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Factors Responsible for Cerebral Hypoxia in Hemodialysis Population

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Summary

Brain tissue oxygenation (rSO_2) measured by near-infrared spectroscopy (NIRS) is lower in hemodialysis patients than in the healthy population and is associated with cognitive dysfunction. The involved mechanisms are not known. We conducted this study to identify the factors that influence the rSO_2 values in end-stage renal disease (ESRD) patients and to describe rSO_2 changes during hemodialysis. We included a cohort of ESRD patients hemodialyzed in our institution. We recorded rSO_2 using INVOS 5100C oximetry system (Medtronic, Essex, U.K.) and analyzed changes in basic laboratory values and hemodynamic fluctuations. Baseline rSO_2 was lower in patients with heart failure (45.2±8.3 % vs. 54.1±7.8 %, p=0.006) and was significantly linked to higher red cell distribution width (RDW) (r=-0.53, p<0.001) and higher BNP level (r=-0.45, p=0.01). The rSO_2 value decreased in first 15 min of hemodialysis, this decrease correlated with drop in white blood count during the same period (r=0.43, p=0.02 in 10 min, r=0.43, p=0.02 in 20 min). Lower rSO_2 values in patients with heart failure and higher RDW suggest that hemodynamic instability combined with vascular changes probably leads to worse cerebral oxygenation in these patients. Decrease of rSO_2 in 15th minute of hemodialysis accompanied with a significant drop in leukocyte count could be explained by complement activation.

Key words

Heart failure • Chronic renal failure • Hemodialysis • Cerebral hypoxia

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Introduction

End-stage renal disease (ESRD) patients treated by hemodialysis suffer from tissue ischemia (brain, peripheral muscle), which is aggravated by hemodialysis sessions (Malik *et al.* 2017). Brain ischemia leads to cognitive decline in hemodialysis patients (Kovarova *et al.* 2018). Brain oxygenation can be measured non-invasively by the near-infrared spectroscopy (NIRS), which gives the cerebral tissue oxygenation (rSO_2) (Ito *et al.* 2015, Matsukawa *et al.* 2017, Papadopoulos *et al.* 2013, Hoshino *et al.* 2014). The near-infrared spectroscopy (NIRS) is a method that estimates regional tissue oxygenation by transcutaneous measurement. It differs from the finger oximetry by using two photo-electrodes – shallow and deep. The data from the shallow electrode is subtracted from the data from the deep electrode. The result (rSO_2) combines venous, microcirculatory and arterial hemoglobin saturation (McCormick *et al.* 1991). Although it is known that dialysis patients have considerably lower rSO_2 values than healthy controls (Malik *et al.* 2017, Ito *et al.* 2015, Hoshino *et al.* 2014) and that this finding is related to cognitive impairment, responsible mechanisms are not completely understood. Otherwise, NIRS is used mostly for non-invasive cerebral oxygenation monitoring during surgery or critical states (McCormick *et al.* 1991, Douchet *et al.* 1996). Lower rSO_2 values were linked with worse neurological prognosis in patients after cardiac surgery (Yao *et al.* 2004, Slater *et al.* 2009), and with worse survival and neurological outcome in patients after cardiopulmonary resuscitation (Ibrahim *et al.* 2015,

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Ito *et al.* 2014). Lower brain oxygenation was also related to symptoms of cerebral hypoxia in de-compensated heart failure patients (Madsen *et al.* 2000). Anyway, it should be stressed out that there is no threshold value of the "pathological" rSO_2 values (Jonsson *et al.* 2017, Bickler *et al.* 2017).

Thus, cerebral rSO_2 is decreased in ESRD patients and further falls after the initiation of hemodialysis according to our pilot study, but the involved mechanisms are to be elucidated. Therefore, we extended our pilot study with the attempt to get more robust data describing rSO_2 changes in ESRD patients and to understand the mechanisms responsible for both lower rSO_2 values at baseline and during hemodialysis.

Methods

We included a cohort of patients in chronic hemodialysis program in our university hospital, who agreed to take part in this study and signed the informed consent. Inclusion criteria were presence of ESRD, clinically stable state and lack of overt dementia or history of stroke. The study was approved by local ethical committee and conforms with the Helsinki Declaration.

The measurements were performed during regular hemodialysis session with no changes of patients' dry weight, medication, or compliance to therapeutic regime.

Recorded demographic characteristics included gender, age, weight, height, comorbidities - coronary artery disease, heart failure, diabetes mellitus, arterial hypertension, dyslipidemia, previous thrombosis or pulmonary embolism - and smoking status.

Basic hemodialysis data was collected (ultrafiltration rate, dry weight, length of dialysis session). We recorded the course of frontal lobe tissue oxygen saturation for 5 min prior to hemodialysis (= baseline) and then during hemodialysis session, measured by near-infrared spectroscopy (NIRS) using the INVOS 5100C oximetry system (Medtronic, Essex, U.K.). The sampling frequency of this device is 6 seconds. The signal was recorded using one probe placed over the dominant frontal lobe. The data was averaged in 1-minute interval and visualized in a chart. Basic hemodynamic parameters (blood pressure, heart rate) were recorded every 10 min during first 30 min of hemodialysis session and then every 60 min until the end of the dialysis session. The blood pressure (BP) was taken by non-invasive measurement on the non-access upper extremity. The mean arterial blood pressure (MAP) was calculated by the equation: MAP=2/3 diastolic BP + 1/3 systolic BP. Blood samples were taken from the dialysis arteriovenous access before the start of dialysis session, in 10, 20 and 30 min and at the end of the dialysis session. We analyzed the blood count including red cell distribution width – RDW, the acid base status (pH, partial pressure of carbon dioxide – pCO_2, serum total carbon dioxide, partial pressure of oxygen – pO_2, hemoglobin saturation with oxygen – $SatO_2$), serum lactate, brain natriuretic peptide (BNP), serum albumin and protein levels. The measured BNP values were logarithmically transformed to get Gaussian distribution for analysis, the original BNP results are presented as median and quartile range.

The statistical analysis was performed using the STATISTICA Software, version 12 (StatSoft, Inc.). We used the univariate correlation analysis, Chi-square test, paired t-test, ANOVA as appropriate and multiple linear regression analysis. $P<0.01$ was considered significant for univariate correlation analysis and $p<0.05$ for the multiple linear regression analysis.

Results

We included 46 patients in our study, 24 men and 22 women, aged 63.3±15.6 years. Dialysis vintage was 46.8±54.4 months (range 1-207 months, median 24.4 months), dialysis access flow volume 1076±548 ml/min. The cause of end stage renal disease was hypertensive nephropathy in 11 patients, diabetic nephropathy in 7 patients, polycystic kidney disease in 5 patients, IgA nephropathy, multiple myeloma and infection in 4 patients, systemic lupus erythematosus, renal cell carcinoma, rapidly progressive glomerulonephritis and tubulointerstitial nephritis in 2 patients, focal segmental nephrosclerosis, membranous glomerulopathy and amyloidosis in 1 patient. Eleven patients (24 %) had history of coronary artery disease, 8 patients (17 %) of chronic heart failure, 18 patients (39 %) of diabetes mellitus, 37 patients (80 %) of arterial hypertension, 19 patients (41 %) had dyslipidemia, 10 patients (22 %) had history of previous venous thrombosis or pulmonary embolism. Twenty-two patients (48 %) were current or former smokers.

Baseline rSO_2 measurement

Mean rSO_2 values at baseline were 53±8 % in our study, which differed only slightly from the pilot study (where it was 52±8 %) (Malik *et al.* 2017).

Of the comorbidities, only the presence of heart failure was associated with significantly lower rSO_2 values (45.2±8.3 % vs. 54.1±7.8 %, p=0.006).

There was no significant relation between rSO_2 value and dialysis vintage, dialysis access blood flow volume, blood pressure or heart rate. Of the laboratory values, rSO_2 decreased significantly with increasing both RDW (r=-0.53, p<0.001) and BNP (r=-0.45, p=0.01) for all baseline values and results of univariate analysis (Table 1).

We tested several multiple regression models by adding age, heart failure, BNP and RDW (2-3 variables for each model). In all of them, age was not significantly related to rSO_2. The presence of heart failure and higher BNP lost significance when RDW was added, RDW remained the strongest determinant of rSO_2.

rSO_2 changes during hemodialysis

Baseline and end-of dialysis rSO_2 values did not differ significantly (52.6±8.5 % vs. 52.1±9.0 %, p=0.53). The time course of rSO_2 during hemodialysis is depicted in Figure 1. We observed two drops of rSO_2 value during hemodialysis, the first one in 15th minute after the start of hemodialysis (to 51.3±8.7 %, p=0.003 vs. baseline), the second one after 3 hours (50.7±9.6 %, p=0.01 vs. baseline).

The decrease in brain tissue oxygenation 10 and 20 min after the start of hemodialysis was significantly accompanied by the decrease of leukocyte count (r=0.43, p=0.02 in 10 min, r=0.43, p=0.02 in 20 min). The leukocyte count dropped significantly in 10th and 20th minute (from 6.2±2 $x10^3$/µl at baseline, to 5.2±2.0 $x10^3$/µl, p=0.00001 in 10th minute and 5.4±1.9 $x10^3$/µl, p<0.0000001 in 20th minute, respectively, compared to baseline). Apart from this, the changes of rSO_2 in 10th, 20th and 30th minute of hemodialysis and at the end of hemodialysis did not have any significant relation with any of the measured laboratory and hemodynamic parameters (Table 2).

Table 1. Baseline data and their relation to rSO_2 changes

Parameter	Baseline value mean ± SD	Correlation with rSO_2 r	p
Age (years)	63 ± 16	-0.27	0.07
Dialysis vintage (months)	46.8 ± 54.4	-0.19	0.20
Qva (ml/min)	1076 ± 548	0.12	0.46
Residual diuresis (ml/day)	464 ± 507	0.32	0.03
White blood count (x103/µl)	6.5 ± 2.5	0.20	0.18
Red blood count (x106/µl)	3.2 ± 0.6	0.27	0.07
Hematocrit (%)	31 ± 4	0.21	0.17
Hemoglobin (g/l)	98.7 ± 14.8	0.18	0.24
Red cell distribution width (%)	15.5 ± 1.9	-0.53	<0.001
Platelet count (x103/µl)	196 ± 67	0.03	0.84
pH	7.35 ± 0.04	-0.36	0.04
pCO_2 (kPa)	5.1 ± 0.6	0.31	0.08
pO_2 (kPa)	10.8 ± 3.1	-0.08	0.68
Hemoglobin saturation by O_2	90.2 ± 14.3	-0.08	0.67
Lactate (mmol/l)	1.1 ± 0.5	-0.18	0.35
Serum protein (g/l)	63.3 ± 6.6	0.17	0.26
Albumin (g/l)	38 ± 5.8	0.30	0.04
Brain natriuretic peptide (ng/l)*	573 (1165)	-0.45	0.01
Systolic BP (mmHg)	148 ± 24	0.13	0.38
Diastolic BP (mmHg)	77 ± 16	0.27	0.07
Mean BP (mmHg)	89 ± 16	0.23	0.12
Heart rate (bpm)	78 ± 13	-0.02	0.87

BP = blood pressure, pO_2 = partial pressure of oxygen, pCO_2 = partial pressure of carbon dioxide, rSO_2 = regional oxygen saturation, Significant results are in bold. * Brain natriuretic peptide results are presented as median (quartile range).

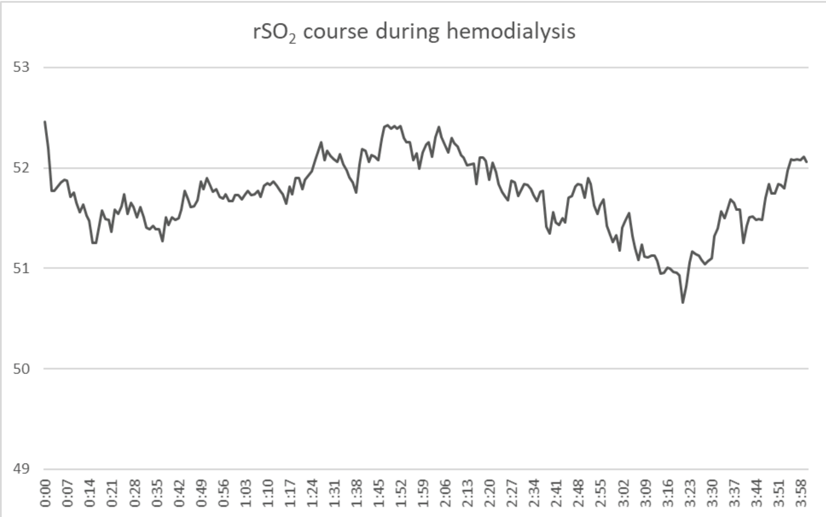

Fig. 1. Cerebral oxygenation course during hemodialysis. The graph depicts the averaged rSO_2 values. Individual courses of rSO_2 values during hemodialysis vary.

Table 2. Changes of cerebral oxygenation, laboratory and hemodynamic parameters during hemodialysis

Parameter	Time				
	Baseline	10 min	20 min	30 min	End
rSO_2 (%)	52.6 ± 8.4	51.8 ± 8.8*	51.5 ± 8.8*	51.7 ± 8.8	52.1 ± 8.9
White blood count (x103/µl)	6.2 ± 2.0	5.2 ± 2.0†	5.4 ± 1.9†	5.8 ± 2.0†	6.0 ± 2.2
Red blood count (x106/µl)	3.2 ± 0.4	3.2 ± 0.4	3.2 ± 0.4	3.3 ± 0.5	3.6 ± 0.6†
Hemoglobin (g/l)	98.6 ± 12.7	97.8 ± 12.0	98.8 ± 11.5	101.4 ± 15.1	110.2 ± 16.1†
Hematocrit (%)	31 ± 5	30 ± 4*	31 ± 4	31 ± 5	34 ± 5†
pH	7.35 ± 0.03	7.34 ± 0.04	7.35 ± 0.04	7.37 ± 0.04**	7.46 ± 0.05†
pCO_2 (kPa)	5.0 ± 0.6	5.4 ± 0.5†	5.5 ± 0.6†	5.4 ± 0.5†	5.0 ± 0.5
pO_2	11.6 ± 2.5	12.2 ± 2.8	11.9 ± 2.6	11.7 ± 2.3	11.5 ± 2.6
Systolic BP (mmHg)	149 ± 22	134 ± 17†	136 ± 17†	139 ± 20†	127 ± 23†
Diastolic BP (mmHg)	78 ± 13	73 ± 13**	72 ± 11†	72 ± 13†	70 ± 15†
Mean BP (mmHg)	102 ± 14	94 ± 12†	93 ± 11†	95 ± 13†	89 ± 16†
Heart rate (bpm)	76 ± 13	70 ± 12†	70 ± 12**	72 ± 11	76 ± 14

Continuous variables are shown as mean ± SD. * $p<0.05$ for the comparison with baseline, ** $p<0.01$ for the comparison with baseline, † $p<0.001$ for the comparison with baseline

We observed that some patients had more pronounced rSO_2 changes during hemodialysis than others. To analyze possible physiological importance, we divided the patients into two groups according to the stability of rSO_2 value during the hemodialysis sessions ("stable" vs. "unstable"). The median value of rSO_2 fluctuation and thus the cut-off value was 10 percent points. The "unstable" patients had lower rSO_2 values before hemodialysis (49.9±8.6 % vs. 56.1±7.3 %, p=0.01), during hemodialysis and at the end of hemodialysis session (56.9±6.6 % vs. 48.3±8.9 %, p=0.001) (Table 3). for details. The "unstable" group had significantly higher RDW than the stable group (16.0±2.2 vs. 14.8±1.4, p=0.04) and significantly higher BNP level (p=0.002). There was no other significant difference in observed laboratory and hemodynamic parameters or ultrafiltration. Patients with known chronic heart failure were more likely to be in the unstable group (88 % vs. 50 %, p=0.05).

Discussion

This study confirmed low baseline cerebral rSO_2 values in one a large of the largest hemodialysis patients' cohorts. Of potential involved mechanisms, higher RDW values were the strongest determinant of lower baseline

Table 3. Differences in cerebral rSO_2 value during hemodialysis in "stable" and "unstable" group of patients.

Time of hemodialysis	rSO_2 (%) "Stable" group	rSO_2 (%) "Unstable" group	P value
Baseline	56.1 ± 7.3	49.9 ± 8.6	0.01
10 minutes	55.9 ± 7.1	48.5 ± 9.0	0.005
20 minutes	55.8 ± 6.5	48.0 ± 9.2	0.003
30 minutes	56.1 ± 6.5	48.3 ± 9.1	0.002
1 hour	56.3 ± 6.7	48.3 ± 9.2	0.002
2 hours	56.4 ± 6.0	49.1 ± 9.4	0.004
3 hours	55.8 ± 7.3	48.1 ± 9.4	0.005
End	56.9 ± 6.6	48.3 ± 8.9	0.001

Unpaired t-test was used for comparison. "Stable" patients had rSO_2 variation <10 %, unstable >10 %; see the text for further explanation

rSO_2, presence of congestive heart failure and higher values of BNP also predicted lower rSO_2. The values of rSO_2 decreased at the beginning of hemodialysis and then after the 3rd hour, the first rSO_2 decline was related to the decrease of leukocyte count. Patients with congestive heart failure, higher BNP values and higher RDW had more pronounced rSO_2 fluctuation during hemodialysis.

It is already known that decompensated heart failure leads to rSO_2 decrease in non-CKD patients (Madsen *et al.* 2000). Thus, patients with cardiorenal syndrome type 2 or 4 according to Ronco (Granata *et al.* 2009), characterized by the presence of both heart failure and CKD (Cruz *et al.* 2013), are prone to circulatory instability. Two mechanisms could explain lower rSO_2 values in these patients: cerebral blood flow decrease due to lower cardiac output and dysfunction of cerebral vascular autoregulation, especially in response to changes of carbon dioxide level (Havakuk *et al.* 2017). Described changes could prolong cerebral blood transition time, which may be responsible for increased oxygen uptake by the brain tissue. NIRS combines arterial and venous blood hemoglobin saturation with the ratio 1:3, so rSO_2 was decreased mainly due to lower blood hemoglobin saturation in the venous blood due to slower blood flow and thus higher extraction of oxygen from hemoglobin.

Interestingly, rSO_2 values were lower in patients with higher red cell distribution width (RDW), higher RDW was also associated with bigger rSO_2 fluctuations during hemodialysis. Increase in RDW was previously reported in CKD patients (Ujszaszi *et al.* 2013, Docci *et al.* 1989). RDW describes the heterogeneity in erythrocytes size, high variability indicates dysfunctional erythropoiesis or shorter erythrocyte lifespan (Ujszaszi *et al.* 2013). RDW has been extensively studied recently: it was linked to malnutrition, inflammation, oxidative stress (Tekce *et al.* 2014) – all these states are present in ESRD patients on hemodialysis. Shorter erythrocyte lifespan has been documented in hemodialysis patients, it was linked to intradialytic hypoxemia resulting in lower erythrocyte resilience to oxidative stress (Meyring-Wösten *et al.* 2016). Higher RDW is a strong predictor of increased all-cause mortality, similar to albumin and even stronger than hemoglobin or ferritin in ESRD (Vashistha *et al.* 2016), coronary artery disease or other conditions. Nevertheless, no clear explanation of the detrimental effect of higher RDW is available – although some authors linked higher RDW to decreased red cell deformability and thus slower capillary flow (Patel *et al.* 2013), others did not confirm such association (Vaya *et al.* 2015). Therefore, higher RDW could be only an epiphenomenon instead of having direct causative role.

We observed a decrease of brain rSO_2 after the start of dialysis session, reaching its minimum in 15 min. These results confirm the observation made in our pilot study (Malik *et al.* 2017), although the decrease seems to occur sooner in the larger group and is less steep. A decrease in arterial oxygen saturation (SaO_2) after the beginning of hemodialysis was described previously by Campos *et al.* (2016), however, the SaO_2 value reached the minimum later in his study. In our study, the drop in rSO_2 value was significantly related only to the drop in leukocytes. Possible explanation is the activation of complement – its maximal activation develops 15 min after the start of hemodialysis (Yigla *et al.* 2006) and it is affected by the contact of blood with dialysis membrane.

The transient leukopenia during hemodialysis is usually explained by transient sequestration of leukocytes in pulmonary circulation mediated by complement activation (Remuzzi *et al.* 2014). The activation of complement may result in pulmonary dysfunction in dialysis patients (Craddock *et al.* 1977), however, we do not have any record of respiration problems in our patient group. In this study, we observed a second and even more pronounced drop of rSO_2 values after 3 hours since hemodialysis initiation. As far as this is a new observation, not apparent in our pilot study, we did not have related laboratory data that could explain it. We did not observe any significant relation with changes of blood pressure either. Anyway, in a recently published study using position-emission tomography (Polinder-Bos *et al.* 2018), cerebral blood flow significantly decreases towards the end of hemodialysis session.

Blood pressure dropped significantly after the start of hemodialysis and further decreased till its end, as is typical. Statistically, we did not find any relation between blood pressure (changes) and rSO_2. This finding suggests that even in this multimorbid elderly population, the cerebral autoregulation mechanisms are able to maintain stable cerebral blood flow in the wide range of blood pressure values, as in physiological conditions (Lassen 1959).

We are aware that the study has some limitations. Mainly it is its cross-sectional character that does not allow us to evaluate the changes of rSO_2 in longer time period. Nevertheless, up to now there is very limited data about rSO_2 in hemodialysis population and thus cross-sectional studies are important first steps.

Conflict of Interest

There is no conflict of interest.

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