Volume excess in chronic haemodialysis patients—effects of treatment frequency and treatment spacing

Jakob Stockinger¹, Werner Ribitsch² and Daniel Schneditz¹

¹Institute of Physiology, Medical University of Graz, Graz, Austria and ²Division of Nephrology, Department of Internal Medicine, Medical University of Graz, Graz, Austria

Correspondence and offprint requests to: Daniel Schneditz; E-mail: daniel.schneditz@medunigraz.at

Abstract

Background. The main objective of this study was to theoretically quantify the fluctuations of fluid volume excess for different modes of intermittent ultrafiltration schedules and to compare the prediction for the typical and asymmetric thrice-weekly schedule to clinical, physiological and biophysical markers of volume expansion in a group of stable haemodialysis patients.

Methods. Overall volume excess \((\overline{V_{OVE}})\) was described as the sum of a time-independent \((\overline{V_0})\) and a time-dependent component \((\overline{V})\). An exact relationship was developed to relate \(\overline{V}\) to variable treatment frequency, treatment spacing and net volume accumulation rate. In a single-centre haemodialysis population, body mass profiling was combined with volume state evaluation by bioimpedance analysis, N-terminal pro-B-type natriuretic peptide (NT-pro BNP) levels, clinical signs, a volume questionnaire and blood pressure levels.

Results. In 23 patients following the typical thrice-weekly schedule, the time-averaged volume excess \((\overline{V})\) during the whole week \((1.1 \pm 0.5 \text{ L})\) was significantly larger than that during the midweek interval \((0.9 \pm 0.4 \text{ L})\) \((P < 0.002)\) by a factor comparable to that of 1.21 obtained from the theoretical analysis. \(\overline{V_{OVE}}\) was \(1.3 \pm 1.7 \text{ L}\) and significantly related to pre- \((P < 0.001)\) and post-dialysis levels of NT-pro BNP \((P < 0.001)\).

Conclusion. Asymmetric treatment spacing such as with the typical thrice-weekly treatment schedule leads to a significant increase in time-averaged volume excess. The theoretical analysis allows for comparison of time-averaged volume excess in treatments varying with regard to treatment frequency and regularity and could be helpful to prescribe post-treatment volume (target weight) for such variable treatment modes.

Keywords: dry body mass; time-averaged volume deviation; time-averaged volume excess; ultrafiltration

Introduction

One essential aspect of total body water mass and volume in haemodialysis patients is their variability. Even in the steady state, body mass is highly time dependent and characterized by periodic changes of volume expansion and volume contraction [1]. Slow accumulation of fluid volume between ultrafiltration treatments is followed by rapid elimination within treatments. Volume changes ideally occur under iso-osmotic or close to iso-osmotic conditions so that they are largely confined to changes in extracellular volume [2].

Fluid volume excess in intermittent renal replacement therapy comprises a time-dependent and a time-independent component. The volume excess (or deficit) measured at the end of a given therapy refers to the time-independent component because it represents a constant positive (or negative) offset from the reference value. The determination of this constant offset has been the focus of previous studies [3–6] reviewed in [7]. However, there is a component of volume excess that varies with time and hence with duration, frequency and spacing of treatments. This is well known in everyday practice [1, 8], but to our knowledge, this aspect of volume excess has not been formally examined in more detail.

In this study, we develop an approach to account for the variability of volume expansion inherent to intermittent treatment modes and propose time-averaged volume excess \((\overline{V})\) and time-averaged volume deviation \((\Delta \overline{V})\) as measures of volume expansion and fluctuation in haemodialysis patients undergoing intermittent fluid adjustment.

Materials and methods

Model

In the steady state, net accumulation of volume between treatments defined as the difference between volume intake by ingestion of food and fluids and sensible as well as insensible volume loss is matched by ultrafiltration volume removed within treatments. Common treatment schedules are unsymmetric because of constraints determined by the work week. If net fluid accumulation is independent of treatment frequency and treatment regularity, ultrafiltration volumes are usually larger after long weekend intervals [9]. For treatment schedules with only one treatment per day (done around the same time of the day) and two different treatment intervals (the most common case), the time-averaged volume excess \(\overline{V}\) is given as:

\[
\overline{V} = \frac{Q}{2T} \left( n_2 \overline{r}_2^2 + n_1 \overline{r}_1^2 \right),
\]
**Results**

The study population comprised 23 patients, 10 of them female, whose characteristics are summarized in Table 1. Five patients (21.7%) were diabetic and 16 patients (69.6%) took anti-hypertensive medication.

The weekly volume profile revealed the expected pattern (Figure 1, Table 2). A positive overall volume excess was found in 16 subjects (69.6%). Five subjects (21.7%) presented a relative overall volume excess of >15% before dialysis treatment. Twelve subjects (52.2%) were volume contracted at the end of dialysis. The average net volume accumulation rate and the time-averaged volume excess of the measurement week were close to the corresponding values of the validation week. Moreover, variations of post-dialysis body mass were minimal (Table 3).

Time-averaged volume excess for the midweek treatment was equal to the daily net volume accumulation, ~0.9 L in this study (Table 2) and significantly lower (P < 0.002) than the weekly average, which was derived from Equation (4). Relative overall volume excess before ultrafiltration was significantly related to the pre- and post-dialysis NT-pro BNP levels and the blood pressure at the end of dialysis (Table 4). Furthermore, overall volume excess normalized to extracellular volume was significantly higher in patients with moist lung rales (Table 5), while other volume indicators did not reach a significant level.

The expected impact of different treatment schedules on volume excess and time-averaged volume deviation is shown in Figure 2. Overall volume excess and time-averaged volume deviation increase with treatment asymmetry and decrease with treatment frequency. With daily dialysis done six times per week, time-averaged volume excess is expected to fall to 53% of that of the typical thrice-weekly schedule (Monday–Wednesday–Friday or Tuesday–Thursday–Saturday schedule).

A comparison of effects caused by changes in treatment schedule and ultrafiltration volumes is shown in Figure 3 and summarized in Table 6. While an increase in ultrafiltration volume decreases overall volume excess by decreasing post-dialysis volume (and post-dialysis mass), an increase in treatment frequency alone decreases both overall volume excess as well as time-averaged volume deviation.

**Discussion**

Haemodialysis patients were examined with regard to time-dependent and time-independent components of

---

**Table 1. Patient characteristics (N = 23)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.3 ± 12.6</td>
<td>18–73</td>
</tr>
<tr>
<td>Body height (cm)</td>
<td>168 ± 8</td>
<td>156–181</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.3 ± 5.7</td>
<td>18.5–40.9</td>
</tr>
<tr>
<td>Pre-dialysis mass (kg)</td>
<td>74.3 ± 18.1</td>
<td>45.2–122.0</td>
</tr>
<tr>
<td>Treatment duration (h:min)</td>
<td>4:09 ± 0.25</td>
<td>2:54–5:00</td>
</tr>
</tbody>
</table>

---

where \( Q_0 \) refers to the net volume accumulation rate per day (in L/day), \( T \) is the duration of the weekly cycle (7 days), \( n_l, n_s \) refer to the number of treatments with long and short intervals and where \( t_l \) and \( t_s \) refer to the durations of short or long treatment interval in days (see Appendix).

Time-averaged deviation which measures the average amplitude of the volume oscillations depends on \( V' \) and is given as:

\[
\Delta V = \begin{cases} 
\frac{n_l + n_s}{T} \times \frac{Q_a}{Q_a} & \text{if } V' \leq t_s Q_a, \\
\frac{n_l}{T} \left( t_s Q_a - V' \right) & \text{if } V' > t_s Q_a.
\end{cases}
\]

Overall volume excess comprising both a time-dependent \( V' \) and a time-independent components \( V_0 \) is determined by the sum of both components:

\[
V_{OVE} = V + V_0.
\]

---

**Protocol**

Haemodialysis patients from the out-patient programme of the Division of Nephrology, Department of Internal Medicine, Medical University of Graz, provided written informed consent for the study which was designed in adherence to the Declaration of Helsinki and approved by the University’s Internal Review Board. Patients with pacemakers, implantable cardioverter-defibrillators, limb amputations as well as local wrist and/or ankle oedema were excluded because bioimpedance measurements are not indicated in that situation. Haemodialysis was delivered as prescribed. Patients followed their normal thrice-weekly treatment schedule. Pre- and post-dialysis body masses were collected for a period of 2 weeks, 1 week serving for model development and the other week serving for model validation.

**Measurements**

The time-averaged volume excess for the typical thrice-weekly schedule was derived from Equation (1) with \( n_l = 2, n_s = 1, t_s = 2, t_l = 3 \) and \( T = 7 \) and is therefore given as:

\[
V = \frac{17}{14} Q_0 \approx 1.21 Q_0.
\]

The net volume accumulation rate \( Q_0 \) was determined from the average interdialytic body mass gain per day.

For validation periods, volumes were calculated according to the measured body mass profiles. Markers of volume expansion were obtained using physiological, clinical and bioelectrical data as described in a companion study [10]. Blood samples were taken at the beginning and end of dialysis, and N-terminal pro-B-type natriuretic peptide (NT-pro BNP) was measured by Modular Analytics Evo (F. Hoffmann-La Roche AG, Basel, Switzerland). A volume score validated in previous studies was used for a clinical volume assessment [11, 12]. Extracellular volume \( (V_E) \), time-independent volume excess \( (V_a) \) and relative volume excess \( (V_\text{rel}) \) were obtained from bioimpedance data according to Chumney et al. [3] using the Body Composition Monitor (BCM, Fresenius Medical Care, Bad Homburg, Germany). Relative overall volume excess \( (\text{OVE}) \) was determined by relating overall volume excess \( (V_{OVE}) \) to pre-dialytic extracellular volume \( (V_{OVE} = V_{OVE}/V_E) \).

**Data analysis**

Data were analysed using MS-Excel (Microsoft Corporation, Seattle, WA) and SPSS (IBM Corporation, New York, NY). Values are presented as arithmetic mean ± SD and correlations were examined according to Pearson, unless otherwise specified. Normal distribution was tested by Shapiro–Wilks, whereas equal variances in the groups were assumed. Groups consisted of normally distributed numeric values and were compared by two-sided t-test, unless mentioned otherwise. For all tests, a probability \( P < 0.05 \) was considered significant to reject the null hypothesis.
volume expansion and these components were compared to clinical, physiological and biophysical volume markers. The main result revealed a significant correlation between NT-pro BNP and the overall volume excess $V_{OVE}$, expressed as the sum of time-independent volume excess $V_0$ and time-averaged volume excess $V^T$. Furthermore, the exact relationships derived in this study allowed for calculating the volume excess for treatment modes with regard to variations in treatment frequency and/or treatment spacing from first principles. This could be helpful to compare the volume status of haemodialysis patients undergoing different treatment schedules.
The approach to describe time-averaged volume excess resembles the analysis of time-averaged concentration in haemodialysis solute kinetics [13–18]. With continuous ultrafiltration in healthy subjects, the time-averaged volume excess is zero in the steady state, and the fluid volume under these conditions can be assumed as a reference volume. With intermittent ultrafiltration, however, time-averaged volume increases above the reference volume. The increase is quantified by Equation (1).

The intermittency of extracorporeal clearance results in a seesaw pattern of solute concentrations and the amplitude of the concentration peaks has been quantified by the time-averaged deviation [19–21]. In analogy, time-averaged volume deviation is zero for continuous ultrafiltration and increases with intermittent and unevenly spaced treatments. For evenly spaced treatments, time-averaged volume deviation and inter-dialytic volume gain are related by a constant factor of 0.5 [Equation (A.3)] and are easily converted. Time-averaged volume deviation, however, increases with treatment asymmetry (Table 6, Figure 2).

### Table 4. Volume indicators compared to relative overall volume excess (N = 23)*

<table>
<thead>
<tr>
<th>Volume indicator</th>
<th>Mean ±SD</th>
<th>Range</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dialysis NT-pro BNP (pg/mL)</td>
<td>5157b</td>
<td>2436 to 17 145c</td>
<td>566 to 35 000</td>
<td>0.651</td>
</tr>
<tr>
<td>Post-dialysis NT-pro BNP (pg/mL)</td>
<td>4900b</td>
<td>747 to 11 311c</td>
<td>372 to 35 000</td>
<td>0.644</td>
</tr>
<tr>
<td>Pre-dialysis MAP (mmHg)</td>
<td>105 ±14</td>
<td>83 to 130</td>
<td>0.183</td>
<td>0.403</td>
</tr>
<tr>
<td>First intra-dialytic MAP (mmHg)</td>
<td>101 ±15</td>
<td>76 to 123</td>
<td>0.096</td>
<td>0.664</td>
</tr>
<tr>
<td>Last intra-dialytic MAP (mmHg)</td>
<td>95 ±17</td>
<td>69 to 127</td>
<td>0.446</td>
<td>0.033d</td>
</tr>
<tr>
<td>Clinical volume score</td>
<td>0b0 to 0c</td>
<td>−4 to +8</td>
<td>0.303</td>
<td>0.160f</td>
</tr>
</tbody>
</table>

*MAP, mean arterial pressure.
abMedian.
cInterquartile range.
dSignificant correlation.
eAfter logarithmic transformation of the NT-pro BNP values.
fSpearman coefficient.

### Table 5. Volume indicators and clinical signs (N = 23)*

<table>
<thead>
<tr>
<th>IOVE,223 (%)</th>
<th>IOVE,223 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema</td>
<td>11.3 ± 10.3</td>
<td>5.5 ± 8.6</td>
</tr>
<tr>
<td>Rales</td>
<td>16.9 ± 5.3</td>
<td>5.7 ± 8.5</td>
</tr>
<tr>
<td>Cramps</td>
<td>1.1 ± 8.4</td>
<td>8.7 ± 9.4</td>
</tr>
<tr>
<td>Hypotension</td>
<td>13.4 ± 9.2</td>
<td>5.7 ± 9.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10.5 ± 10.8</td>
<td>6.2 ± 9.2</td>
</tr>
</tbody>
</table>

*OVE,223, relative overall volume excess.
*Significant difference.

### Fig. 2. Time-averaged volume data. Time-averaged volume excess (V̅, full circles) and time-averaged volume deviation (ΔV̅, error bars) calculated for common treatment schedules, if other treatment parameters remain unchanged. Treatment frequency: 1 (dialysis done once a week), 2 (one 4-day interval and one 3-day interval), 3 (two 2-day intervals and one 3-day interval; typical thrice-weekly schedule), 4 (one 1-day interval and three 2-day intervals), 6 (five 1-day intervals and one 2-day interval) and 7 (daily dialysis).

### Fig. 3. Volume excess map. Effect of different treatment strategies for a patient in the typical thrice-weekly haemodialysis schedule with an overall volume excess (VOVE) of 0.91 L and a time-averaged volume deviation (ΔV̅) of 0.73 L (full circle): (1) a reduction in post-dialysis volume by 0.8 L changes V̅ but maintains ΔV̅. (2) A switch to five asymmetric treatments per week with four 1-day intervals and one 3-day interval reduces overall volume excess but maintains a similar ΔV̅. (3) A switch to five more evenly spaced treatments per week with three 1-day and two 2-day intervals reduces both overall volume excess and ΔV̅. (4) A decrease of volume influx by 0.4 L reduces both overall volume excess and time-averaged volume deviation.
The analysis of time-averaged concentration and related measures has its merits in comparing treatment dose delivered with different treatment schedules and has led to measures such as equivalent urea clearance and standard Kt/V. Similar considerations apply to an analysis of volumes. The analysis is simpler in the case of volume, but to our knowledge, a formal analysis of intermittent volume removal and its effect on average volume excess has not yet been presented. This is even more surprising as volume information is available with every treatment so that time-averaged volumes are easily computed for every patient and every week.

As a result from this analysis, one could postulate that treatments with different treatment schedules are comparable with regard to volume state for comparable time-averaged volume excess. As the overall volume excess is given by the sum of the time-averaged volume excess \( V \) and the post-treatment volume excess \( V_0 \) (Equation (3)), the sum remains constant by increasing one component, for example \( V \), while decreasing the other component, in this case \( V_0 \). In order to maintain a state of average euvoalma (an overall volume excess of zero L), the post-treatment volume excess \( V_0 \) must be lowered by a magnitude given by Equation (1) so that, for the common thrice-weekly schedule, the post-dialysis volume would have to be reduced below the reference volume by 1.2 times the daily fluid intake [Equation (4)]. For daily dialysis done six times per week, time-averaged volume would have to be reduced only by half of that value. In other words, post-dialysis volume can be increased with increased treatment frequency. This could be a major factor for improved outcome observed with daily dialysis [22, 23].

While it is possible to obtain comparable time-averaged volumes using different treatment schedules by adjusting the post-dialysis volume, the time-averaged volume deviation will be different for any two protocols chosen and it will be smaller for the protocol with higher treatment frequency and treatment symmetry. Thus, time-averaged volume deviation is a measure of treatment un-physiology comparable to the concept advocated by Lopot et al. many years ago [19, 20].

Novel technologies attempt to quantify the volume excess by comparing the volume state of dialysis patients to that of the healthy population [24, 25]. Such a comparison inherently underestimates the volume excess if measured post-dialysis: in this regard, it would be normal for patients treated by intermittent treatment modes to be volume contracted at the end of dialysis. Post-dialysis volume excess was more or less zero in the present study population and most studies even found volume depletion at treatment end [26–29].

The intuitive assumption that symmetric and short treatment intervals are favourable with regard to volume excess was also confirmed by the analysis presented in this study. Time-averaged volume excess for the typical midweek treatment was equal to the daily fluid accumulation, \(-0.9\) L in this study (Table 2). The weekly average was \(-21\%\) [Equation (4)] higher, essentially because of asymmetric treatment spacing. Indeed, symmetric treatment modes have been shown to reduce left ventricular mass and to improve the ejection fraction [30].

Different components of volume excess have been related to increased mortality: pre-dialysis volume excess has been shown as one of the significant predictors of mortality in 269 prevalent haemodialysis patients after 3.5 years of follow-up [27]. The relationship between inter-dialytic volume gain, an easily assessable indicator, and mortality has been sufficiently demonstrated in large study populations [31, 32]. Other authors found mortality to be related to volume state without specifying the time aspects of volume evaluation [33].

Volume excess prevailed in our study population. Overall volume excess agreed well with NT-pro BNP but failed to clearly correlate with other volume indicators, probably because of a lack in specificity or because of different time scales of the indicators used: overall volume excess and, to some degree, the clinical score refer to the whole cycle of volume contraction and expansion. NT-pro BNP whose half-life lies within 60 and 120 min [34] reflects the volume during the hours before its measurement.

In conclusion, time-averaged volume excess is a measure of ultrafiltration adequacy accounting for effects caused by treatment frequency and treatment spacing. The concept presented here is the first formal and quantitative analysis of volume and volume changes that allows for a comparison between individuals regardless of volume accumulation rate, ultrafiltration frequency and treatment symmetry. This is important because alternative treatment schedules have gained attention and because new techniques to measure proper reference volumes need to account for treatment frequency and symmetry. Further research in larger studies is needed to show the benefit of such an approach in patient outcome.

**Acknowledgements.** We thank Dr C. Weber from Fresenius Medical Care Austria for providing the Body Composition Monitor. This work was in part supported by the Austrian Research Promotion Agency (FFG) and by a research grant to Dr W.R. from Baxter Healthcare Austria.

**Conflict of interest statement.** None declared.

**Appendix**

With a constant net volume accumulation rate \( Q_a \) (in L/day), the area under the volume curve \( A \) (in L × day) during one...
treatment cycle with the duration $t$ (in days) is given as:

$$A = \frac{Q_s}{2} t^2 \quad \text{(A.1)}$$

The time-averaged volume excess $V$ (in L) over the period $T$ (in days) is then given as the sum of the areas $A$ divided by $T$ so that

$$\hat{V} = \frac{1}{T} \sum_{j=1}^{n} A_j = \frac{Q_s}{2T} \sum_{j=1}^{n} t_j^2. \quad \text{(A.2)}$$

A graphical explanation of this equation is given in Figure 1. For treatment schedules with two different treatment intervals, Equation (A.2) is easily converted into Equation (1). For symmetric and evenly spaced treatments, Equation (A.2) simplifies to

$$\hat{V} = \frac{Q_s}{2} t = \frac{V_u}{2}, \quad \text{(A.3)}$$

where $V_u$ is the ultrafiltration volume. Time-averaged volume deviation $\Delta V$ is then given as:

$$\Delta \hat{V} = \frac{Q_s}{4} t = \frac{V_u}{4}. \quad \text{(A.4)}$$

References


17. Daugirdas JT, Tattersall J. Effect of treatment spacing and frequency on three measures of equivalent clearance, including standard Kt/V. Nephrol Dial Transplant 2010; 25: 558–561


Received for publication: 27.1.2011; Accepted in revised form: 25.10.2011

Downloaded from https://academic.oup.com/ndt/article-pdf/28/1/170/1825831 by guest on 10 January 2019