Cerebral blood flow decreases during intermittent hemodialysis in patients with acute kidney injury, but not in patients with end-stage renal disease

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Abstract

Background. Cerebral blood flow (CBF) may decrease during intermittent hemodialysis (IHD). Patients with acute kidney injury (AKI) may be more vulnerable to cerebral hypoperfusion than patients with end-stage renal disease (ESRD), due to concomitant critical illness and hemodynamic instability.

Methods. In this observational, prospective study, we measured mean flow velocity at the level of the middle cerebral artery by transcranial Doppler at the start, after 2 h and at the end of a hemodialysis session in 15 consecutive patients with AKI and critical illness referred to the nephrological intensive care unit of a university hospital and in 12 patients with ESRD on regular treatment thrice weekly, who served as controls. We compared end-dialysis changes from baseline in mean flow velocity between the study groups and examined the correlation between this change and that of other relevant clinical parameters.

Results. Mean flow velocity decreased significantly at end-dialysis in the patients with AKI, but not in those with ESRD (P = 0.02). This difference persisted after adjusting for baseline mean flow velocity and net ultrafiltration volume. No significant correlations were found in either group between changes in mean flow velocity and changes in mean blood pressure (AKI: \( r = -0.27, P = 0.34 \); ESRD: \( r = 0.15, P = 0.68 \)), SUN (AKI: \( r = -0.33, P = 0.25 \); ESRD: \( r = 0.06, P = 0.85 \)), plasma HCO3\textsuperscript{-} (AKI: \( r = -0.52, P = 0.24 \); ESRD: \( r = -0.18, P = 0.59 \)), hematocrit (AKI: \( r = 0.08, P = 0.71 \); ESRD: \( r = -0.19, P = 0.65 \)) or arterial oxygen content (AKI: \( r = -0.17, P = 0.36 \); ESRD: \( r = -0.33, P = 0.43 \)).

Conclusions. Our data suggest that AKI patients may be more vulnerable than ESRD patients to cerebral hypoperfusion during IHD. Our findings do not support a clear-cut role of rapid changes in blood osmolarity, rheological properties or vasoreactivity of the cerebral circulation to \( O_2 \) supply in modulating CBF during hemodialysis.

Keywords: acute kidney injury; cerebral blood flow; hemodialysis; transcranial Doppler

Introduction

IHD may impair cerebral blood flow (CBF) in patients with ESRD, as shown by early studies based on \(^{133}\)Xe injection or inhalation techniques \([1, 2]\). Moreover, recent investigations based on transcranial Doppler (TCD) have reported a decrease in the mean flow velocity (mfv) at the level of the middle cerebral artery (MCA) during the procedure \([3–7]\). MCAmfv has been proposed as a reliable proxy for CBF; indeed, comparisons of recordings of blood flow velocities obtained with electromagnetic flowmetry in the MCA have shown reasonable agreement between velocity estimates and volume flow \([8, 9]\). Since intradialytic hypotension may complicate up to 20% of IHD sessions due to ultrafiltration exceeding the refilling rate \([10]\), hence potentially jeopardizing blood flow in vital organs, the availability of a non-invasive tool to monitor cerebral perfusion during dialytic sessions is of utmost importance. Actually, changes in hemodynamic \([5, 11]\), rheologic \([3, 4, 6]\) and metabolic \([3, 6]\) factors have been related to MCAmfv variations following single IHD sessions. Intradialytic hypotension \([12]\), or the disequilibrium syndrome caused by acute changes in urea and/or bicarbonate plasma concentration \([13]\), may contribute to impairment of cerebral perfusion pressure (CPP) leading to a decrease in CBF.
Compared with ESRD patients on a regular weekly HD schedule, patients with AKI may be more vulnerable to the risk of cerebral hypoperfusion during IHD, due to their having more critical clinical conditions often associated with hemodynamic instability [14].

In this study, we evaluated non-invasively the CBF in patients with oliguric AKI during a single 4-h hemodialysis session having as controls patients with ESRD on a regular IHD schedule.

Methods

Patients

Fifteen consecutive patients (mean age 79 years, range 69–92) admitted for oliguric (<0.5 mL/kg/h for ≥12 h) AKI requiring urgent hemodialysis for uremia, hyperkalemia, metabolic acidosis and/or fluid overload were enrolled. AKI was accounted for by hemodynamic causes (low effective arterial blood volume and venous congestion due to congestive heart failure) in six patients, sepsis in six patients (three with bacterial pneumonia, two with urinary tract infection, one with Clostridium difficile colitis), and colonic ischemia in three patients. None of the patients was mechanically ventilated.

Twelve patients with ESRD (mean age 72 years, range 36–89; five with chronic glomerulonephritis, four with diabetic nephropathy, three with nephroangioleiomyosclerosis/iscemic nephropathy) on regular (2–5 years) thrice weekly hemodialysis served as controls. None of the patients was treated with antihypertensive or diuretic drugs; all of the patients were treated with erythropoiesis-stimulating agents (10 received recombinant human beta-erythropoietin and two received darbepoetin).

Protocol

In AKI patients, the study was performed during the very first hemodialysis session (4 h); Qb was set at 200 mL/min and Qd at 300 mL/min, with parallel flows. Low blood and dialysate flows were chosen to minimize dialytic efficiency, since in order to reduce the risk of dialysis disequilibrium syndrome, High-flux heparin-coated AN69 ST dialyzers (EVODIAL 1.6 m², Gambro-Hospital, Meyzieux, France) and AK200 ultra dialysis monitors (Gambro Hospital, Bologna, Italy) were used. Dialysis fluid composition was as follows: Na 140 mmol/L, K 3 or 4 mmol/L, HCO₃⁻ 34 mmol/L, Cl⁻ 110 mmol/L, Ca²⁺ 1.25 mmol/L, Mg²⁺ 0.5 mmol/L, glucose 5.55 mmol/L, acetate 3.0 mmol/L; no heparin was used. Dialysis fluid temperature was set at 35°C. The attending physician autonomously prescribed the ultrafiltration rate based on the clinical evaluation of fluid balance and hemodynamic status.

In ESRD patients, the study was conducted during the first hemodialysis session of the week (4 h); Qb was set at 300 mL/min, Qd at 300 mL/min, counter-current flow, with the same filters, dialysis machines and dialysis fluid composition as detailed above for the AKI patients. Dalteparin 2500 UI was administered at the start of hemodialysis in the arterial line of the circuit. Dialysis fluid temperature was set at 36°C. The ultrafiltration rate was chosen by the attending physician to attain the usual ‘dry weight’ for each patient. Antihypertensive treatment, if any, was not administered on the study day.

At the start, at midtime and at the end of each hemodialysis session, transcranial Doppler measurements of MCAmvf were performed by the same experienced operator through the anterior temporal window, with exclusion of hemodynamically relevant stenoses.

Both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured non-invasively at 30-min intervals by an automatic oscillometric device; mean blood pressure (MBP) was calculated as DBP + (SBP − DBP)/3. The ECG trace was monitored throughout the procedure (IntelliVueMP70, Philips Healthcare, Andover, MA, USA). Blood was drawn from a peripheral vein at start and end HD for measurements of serum urea nitrogen (SUN) and complete blood count; arterial blood gas analysis was also performed at start and end of the dialysis session. Arterial oxygen content was calculated as the product of hemoglobin concentration and arterial oxygen saturation.

Informed consent was obtained from all patients or the closest available next-of-kin. The protocol was approved by the Ethical Committee of Parma University Medical School.

Statistics

We compared the two groups (AKI and ESRD) with respect to the absolute change from the baseline MCAmvf value at each time point (midtime and end of dialysis). These comparisons were carried out with the use of the Mann–Whitney test. Additionally, we compared the two groups with respect to the mean MCAmvf during dialysis after adjustment for net ultrafiltration volume. This analysis was performed using an analysis of covariance (ANCOVA) model with post-baseline MCAmvf values as the response and the baseline value as a covariate. The estimation method used was Restricted Maximum Likelihood (SPSS MIXED procedure). The model for analysis included fixed, categorical effects of group (AKI and ESRD) and of time of measurement (midtime and end-dialysis), as well as the continuous, fixed covariates of baseline MCAmvf value and net ultrafiltration volume. Patient identification number was included as a random factor. The analysis was repeated after exclusion of two patients (one in the AKI group and one in the ESRD group) with extreme MCAmvf changes at end-dialysis (‘outliers’), but the results were similar. Therefore, we report the results of the analyses on the full dataset. The results of the analyses on all other continuous variables were also similar after exclusion of the data from two potentially outlying subjects, unless otherwise reported. For other continuous variables, we used two-sample t-tests or Mann–Whitney test, as appropriate, to compare the differences between groups at baseline and the differences between groups in an absolute change from baseline at the end of dialysis. For baseline differences in categorical variables, we used Fisher’s exact test. Ordinary least squares regression was used to examine the linear relationship between changes in MCAmvf and changes in SBP, DBP, MBP, heart rate, SUN, hematocrit, arterial oxygen content or HCO₃⁻ concentration. A two-tailed P-value of <0.05 was regarded as statistically significant. SPSS (version 17.0, SPSS Inc, Chicago, IL, USA) was used to perform all of the analyses.

Results

Clinical and laboratory data of the two groups of patients are shown in Table 1. Diastolic blood pressure values were slightly lower in the AKI group; in ESRD patients, SUN values were lower and plasma HCO₃⁻ higher than in AKI patients. Female sex and diabetes were slightly but not significantly more prevalent in the former group.

Net ultrafiltration volume was greater in the patients with ESRD than in those with AKI (1900 ± 420 versus 920 ± 23 mL; P = 0.03). No symptomatic hypertensive episodes occurred in either group, although 3 out of 15 patients with AKI needed the start of noradrenaline infusion at some time during the hemodialysis session; the infusion rate was adjusted to maintain SBP >90 mmHg until the end of the dialytic session. As a result, the average change in MBP from start to end of the hemodialysis session did not differ significantly between ESRD and AKI patients (Table 2).

At end-dialysis, MCAmvf had decreased by −6.8 (SEM 1.2) cm/s in the AKI group and by −2.9 (SEM 2.6) cm/s in the ESRD group (P = 0.02). At end-dialysis, the difference between the mean of the two groups, adjusted for baseline MCAmvf and net ultrafiltration volume, was −5.7 (95% CI −10.6 to −0.7) cm/s.
Adjusted midtime and end-dialysis average MCAmfv was higher in the patients with ESRD than in those with AKI (P = 0.03). Furthermore, as reported in Figure 1, which shows the average as well as individual MCAmfv values for both groups, MCAmfv decreased during dialysis in most of the AKI patients unlike in ESRD patients. The average MBP values, as well as individual MBP trajectories at different time points in both groups of patients, are depicted in Figure 2; it can be seen that the average MBP values were stable and similar during dialysis in the patients with AKI and in those with ESRD, even though a greater variability in baseline values was evident in the former group.

Absolute changes in hemodynamic and biochemical data of interest are reported in Table 2.

No significant correlations were found in either group between absolute changes in MCAmfv and absolute changes in SBP (AKI: \( r = -0.28, P = 0.32 \); ESRD: \( r = 0.36, P = 0.30 \)), DBP (AKI: \( r = -0.18, P = 0.53 \); ESRD: \( r = -0.13, P = 0.73 \)), MBP (AKI: \( r = -0.27, P = 0.34 \); ESRD: \( r = 0.15, P = 0.68 \)), or heart rate (AKI: \( r = -0.36, P = 0.19 \); ESRD: \( r = 0.54, P = 0.07 \)).

The urea reduction ratio was higher in ESRD than that in AKI patients. However, no significant correlation was found in either group (AKI: \( r = -0.33, P = 0.25 \); ESRD: \( r = 0.06, P = 0.85 \)) between absolute changes in MCAmfv and absolute changes in SUN (AKI: \( -49.1 \pm 7.0 \) mg/dL; ESRD: \( -38.3 \pm 2.4 \) mg/dL) at the end of the hemodialysis session. Plasma HCO\(_3\) value increased more in the AKI than that in the ESRD group at the end of the hemodialysis session compared with baseline; conversely, the changes in hematocrit and arterial oxygen content were lower in the AKI than those in the ESRD group. No significant correlations were found in either group between changes in MCAmfv and changes in plasma HCO\(_3\) (AKI: \( r = -0.52, P = 0.24 \); ESRD: \( r = -0.18, P = 0.59 \)), hematocrit (AKI: \( r = 0.08, P = 0.71 \); ESRD: \( r = -0.19, P = 0.65 \)) or arterial oxygen content (AKI: \( r = -0.17, P = 0.36 \); ESRD: \( r = -0.33, P = 0.43 \)) when the full patient dataset was examined. However, after exclusion of data from the

### Table 1. Baseline characteristics of the enrolled patients

<table>
<thead>
<tr>
<th></th>
<th>AKI (N = 15)</th>
<th>Median (IQR)</th>
<th>ESRD (N = 12)</th>
<th>Median (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>78.9 ± 1.6</td>
<td>77.0 (75.0–82.0)</td>
<td>72.3 ± 4.7</td>
<td>74.5 (61.3–86.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Sex (% males)</td>
<td>53.3</td>
<td></td>
<td>33.3</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetics (%)</td>
<td>20.0</td>
<td></td>
<td>33.3</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>6.7</td>
<td></td>
<td>0</td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122.8 ± 6.8</td>
<td>120.0 (100.0–147.0)</td>
<td>129.6 ± 4.3</td>
<td>122.5 (120.0–140.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>62.5 ± 3.5</td>
<td>67.0 (50.0–73.0)</td>
<td>70.0 ± 2.1</td>
<td>70.0 (62.5–77.5)</td>
<td>0.08</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>87.8 ± 5.2</td>
<td>85.0 (73.0–97.0)</td>
<td>89.4 ± 2.0</td>
<td>88.0 (86.0–93.0)</td>
<td>0.78</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>77.5 ± 6.1</td>
<td>80.0 (59.0–88.8)</td>
<td>69.3 ± 1.1</td>
<td>70.0 (60.0–82.0)</td>
<td>0.26</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>19.3 ± 1.6</td>
<td>18.0 (15.0–27.0)</td>
<td>NA</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>White blood cells (×10(^3)/mL)</td>
<td>9.5 ± 1.2</td>
<td>7.3 (6.0–10.4)</td>
<td>6.2 ± 0.4</td>
<td>6.5 (3.7–7.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Platelets (×10(^9)/mL)</td>
<td>195.2 ± 20.7</td>
<td>189.0 (150.0–260.0)</td>
<td>233.3 ± 15.9</td>
<td>213.5 (189.0–276.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.8 ± 0.5</td>
<td>10.4 (9.1–12.7)</td>
<td>11.2 ± 0.3</td>
<td>11.3 (10.7–12.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>33.8 ± 1.6</td>
<td>33.9 (28.1–39.9)</td>
<td>35.9 ± 1.1</td>
<td>36.5 (34.3–38.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Serum urea nitrogen (mg/dL)</td>
<td>106.4 ± 10.7</td>
<td>98.6 (70.1–126.6)</td>
<td>53.1 ± 3.3</td>
<td>52.8 (42.5–64.1)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>6.4 ± 0.6</td>
<td>6.5 (5.2–7.4)</td>
<td>6.7 ± 0.6</td>
<td>6.2 (5.6–8.8)</td>
<td>0.73</td>
</tr>
<tr>
<td>Plasma HCO(_3) (mmol/L)</td>
<td>17.4 ± 3.4</td>
<td>16.7 (14.0–19.4)</td>
<td>24.9 ± 0.9</td>
<td>24.3 (22.7–26.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Arterial oxygen content (mL/100 mL)</td>
<td>14.3 ± 0.7</td>
<td>13.9 (12.3–17.3)</td>
<td>14.5 ± 0.6</td>
<td>14.3 (13.8–16.2)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

*APACHE, Acute Physiology and Chronic Health Evaluation.

### Table 2. Absolute change from baseline in hemodynamic and biochemical parameters at the end of the dialysis session

<table>
<thead>
<tr>
<th></th>
<th>AKI (N = 15)</th>
<th>Median (IQR)</th>
<th>ESRD (N = 12)</th>
<th>Median (IQR)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta ) Systolic blood pressure (mmHg)</td>
<td>–3.2 ± 6.0</td>
<td>2.0 (–18.0–13.0)</td>
<td>4.4 ± 6.0</td>
<td>0.0 (–7.5–14.0)</td>
<td>0.39</td>
</tr>
<tr>
<td>( \Delta ) Diastolic blood pressure (mmHg)</td>
<td>3.2 ± 3.6</td>
<td>7.0 (–5.0–12.0)</td>
<td>4.8 ± 2.5</td>
<td>0.0 (0.0–11.5)</td>
<td>0.73</td>
</tr>
<tr>
<td>( \Delta ) Mean blood pressure (mmHg)</td>
<td>–0.5 ± 4.3</td>
<td>0.0 (–11.0–13.0)</td>
<td>4.9 ± 3.0</td>
<td>0.0 (–3.0–12.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>( \Delta ) Heart rate (bpm)</td>
<td>13.8 ± 6.9</td>
<td>12.7 (–12.1–39.7)</td>
<td>–2.4 ± 1.1</td>
<td>–3.6 (–5.2–2.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Urea reduction ratio</td>
<td>0.45 ± 0.05</td>
<td>0.48 (0.38–0.52)</td>
<td>0.73 ± 0.03</td>
<td>0.76 (0.65–0.80)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>( \Delta ) plasma HCO(_3) (mmol/L)</td>
<td>8.5 ± 1.5</td>
<td>7.5 (4.8–10.4)</td>
<td>4.4 ± 0.6</td>
<td>4.4 (3.9–6.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>( \Delta ) Hematocrit (%)</td>
<td>0.3 ± 0.9</td>
<td>0.6 (0.0–1.6)</td>
<td>2.1 ± 0.6</td>
<td>1.8 (0.4–3.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>( \Delta ) Arterial oxygen content (mL/100 mL)</td>
<td>0.5 ± 0.4</td>
<td>0.7 (0.2–1.7)</td>
<td>2.0 ± 0.3</td>
<td>1.9 (1.3–2.7)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
two patients suspected to be ‘outliers’, a trend towards a negative correlation appeared between the decrease in MCAfvm and the increase in plasma $\text{HCO}_3^-$ (AKI: $r = -0.50$, $P = 0.07$; ESRD: $r = -0.63$, $P = 0.05$).

**Discussion**

The main finding of this study is that a single hemodialysis session induced a significant decrease of MCAfvm in patients admitted for oliguric AKI, but not in patients with ESRD on a regular IHD schedule.

Patients with AKI may be at increased risk of cerebral hypoperfusion during IHD, related to intradialytic hypotension and/or rapid changes in serum urea or blood/brain pH that may result in cerebral edema and hence alter CPP [12, 13, 15]. Indeed, decreased CPP and increased intracranial pressure due to worsening cerebral edema have been demonstrated during IHD in patients with AKI in the setting of traumatic brain injury [16]; this
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phenomenon was attenuated when continuous modalities of renal replacement therapy were used [12, 17].

In the present study no significant decrease in MBP was observed in either group at the end of the hemodialysis session compared with baseline; yet, three AKI patients needed vasoactive support during treatment despite significantly lower net ultrafiltration volume compared with ESRD patients. Several investigators failed to observe significant correlations between changes in Doppler-derived estimates of CBF and changes in MBP after a single hemodialysis session in patients with ESRD [3–6, 11]; this observation is consistent with the expected constancy of CBF over a wide range of MBP values due to the autoregulation phenomenon [18]. In the present study we also did not find a significant correlation between the change in MCAmfv and the changes in SBP, DBP, MBP or heart rate in either AKI or ESRD patients, suggesting that CBF autoregulation was substantially preserved before and after hemodialysis. Indeed, both dynamic pressure autoregulation and carbon dioxide reactivity were found to be intact in ESRD patients before and after a single hemodialysis session [7]. Conversely, studies on patients with AKI associated with traumatic brain injury [16] or severe/fulminant hepatic failure [19–21] indicated that cerebral autoregulation is impaired in these clinical conditions, as pointed out by the occurrence of cerebral hypoperfusion due to a fall in CPP secondary to decreased systemic blood pressure during IHD. Furthermore, impairment of both dynamic pressure autoregulation and carbon dioxide reactivity was formally demonstrated in patients with fulminant liver failure and hepatic encephalopathy [20, 22, 23]. None of the patients with AKI enrolled in the present study had traumatic brain injury or clinical or laboratory signs of advanced liver disease, but we did not formally test the efficiency of dynamic pressure autoregulation, nor CO2 reactivity; smoking status was also not recorded in our patients. In fact, in smokers, the regional CBF distribution following 5% CO2 breathing may vary after cigarette smoking following overnight tobacco abstinence [24, 25]. Therefore, we cannot rule out the possibility of subtle derangements in cerebral vasomotor adaptation to changes in systemic hemodynamics and/or changes in arterial CO2 during the hemodialysis session. Gabegdeku et al. [11] provided convincing evidence that ultrafiltration during hemodialysis is associated with decreases in stroke volume up to 30% even in the absence of significant changes in systemic blood pressure. Thus, if cerebral autoregulation fails to preserve constant CBF in response to a decrease in stroke volume and CPP during IHD in patients with AKI, MCAmfv—which has been proved to be a reasonable estimate of CBF [26]—is also expected to decrease. Defective CBF autoregulation was demonstrated by Pfister et al. [27] and by Taccone et al. [28] in severe sepsis, albeit others investigators [29] failed to confirm this finding. Moreover, evidence in humans exists that during sepsis CBF may decrease before a fall in MBP, due to an increase in cerebral vascular resistance [30, 31]. Six of the 15 patients (40%) with AKI in our series were septic at presentation, and other 3 (20%) had colonic ischemia, a condition associated with increased risk of bacterial translocation. However, we did not observe a different pattern of MCAmfv time-course during the hemodialysis session in those nine patients and the five patients with AKI associated with congestive heart failure. As an alternative explanation, in case of preserved cerebral autoregulation, a decreased MCAmfv would have been expected only if MCA vasodilation had occurred and CBF had remained constant. However, this hypothesis seems unlikely for at least two reasons. First, since net ultrafiltration volume was greater in the patients with ESRD than in those with AKI, the greater fluid loss should have caused a more pronounced MCA vasodilatation and therefore a greater decrease in MCAmfv in the former group; secondly, some evidence exists that MCA diameter does not change significantly following moderate changes in mean arterial pressure [32, 33].

After adjusting for the differences in net ultrafiltration volume, a clear-cut decrease in MCAmfv was recorded only in the AKI group. In an attempt to elucidate further possible mechanisms of this decrease beyond changes in systemic hemodynamics, we explored the relationship between the changes in MCAmfv and those in potentially meaningful metabolic parameters at the end of the hemodialysis session. Given the intentionally low-efficiency hemodialysis settings in AKI patients, the urea reduction ratio was lower in these patients compared with that obtained in ESRD patients (0.45 versus 0.73); thus, reverse urea effect [34–36] causing an imbalance in blood/brain osmolality and consequent transient cerebral edema was unlikely to account for the observed fall in MCAmfv in the former group. Moreover, we failed to detect a significant correlation between the MCAmfv changes and urea reduction ratio either in the patients with AKI or in those with ESRD. Since AKI patients were slightly more acidoemic at baseline, plasma HCO3− values increased more at the end of the hemodialysis session in them than in those with ESRD; therefore, one might speculate that the ensuing greater ‘paradoxical’ brain acidification [37] in patients with AKI may have produced increased intracellular brain osmolality and thus, again, transient cerebral edema. No clear-cut relationship was found in either group between MCAmfv changes and plasma HCO3− changes, even though a trend towards a negative correlation seemed to emerge between the decrease in MCAmfv and the increase in plasma HCO3− after exclusion of two patients (one in the AKI group and one in the ESRD group) with extreme MCAmfv changes at end-dialysis. A rapid correction of metabolic acidosis during IHD is associated with increased plasma and cerebrospinal fluid (CSF) CO2, with ensuing fall in CSF pH; this, in turn, would lead to an increased brain H+ concentration due to increased organic acid production. The resulting increase in intracellular osmolality in the brain would cause intracellular water translocation and brain edema [10], albeit a definitive demonstration of this hypothesis is still lacking in humans. Finally, due to lower net ultrafiltration volume in AKI than in ESRD patients, hematocrit and arterial oxygen content increased less in the former group. All of the ESRD patients in this study were being treated with erythropoiesis-stimulating agents; in fact, these patients had slightly though not significantly higher
hematocrit values at baseline compared with AKI patients. Because blood viscosity and arterial oxygen content [6, 38] have been recognized as important modulators of MCA blood flow velocity, we would have rather expected a greater decrease in MCAmfv in the ESRD patients, i.e. the opposite of what we observed. Again, in neither group significant correlations were detected between the changes in MCAmfv and the changes in hematocrit or arterial oxygen content.

The lower dialysate temperature prescribed for the AKI compared with the ESRD patients (35°C versus 36°C, respectively) may have affected MCAmfv values throughout the hemodialysis session in the former group. Indeed, CBF velocity decreased significantly during the cooling (i.e. <33°C) phase, and was restored to baseline values during the rewarming (i.e. >36°C) phase, of cardiopulmonary bypass in patients undergoing major heart surgery [39]. Although MCAmfv values were already significantly lower at the start of the hemodialysis session in AKI compared with ESRD patients, we did not measure body temperature during the dialytic session, and therefore cannot exclude that the observed MCAmfv decrease in AKI patients might have been related, at least in part, to blood cooling.

We also considered the possibility that the observed difference in the time-course of MCAmfv between the two groups may have been related to the use of low-molecular-weight heparin (LMWH) to ensure circuit patency in the patients with ESRD. In fact, Ruggiero et al. [40] demonstrated that intravenous heparin acutely reduces plasma viscosity. Moreover, some experimental data suggest that LMWH may reduce the intensity of the no-reflow phenomenon and cerebral hyperperfusion after transient occlusion of either one MCA [41] or both carotid arteries [42]. Furthermore, data obtained in isolated rabbit cerebral artery myocytes support the hypothesis that unfractionated heparin may be able to modulate the cerebral vasoconstriction triggered by endothelial growth factor receptor activation via inhibition of the outward-rectifying K channels [43]. However, in this study, AKI patients displayed lower values of MCAmfv compared with ESRD patients already at the start of the dialysis session; hence, a clinically meaningful role of dalteparin administration in preventing MCAmfv decrease during the hemodialysis session in the latter group seems unlikely.

In conclusion, our data suggest that IHD can decrease CBF in patients with AKI but not in patients with ESRD on a regular hemodialysis schedule. We could not demonstrate any convincing relationships between the changes in MCAmfv and changes in non-hemodynamic parameters in either group of patients, with a possible exception for changes in plasma HCO₃⁻. Thus, our findings do not support a clear-cut role of rapid changes in blood osmolarity or vasoreactivity of the cerebral circulation to oxygen supply in modulating CBF during IHD, albeit we cannot exclude the possibility that an increased brain water content produced by a more pronounced plasma alkalization in our patients with AKI might have played a role in the observed decrease in MCAmfv via an increase in intracerebral pressure and an ensuing decrease in CPP. Some limitations of the present study should be acknowledged. First, echocardiography was not performed in our patients; hence, data on the effects of ultrafiltration volume on stroke volume or ejection fraction were not available. Secondly, plasma fibrinogen and serum C-reactive protein were not systematically collected in this study; therefore, we cannot exclude that changes in plasma viscosity may have exerted some role in the observed MCAmfv decrease during IHD in AKI patients. Finally, our AKI patients’ clinical conditions, albeit in the setting of critical illness, were not as severe as those more commonly found in patients admitted to intensive care units. In fact, none of the patients of the present study was being mechanically ventilated, nor had profound hemodynamic instability, even though central venous oxygen saturation and serum lactate were not systematically recorded. Accordingly, we regarded as ethically acceptable to prescribe IHD rather than continuous renal replacement therapies (CRRT) or sustained low efficiency dialysis (SLED) for these patients; furthermore, we reasoned that a relatively ‘healthy’ group of AKI patients could be more appropriately compared with a control group of ESRD patients. Further studies are needed to investigate whether CRRT or prolonged intermittent techniques (e.g. sustained low-efficiency dialysis), which afford a better hemodynamic tolerance and a lower risk of disequilibrium syndrome [44], might also better preserve transcranial Doppler-derived indices of CBF in patients with AKI.

Conflict of Interest statement. None declared.

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