Noninvasive Cerebrovascular Autoregulation Monitoring in Hemodialysis Patients: A Pilot Study

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Abstract. *Background and objective: The hemodialysis (HD) is one of the main treatment options at end-stage renal disease (ESRD) used to remove uremic toxins from the body. Although HD procedures are individualized, they frequently lead to the removal of large quantities of fluid and electrolytes. This might provoke different impairments in the body. Previous studies have proven that chronic kidney diseases cause dysfunction of the central and peripheral nervous system. However, the pathophysiological mechanisms are not clear yet.*

The aim of our study was to employ the method of noninvasive cerebrovascular autoregulation (CA) monitoring for dialysis patients during HD, to assess CA dynamics and to explore the association between changes of the level of uremic toxins, electrolytes and CA during an HD session.

Materials and methods: Noninvasive CA monitoring of 15 HD patients was performed during an HD session. Pre-dialysis and post-dialysis blood samples were taken and levels of uremic toxins and electrolytes were analyzed. The CA status was estimated by calculating the pressure reactivity index (vPRx) as the moving correlation coefficient between slow waves of noninvasively measured arterial blood pressure and noninvasively measured slow fluctuations of intracranial blood volume. The associations between the duration of the longest CA impairment (LCAI) and changes of the level of uremic toxins and electrolytes during an HD session were analyzed.

Results: There were 9 male (60%) and 6 female (40%) HD patients in the study. The mean age was 58 ± 10.9 years, and the mean HD vintage was 31 ± 24 months. There was a negative correlation between the duration of LCAI during an HD session and duration on HD treatment in months ($r = -0.526$, $P = 0.044$), post-dialysis potassium ($r = -0.652$, $P = 0.006$) and calcium ($r = -0.610$, $P = 0.016$) levels in the blood. The post-dialysis bicarbonate level in the blood and the duration of an LCAI event during an HD session correlated directly ($r = 0.586$, $P = 0.027$). There were no significant associations between the duration of LCAI and blood flow, dialysate flow, fluid ultrafiltration rate during HD, post-dialysis urea, creatinine, sodium, and magnesium levels in the blood.

Conclusions: The longer duration of CA impairment events has been associated with a shorter duration time on HD treatment in months, lower post-dialysis potassium and calcium levels in the blood and a higher bicarbonate level. These preliminary results allows us to formulate the hypothesis that HD procedures can cause excessive changes of the electrolyte level and these changes are associated with the appearance of CA impairment events during an HD procedure. Impaired CA was detected more often due to the electrolyte changes during an HD procedure in patients having less HD vintage.

Introduction

Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are two main global health concerns with prevalence as high as 11–13% and 0.1% in the general population, respectively [1]. ESRD is the last stage (stage 5) of CKD when a requirement of renal replacement therapy appears. Hemodialysis (HD) is one of the main treatment options at ESRD [2, 3]. HD procedures are minimally individualized and frequently lead to the removal of large quantities of fluid and electrolytes and, thus, provoke large variations in arterial blood pressure and blood volume, associated with different impairments in the body. Previous studies have proven that CKD causes dysfunction of central and peripheral nervous systems, which is particularly severe in HD patients (diverse encephalopathy and disequilibrium syndrome are observed) [4, 5]. Consequently, cognitive function impairment and depression develop, the life quality deteriorates, and the lifespan decreases [6]. However, the pathophysiological mechanisms are not clear yet. An HD procedure, when large

quantities of fluid, electrolytes and toxic products are removed, is one of the probable mechanisms. The number of reports about possible brain damages and subsequent impairment of cognitive functions, development of depression, deterioration of life quality and lifespan decrease is growing. Brain damage mechanisms are unclear; thus, researchers more and more often pay attention to them. In previous studies, cerebral blood flow in HD patients was assessed using a variety of visual imaging techniques such as magnetic resonance imaging [7, 8, 9], transcranial Doppler ultrasound [10], computer tomography [9], positron emission tomography [11], and near-infrared spectroscopy [12]. However, the data obtained in these studies vary greatly. Mostly, brain circulation is evaluated once, and changes during HD are not recorded. Meanwhile, until now, noninvasive methods for monitoring of cerebral blood flow changes have not been applied for brain state investigation during HD. It is important to introduce the innovative noninvasive imaging technologies to clinical practice, to investigate the brain state during HD and to find possibilities to individualize HD procedures for patients in order to avoid brain injuries during this procedure. One of the main mechanisms of a possible brain injury is disorder of cerebrovascular autoregulation (CA). In the human brain, it is a vital protective function of the cerebral vasculature. CA protects the brain against hypoperfusion caused by hypotension, as well as against hypertension-induced hyperemia [13]. Four mechanisms regulate cerebral blood flow, including myogenic, neurogenic, endothelial, and metabolic responses [14]. CA monitoring during HD might be extremely useful for detection of episodes of its impairment and for determination of factors influencing it.

The aim of our study was to employ the method of noninvasive CA monitoring for dialysis patients during HD, to assess CA dynamics and to explore the association between changes of levels of uremic toxins, electrolytes and CA during an HD session.

Methods

The ongoing prospective study was performed at the Department of Detoxication at the Hospital of the Lithuanian University of Health Sciences (LUHS) Kauno klinikos. The study was approved by Kaunas Regional Biomedical Research Ethics Committee (protocol No. P2-BE-2-9/2014). Written informed consent was obtained from all patients at the time of study enrollment.

Fifteen HD patients (18 years old and over) with ESRD receiving regular HD therapy thrice weekly or more were included in the prospective observational study. The exclusion criteria were as follows: patients with dementia or Alzheimer's disease, ischemic or hemorrhagic stroke, or other neurological disease in the past. For all the patients, study questionnaires were filled in. From the outpatient cards of the patients, the demographic data, information about primary kidney disease, HD vintage, and HD regimen were collected. Pre-dialysis and post-dialysis blood samples were taken (to examine blood urea nitrogen, creatinine, potassium, sodium, magnesium, calcium, and bicarbonate concentrations).

The monitoring of patients' physiological parameters was performed during one HD procedure:

- arterial blood pressure (ABP) was monitored by using a noninvasive Finapres monitor;
- CA was monitored by using a noninvasive CA monitor (developed at Kaunas University of Technology) based on the intracranial blood volume (IBV) fluctuation measurement in the brain parenchymal vessels by means of the ultrasonic time-of-flight measurement principle [15, 16]. A head frame with a pair of ultrasonic transducers on either side of the head is positioned so that the ultrasonic signals are transmitted across smaller brain vessels and arterioles. The measured ultrasound wave propagation speed between face-to-face positioned ultrasonic transducers reflects over whole brain integrated fluctuation of intracranial blood volumes [17].

The CA status was estimated by calculating noninvasively the pressure reactivity index (vPRx) as a moving correlation coefficient between the slow waves of ABP(t) and IBV(t) [17] within 2-min averaging time window. Negative values $vPRx(t) < 0$ correspond to the intact CA status (normal reactivity of cerebral vessels) and positive $vPRx(t) > 0$ indicate CA impairment (impaired reactivity of vascular bed) [17, 18]. For each episode of CA impairment, we estimated the duration of the longest CA impairment (LCAI) event. The LCAI event was chosen for evaluation in order to find the relationship between the CA impairment length and changes of the level of uremic toxins and electrolytes during an HD session. The duration of CA impairment events was calculated at the level $vPRx(t) > 0$ assuming that the vPRx value above 0 corresponds to the mathematical threshold for CA impairment [18, 19, 20]. CA impairment episodes were registered during an HD procedure by using noninvasive CA monitoring methodology.

Statistical analysis

The statistical data analysis was made employing the software package of data accumulation and analysis SPSS 22.0 (Statistical Package for Social Science 22 for Windows). All parametric data are expressed as the mean ± SD (standard deviation). Differences between continuous variables were calculated using the Mann-Whitney U test as appropriate. The paired t test or Wilcoxon matched-pairs

were used to compare variables pre- and post-dialysis, as appropriate. To analyze the univariate associations, the Spearman correlation coefficient was examined. Spearman correlation analysis between demographic characteristics of study patients, parameters of the HD regimen, dialysis solution components and duration of the LCAI was done. A *P* value < 0.05 was considered significant.

Results

There were 9 men (60%) and 6 women (40%) patients in our study. Primary kidney disease was distributed as follows: chronic pyelonephritis in 13.3% of patients (n = 2), chronic glomerulonephritis in 20% (n = 3), hypertensive nephropathy in 6.7% (n = 1), polycystic kidney disease in 33.3% (n = 5), other diseases in 26.7% (n = 4). The mean age of the study patients was 58 ± 10.9 years, and the mean HD vintage was 31 ± 24 months. The average dialysis dose (according to the mean spKt/V) was within recommended targets (1.46 ± 0.25). The detailed baseline demographic characteristics of the study patients and HD regimen parameters are shown in Table 1. Composition of dialysis solution electrolytes varied according to previous patient blood tests; thus, it was selected individually by an attending nephrologist. Only the concentration of magnesium was the same for all the patients (0.5 mmol/L), as this concentration is standard in all dialysis solutions.

There were no significant associations between the duration of LCAI and age of patients, blood flow, dialysate flow, fluid ultrafiltration rate during HD, spKt/V and composition of dialysis solution. A significant negative correlation was found between HD vintage and an LCAI event (r = –0.526; *P* = 0.044) (Fig. 1).

Statistically significant changes in the levels of uremic toxins and electrolytes during HD procedures were observed (Table 2). There was no significant association between pre-dialysis laboratory values and the duration of LCAI. The duration of LCAI significantly negatively correlated with post-dialysis blood levels of potassium (Fig. 2) and calcium (Fig. 3) and a positive correlation was found with the post-dialysis bicarbonate concentration in the blood (Fig. 4). There was a tendency of a negative correlation with post-dialysis magnesium value

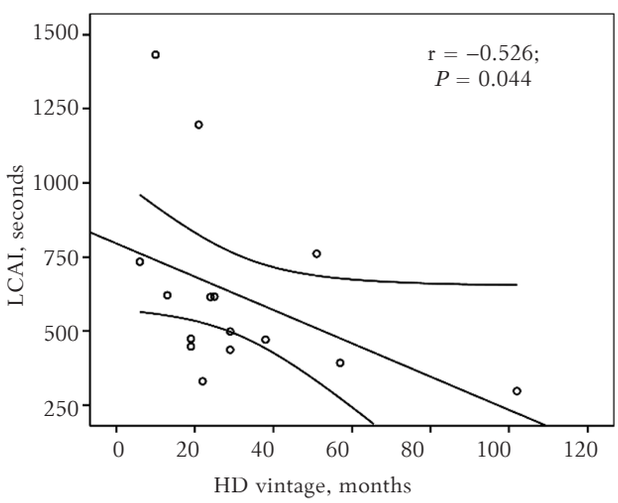

Fig. 1. The association between hemodialysis vintage and the longest cerebrovascular autoregulation impairment.

Table 1. Baseline demographic characteristics of study patients, data of the hemodialysis regimen and correlation with the longest cerebrovascular autoregulation impairment event

Parameter	Mean ± SD	Minimum value	Maximum value	Correlation with LCAI (r; *P* value) (insignificant results)
Age (years)	58 ± 10.9	35	75	0.496; 0.06
HD vintage (months)	31 ± 24	6	102	statistically significant (Fig. 1)
Ultrafiltration rate during HD (L)	1.86 ± 1.17	0.1	3.6	–0.009; 0.487
spKt/V	1.46 ± 0.25	0.99	1.96	0.146; 0.603
Blood flow (mL/min)	315.33 ± 44.38	250	400	–0.159; 0.285
Dialysate flow (mL/min)	566.67 ± 97.59	500	700	–0.193; 0.391
Composition of hemodialysis solution				
Sodium (mmol/L)	139.4 ± 1.4	135	140	–0.063; 0.774
Potasium (mmol/L)	2.6 ± 0.73	2	4	–0.12; 0.579
Calcium (mmol/L)	1.55 ± 0.10	1.5	1.75	–0.39; 0.083
Bicarbonate (mmol/L)	32.4 ± 2.4	28	34	0.106; 0.353
Magnesium (mmol/L)	0.5 (standard value)			NA

SD, standard deviation; LCAI, longest cerebrovascular autoregulation impairment; r, Spearman correlation coefficient; *P* value, significance level; HD, hemodialysis; NA, not applicable.

Table 2. Pre-dialysis and post-dialysis laboratory data, their correlations with the longest cerebrovascular autoregulation impairment event

Parameter	Pre-dialysis value		Post-dialysis value		*P* value (in comparison between pre-dialysis and post-dialysis values)
	Mean ± SD	Correlation with duration of LCAI (r; *P* value)	Mean ± SD	Correlation with duration of LCAI (r; *P* value) (insignificant results)	
Urea (mmol/L)	22 ± 4.9*	–0.254; 0.362	6.29 ± 1.86*	–0.339; 0.216	0.001*
Creatinine (μmol/L)	911.53 ± 224.66*	–0.429; 0.111	344.47 ± 104.9*	–0.443; 0.098	0.001*
Sodium (mmol/L)	136.47 ± 3.31*	0.337; 0.219	133.73 ± 2.43*	–0.063; 0.823	0.013*
Potassium (mmol/L)	5.28 ± 1.04*	–0.438; 0.102	3.6 ± 0.44*	statistically significant (Fig. 2)	0.001*
Calcium (mmol/L)	2.24 ± 0.12*	–0.311; 0.259	2.38 ± 0.13*	statistically significant (Fig. 3)	0.003*
Magnesium (mmol/L)	0.99 ± 0.11*	–0.228; 0.414	0.76 ± 0.45*	–0.228; 0.052	0.001*
Bicarbonate (mmol/L)	21.31 ± 2.53*	0.143; 0.611	28.91 ± 2.89*	statistically significant (Fig. 4)	0.001*

SD, standard deviation; LCAI, longest cerebrovascular autoregulation impairment; r, Spearman correlation coefficient; *P* value, significance level.

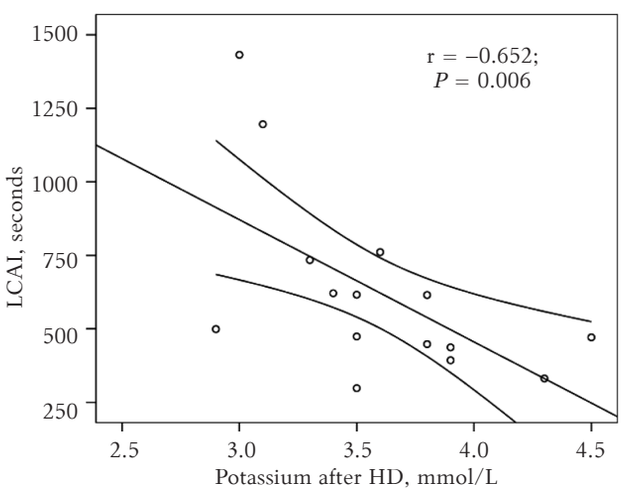

Fig. 2. The association between the post-dialysis potassium level in the blood and the longest cerebrovascular autoregulation impairment.

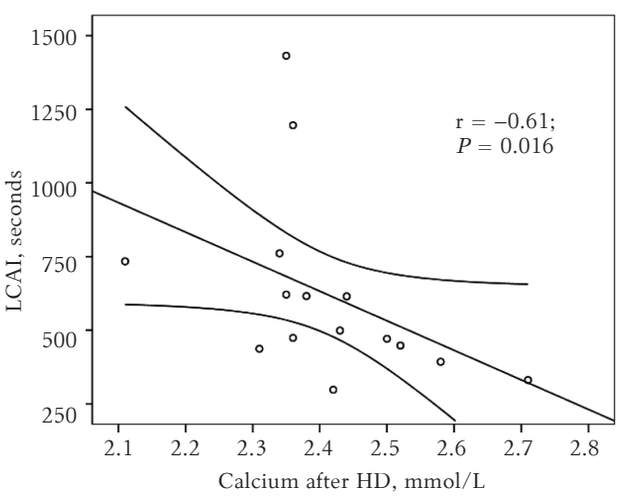

Fig. 3. The association between the post-dialysis calcium level in the blood and the longest cerebrovascular autoregulation impairment.

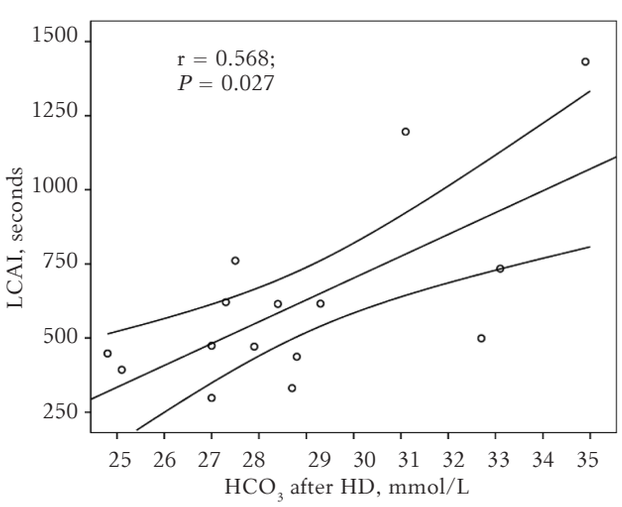

Fig. 4. The association between the post-dialysis bicarbonate level in the blood and the longest cerebrovascular autoregulation impairment.

(r = –0.228; *P* = 0.052). There were no significant associations with post-dialysis urea, creatinine, and sodium concentrations.

Discussion

In our study, noninvasive CA monitoring for HD patients during an HD session was performed for the first time. We gained new scientific knowledge about dynamics and disorders of CA during HD and associations with changes of the level of uremic toxins and electrolytes. There are only a few studies examining the condition of the brain during dialysis, with CA being most often studied parameter. The methods of investigation were different [7–12], but there is no one reliable method. Noninvasive CA monitoring during the whole dialysis procedure could be a step forward, because the state of CA was monitored in real time during the whole HD process.

Previous studies of noninvasive CA monitoring (developed at Kaunas University of Technology) showed that prolonged CA impairment events are the risk factors associated with deteriorated cognition for patients undergoing cardiac surgery with cardiopulmonary bypass as well as for traumatic brain injury patients [21, 22]. The critical duration for the single LCAI episode occurring for patients undergoing cardiac surgery exceeding ~300 seconds was found to be associated with postoperative cognitive dysfunction [21]. According to the experience gained in previous studies, investigation of an LCAI episode was also chosen in our work. Sensitive noninvasive technologies, created at Kaunas University of Technology Health Telematics Science Institute, were used for the first time worldwide for HD patients. Thus, there are no possibilities to compare our results with similar ones in other countries.

A negative correlation was found between dialysis vintage and duration of LCAI in our study. It has been shown in studies of other investigators that in certain parts of the brain of HD patients there is a higher amount of water than in healthy subjects and in patients with CKD who are not yet undergoing HD. These changes correlated with HD vintage and cognitive impairment [8, 23]. Our experience showed that patients with higher dialysis vintage had less LCAI episodes. We can explain it by assuming that patients having higher dialysis vintage adapt to changes occurring during an HD session over time.

In the study by Skinner H. and co-authors, middle cerebral artery flow velocity was measured in HD patients by transcranial Doppler ultrasound. Cerebral artery flow velocity decreased significantly after dialysis, but dynamic pressure autoregulation remained normal and was not altered significantly by HD [10]. Farhoudi M. and co-authors found that cerebrovascular blood flow was more active in HD patients in comparison with healthy subjects [24]. All investigations in other studies were performed before and after HD, and the changes were not monitored during the procedure itself, as it is technically difficult to do this. Measurements during our study were carried out during the whole HD procedure, dynamics of CA were registered and temporal disorders of CA were found.

The intended function of dialysate fluid is to reduce the concentration of uremic toxins and to correct electrolyte and acid-base abnormalities. Dialysis fluid is produced by the blending of treated water with electrolytes at the patient's bedside. Its preparation and composition are important elements of treatment optimization since many of the constituents play a role in patient's well-being. Ideally, the dialysis fluid electrolyte and buffer composition should be adapted to the needs of patients. Such individualization is facilitated by the availability of technology; however, it is not yet possible to individualize minor electrolytes, such as potassium, calcium, and magnesium [25]. We did not find associations between CA disorders and the dialysis fluid composition, post-dialysis uremic toxins, such as urea, creatinine, concentrations and spKt/V, but our results indicate that the duration of an LCAI event was associated with post-dialysis potassium, calcium, and bicarbonate concentrations in the blood of HD patients.

Sudden cardiac death is the leading cause of death in HD patients [26]. Several observational studies have indicated that HD with low potassium dialysate might increase the risk of it [27, 28]. Rapid changes in electrolyte concentrations during HD may contribute to arrhythmias and sudden death [26, 29]. We did not study associations between the potassium level and the rate of arrhythmias, but we found significant associations between the low post-dialysis potassium level in the blood and the duration of LCAI.

The optimal dialysate calcium concentration to maintain normal mineralization and reduce the risk of a cardiovascular event in HD patients is debated. Guidelines suggest that dialysate calcium concentration should be lowered to avoid vascular calcification, but cardiac arrhythmias and sudden cardiac arrest may be more likely to occur at lower dialysate calcium [30]. On the other hand, a study with 1182 incident HD patients showed that using a high dialysis fluid calcium was a significant risk for all-cause mortality [31]. However, the authors of this study at the same time predicate that the prescription of dialysate calcium should be individualized to meet the specific condition of HD patients [31]. We did not find significant associations between CA disorders and the dialysate calcium concentration, but our results showed a negative correlation between the duration of LCAI and the post-dialysis calcium level in the blood of HD patients. Too low calcium after dialysis may cause appearance of temporal CA impairments during an HD procedure.

Most HD patients worldwide are treated with bicarbonate dialysis using sodium bicarbonate at the base. The optimal concentration remains uncertain until now [32]. When mortality risk has been evaluated in HD patients in relation to their serum bicarbonates, an increase in the risk has been noted with low values [33–35] and high values [35, 36] of bicarbonates. A cohort study using the DOPPS database suggests that an increasing dialysate bicarbonate concentration increases the hazard risk for all-cause mortality regardless of a pre-dialysis serum bicarbonate concentration [32]. There are no studies that examined the relation between CA and the amount of bicarbonate in the blood. Afsar B. and co-authors in their study did not find any asso-

ciation between metabolic acidosis and bicarbonate levels with cognitive function and depression, but interdialytic changes in acid-base status were not evaluated [37]. The results of our study showed that the high post-dialysis bicarbonate level was associated with the duration of an LCAI event.

The results of our study showed the importance of a regular checking of electrolytes after dialysis and individual correction of the dialysate composition in order to reduce the likelihood of CA impairment during an HD procedure.

The main limitation of our study is a small number of study patients. Possibly, because of a small sample size, we could not get significant associations between the duration of LCAI and some characteristics of HD patients. However, the novel method and the device for noninvasive CA status monitoring of HD patients in real time during an HD session was applied for the first time. It was a pilot study and the first experience in the field of noninvasive investigation of physiology of cerebral parameters. As the study is ongoing yet, we hope to obtain new results, which will help to individualize HD procedures in order to avoid brain injuries during HD.

Conclusions

A longer duration of CA impairment events has been associated with a shorter duration time on HD treatment in months, lower post-dialysis potassium and calcium levels in the blood and a higher bicarbonate level. These preliminary results allows us to formulate the hypothesis that HD procedures can cause excessive changes in electrolyte levels and these changes are associated with the appearance of CA impairment events during an HD procedure. Impaired CA was detected more often due to electrolyte changes during an HD procedure in patients having less HD vintage.

Conflict of interest

The authors state no conflict of interest.

Acknowledgments

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