Differences in heart rate variability during haemodialysis and haemofiltration

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Abstract

Background. The aim of our study was to evaluate whether convective (haemofiltration, Hf) and diffusive (haemodialysis, Hd) dialysis techniques induce different patterns of long- and short-term autonomic adjustments in haemodynamically stable dialysis patients.

Methods: Ten haemodynamically stable Hd patients were studied. Each patient underwent a block of six Hd sessions, then was switched to six Hf. During the last session of each dialytic treatment, continuous beat to beat measurements of systolic arterial pressure (SAP) and heart rate (HR) were performed. Spectral analysis of heart rate variability (HRV) was made before and during the treatment to evaluate the modification of autonomic nervous system activity.

Results: Baseline values of plasma sodium, body weight, HR and SAP were not different for the two considered methods of dialysis, while the baseline values of normalized LF were significantly higher in Hf as compared to Hd and the opposite was observed for HF powers (P < 0.001). Sodium balance and body weight loss per hour did not differ between Hd and Hf while body temperature was kept constant in all sessions. Throughout the dialytic procedures, with both techniques, SAP was constant, while HR diminished from the first hour till the end of the procedure (P < 0.05). An increase in LF (and decrease in HF) was noticed only in the case of Hd, considering normalized units (P < 0.05). These selective changes were maintained also during the recovery after the procedure.

Conclusions: The spectral analysis of RR interval variability during Hd and Hf suggests a potential autonomic advantage with Hf, to be added to the well-recognized intrinsic greater haemodynamic stability.

Keywords: haemodialysis; haemofiltration; heart rate variability; hemodynamic stability; spectral analysis

Introduction

The Intradialytic hypotension, occurring in 20–35% of dialytic sessions [1], is the major clinical problem faced in dialytic treatment.

Diffusive and convective dialytic approaches have been extensively investigated, suggesting that haemofiltration (Hf) represents the best intermittent renal replacement therapy for cardiovascular stability, resulting in a reduction of intradialytic hypotension compared to haemodialysis (Hd) [2,3]. Traditionally, volume removal during Hf is considered more physiologic than in Hd due to the smaller decrease in plasma osmolality resulting in a less negative sodium balance. Furthermore, during Hf the extracorporeal blood temperature is usually constantly lower than during Hd and this may favour a better vascular response. To gain a mechanistic understanding of the improved performance of Hf, several investigators addressed separately the role of temperature [4] and of osmolality [5,6], however results are far from definitive.

An additional potential role for the autonomic nervous system has been suggested since 1984 by clinical observations by Zucchelli et al. [7], and more recently by Santoro et al. [8], on the basis of in vitro experiments but to the best of our knowledge no studies have been conducted to investigate whether Hd and Hf may have different effects on autonomic nervous system activity, independently from sodium and variations in body temperature.

Previous studies on the autonomic effects of diffusive dialysis during haemodynamically stable sessions, reported that the normalized power of the low-frequency (LF) component (marker of sympathetic oscillatory regulation) of the heart rate variability tends to increase whereas the high-frequency (HF)
component (marker of vagal oscillatory regulation) falls progressively [9]. Conversely, during intradialytic hypotension, autonomic adjustments are largely different, and consist in sympathetic withdrawal [10] and vagal activation, as suggested by transient rises in the power of HF component [11].

The end stage renal disease (ESRD) is associated to an array of functional disturbances, among which various degrees of autonomic dysregulation have been described since the early 1970s [12,13]. In this context, some authors observed a reduced LF power of HRV [14], while other groups reported increased LF power [15], possibly related to clinical or methodological differences. Few studies indicated that recovery of renal function restores autonomic regulation [16,17]; however, there is essentially no information whether different dialysis techniques lead to different baseline autonomic indices during the subsequent interdialytic period.

Accordingly, the aim of our study was to evaluate whether convective (haemofiltration, Hf) and diffusive (haemodialysis, Hd) dialysis techniques induce different patterns of intradialytic (acute effects) and interdialytic (short-term effects) autonomic adjustments in haemodynamically stable ESRD patients, undergoing chronic dialysis.

**Subjects and methods**

The protocol of the study was approved by the Ethics Committee of Ospedale S. Gerardo (Monza) and Ospedale Ubboldo (Cernusco Sul Naviglio) and was in accordance with the Helsinki declaration of 1975 (and as revised in 1983). All patients provided informed consent before participation.

**Patients**

Ten haemodynamically stable haemodialysis patients (six women and four men), aged 60 ± 11 were selected for the study. Haemodynamic stability was defined as a lack of episodes of hypotension during the last 3 months, with three weekly dialytic sessions.

The median time of haemodialysis was 23 months (range 10–39 months). The underlying causes of end-stage renal disease were polycystic kidney disease (n = 3), chronic glomerulonephritis (n = 2), nephroangiosclerosis (n = 1), chronic pyelonephritis (n = 3), renal tuberculosis (n = 1). Exclusion criteria are reported in Table 1. A control group of healthy subjects was considered for comparison of baseline values. The group was matched for sex and age to dialytic patients (six women and four men, aged 57.5 ± 3.0).

**Study procedure**

In this study, each patient first underwent a block of six consecutive bicarbonate haemodialysis (i.e. diffusive, Hd) sessions, then was switched to a block of six consecutive predilution on-line haemofiltration (i.e. convective, Hf) sessions. During Hd sessions, hourly body weight loss, Kt/V, Na and body temperature were constantly monitored. In the last (sixth) session, haemodynamic and autonomic recordings were performed. Hf prescriptions were balanced according to individual results (Kt/V, Na balance and body temperature) previously obtained with Hd and on Hf number six the haemodynamic and autonomic registrations were repeated. In each patient, dry weight was achieved in every session and was constant throughout the study.

**Table 1. Exclusion criteria**

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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<tbody>
<tr>
<td>Dialysis age &gt;5 years</td>
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<tr>
<td>Obesity (BMI &gt;30 kg/m²)</td>
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<tr>
<td>Anemia (Hb &lt;10 g/dl)</td>
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<tr>
<td>Diabetes (FPG &gt;126 mg%)</td>
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<tr>
<td>Ischaemic heart disease</td>
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<tr>
<td>Ejection fraction &lt;40%</td>
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<tr>
<td>Arrhythmias</td>
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<tr>
<td>Cerebrovascular diseases</td>
</tr>
<tr>
<td>Clinical autonomic neuropathy</td>
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<td>Use of antiadrenergic drugs</td>
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FPG: fasting plasma glucose.

**Adequacy**

Dialytic adequacy was calculated according to the simplified Daugirdas formula [18]. Our target was to maintain a Kt/V value above 1.2 both in Hd and in Hf.

**Sodium balance**

Total body volume was determined in every Hd using the K-DOQI single-pool variable volume (SPVV) Gotch’s theory [19]. Urea distribution volume and urea generation were calculated according to equations (1) and (2) iteratively solved till V and G differed by no more than 1%. Initial and end dialysis plasma water urea concentrations were determined by direct potentiometry in blood samples drawn at the beginning and at the end of the treatment. The end blood sample was performed after 5 min of reduced blood flow to 100 ml/min. Dialyser clearance (K) was considered constant throughout the treatment. Sodium balance was then calculated according to the formula, Na balance = (V₀ × Na₀ − Vᵣ × Naᵣ); where V₀/Vᵣ and Na₀/Naᵣ represent the volume and sodium at the beginning and at the end of the dialysis treatment. During Hf, Gotch’s formula can not be used due to the rapid changes of the dialyser clearances throughout the session. We hypothesized no changes in patients volume during Hf period and to confirm this hypothesis we performed a successive Hd session in which volume was calculated according to SPVV-UKM.

**Isothermic dialysis**

Isothermic Hd (i.e. maintenance of estimated body temperature throughout the Hd session) was obtained using a properly designed automatic device associated to the dialysis monitor (BTM- Fresenius). The operation of this module has been described previously [20].

Conversely, during Hf the temperature of the reinfusion fluid was settled at 36°C and approximate constancy of body temperature was inferred from the stability of the temperature of the arterial line, as indicated by BTM monitor.
No patients felt cold or had shivers. Energetic balance was not considered in the study.

**Autonomic evaluation**

Autonomic cardiac regulation was inferred from spectral analysis of HRV that provides indices of sympathetic and parasympathetic regulatory activities, by separate examination of low- (LF) and high-frequency (HF) components, employing normalized units. These spectral components of HRV can be easily acutely modulated by standard laboratory maneuvers. An increased sympathetic modulation elicited by standing, moderate exercise or mental stress determines an increased power of the LF spectral component, expressed in normalized units. Other physiological stimuli, recognized to increase vagal drive, such as controlled respiration, low dose atropine or cold facial stimulation, result in an increase in HF peak [21,22].

During session 6 of each dialytic block, the following variables were continuously recorded in each patient:

- electrocardiogram (chest-chest electrode) and respiratory movements by means of a two channel amplifier,
- arterial pressure waveform by a Finapres device (Finapres, Ohmeda, Englewood, Colorado, USA). The accuracy of this device in tracking minute-by-minute blood pressure changes has been previously documented also during dialysis.

After a preliminary rest to allow stabilization, a 10 min rest period was registered followed by 10 min of active standing. The dialysis procedure was started only after another rest period of 10 min. Subsequently, data were collected for a 10 min period at hourly intervals (1, 2, and 3 h) and finally, shortly after the end of the procedure.

Data were acquired with a personal computer, using an acquisition rate of 300 samples/channel/second. As previously described, an autoregressive algorithm (Heart Scope) was used to analyse the RR variability series providing the following frequency domain data: RR variability total variance (VARRR [ms²], equivalent to SD²), the power of the low frequency (LF, 0.03–0.14 Hz) and the high-frequency (HF, 0.15–0.35 Hz) components, both in absolute (i.e. ms²) and normalized units (nu). LF spectral powers were normalized according to the formula PLF [nu] = [(PLF [ms²]) / (VARRR [ms²] – VLF [ms²])]100, (where PLF [nu] = LF powers in normalized unit, VARRR [ms²] = total variance; VLF = very low-frequency component, i.e. the component <0.03 Hz); similar normalization was performed for HF powers. LF/HF of RR interval variability power ratio was also computed.

Simultaneous spectral analysis of RR interval variability and respiration were employed to ensure that in all subjects included in the study respiratory rate coincided with the HF component of RR variability and no respiratory entrainment was present. The Finapres signal provided minute by minute average values of systolic arterial pressure.

**Statistical analysis**

All data are expressed as mean ± SE. Comparison of baseline and standing values in both Hd and Hf and of Hd and Hf patients versus control group were performed with the Student’s t-test. Time effects during dialytic sessions were assessed with analysis of variance for repeated measures and Bonferroni’s correction. (Statview, Abacus Concept, v 4.5). A P value <0.05 was considered significant.

**Results**

Both Hd and Hf ensured dialytic adequacy, however Kt/V was higher in Hd. Moreover sodium balance and reduction in body weight/hour were similar (Table 2).

**Short-term effects of haemodialysis and haemofiltration**

Regarding baseline evaluation, the two considered methods of dialysis did not differ significantly in plasma sodium (138.4 ± 1.3 vs 138.5 ± 0.9 mEq/l), predialysis body weight (59.7 ± 3.0 vs 59.3 ± 2.9 Kg), heart rate (74.6 ± 5.1 vs 75.4 ± 0.6 bpm) and systolic arterial pressure (147.9 ± 5.6 vs 146.8 ± 4.2 mmHg).

Conversely, a significant (P <0.01) difference was observed in normalized powers of RR variability. After the run-in period, the baseline values of normalized LF were significantly higher in Hf modality as compared to the Hd approach; the opposite was observed for HF powers (respectively, LF = 65.5 ± 6.5 vs 48.1 ± 7.0 nu; HF = 24.4 ± 7.0 vs 38.8 ± 6.2 nu). LF absolute power baseline values were higher before Hf compared to Hd, while no differences in absolute powers for HF were found. No differences were observed for RR interval (as well as heart rate (HR)) and its variance (Table 3).

### Table 2. Dialytic parameters of haemodialysis and haemofiltration

<table>
<thead>
<tr>
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<th>Kt/V</th>
<th>Sodium balance</th>
<th>UF (ml/h)</th>
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<tbody>
<tr>
<td>Haemodialysis</td>
<td>1.5 ± 0.03</td>
<td>240.9 ± 31.3</td>
<td>571.3 ± 61.1</td>
</tr>
<tr>
<td>Haemofiltration</td>
<td>1.3 ± 0.02*</td>
<td>282.9 ± 40.2</td>
<td>538.2 ± 73.8</td>
</tr>
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</table>

Data are presented as mean ± SE. UF: ultrafiltration. *P < 0.05 vs haemodialysis.

### Table 3. Baseline values of autonomic nervous system indexes before haemodialysis and haemofiltration sessions

<table>
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<tr>
<th></th>
<th>Haemodialysis</th>
<th>Haemofiltration</th>
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<tr>
<td>RR (ms)</td>
<td>833 ± 48</td>
<td>839 ± 66</td>
</tr>
<tr>
<td>VARrr (ms²)</td>
<td>844 ± 225</td>
<td>1358 ± 319</td>
</tr>
<tr>
<td>Low-frequency (LF) (ms²)</td>
<td>235 ± 86</td>
<td>571 ± 158*</td>
</tr>
<tr>
<td>High-frequency (HF) (ms²)</td>
<td>158 ± 46</td>
<td>243 ± 118</td>
</tr>
<tr>
<td>LF (nu)</td>
<td>48.1 ± 7.1</td>
<td>65.5 ± 6.5*</td>
</tr>
<tr>
<td>HF (nu)</td>
<td>38.8 ± 6.2</td>
<td>24.4 ± 4.7*</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.1 ± 0.7</td>
<td>5.0 ± 1.7</td>
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</table>

Data are presented as mean ± SE. *P < 0.05 vs haemodialysis.
The control group did not differ from neither Hd nor Hf patients considering both LF and HF components of RR interval variability (respectively $52.6 \pm 14.2$ and $33.0 \pm 13.7\ \text{nu}$). Also, RR interval variance of control group ($1172 \pm 316\ \text{ms}^2$) was not statistically different from haemodialysis groups.

**Active standing effects**

In Hd modality, the standing procedure induced a significant increment of normalized LF component, and normalized HF component significantly decreased. (LF $= 45.1 \pm 7.1$ vs $64.4 \pm 6.6\ \text{and}\ \text{HF} = 42.1 \pm 5.9$ vs $22.0 \pm 5.0\ \text{nu}$, respectively, $P < 0.05$). On the contrary, in Hf patients, both, LF and HF nu did not change during the standing period. (LF $= 68.6 \pm 6.9$ vs $64.01 \pm 8.1\ \text{and}\ \text{HF} = 23.2 \pm 5.5$ vs $24.5 \pm 6.0\ \text{nu}$, respectively). None of the subjects had symptomatic hypotension during the standing period and the HR significantly increased in all patients (Figure 1).

**Acute effects of haemodialysis and haemofiltration**

Throughout the dialytic procedures, with both techniques, arterial blood line temperature remained constant ($36.5 \pm 0.1$ vs $36.5 \pm 0.1\ \text{in}\ \text{Hd}\ 36.5 \pm 0.1$ vs $36.6 \pm 0.1\ \text{in}\ \text{Hf}$), arterial systolic pressure was transiently reduced during the first hour, while heart rate was diminished from the first hour till the end of the procedure (Figure 2).

Indices of heart rate variability showed small insignificant changes in the initial phases of the dialysis,

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Fig. 1. Active standing effects. Data are presented as mean ± SE. Striped bars indicate baseline values. Solid bars indicate values during active standing. *$P < 0.05$ vs baseline.

Fig. 2. Cardiovascular parameters during haemodialysis and haemofiltration sessions. Data are presented as mean±SE. HR: heart rate; SAP: systolic arterial pressure; Bas: before start of dialysis; Post: after end of dialysis. Filled triangles denote systolic arterial pressure (SAP) in mmHg; filled squares denote heart rate (HR) expressed as beats per minute (Bpm). *$P < 0.05$ vs baseline. #*$P < 0.05$ vs first hour of treatment.
for both techniques, while a clear increase in LF (and decrease in HF) was noticed only in the case of Hd, considering normalized units. These selective changes were maintained also during the recovery after the procedure (Table 4 and Figure 3). RR variance and spectral components in absolute units did not change significantly throughout the procedure (data not shown for simplicity).

Discussion

In this study we observed that in haemodynamically stable haemodialysis patients, diffusive and convective techniques induce different patterns of acute and short term autonomic adjustments.

Considering the interdialytic period (short-term effects), Hd patients were characterized by a slightly smaller RR variance, a reduced power of LF component (in both absolute and normalized units) together with an increase in HF. Heart rate and arterial pressure were in the normal range and similar in the two dialysis modalities Cavalcanti et al. [11], showed that in dialysis patients, lower LF (and greater HF) powers of RR variability are harbingers of greater haemodynamic instability. According to these results our data may suggest a minor efficacy of Hd in correcting the uremic cardiac autonomic neuropathy of ESRD than Hf. The importance of increases in HRV and in the fraction of LF power as signs of improved ESRD related autonomic dysfunction, is further substantiated by observations in patients with kidney transplantation. [23]. Likewise, it may be surmised that the greater LF

| Table 4. Autonomic indexes during haemodialysis and haemofiltration sessions |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | Bas             | First hour      | Second hour     | Third hour      | Post            |
| (a) Haemodialysis |                 |                 |                 |                 |                 |
| LF (nu)         | 48.1 ± 7.1      | 39.8 ± 5.6      | 51.0 ± 9.7      | 68.4 ± 6.9*     | 65.4 ± 7.7*     |
| HF (nu)         | 38.8 ± 6.2      | 49.0 ± 4.2      | 38.7 ± 8.8      | 29.0 ± 5.1*     | 26.9 ± 6.0*     |
| LF/HF           | 2.1 ± 0.7       | 0.9 ± 0.2       | 4.3 ± 1.9       | 5.8 ± 2.9       | 9.3 ± 5.9       |
| (b) Haemofiltration |              |                 |                 |                 |                 |
| LF (nu)         | 65.5 ± 6.5      | 54.8 ± 6.2      | 58.3 ± 2.8      | 61.1 ± 6.8      | 56.9 ± 7.2      |
| HF (nu)         | 24.4 ± 4.7      | 37.2 ± 5.3      | 34.9 ± 7.7      | 32.6 ± 6.1      | 34.8 ± 5.5      |
| LF/HF           | 5.0 ± 1.7       | 1.9 ± 0.4       | 3.5 ± 1.3       | 6.2 ± 3.6       | 2.7 ± 0.9       |

Data are presented as mean ± SE. LF: low frequency; HF: high frequency; Bas: before start of dialysis; post: after end of dialysis.

*P < 0.05 vs first hour of treatment.

Fig. 3. Dynamic modification of low frequency (LF) and high frequency (HF) during haemodialysis and haemofiltration. Each bar indicate differences between basal condition and each hour of treatment (delta values). *P < 0.05 delta 3 h, haemodialysis vs haemofiltration. **P < 0.05 delta post-haemodialysis vs haemofiltration. ***P < 0.05 vs delta 1 h.
normalized and absolute power observed in our patients with Hf is a sign of a more efficient oscillatory autonomic regulation of the SA node under the convective therapy regime. This hypothesis is in line with previous data of Zucchelli et al. [7], showing an improvement of autonomic cardiovascular regulation after convective dialysis sessions. However, given the indirect nature of autonomic evaluation we can not exclude the presence of some subtle sympathetic activation in patients undergoing Hf.

The registered session of Hd and Hf differed in Kt/V (significantly higher in Hd). Therefore, we can not exclude some differences in osmolality changes during the two different treatments, on the other hand we believe that this difference is unimportant, from a clinical point of view and this opinion is also supported by previous study showing a better cardiovascular stability of Hf vs Hd independently from differences in Kt/V values [24].

Regarding intra-dialytic changes (acute effects), both Hd and Hf produced a decrease in HR, in contrast with studies by others showing either an increase [9] or no modification of HR [25] during treatment. This unexpected bradycardia, although already described [26], is not easily explained: one explanation might be a negative thermal balance also in Hd. Moreover, in our study, arterial pressure was maintained in the normal range by both dialytic techniques, never showing hypotensive episodes.

Notably, Hf and Hd produced different intra-dialytic profiles of oscillatory autonomic markers. In Hd, the LF component, starting from a lower baseline, increased selectively and progressively during the procedure, while it remained constant during Hf (opposite and symmetrical changes occurred for normalized HF). This finding could indicate an increase of oscillatory sympathetic modulation during our haemodynamically stable Hd procedure. As previously suggested by Barnas et al. [9] using a similar technique, the lack of sympathetic activation would lead to haemodynamic imbalance during unstable Hd sessions, in keeping with findings of Cavalcanti et al. [11]. We might hypothesize, therefore, that Hd maintains a haemodynamic stability only if a sympathetic activation is induced. On the contrary, the haemodynamic stability observed with Hf was not accompanied by any intradialytic increase in spectral markers of oscillatory sympathetic modulation, probably because of the already apparent elevated oscillatory sympathetic modulation, combined with a lower vagal drive.

We can also hypothesize that, the elevated LF component baseline value in Hf patients could be an expression of an increment of sympathetic tone, to add to the postulated more efficient oscillatory autonomic regulation of the SA node. If the matter stands like as such, it could represent an advantage for intradialytic haemodynamic stability, but a detriment for the cardiovascular risk at long term [27].

Nevertheless, we should consider that the greater haemodynamic stability of Hf might also depend on a more efficient refilling process [28] or a different pattern of vasoactive substances removal in comparison with Hd [2].

In conclusion, although both Hd and Hf dialysis seem to provide valid treatments for ESRD, spectral analysis of RR interval variability suggests a potential autonomic advantage with Hf during both inter and intradialytic periods, to be added to the well-recognized intrinsic greater haemodynamic stability.

Conflict of interest statement. None declared.


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Appendix

Formula 1:

\[ V = UF \times T \times \left\{ 1 - \left[ \frac{G - C_t \times (K - UF)}{G - C_0 \times (K - UF)} \right]^{\frac{T}{Tid}} - 1 \right\} \]

Formula 2:

\[ G = 10 \times \frac{(BUN_3 \times V_3 - BUN_2 \times V_2)}{T_{id}} \]

where \( C_t \) is the end dialysis plasma water urea concentration (mg/ml); \( C_0 \) the initial plasma water urea concentration (mg/ml); \( T \) the length of treatment (min); \( Tid \) the length of interdialytic period (min); \( BUN_3 \) the blood urea nitrogen concentration before the start of the subsequent dialytic treatment; \( BUN_2 \) the end-dialysis blood urea nitrogen concentration; \( V_2 \) the end-dialysis water body volume; \( V_3 \) the water body volume before the start of the subsequent dialytic treatment; \( UF \) the ultrafiltration rate (ml/min); \( G \) the urea generation rate (mg/min); \( K = \text{dialyser urea clearance (ml/min).} \)