Impact of extracorporeal blood flow rate on blood pressure, pulse rate and cardiac output during haemodialysis

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ABSTRACT

Background. If blood pressure (BP) falls during haemodialysis (HD) [intradialytic hypotension (IDH)] a common clinical practice is to reduce the extracorporeal blood flow rate (EBFR). Consequently the efficacy of the HD (Kt/V) is reduced. However, only very limited knowledge on the effect of reducing EBFR on BP exists and data are conflicting. The aim of this study was to evaluate the effect and the potential mechanism(s) involved by investigating the impact of changes in EBFR on BP, pulse rate (PR) and cardiac output (CO) in HD patients with arteriovenous-fistulas (AV-fistulas).

Methods. We performed a randomized, crossover trial in 22 haemodynamically stable HD patients with AV-fistula. After a conventional HD session each patient was examined during EBFR of 200, 300 and 400 mL/min in random order. After 15 min when steady state was achieved CO, BP and PR were measured at each EBFR, respectively.

Results. Mean (SD) age was 71 (11) years. Systolic BP was significantly higher at an EBFR of 200 mL/min as compared with 300 mL/min [133 (23) versus 128 (24) mmHg; P < 0.05], but not as compared with 400 mL/min [133 (23) versus 130 (19) mmHg; P = 0.20]. At EBFR of 200, 300 and 400 mL/min diastolic BP, mean arterial pressure, PR and CO remained unchanged.
Conclusion. Our study does not show any consistent trend in BP changes by a reduction in EBFR. Reduction in EBFR if BP falls during IDH is thus not supported. However, none of the patients experienced IDH. Further studies are required to evaluate the impact of changes in EBFR on BP during IDH.

Keywords: blood flow rate, cardiac output, extracorporeal circulation, intradialytic hypotension, renal dialysis

INTRODUCTION

Symptomatic hypotension during haemodialysis (HD) [intradialytic hypotension (IDH)] occurs in 15–30% of HD sessions [1, 2] and is an independent predictor of cardiovascular morbidity [3] and mortality [2].

The underlying pathophysiology of IDH seems to be multifactorial. Factors such as inadequate plasma volume during fluid removal [1, 4], rapid reduction in plasma osmolality [5], autonomic dysfunction [6], heart disease [7–9], impaired baroreflexes [10], release of endotoxins [11], adenosine [12] and increased synthesis of endogenous vasodilators have been suggested [13].

IDH is usually treated by discontinuation of fluid removal and volume replacement [2, 14, 15]. Reduction in extracorporeal blood flow rate (EBFR) during HD has been suggested as a supplementary treatment modality [16]. However, data on the impact of changes in EBFR on blood pressure (BP) during HD are conflicting and very limited [17–19]. Interestingly, data from Trivedi et al. [17] demonstrated an increase in systolic (SBP) and diastolic (DBP) blood pressure with increasing EBFR. The underlying mechanism was not investigated.

The aim of the present study was to investigate the impact of changes in EBFR on blood pressure (BP), pulse rate (PR) and cardiac output (CO) in haemodynamically stable patients on chronic HD.

MATERIALS AND METHODS

The study was a prospective, randomized, crossover trial. The local ethics committee approved the study and all patients gave written informed consent.

Patients and randomization

Twenty-two consecutive patients on chronic HD who fulfilled the following inclusion criteria were enrolled in this study: an arteriovenous-fistula (AV-fistula) as vascular access and an age of 18 years or above. Before study examination, the selected patients were not susceptible to symptomatic blood pressure decline during HD. Exclusion criteria were (i) pregnancy, (ii) dementia and (iii) a symptomatic decline in systolic blood pressure below 100 mmHg or a symptomatic decline in systolic blood pressure equal to or above 30 mmHg during study examination.

Each patient was allocated to a combination of the sequence of EBFRs. The combinations were divided into balanced blocks using the generator provided at www.randomization.com. Balanced block means permutations in a block are selected at random without replacement until the set of all permutations is exhausted before advancing to the next block. At www.randomization.com we chose the setting of 48 subjects divided into 8 blocks (and using seed 11224), which meant that a given combination within a block occurred randomly once whereby they became balanced. The sequence of EBFRs was blinded to the patient.

One patient was omitted from all calculations, and another two patients from calculations regarding changes in EBFR, due to missing data (technical failures with the haemodialysis monitor’s ability to estimate CO).

Intervention

Patients were investigated prior to and after one conventional HD session.

Prior to the HD session, an echocardiograph was performed to evaluate left ventricular ejection fraction (LVEF) and establish the degree of potential heart failure. Furthermore, AV-fistula recirculation, a confounder of the measurement of EBFR, was excluded at an EBFR of 400 mL/min (Figure 1). After the HD session with regular ultrafiltration (UF) of a maximum of 1 L/h for the patients to obtain dry weight, UF was stopped, while dialysis continued, to avoid any influence of fluid removal during the investigation. The patient was examined at EBFR of 200, 300 and 400 mL/min in random order. Each EBFR was maintained for 15 min to gain steady state before measurements of BP, PR and CO. BP and PR

![Figure 1: Measurements performed during a single HD session for each patient. Arrows show points of measurements (pulse rate, blood pressure, cardiac output). EBFR, extracorporeal blood flow rate. *Recirculation excluded.](https://academic.oup.com/ndt/article-abstract/30/12/2075/2460052/figure1)
were measured thrice and a mean was calculated while CO was measured twice and a mean was calculated. If there was a difference of >15% a third CO was measured and the mean of the two nearest results was used for calculation. Apart from the assessment of body weight (BW) all measurements were carried out with the patients in the supine position.

**Cardiac output, stroke volume and total peripheral resistance**

CO was estimated with the Transonic’s HD03-CO Flow-QC® Hemodialysis Monitor using the ultrasonic dilution method [20].

The method is validated against thermo dilution in intensive care patients \((R = 0.97) [21]\) and against aortic flow probe and against cardiac bypass pump in pigs \((R = 0.95 \text{ and } 0.97, \text{ respectively}) [22]\). Reproducibility of CO, expressed as absolute percentage deviation from the average of duplicates, is \(4.3 \pm 3.8\% [23]\).

Total peripheral resistance was calculated as mean arterial blood pressure (MAP) divided with CO and stroke volume as CO divided with PR.

**Dialysis, blood pressure and pulse rate**

We used Gambro AK 200 Ultra S. All HD sessions were according to the dialysis units standard with a temperature \(37\degree\text{C}\) and dialysate ion-concentrations consisting of \(\text{Na}^+ \ 140 \text{ mmol/L}, \ \text{HCO}_3^- \ 38 \text{ mmol/L}, \ \text{K}^+ \ 2.0 \text{ mmol/L}, \ \text{Ca}^{2+} \ 1.25 \text{ mmol/L}\). Filters used were PF 170 or PF 210 from Gambro.

BP and PR were measured using the dialysis machine. Accuracy was \(\pm 3 \text{ mmHg}\) for BP measurements and \(\pm 3 \text{ BPM}\) for PR measurements.

No haemodiafiltration was performed.

**Echocardiography**

Two-dimensional (2D) echocardiograph was performed on a General Electric Vivid 9, BT12 ultrasound system. All measurements including the degree of diastolic function (graded 1–3) were assessed according to the European Association of Echocardiography (EAE) and the American Society of Echocardiography (ASE) recommendations [24]. All echocardiographs were performed by one experienced operator who was blinded to any clinical data. Two operators separately evaluated all echocardiographs.

**Statistics**

Based on data from Krivitski and Depner [23] and using a minimal clinically important difference in CO of \(1.7 \text{ L/min}\) and a standard deviation (SD) of \(1.4 \text{ L/min}\) along with a power of \(0.90\) and a risk of type I error of \(0.05\) we calculated a necessary sample size of 17 patients. The sample size was estimated using a sample size tool for crossover studies derived from [http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html](http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html).

Except for stroke volume, time on dialysis and diuresis, none of the variables departed from the assumption of normal distribution when estimated with Shapiro–Wilk tests and QQ-plots. Normally distributed data are presented as mean (SD), while non-normally distributed data are presented as geometric mean; IQ range (stroke volume) or median; IQ range (time on dialysis/diuresis).

Sample means were compared using paired Student’s \(t\)-tests. Simple linear regression was used to test for linear associations between the absolute and relative change in EBFR and MAP and between UF and MAP and CO. For these calculations we used JMP, Statistical Discovery from SAS, version 11, 2013.

Carry-over effects were ruled out using the recommendations in [25] and the author’s S-PLUS code adapted for the statistical software ‘R’ [26].

**RESULTS**

**Patients**

Baseline characteristics are presented in Table 1. Renal failure was due to diabetes \((n = 7)\), hypertension \((n = 3)\), adult polycystic kidney disease \((n = 2)\), myelomatosis \((n = 2)\), bilateral nephrectomy \((n = 2)\), acute kidney injury \((n = 1)\) and of unknown origin \((n = 3)\). Known risk factors for cardiovascular disease were common in investigated patients such as diabetes \((n = 9)\), hypertension \((n = 11)\) and signs of arteriosclerosis: ischaemic heart disease \((n = 8)\), stroke \((n = 2)\) and limb ischaemia \((n = 1)\).

Patients were treated with loop diuretic \((n = 10)\), renin angiotensin system blockers \((n = 7)\), calcium antagonists \((n = 7)\) and beta-blockers \((n = 8)\).

All except one patient had some degree of diastolic dysfunction (grade 1–3).

None of the patients suffered from IDH during measurements.

**Measurements**

**Results of changes in EBFR.** No trend between EBFR and SBP/DBP was found \((R_2 = 0; \text{ not significant})\). However, SBP was significantly higher at an EBFR of 200 mL/min, as compared with 300 mL/min [133 (23) versus 128 (24) mmHg; \(P < 0.05; \text{ mean (SD)}\)], but not as compared with 400 mL/min [133 (23) versus 130 (19) mmHg; \(P = 0.20\)] (Table 2). At EBFR of 200, 300 and 400 mL/min, respectively, DBP, MAP, PR and CO remained unchanged. No carry-over effects were detected for any of the outcomes.

**Table 1. Baseline characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (SD) or median (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N) (female/male)</td>
<td>21 (10/11)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 (11)</td>
</tr>
<tr>
<td>Time on dialysis (months)*</td>
<td>46 (27–60)</td>
</tr>
<tr>
<td>Ultrafiltration (L/dialysis)</td>
<td>1.5 (1.0)</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>139/71 (17/10)</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.3 (1.4)</td>
</tr>
<tr>
<td>LVEF (\geq 40%) (N)</td>
<td>16</td>
</tr>
<tr>
<td>RVEF normal (TAPSE (&gt;18) mm) (N)</td>
<td>16</td>
</tr>
<tr>
<td>Diastolic dysfunction, grade (\geq 2) (N)</td>
<td>7</td>
</tr>
<tr>
<td>Diuresis (L/24 h)*</td>
<td>0.9 (0.0–0.9)*</td>
</tr>
<tr>
<td>Haemoglobin (mmol/L)</td>
<td>7.4 (0.7)</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>39 (4.7)</td>
</tr>
</tbody>
</table>

*TAPSE, tricuspid annular plane systolic excursion. Mean (SD) or *median (interquartile range).
Table 2. Changes in blood pressure, pulse rate, cardiac output, stroke volume, total peripheral resistance (TPR) and body weight during an HD session.

<table>
<thead>
<tr>
<th>At EBFR 400 mL/min</th>
<th>Start HD</th>
<th>End HD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>139 (17)</td>
<td>132 (19)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Diastolic</td>
<td>71 (10)</td>
<td>66 (9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean</td>
<td>94 (10)</td>
<td>88 (11)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>72 (12)</td>
<td>75 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>5.3 (1.4)</td>
<td>5.0 (1.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Stroke volume (mL/min)</td>
<td>71.9 (61.0–86.7)</td>
<td>64.3 (50.7–76.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TPR (mmHg x min/L)</td>
<td>18.8 (5.6)</td>
<td>18.7 (4.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>74.8 (14)</td>
<td>73.7 (14)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean (SD), *Comparing EBFR 200 and 300 mL/min, N = 19. NS, not significant.

Changes in haemodynamic during the HD session. During the HD session we demonstrated a significant decline in SBP, DBP, MAP, BW and stroke volume (SV) while PR, CO and TPR remained unchanged (Table 3). We demonstrated a significant correlation between absolute and relative changes in CO and MAP during HD ($R^2 = 0.45, P < 0.002$); $R^2 = 0.38, P < 0.005$). No significant correlations were found between total ultrafiltration and absolute changes in MAP ($R^2 = 0.13; P = 0.11$) or CO ($R^2 = 0.02; P = 0.49$).

DISCUSSION

The main finding from our prospective, randomized, crossover trial was that changes in EBFR did not show any consistent trend in the changes of systemic BP, PR or CO in normotensive, non-IDH prone HD patients.

Previous data on the present issue are sparse and contradictory. We could not reproduce previous findings by Trivedi et al. [17] who demonstrated an increase in SBP (4.1 mmHg) and DBP (3.0 mmHg) during an increase in EBFR from 200 to 400 mL/min. Similar to our study, the study by Trivedi et al. had a crossover and randomized design, but was carried out on two separate days a week apart. Furthermore, we controlled for a carry-over effect and there was virtually no time delay (15 min) between the changes in EBFR, which excluded other errors of period by treatment interaction, e.g. influence of other potential factors such as fluid intake in the period between the measurements [25]. Finally, we excluded UF to avoid influence on BP from fluid removal.

A randomized study by Alfurayh et al. [18] examined the effect of randomly chosen EBFR of 250 mL/min, 350 mL/min and 450 mL/min in 10 young, stable chronic HD patients free of antihypertensive treatment during three HD sessions a week apart. They found no changes in LVEF or CO evaluated by 2D echocardiography, nor in PR or BP.

Observational studies on the association between EBFR and BP are conflicting. In a prospective, observational study of 218 prevalent HD patients Flythe et al. [19] did not find any association between changes in EBFR and SBP variability (EBFR <400 mL/min versus ≥400 mL/min). In contrast, data from the HEMO study [27] suggested a lower incidence of IDH with increasing EBFR. However, this observation, as stated by the authors, could be confounded by patients being less likely to have cardiovascular disease and diabetes and therefore able to tolerate higher EBFR.

Comparable to previous studies there are several limitations of the present study. None of the patients experienced any IDH during the investigation. Whether a reduction in EBFR during IDH will affect systemic BP is still not established.

All patients in the present study were examined at the end of a conventional dialysis. Previous data by Bergström et al. [5] have demonstrated that a rapid reduction in plasma osmolarity (removal of urea and other solutes) initiated at the onset of HD contributes to IDH, due to osmotic removal of fluid into the cells depleting the extracellular volume and interference with sympathetic responsiveness to volume depletion (UF). Correspondingly, recent data by Dinesh et al. [28] demonstrated a biphasic decline in systemic BP during HD, with an early faster decline in BP of 25.5 mmHg (independent of UF volume/rate) observed within the first 25% of the HD session, followed by a late subsequent decline in BP of 5.8 mmHg (dependent of UF volume/rate). The early faster decline in BP might reflect mechanisms comparable to those reported by Bergström et al.

We speculate that since the clearance of urea is largest early in the HD session and highly dependent on EBFR, a greater impact of changes in EBFR on BP will be present early during HD.

In our study, the majority of patients received antihypertensive medications. Several angiotensin–converting-enzyme inhibitors and beta-blockers are dialysable. Whether there is an
impact of antihypertensive treatment on the association between changes in EBFR and BP is unknown. However, Flythe et al. [19] found that antihypertensive medication had no influence on SBP variability regardless of number, class and dialysability.

During a HD session with UF we demonstrated a significant decline in BP, SV and BW, without significant changes in PR, CO and TPR. However, changes in CO and BP were highly significant associated. These data suggest that the reduction in BP appeared to be due to a fall in SV as found by others [29, 30]. The observed decrease in SV seems to be due to fluid removal during HD, resulting in haemodynamic changes consistent with a decrease in preload [31].

In conclusion, our study does not support of the use of a reduction in EBFR to increase systemic BP during HD. Further studies are required to evaluate the impact of changes in EBFR on BP during IDH.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part, except in abstract format. None of the investigators received any financial or material contribution in any form. There are no conflicts of interests.

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