Solute clearances during continuous venovenous haemofiltration at various ultrafiltration flow rates using Multiflow-100 and HF1000 filters

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Abstract

Background. In continuous venovenous haemofiltration (CVVH), high ultrafiltration rates provide survival benefits in acute renal failure. This study measured clearances obtained at ultrafiltration rates of up to 4.5 l/h.

Methods. Clearances of small solutes (urea, creatinine, phosphate and urate) and of β₂-microglobulin (β₂-M) were measured during CVVH. Five preset Multiflow-100 (M-100) and five HF1000 hollow-fibre filters were compared. For the M-100, clearances obtained by haemofiltration were compared with those obtained by haemodiafiltration at similar total effluent rates from a previous study.

Results. For small solutes, the effluent to plasma ratio (E/P) remained close to 1.0 at all ultrafiltration rates; filter clearances were thus equal to Quf for both filters. Increasing Quf from 1.0 to 4.5 l/h did not significantly modify E/P. Convective clearances of β₂-M were lower than those obtained for small solutes. For the M-100, average β₂-M E/P was 0.62 ± 0.10 and did not significantly change while increasing Quf. For the HF1000, average β₂-M E/P were significantly lower compared with the M-100 (0.42 ± 0.09 at 1.0 l/h) and decreased progressively to 0.26 ± 0.06 while increasing Quf to 4.5 l/h. With pre-dilution, progressive decreases in clearances delivered to patients were observed reaching 40% at a Quf rate of 4.5 l/h. There was no clinically significant adsorption of β₂-M. For the M-100, at similar total effluent flow rates, clearances delivered to patients using haemodiafiltration were significantly higher for small solutes but lower for β₂-M in comparison to haemofiltration only.

Conclusions. Filter clearance for small solutes equaled Quf at evaluated rates. At high ultrafiltration rates there was significant loss of clearances with pre-dilution. At similar total effluent rates with the use of pre-dilution, haemodiafiltration is superior to haemofiltration for small solute clearance but inferior for β₂-M.

Keywords: clearance; continuous renal replacement therapy; haemodiafiltration; haemofiltration; pre-dilution

Introduction

Continuous renal replacement therapy (CRRT) has been performed in intensive care units since the 1980s. Over that time, the technical development it has undergone has made it an accessible and safe procedure. Using new devices, high convective and diffusive solute clearances can be achieved by accurate control of ultrafiltration (Quf) and dialysate (Qd) flow rates.

Much attention has been given to the removal of mixed-molecular-weight solutes, such as pro-inflammatory mediators, β₂-microglobulin (β₂-M) and myoglobin [1–3]. New filter membranes with larger surfaces, higher convective permeability and adsorption capacity have been designed for their removal [4,5]. In contrast to diffusion, convection and membrane adsorption are the only efficient methods for removing mixed-molecular-weight solutes [1,2,6].

Recently, venovenous CRRT using the Prisma pre-dilution system (Gambro, St Leonard, Canada) was modified to allow Quf rates of 4.5 l/h in the haemofiltration mode only [continuous venovenous haemofiltration (CVVH)]. This coincided with data showing high ultrafiltration rates providing survival benefits in intensive care patients [7]. However, gain on small and mixed-molecular-weight solute clearance at these rates has not been measured.

The Prisma system uses a pre-dilution mode to possibly extend the filter’s lifetime. Pre-dilution becomes
theoretically mandatory when comparing blood (and plasma) flow rates to Quf rates of 4.5 l/h in order to prevent rising haematocrits (>60%) inside the hollow fibres of the filter. However, the impact of pre-dilution on solute clearances at Quf > 2 l/h has not been formally evaluated.

The objectives of this study were to measure clearances of small and larger solutes during convective CRRT at Quf rates as high as 4.5 l/h and to determine the impact of pre-dilution on solute clearances at such rates. We also estimated membrane adsorption of \( \beta_2 \)-M. Two hollow-fibre filters were evaluated, one made with AN69 membrane and the other with modified polysulphone. Finally, we compared clearances measured in the present study to those obtained in a similar study we conducted using haemodiafiltration (CVVHDF) [2].

Subjects and methods

Study design

We evaluated 10 filters on seven consecutive critically ill patients with acute renal failure. They were treated by venovenous CVVH using the Prisma pre-dilution system (Gambro, St Leonard, Canada; Figure 1). We compared five preset Multiflow-100 (M-100; 0.9 m\(^2\) AN69 membrane) with five HF1000 (1.1 m\(^2\) polyarylethersulphone membrane) hollow-fibre filters.

Each patient studied suffered from acute renal failure already treated by CRRT. Subjects at risk of bleeding and those with unstable haemodynamics were excluded. Those with marked jaundice were also excluded due to possible interference with laboratory measurements.

Each evaluation protocol was conducted no later than 10 h after filter installation to minimize clearance loss due to hollow fibre wasting. Blood flow rate (Qb) was kept at 150 ml/min. On four occasions (two protocols for each filter), blood flow rate was reduced to 125 ml/min because of catheter malfunction. No net ultrafiltration was applied during the protocol. Heparin was routinely used to maintain the whole blood partial thromboplastin time levels between 60 and 80 s. Reinjection solutions were either bicarbonate- or lactate-based (Hemosol B0 and Hemosol LG2, respectively; Gambro) with supplements of dextrose, potassium and phosphate added as needed.

Measurement of clearances

Filter convective clearance. We initially compared filter performances. Solute convective clearances were measured in CVVH at various Quf rates for urea, creatinine, phosphate, urate and \( \beta_2 \)-M. This was carried out by calculating clearances using blood sampled immediately before the filter (after the pre-dilution port), abstracting the impact of pre-dilution (Figure 1). Convective clearances of the filter itself (Kf) were calculated as follows:

\[
K_f = \frac{E}{P} \times \text{Quf}
\]

where E and P are the solute concentrations measured in the ultrafiltrate (or effluent) and the plasma at the arterial port after pre-dilution, respectively. The sieving coefficient for small solutes (urea, creatinine, phosphate and urate) is the effluent to plasma ratio (E/P).

These measurements were repeated while increasing Quf rates from 1 to 4.5 l/h (in increments of 0.5 l/h). A 15 min interval was allowed before each set of sampling to ensure adequate washout of the circuit’s filling volume.

Clearances delivered to the patient and impact of pre-dilution. Since the M-100 and HF1000 sets use pre-dilution, these clearances overestimate actual clearances delivered to patients in relation to the amount of ultrafiltration. To measure this impact, we obtained actual clearances delivered to patients using blood samples taken before the pre-dilution port of the filter. Clearances delivered to the patient (Kp) were calculated as follows:

\[
K_p = \frac{E}{A} \times \text{Quf}
\]

where A is the solute concentrations measured at the arterial port before pre-dilution.

The relative drop from Kf to Kp represents the pre-dilution impact on solute clearance. This impact can be predicted. It represents dilution of specific solutes (e.g. urea) by the replacement solution. Single pool kinetics assumes that solutes are contained in a single body compartment, the plasma. The predicted single-pool drop in solute clearance is calculated as follows:

\[
\text{Predicted decrease in clearances} = \frac{\text{Plasma flow} \times (1 - \text{Haematocrit}) \times \text{Qb}}{\text{Plasma flow} + \text{Quf}}
\]

where

\[
\text{Plasma flow} = (1 - \text{Haematocrit}) \times \text{Qb}
\]

Fig. 1. A scheme of the pre-dilution Prisma circuit.
This is an approximation since intracellular solutes tend to diffuse towards plasma after pre-dilution so that the observed loss is less than predicted. By comparing predicted and observed drops in clearances with pre-dilution, we can quantify this phenomenon.

Phosphate clearances delivered to the patient were not estimated in every case since phosphate supplement was occasionally added to the reinjection solution.

**Adsorptive clearance of β2-microglobulin.** β2-M adsorption onto filter membranes has been reported to contribute significantly to its clearance [8]. To assess this, total (convective and adsorptive) clearance was estimated using the arteriovenous difference in plasma levels of β2-M. We then subtracted from this the convective clearance (E/A×Quf) to determine if any adsorption had taken place. For each filter, the overall adsorptive clearance was calculated by averaging estimates obtained at every Quf rate.

Total (convective and adsorptive) β2-M clearance was calculated as follows:

\[
\text{β2-M clearance} = \frac{(A - V)}{A} \times \text{Plasma flow}
\]

where V is the β2-M concentration at the venous port.

**Solute clearances comparing CVVH with CVVHDF.** Finally, for the M-100 only, we compared clearances using CVVH to a previous study we reported in 1999 evaluating CVVHDF in pre-dilution mode [2]. Clearances were then measured in haemodiafiltration with the M-100 using a similar methodology. Five protocols were studied at a fixed haemofiltration rate of 2.0 l/h with a varying dialysate rate ranging from 0 to 2.5 l/h. The exclusion criteria, use of heparin, solutions and calculations were the same. The blood flow was kept at 150 ml/min. The M-100 was slightly different in shape from the one used in this study, but with the identical membrane, surface area and priming volume. We compared clearances using CVVH of 2–4.5 l/h to those obtained using CVVHDF with a total effluent flow rate varying from 2.0 to 4.5 l/h.

**Laboratory measurements**

Blood and effluent samples (2.5 ml) were simultaneously drawn in heparin tubes as shown in Figure 1. They were kept on ice, centrifuged at the end of each protocol and then stored at −20°C until time of analysis. Urea, creatinine, phosphate and urate were measured using the ADVIA 1650 system (Bayer Diagnostics, Toronto, Canada). β2-M was determined by nephelometry using the Immage immunochemistry system (Beckman Coulter Canada Inc., Mississauga, Canada) at a 1:6 sample dilution mode to improve the method linearity and analytical sensitivity.

**Statistical analysis**

Variables are presented as means ± SD. Differences in means were tested using Student’s t-tests (paired t-tests when comparing predicted and observed loss of clearance). Confidence intervals were calculated for estimates of clearance by membrane adsorption. All P-values were two-tailed and values of <0.05 were considered statistically significant. Analyses were performed using Statistica (StatSoft, Tulsa, OK).

**Results**

**Filter convective clearances**

For small solutes, the sieving coefficient remained near 1.0 at all ultrafiltration rates for both filters; at a Quf rate of 4.5 l/h, the sieving coefficients for urea, creatinine, urate and phosphate were 0.96 ± 0.05, 1.00 ± 0.06, 1.02 ± 0.09 and 0.98 ± 0.03, respectively. Clearances for small molecules were thus equal to Quf (Figure 2). Small solute clearances were similar for the M-100 and HF1000 and differences between filters were ≤3%. Increasing Quf from 1.0 to 4.5 l/h did not significantly modify the sieving coefficient for small solutes (P > 0.05 for every comparison).

As shown in Figure 2, convective clearances were lower for β2-M compared with small solutes. With the M-100, average E/P for β2-M was 0.62 ± 0.10 and did not significantly change from Quf 1.0 to 4.5 l/h. Hence, M-100 convective clearance of β2-M increased linearly at ~60% of the small solutes clearance rate. For the HF1000, the average E/P was lower compared with the M-100 and decreased significantly from 0.42 ± 0.09 to
Table 1. Predicted and observed decreases in clearances delivered to the patients with pre-dilution at 4.5 l/h of haemofiltration (CVVH)

<table>
<thead>
<tr>
<th>Protocol number</th>
<th>Qb</th>
<th>Ht</th>
<th>Predicted decrease in clearances at 4.5 l/h in pre-dilution</th>
<th>Observed decrease in clearances</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Urea</td>
<td>Creatinine</td>
</tr>
<tr>
<td>M-100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>0.23</td>
<td>39%</td>
<td>31%</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>0.22</td>
<td>39%</td>
<td>33%</td>
</tr>
<tr>
<td>3</td>
<td>125</td>
<td>0.31</td>
<td>46%</td>
<td>38%</td>
</tr>
<tr>
<td>4</td>
<td>125</td>
<td>0.25</td>
<td>44%</td>
<td>33%</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>0.27</td>
<td>41%</td>
<td>34%</td>
</tr>
<tr>
<td>HF1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>0.29</td>
<td>41%</td>
<td>33%</td>
</tr>
<tr>
<td>2</td>
<td>125</td>
<td>0.24</td>
<td>44%</td>
<td>36%</td>
</tr>
<tr>
<td>3</td>
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<td>0.37</td>
<td>49%</td>
<td>36%</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
<td>0.27</td>
<td>41%</td>
<td>36%</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>0.31</td>
<td>42%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Ht, haematocrit.

Table 2. Mean clearances (ml/min) delivered to patients for various solutes with M-100 and HF1000 at different ultrafiltration rates

<table>
<thead>
<tr>
<th>Quf (l/h)</th>
<th>Urea</th>
<th>Creatinine</th>
<th>Urate</th>
<th>Phosphate</th>
<th>β2-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>150</td>
<td>13.5±1.1</td>
<td>14.3±1.8</td>
<td>15.1±0.9</td>
<td>14.0±1.6</td>
</tr>
<tr>
<td>1</td>
<td>125</td>
<td>20.4±0.7</td>
<td>21.1±1.8</td>
<td>21.6±1.9</td>
<td>20.0±1.4</td>
</tr>
<tr>
<td>2</td>
<td>125</td>
<td>25.6±2.1</td>
<td>26.8±2.2</td>
<td>27.1±2.0</td>
<td>25.8±0.9</td>
</tr>
<tr>
<td>3</td>
<td>125</td>
<td>30.7±2.4</td>
<td>31.4±2.4</td>
<td>31.4±2.7</td>
<td>29.5±2.3</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
<td>34.8±2.2</td>
<td>35.1±2.8</td>
<td>36.0±2.8</td>
<td>34.3±1.1</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>39.2±2.2</td>
<td>40.1±3.7</td>
<td>42.6±2.8</td>
<td>39.2±0.9</td>
</tr>
<tr>
<td>4.5</td>
<td>42.9±2.8</td>
<td>43.3±3.6</td>
<td>44.1±3.6</td>
<td>43.1±3.7</td>
<td>24.1±2.8</td>
</tr>
<tr>
<td>4.1</td>
<td>47.5±2.8</td>
<td>47.2±3.1</td>
<td>46.0±4.1</td>
<td>44.7±4.0</td>
<td>28.6±2.3</td>
</tr>
<tr>
<td>HF1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>150</td>
<td>14.5±0.4</td>
<td>15.0±0.7</td>
<td>15.4±1.1</td>
<td>15.9</td>
</tr>
<tr>
<td>1</td>
<td>125</td>
<td>21.2±1.2</td>
<td>21.6±0.4</td>
<td>22.4±1.7</td>
<td>21.0</td>
</tr>
<tr>
<td>2</td>
<td>125</td>
<td>26.0±1.2</td>
<td>26.3±0.9</td>
<td>27.3±2.1</td>
<td>25.7</td>
</tr>
<tr>
<td>3</td>
<td>125</td>
<td>30.3±1.3</td>
<td>30.2±2.3</td>
<td>31.7±2.6</td>
<td>30.4</td>
</tr>
<tr>
<td>4</td>
<td>150</td>
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<td>35.2±1.7</td>
<td>36.8±3.5</td>
<td>34.5</td>
</tr>
<tr>
<td>5</td>
<td>150</td>
<td>40.0±2.9</td>
<td>38.8±2.0</td>
<td>40.5±4.2</td>
<td>37.1</td>
</tr>
<tr>
<td>4.5</td>
<td>44.2±2.8</td>
<td>42.0±2.1</td>
<td>43.6±5.0</td>
<td>40.2</td>
<td>10.3±3.1</td>
</tr>
<tr>
<td>4.1</td>
<td>47.4±2.5</td>
<td>44.9±1.9</td>
<td>45.7±5.1</td>
<td>42.3</td>
<td>10.9±2.3</td>
</tr>
</tbody>
</table>

*Phosphate clearances delivered to patients were not measured when phosphate supplement had to be added to the reinjection solution.

0.26±0.06 while increasing Quf from 1 to 4.5 l/h (P < 0.01).

Convective clearances delivered to the patients and impact of pre-dilution

With pre-dilution, progressive decreases in clearances delivered to the patient were observed, reaching maximum values of 34, 39, 40, 39 and 42% for urea, creatinine, urate, phosphate and β2-M, respectively, on average for both filters and at a Quf rate of 4.5 l/h in pre-dilution. Since blood flow rate and haematocrit influenced these results, we report observed drops in clearance for every solute in each protocol (Table 1). The impact of pre-dilution on urea and creatinine was significantly less than predicted (P < 0.01 by paired t-test for both solutes compared with predicted loss), probably accounting for passive diffusion of smaller solutes within red blood cells towards plasma. Furthermore, the impact of pre-dilution on urea (60 Da) was smaller than for creatinine (113 Da) (P < 0.01). Differences between observed and predicted loss of clearances were similar for both filters (P < 0.1 between filters for each solute). By comparison, at a more usual ultrafiltration rate of 2.0 l/h, we found an average 22% loss of clearance with pre-dilution for both filters. Final clearances delivered to the patient are shown in Table 2.

Adsortive β2-M clearance

For each studied filter, we estimated the adsorptive clearance of β2-M at every ultrafiltration rate by subtracting convective clearance from total clearance obtained by arteriovenous difference of plasma levels of β2-M. These estimates did not correlate with ultrafiltration rate (P > 0.05 for each filter, data not shown). Hence, adsorption seemed independent of ultrafiltration rate. We then calculated for each filter the average adsorptive clearance from all ultrafiltration flow rates and corresponding confidence intervals. Two M-100 and two HF1000 filters had average adsorption significantly different from 0. We plotted the average filter adsorption against the corresponding time elapsed since its installation. It is evident from Figure 3 that no clinically significant adsorption occurred in this study.

Solute clearances comparing CVVH with CVVHDF

We compared our results with those of a similar study we performed recently using a combination of diffusion and convection in pre-dilution mode with M-100 filters [2]. Clearances in CVVHDF mode were evaluated at a fixed Quf rate (2.0 l/h) and a Qd rate increasing from 0 to 2.5 l/h (in increments of 0.5 l/h of Qd), hence with a total effluent rate varying from 2.0 to...
4.5 l/h. Solute clearances delivered to patients comparing CVVH with CVVHDF are shown in Figure 4. Since there was less pre-dilution with the use of CVVHDF, small solute clearances delivered to the patient were significantly higher with that modality. However, since diffusion (or dialysis) is an inefficient method for removing larger solute, CVVH was superior to CVVHDF for β2-M clearance at an effluent flow rate of 4.5 l/h.

Discussion

The present study on solute clearances during CVVH at ultrafiltration rates up to 4.5 l/h showed that: (i) filter clearances equalled Quf rates for small solutes for M-100 and HF1000 filters; (ii) β2-M clearances were significantly better using M-100 compared with HF1000; (iii) on average, the use of pre-dilution resulted for both filters in a 40% drop in clearances at a Quf rate of 4.5 l/h; (iv) for urea and creatinine, observed losses of clearances with pre-dilution were less than those predicted using single pool kinetics; (v) membrane adsorption was not clinically significant; and (vi) for the M-100, at similar total effluent flow rates with the use of pre-dilation, clearances delivered to patients using CVVHDF were significantly higher for small solutes but lower for β2-M when compared with CVVH.

Filter clearances of small solutes remained equal to reinjection flow rates for both filters. As shown in our previous study [2], effluent flow rate is the most important determinant of clearance in CRRT contrary to standard haemodialysis. β2-M clearances were significantly better with the M-100 (AN69) compared with the HF1000 (polyarylethersulphone). Other studies have found significant gain of β2-M clearances with polyarylethersulphone membranes, but these were measured in intermittent haemodialysis [4]. These findings could be consequent to greater adsorption of β2-M with larger surfaces. Finally, these results may not represent clearances of other mixed-molecular-weight solutes, such as cytokines and myoglobin.

With high rate haemofiltration, pre-dilution becomes theoretically mandatory when comparing blood (and plasma) flow rates to Quf rates of 4.5 l/h in order to prevent rising haematocrits (>60%) inside the hollow fibres of the filter. Clearances delivered to the patient were necessarily reduced compared with filter clearances. We were able to predict this by calculating the percentage drop in specific plasma solute concentration with the addition of the replacement solution. Observed drops in clearances were less than predicted for lower molecular weight solutes (urea and creatinine). Also there was a lower loss of clearance for
urea compared with creatinine. These observations illustrate the diffusive behaviour of intracellular solutes towards plasma, one that is mainly influenced by the molecular size. A recent study has looked at the impact of pre-dilution (compared with post-dilution) on solute clearances in CVVH for various solutes, including inulin, vancomycin and myoglobin [9]. These authors found a similar impact on clearances of small solutes using pre-dilution.

Surprisingly, we did not find a clinically significant adsorption of $\beta_2$-M, even for the six filters studied within the first hour after their installation (Figure 4). This observation is possibly consequent to complete saturation of the adsorption capacity of both filters in the first few minutes following CRRT initiation.

We finally compared results from our study with a study we conducted previously using the same protocol [2]. As predicted, the use of diffusion allows greater clearances of small solutes by avoiding pre-dilution with convection. Hence, at the same total effluent rate with the use of pre-dilution, CVVHDF is superior to CVVH for elimination of small molecules. However, since diffusion is an inefficient way of clearing mixed-molecular-weight solutes, CVVH is superior to CVVHDF for $\beta_2$-M removal. Nevertheless, unless future studies are able to identify or confirm clinical gains in removing mixed-molecular-weight solutes such as cytokines in critical illness [1], CVVHDF could be a more efficient epuration method in the intensive care unit than pre-dilution CVVH at equal total effluent rates. However, in situations such as rhabdomyolysis, CVVH would definitely be preferable to CVVHDF because of the greater clearance of myoglobin, which is a rather large solute of 17 kDa [3].

We hope that our results will be useful to optimize solute clearances achieved by CRRT in the critically ill patient and that data measured will provide a more rational approach for treatment prescription.

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Conflict of interest statement. None declared.

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