in the present study? This question remains. Recently, we have demonstrated that fatigue in patients on CHD was significantly associated with the serum concentrations of in-
terleukin-6, independently of the presence of symptoms of depression [16]. It can be hypothesized that the UFR may influence the production of cytokines or their removal and consequently the recovery time. In the study of Müller-Steinhardt et al. [17], a stepwise reduction in UFR from 40–46 to 7–10 mL/min resulted in a significant increase in IL-10 concentrations ($p = 0.012$) and decrease in Interleukin-1 beta (IL-1β) concentrations. Unfortunately, there is no other evidence about the effect of UFR on cytokine production and removal, unlike data on removal of cytokines and type of hemodialysis filter [18]. Alternatively, it may be suggested that patients with a high UFR might have been selected to receive a high UFR because of their capacity to tolerate a high UFR and that consequently these patients had a short recovery time.

It remains to be investigated whether the reduction of recovery time may be obtained with the increase of the UFR in the routine clinical practice and whether this is appropriate. In fact, it is well known that a higher UFR has been associated with increased mortality [19–21] and with hemodynamic effects such as reduced myocardial blood and myocardial stunning [22–24]. Nevertheless, an ideal UFR has not yet been identified [25].

We also found that the dialysate sodium concentration did not differ significantly between patients with recovery time below and above the median value. An opposite result has been reported by Rayner et al. [4] who demonstrated that a prescription of dialysate sodium concentration <140 vs. 140 mEq/L was associated significantly with longer recovery time. Nevertheless, the dialysate sodium concentration did not differ significantly across the recovery time categories in the study of Hussein et al. [9]. Indeed, there is evidence that the intradialytic reduction in osmolarity is no different between patients with and without post-dialysis fatigue and studies comparing high-sodium (142–146 mEq/L) and low-sodium (131–137 mEq/L) baths have led to conflicting results [26–35].

The observation that the odds ratio of having a recovery time below the median value was higher in patients with IADL disability is in accordance with that of the study of Rayner et al. [4] that reported that patients reporting fewer ADL tended to report a longer recovery time.

Surprisingly, DRT was not related to sex in the present study. This finding is in disagreement with that of previous studies that have demonstrated a significant association between a longer recovery time and the female sex [4–5, 9].

In accordance with previous studies, recovery time was unrelated to age [7, 9] and some clinical variables such as the Charlson comorbidity index [7] and insomnia [36].

We also found that recovery time was unrelated to the dialysate temperature. In fact, the mean dialysate temperature was similar in patients with recovery time below and above the median value. It is well known that low dialysate temperature increases arterial pressure in hypertensive hemodialysis patients and reduces the prevalence

### Table 3. Characteristics of patients according to the UFR

<table>
<thead>
<tr>
<th>UFR, mL/kg/h</th>
<th>$&lt;10$ ($n = 125$)</th>
<th>$10–13$ ($n = 63$)</th>
<th>$&gt;13$ ($n = 22$)</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>71.1±12.2</td>
<td>69.9±15.5</td>
<td>66.5±18.5</td>
<td>0.337</td>
</tr>
<tr>
<td>Dialytic age, months</td>
<td>66.1±70.7</td>
<td>74.3±76.2</td>
<td>84.1±65.8</td>
<td>0.445</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.1±5.3</td>
<td>24.1±1.5</td>
<td>20.8±2.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADL</td>
<td>6 (6–6)</td>
<td>6 (6–6)</td>
<td>6 (6–6)</td>
<td>0.266</td>
</tr>
<tr>
<td>IADL</td>
<td>6 (5–7)</td>
<td>7 (5–8)</td>
<td>7 (4.9–8)</td>
<td>0.490</td>
</tr>
<tr>
<td>CCI</td>
<td>2.2±1.7</td>
<td>2.3±1.5</td>
<td>1.7±1.5</td>
<td>0.334</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>3.98±0.4</td>
<td>3.51±0.4</td>
<td>3.65±0.5</td>
<td>0.348</td>
</tr>
<tr>
<td>Hb, g/dL</td>
<td>11.2±1</td>
<td>11.3±1</td>
<td>11.3±1.2</td>
<td>0.189</td>
</tr>
<tr>
<td>Ht, %</td>
<td>34.4±3.5</td>
<td>35.3±3.4</td>
<td>35.6±4.1</td>
<td>0.149</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>8.6±2.7</td>
<td>9.1±2.3</td>
<td>8.9±2.6</td>
<td>0.450</td>
</tr>
<tr>
<td>Dialysis session time, min</td>
<td>240</td>
<td>240</td>
<td>240</td>
<td>1.000</td>
</tr>
<tr>
<td>Dialysate Na concentration, mEq/L</td>
<td>139.7±1.7</td>
<td>140.3±1.8</td>
<td>140.1±1.8</td>
<td>0.089</td>
</tr>
<tr>
<td>Dialysate temperature, °C</td>
<td>36.6±0.4</td>
<td>36.5±0.5</td>
<td>36.5±0.4</td>
<td>0.109</td>
</tr>
</tbody>
</table>

BMI, body mass index; ADL, activities of daily living; IADL, instrumental activities of daily living; CCI, Charlson comorbidity index score.
of intradialytic hypotensive events [37]. Recently, one study has investigated the effect of low temperature on fatigue showing that the switch from 37 to 35°C dialysate temperature determined lower severity and duration of fatigue [38].

Unsurprisingly, recovery time was also not associated with any of the laboratory parameters collected (i.e., hemoglobin, creatinine, albumin, Kt/V). This finding may be due to the fact that all patients were treated to target hemoglobin, albumin and Kt/V according to the Kidney Disease Outcomes Quality Initiative guidelines [39].

We found a striking difference in BMI among the groups of UFR shown in Table 3. This may reflect the lack of a linear relationship between fluid intake and BMI. Undoubtedly, this finding requires further investigation in the future.

The present study has some limitations. First, the sample size was relatively small and this may have masked other possible interactions. Second, recovery time is a subjective measure and may be related to various symptoms such as post-dialysis fatigue, sickness, headache, exhaustion, or weakness. Second, no circulating inflammatory biomarkers were measured, and this did not allow the possibility to explore the association between recovery time and systemic inflammation. Third, we did not assess and compare the changes of serum potassium between patients with low and high recovery time.

In conclusion, the present study shows that the recovery time is inversely associated with UFR in patients on CHD. Whether this is an indication that a high UFR is recommended to reduce the DRT needs to be elucidated through an adequate prospective randomised study.

Disclosure Statement

None of the authors has conflicts of interest to disclose.

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References


32 Barré PE, Brunelle G, Gascon-Barré M: A randomized double blind trial of dialysate sodiums of 145 mEq/L, 150 mEq/L, and 155 mEq/L. ASAIO Trans 1988;34:338–341.


