Cerebrovascular autoregulation in critically ill patients during continuous hemodialysis

L'autorégulation vasculaire cérébrale chez les patients gravement malades pendant l'hémodialyse continue

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Abstract

Purpose In chronic renal failure, intermittent hemodialysis decreases cerebral blood flow velocity (CBFV); however, in critically ill patients with acute renal failure, the effect of continuous venovenous hemodialysis (CVVHD) on CBFV and cerebrovascular autoregulation (AR) is unknown. Therefore, a study was undertaken to investigate the potential effect of CVVHD on CBFV and AR in patients with acute renal failure.

Methods This cohort study investigated 20 patients with acute renal failure who required CVVHD. In these patients,

the CBFV and index of AR (Mx) were measured using transcranial Doppler before and during CVVHD.

Results The median Mx values at baseline were 0.33 [interquartile range (IQR): 0.02–0.55], and during CVVHD, they were 0.20 [0.07–0.40]. The differences in Mx (CVVHD – baseline) was (median [IQR]) –0.015 [–0.19–0.05], 95% confidence interval (CI) –0.16 to 0.05. The Mx was > 0.3 in 11/20 patients at baseline measurement. Six of these patients recovered to Mx < 0.3 during CVVHD. The CBFV was (median [IQR]) 47 [36–59] cm·sec^{–1} at baseline and 49 [36–66] cm·sec^{–1} during CVVHD. The difference of CBFV was 0.0 [–4 – 2.7], 95% CI –2.5 to 4.2.

Conclusion Compared with patients with intermittent hemodialysis, CVVHD did not influence CBFV and AR in critically ill patients with acute renal failure, possibly due to lower extracorporeal blood flow, slower change of plasma osmolarity, and a lower fluid extraction rate. In a subgroup of patients with sepsis, the AR was impaired at baseline in more than half of the patients, and this was reversed during CVVHD. The trial was registered at ClinicalTrials.gov ID: NCT01376531.

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Résumé

Objectif Lors d'insuffisance rénale chronique, l'hémodialyse intermittente réduit la vitesse du débit sanguin cérébral (VDSC); toutefois, nous ne connaissons pas l'effet d'une hémodialyse veino-veineuse continue (HDVVC) sur la VDSC et sur l'autorégulation (AR) vasculaire cérébrale chez les patients gravement malades présentant une insuffisance rénale aiguë. Par conséquent, une étude a été réalisée pour étudier l'effet potentiel d'une HDVVC sur la VDSC et l'AR chez les patients atteints d'insuffisance rénale aiguë.

Méthode Cette étude de cohorte a porté sur 20 patients souffrant d'insuffisance rénale aiguë et nécessitant une HDVVC. Nous avons mesuré la VDSC et l'indice d'AR (Mx) chez ces patients à l'aide d'un Doppler transcrânien avant et pendant la HDVVC.

Résultats Les valeurs Mx médianes de base étaient [écart interquartile (ÉIQ)] 0,33 [0,02-0,55] et, pendant la HDVVC, elles étaient de 0,20 [0,07-0,40]. Les différences de Mx (HDVVC – valeurs de base) étaient de $-0,015$ [$-0,19 - 0,05$], intervalle de confiance (IC) 95 % $-0,16$ à $0,05$. Le Mx était $> 0,3$ chez 11/30 patients lors des mesures de base. Six de ces patients ont atteint un Mx $< 0,3$ pendant la HDVVC. La VDSC était de (médiane [ÉIQ]) 47 [$36-59$] $\text{cm}\cdot\text{sec}^{-1}$ avant l'intervention et de 49 [$36-66$] $\text{cm}\cdot\text{sec}^{-1}$ pendant la HDVVC. La différence de VDSC était de $0,0$ [$-4 - 2,7$], IC 95 % $-2,5$ à $4,2$.

Conclusion Par rapport aux patients recevant une hémodialyse intermittente, la HDVVC n'a pas influencé la VDSC et l'AR chez les patients gravement malades souffrant d'insuffisance rénale aiguë; possiblement en raison d'un débit sanguin extracorporel plus faible, d'un changement d'osmolarité plasmatique plus lent, et d'un taux d'extraction liquidienne plus faible. Dans un sous-groupe de patients atteints de sepsis, l'AR était altérée au départ chez plus de la moitié des patients, une situation qui a été renversée pendant la HDVVC. Cette étude est enregistrée sous ClinicalTrials.gov, ID : NCT01376531.

To avoid adverse effects of cerebral hypo- and hyperperfusion, cerebral blood flow is autoregulated within a wide range of arterial blood pressure changes. This so-called cerebrovascular autoregulation (AR) is impaired in patients with intracranial pathology^{1,2} and, likewise, in critically ill septic patients without cerebral pathologies.³ These patients often develop further organ dysfunction, such as acute renal failure with the consequent need for renal replacement therapy. Extracorporeal continuous venovenous hemodialysis (CVVHD) is one kind of renal replacement therapy used in the intensive care unit (ICU) in critically ill patients.

Intermittent ambulant hemodialysis, which is necessary in patients with chronic renal failure, decreases cerebral blood flow velocity (CBFV);⁴ therefore, it is possible that CVVHD, which is used in ICU in patients with acute renal failure, might also compromise CBFV. The AR in many of these patients might already be impaired, and it is possible that the CVVHD itself further compromises AR due to the high fluid turnover and hemoconcentration. Although the status of AR is very important for the management of cerebral perfusion pressure in patients with acute renal failure and CVVHD in the ICU, there is a lack of studies examining CBFV and AR in these patients. Consequently, the present cohort study was undertaken to investigate AR at baseline and during CVVHD in the same critically ill patients with acute renal failure, and the primary end point was to investigate the change in AR due to CVVHD, with the hypothesis that there are no changes in AR during CVVHD.

Methods

Patient recruitment

The study was conducted at the University Medical Center Mainz, Germany. The Ethical Care Committee (Institutional Review Board [IRB]) of the Federal State of Rhineland-Palatinate, Germany approved the study (IRB approval number: 837.041.10, June 2010). Written informed consent was obtained from the legal surrogate of all patients. Adult ICU patients (age > 18 yr) suffering from acute renal failure (defined by a decrease of glomerular filtration rate, an increase of serum creatinine, or insufficient urine output)⁵ and undergoing renal replacement therapy were eligible for inclusion in the study. Renal replacement therapy was indicated when fluid extraction during oliguria or anuria was necessary or in patients with hyperkalemia or severely elevated serum creatinine. Exclusion criteria were preexisting neurological or psychiatric diseases, intracranial infection, brain trauma, or pregnancy. Recruitment was performed daily by one of the authors.

Patient treatment

The study was performed after cardiopulmonary stability was achieved. All patients were sedated and ventilated in the ICU. Sedation was performed using propofol ($1-4 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ iv) and sufentanil ($0.1-0.6 \text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ iv) to achieve a target Richmond Agitation and Sedation Scale of -3 to -1 . Mandatory or assisted ventilation with a tidal volume of $6 \text{ mL}\cdot\text{kg}^{-1}$ predicted body weight was performed. Ventilator frequency was adapted to maintain PaCO_2 in the range of $35-45 \text{ mmHg}$. The PaCO_2 levels of the

individual patients were intended to be held constant throughout the study (maximal difference = 5 mmHg). Inspiratory oxygen fraction ($F_{I}O_2$) and positive end-expiratory pressure were individually adjusted to achieve a $PaO_2 > 70$ mmHg.

According to the standard operating procedures, the mean arterial blood pressure was invasively measured and maintained in the range of 65–90 mmHg using the vasopressor, norepinephrine, or the inotropic drug, dobutamine, guided by pulse contour cardiac output measurement using PiCCO Technology (PULSION Medical Systems, Feldkirchen, Germany). Further physiologic variables, such as heart rate, blood glucose concentration, electrolytes, hemoglobin concentration, and bladder temperature were controlled and actively maintained within the normal range. To minimize the possible confounding factors on the measurement, no drugs were changed or newly added, and no changes in infusion rates were performed between both measurements, with the exception of the catecholamine therapy and the use of anticoagulant drugs in non-citrate anticoagulation CVVHD.

CVVHD

The multiFiltrate® system (Fresenius Medical Care, Bad Homburg, Germany) was used in CVVHD modality with citrate anticoagulation (CiCa®), or with systemic anticoagulation with heparin ($100 \text{ IU} \cdot \text{mL}^{-1}$) or argatroban ($10 \text{ mg} \cdot \text{mL}^{-1}$) and a target of partial thromboplastin time of 40–60 sec. Citrate anticoagulation uses sodium citrate applied to the extracorporeal blood in the dialysis catheter after the blood is withdrawn from the body. This citrate ligates serum Ca^{2+} and reduces free Ca^{2+} , thereby inhibiting the plasmatic coagulation. Before the extracorporeal blood returns to the patient's vascular system via the dialysis catheter, Ca^{2+} is added to attain normal serum Ca^{2+} concentration. The effluent flow is about $25 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$. During citrate anticoagulation, the blood flow is adapted at the effluent flow to control plasma HCO_3^- and pH. The fluid replacement is adapted to minimize cardiovascular depression during fluid exchange. The Ultraflux® AV1000S filter (Fresenius Medical Care, Bad Homburg, Germany) was used. For the citrate anticoagulation Ci-Ca Dialysate K2 fluid, which containing potassium ($2 \text{ mmol} \cdot \text{L}^{-1}$) (Fresenius Medical Care, Bad Homburg, Germany), sodium citrate (4%), and calcium chloride ($0.5 \text{ mmol} \cdot \text{L}^{-1}$). Duosol™ dialysate solution containing potassium ($2 \text{ mmol} \cdot \text{L}^{-1}$) was used for systemic anticoagulation; the anticoagulants were applied before the Ultraflux AV1000S filter (all fluids from B. Braun, Melsungen, Germany).

Transcranial Doppler (TCD) ultrasound and AR

Measurement of AR was performed using TCD. The baseline measurement was performed before CVVHD was

started, followed by the measurement during CVVHD. Measurement of the index of AR (Mx) was performed over a period of 45 min according to the manufacturer's recommendation (30–60 min) and previous descriptions of critically ill patients with sepsis.³ Physiological variables, e.g., oxygenation and blood pressure, were held within physiological limits, and both measurements were performed on the same day to avoid further influencing factors such as progress or regress of the underlying illness.

The CBFV in one middle cerebral artery was measured using a 2-MHz TCD probe (Doppler Box®, DWL, Sipplingen, Germany). The probe was positioned over the temporal bone window above the zygomatic arch and fixed with a special frame (DiaMon®, DWL, Sipplingen, Germany). This ensured that the angle and the individual depth of insonation were constant during the investigation.

The Mx was calculated using the software ICM + (University Cambridge, UK, www.neurosurg.cam.ac.uk/icmpls). The CBFV and arterial blood pressure were measured over a period of 45 min, digitized, and then processed calculating the time-averaged values using waveform time integration based on six-second intervals. The Mx was calculated as a Pearson's moving correlation coefficient between 30 samples of mean CBFV and mean arterial blood pressure.⁶ To obtain a reliable value, the mean of Mx over the measurement period of 45 min was used for analysis. A positive association between blood pressure and CBFV (positive values of Mx) indicates passive dependence of blood flow and, therefore, impaired AR. Negative or zero values of Mx imply active cerebrovascular response to changes in blood pressure and, therefore, preserved AR. For clinical interpretation, impaired vs intact AR was dichotomized using 0.3 as the cut-off level. Values > 0.3 show impaired AR.⁷

Statistical analysis

Physiological data are expressed as the mean and standard deviation (SD) or median and interquartile range [IQR]. The primary end point in the study was the change in the Mx due to CVVHD. We hypothesized that any changes in Mx during CVVHD would be small and clinically unimportant. A test of equivalence composed of two one-sided tests was applied for this purpose.⁸ Differences in the Mx of < 0.2 were defined as having no relevance, but this definition was not validated in previous studies. A difference in the Mx of > 0.3 in patients with head injury showed clinical relevance,⁹ while in another study comparing young vs old patients, a difference in the Mx of 0.1 was assumed to be clinically irrelevant.¹⁰ Furthermore, the standard deviation in previously reported studies was about 0.2.^{10,11} Consequently, in the present study, a change in Mx

of ≥ 0.2 between baseline and CVVHD measurement was defined as clinically relevant.

The null hypothesis of the equivalence test states that the Mx changes by > 0.2 ; the alternative hypothesis maintains that this change is < 0.2 . This test of equivalence was performed with two one-sided Wilcoxon signed-rank tests with the null hypothesis shifted by 0.2 to either side. The confidence interval of the median is based on the fact that the number of observations greater than the true median is binomially distributed with $P = 0.5$. The sample size was estimated using a Student's t test for paired samples with an alpha of 0.05 (one-sided), a power of 0.8, an estimated mean difference of 0.2, and a standard deviation of 0.3. It revealed that 16 patients should be investigated. Changes in CBFV were analyzed by a two-sided Wilcoxon signed-ranks test.

All analyses were conducted with SPSS® version 19 (SPSS Inc., Chicago, Illinois, USA).

Results

Patients

Twenty adult patients with acute renal failure were included in the study from October 2010 to April 2011. There were 17 male and three female patients with a mean (SD) age of 67 (10) yr and an age range of 48–80 yr. At the time of recruitment, not all patients fulfilling the inclusion and exclusion criteria could be entered into the study because of the lack of informed consent or other reasons, and a detailed analysis of the number of potentially eligible patients could not be included because no screening log was kept. The measurement was performed about eight days after patient admission to the ICU. During the measurement period, patients remained cardiovascularly stable with supplementation of norepinephrine in 15 patients (median 0.1; IQR [0.05–0.30] $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and additional dobutamine in four of the 15 patients (median 2.84; IQR [1.89–3.15] $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). In seven patients, CVVHD was performed for the first time, and in the other patients, there was more than a 12-hr interval since the previous CVVHD. The underlying diseases were distributed as follows: 11 patients suffered from sepsis (seven septic shock, four severe sepsis); five patients had a systemic inflammatory response syndrome (SIRS);¹² two patients had multiple trauma (no head trauma); and two patients had hepatorenal syndrome. No data were missing in the 20 patients studied. Long-term follow-up was not part of the study protocol.

The CVVHD was performed with citrate anticoagulation in 16 patients and with systemic anticoagulation in four patients. The median [IQR] blood flow was 100 [100–100] $\text{mL}\cdot\text{min}^{-1}$; the median effluent flow was 2,000

[2,000–2,000] $\text{mL}\cdot\text{hr}^{-1}$, and the median fluid extraction was 200 [100–250] $\text{mL}\cdot\text{hr}^{-1}$. The median [IQR] delay from the end of the baseline measurement to the start of the CVVHD measurement was 15 [10–20] min, followed by a measurement time of 45 min. In one patient, the delay was ten minutes, and in two patients, the start of the CVVHD was delayed for more than 60 min (70–290 min) due to technical reasons.

Cerebrovascular autoregulation

The median [IQR] Mx at baseline measurement was 0.33 [0.02–0.55], and it was 0.20 [0.07–0.40] during CVVHD. The median [IQR] for differences in Mx (CVVHD – baseline) was -0.015 [-0.19 – 0.05], 95% CI -0.16 to 0.05 . The results of the tests of equivalence of Mx between baseline and CVVHD were $P = 0.01$ for negative and $P < 0.01$ for positive differences. The Mx was > 0.3 in 11 of the 20 patients during baseline measurement, indicating an impaired AR (Figure). In six of these 11 patients, the Mx decreased from impaired AR to intact AR during CVVHD, while AR remained impaired in five patients. Ten of the eleven patients with initially impaired AR had sepsis or SIRS as the underlying disease, and one patient suffered from trauma. In two patients with sepsis, the Mx increased from < 0.3 during baseline to > 0.3 during CVVHD, hence the AR changed from intact to impaired. Seven patients showed intact AR throughout the study. Further

Figure Cerebrovascular autoregulation at baseline and during continuous venovenous hemodialysis. This figure shows the parallel line plot of the index of cerebrovascular autoregulation (Mx) as a function of the individual patients ordered by baseline Mx. Baseline measurement without continuous venovenous hemodialysis (CVVHD) is represented by a large point and measurement during CVVHD is represented by a small point

influencing factors could not be evaluated due to the limited sample size.

CBFV and physiological variables

At baseline measurement, the median [IQR] CBFV was 47 [36–59] $\text{cm}\cdot\text{sec}^{-1}$, and during CVVHD, it was 49 [36–66] $\text{cm}\cdot\text{sec}^{-1}$ with no statistically significant changes (median difference 0.0; IQR [−4.0–2.7]; 95% CI −2.5 to 4.2; $P = 0.84$). Furthermore, PaCO_2 , PaO_2 , mean arterial blood pressure, hematocrit, and heart rate were not influenced by CVVHD in the individual patients (Table). Although the target was to keep an individual PaCO_2 difference of < 5 mmHg between the two measurements, a higher difference occurred in four patients (6–11 mmHg).

Discussion

This study shows that CVVHD in a heterogeneous group of critically ill patients with acute renal failure does not influence the CBFV and the AR to a clinically relevant extent. Surprisingly, AR was already impaired in 11 of the 20 patients at baseline assessment before the CVVHD was started.

The mean Mx at baseline decreased slightly during CVVHD. This change is below the prospectively defined clinically relevant threshold, and therefore has no clinical relevance. Patients with chronic renal failure showed intact AR before and after intermittent hemodialysis.⁴ Surprisingly, the level of Mx in 11/20 patients with acute renal failure was already above the threshold of 0.3 for intact AR and, therefore, showed impaired AR at baseline measurement. Ten of these patients with impaired AR suffered from sepsis or SIRS. Six of the septic patients with impaired AR at baseline showed recovery during the CVVHD by lowering the index of AR to levels < 0.3 ,

while CBFV was comparable. Our data show that the CVVHD in patients with acute renal failure does not negatively influence the AR; on the contrary, it has the potential to recover impaired AR.

The mean CBFV did not change between the baseline measurement and CVVHD; in contrast, intermittent hemodialysis, which is used in patients with chronic renal failure, significantly influenced CBFV.^{4,13,14} This can possibly be explained by different settings used for chronic vs intermittent hemodialysis strategies. Compared with CVVHD, intermittent hemodialysis uses higher blood flow, faster changes in plasma osmolarity, and fluid extraction, which might have greater influence on cerebral perfusion pressure and intracranial pressure.¹⁵

This study has several limitations. The mean levels of PaCO_2 in the present study, with 45 (7) mmHg during baseline and 46 (9) mmHg during CVVHD, were at the upper normal range and might influence the AR.¹¹ There was no difference between the PaCO_2 levels at baseline and CVVHD ($P = 0.65$), hence, the observed changes in Mx do not seem to be caused by changes in PaCO_2 . Despite the aim to keep the PaCO_2 difference between the first and second measurement in each patient < 5 mmHg; unfortunately, this aim was not achieved in four patients as the difference between the two measurements was > 5 mmHg. One patient with decreased PaCO_2 showed $\text{Mx} > 0.3$ during both measurement periods, and one patient had very high levels of Mx (0.84), which implied severely impaired AR with no further deterioration in PaCO_2 elevation. In another patient with sepsis, the Mx was 0.42 at baseline and 0.36 during CVVHD, which might have been a recovery effect of AR by CVVHD, but this was possibly eliminated by the elevated PaCO_2 . In the remaining two patients with elevated PaCO_2 , AR recovered during CVVHD, which might reflect a pronounced effect of CVVHD despite high PaCO_2 . Consequently, it is unlikely that the main result, the influence of CVVHD on AR, would be affected by the different levels of PaCO_2 in these four patients.

Another limitation of the study is that we considered only the average value of Mx; we did not investigate whether there were differences in the variability of Mx before and during CVVHD.

One further potential confounding factor is that measurements were performed on a wide range of days after admission (1–60 days); however, the main target was to characterize the influence of CVVHD on AR, and each patient served as her/his own control.

The sedation management with propofol (1–4 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ *iv*) and the infusion of catecholamines may potentially affect AR; however, previous clinical studies have shown that propofol and norepinephrine do not influence AR when used in the concentrations in the present study.^{16–19} As a

Table Physiologic variables

	Baseline	During CVVHD
Mx	0.33 [0.02 - 0.55]	0.20 [0.07 - 0.40]
CBFV ($\text{cm}\cdot\text{sec}^{-1}$)	47 [36 - 59]	49 [36 - 66]
PaCO_2 (mmHg)	43 [39 - 50]	44 [40 to 51]
PaO_2 (mmHg)	109 [99 - 126]	97 [81 - 117]
MAP (mmHg)	75 [67 - 83]	72 [66 - 83]
Hk (%)	30 [28 - 33]	30 [28 - 32]
HR (min^{-1})	95 [82 - 106]	98 [84 - 106]

CVVHD = continuous venovenous hemodialysis; Mx = index of cerebrovascular autoregulation; CBFV = cerebral blood flow velocity; MAP = mean arterial pressure; Hk = hematocrit; HR = heart rate. Data are expressed as median [interquartile range]

result, it is unlikely that the sedative regime affected AR during this investigation.

In conclusion, the present study suggests that CVVHD, as it relates to CBFV and AR, can be used safely in critically ill patients with acute renal failure.

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Competing interests All authors declare they have no competing interests.

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