



## Research paper

## EEG spectral changes induced by hemodialysis

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## ABSTRACT

**Objective:** To investigate the EEG spectral changes induced during hemodialysis in patients with chronic kidney disease (CKD), and to identify the risk factors associated with changes in the Central Nervous System (CNS) during hemodialysis. Paradoxical neurological deterioration at the end of hemodialysis sessions, known as dialysis disequilibrium syndrome (DDS) has been described, but previous studies on EEG spectral changes during hemodialysis were controversial.

**Methods:** We performed quantitative EEG spectral analysis in 56 consecutive patients who underwent hemodialysis. We compared EEG at the start and at the end of the hemodialysis, and we correlated the spectral changes with the biochemical and clinical characteristics of the patients, using multivariate analysis.

**Results:** At the end of hemodialysis sessions, we found a significant increase in total EEG power, relative power in delta frequency band and the ratio of delta-theta/alpha–beta power. EEG spectral changes were associated with younger age, recent start of hemodialysis therapy, level of uremia and lower level of glycaemia.

**Conclusions:** Quantitative EEG spectral analysis showed that hemodialysis induced slowing of the EEG background activity. These changes were associated with risk factors of DDS.

**Significance:** EEG spectral changes are potential biomarkers for monitoring CNS function during hemodialysis.

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## 1. Introduction

There have been controversial reports on EEG changes induced during hemodialysis in patients with chronic kidney disease (CKD). Early observational studies based on visual assessment of the recordings, reported increase in the slow EEG frequency components following hemodialysis: increase in theta activity and appearance of high amplitude delta potentials (Kennedy et al., 1963; Hampers et al., 1966). However, later studies using quantitative spectral analysis methods were not able to confirm these

observations (Kiley et al., 1976; Teschan et al., 1979; Basile et al., 1987; Arieff, 1994).

EEG changes induced during hemodialysis are important because they may elucidate the pathomechanisms and highlight the risk factors of a neurological complication occurring during or immediately after hemodialysis, coined dialysis disequilibrium syndrome (DDS) (Arieff, 1994; Patel et al., 2008; Zepeda-Orozco and Quigley, 2012; Mistry, 2019). Paradoxically, patients may show deterioration in their general condition toward the end of or immediately following hemodialysis: headache, nausea and vomiting, disorientation, asterixis and involuntary jerking movements. In rare cases, psychosis, generalized tonic-clonic seizures and coma may be seen.

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Our goal was to evaluate quantitative EEG changes induced during hemodialysis, using spectral analysis methods, and to identify risk factors associated with these changes.

## 2. Methods

We included consecutive patients with CKD, undergoing hemodialysis treatment three times per week. Patients gave their informed consent and the study has been approved by the Ethics Committee of Nefromed Dialysis Centers Cluj-Napoca.

Hemodialysis treatments were performed on 5008 Fresenius machines with synthetic (helixone) high flux membranes with surfaces adapted to body weight and blood-flow to achieve Kt/V at least 1.4 in 240 min. Kt/V is a way of measuring dialysis adequacy: K stands for urea clearance, (volume of blood water cleared of urea in time unit), t stands for time, V represents the distribution volume of urea, close of total water a patient's body contains. One third of the patients had online-hemodiafiltration targeting at least 21 l substitution per treatment. Bicarbonate solutions with glucose were used: Na = 138 mmol/l, K = 2 mmol/l, Ca = 1,5 mg/dl, bicarbonate = 30–34 mEq/l, glucose = 1 g/l. Each hemodialysis session had a duration of 210–270 min. At the end of the hemodialysis sessions, patients generally experienced mild symptoms, such as malaise and fatigue, but these were not severe and specific enough to be considered as DDS.

EEGs were recorded for the entire duration of the hemodialysis sessions (210–240 min), with an EBNeuro Galileo EEG equipment, using scalp electrodes Ag/AgCl EasyCap (B10-S-200) placed according to the international 10–20 system (Jasper 1958). Normal awake activities such as speaking, eating or watching television were allowed. The sampling frequency was 256 per second.

At the beginning and at the end of each hemodialysis sessions, an experimenter verbally alerted the patients and, after a short conversation with them, to keep vigilance, the patients were required to stay relaxed with open eyes for 2–3 min. Patients and EEGs were real-time monitored by the experimenter, to assess the vigilance. Of these periods, where the patient was awake, with open eyes, artifact-free epochs of 12 s (Kim, 2007) were identified and subsequently analyzed.

EEG was evaluated by two board-certified clinical neurophysiologists (BF and SB), in joint reading sessions, blinded to all clinical data. Signals were digitally filtered 0.5–30 Hz. In order to minimize any muscle artefacts, the central electrodes have been chosen for quantitative analysis: C3 (central left) and C4 (central right). An average of the values was calculated  $C_m = (C3 + C4)/2$ , for all the further studies. We used common average reference. We analyzed the following frequency bands: Delta (0.5–4 Hz), Theta (4–8 Hz), Alpha (8–13 Hz) and Beta (13–30 Hz). We calculated the Total Power (all bands), the Relative Power for each band (ratio of the power in the frequency band and the Total Power), and the Power Ratio between the slow and the high frequency powers:  $(\text{Delta} + \text{Theta})/(\text{Alpha} + \text{Beta})$ .

We measured End-Tidal Carbon Dioxide (EtCO<sub>2</sub>) – CO<sub>2</sub> concentration of the expired air through Stardust nasal cannula, pulse, EKG, respiratory rate (RR), pulseoximetry with a LifeSense Nonin Capnograph. At the start of the hemodialysis sessions the body mass was recorded, blood tests for Bicarbonate (ECO<sub>2</sub>), serum Na, K, Ca, serum creatinine, glucose and urea were performed and blood pressure (BP) was measured. The pH was recorded on the left anatomical snuffbox with a portable dermatology pH-meter Hanna Instruments (model HI 99181). The comorbidities of the patients were registered.

For statistical analysis, we calculated the median ( $\pm$ standard deviation) for those parameters with normal distribution and with median 25th–75th percentile) for parameters that did not have

normal distribution. We used Kolmogorov-Smirnov test for assessment of the normality of distribution. For each patient, two values for the Alpha, Theta, Delta and Beta parameters were obtained from the spectral analysis, one at the beginning and one at the end of hemodialysis. The initial and final values were compared by calculating the difference of each data-pair and comparing it to zero, using Student test for paired samples when data had normal distribution, and Wilcoxon test when distribution was not normal. In univariate analysis Pearson or Spearman coefficient of correlation were used to analyze the relationship between two quantitative variables. The univariate analysis was followed by multivariate analysis. We used linear regression model for multivariate analysis. Each EEG measurement parameter was the dependent variable, in a separate linear regression model. As independent variables, we used the variables that proved to be significantly correlated with the EEG measurement parameters in the univariate analysis. Probability p less than 0.05 was considered significant. The analysis was made using SPSS and Microsoft Excel.

## 3. Results

We included and analyzed 56 consecutive patients (20 female), aged between 32 and 86 years (mean: 59.82  $\pm$  12.76, median: 60.5 years). The patients had been treated with hemodialysis, between 1 month and 192 months (mean: 61.41  $\pm$  51.60, median: 42 months), and had the following comorbidities: high blood pressure (50 patients; 50.0%), diabetes (18 patients; 32.1%), hepatopathies (10 patients; 17.9%), thyroid disease (8 patients; 14.3%), epilepsy (3 patients; 5.4%), history of traumatic brain injury (3 patients; 5.4%). [Supplementary document 1](#) shows the biochemical and clinical parameters of the patients.

Hemodialysis resulted in a significant increase in Total EEG Power ([Table 1](#)). Spectral analysis showed increase in Relative Power of Delta band and an increase in the Power Ratio of the slow EEG components toward the end of hemodialysis ([Table 1](#)). Multivariate analysis showed that EEG changes induced by hemodialysis were associated with younger age, recent start of hemodialysis therapy, uremia and lower level of glycaemia ([Table 2](#)).

## 4. Discussion

Using EEG spectral analysis, we confirmed the early observations, based on visual evaluation, that reported increase in the slow EEG components, at the end of hemodialysis (Kennedy et al., 1963; Hampers et al., 1966). Previous studies using spectral analysis were not able to find such changes (Kiley et al, 1976; Teschan et al., 1979; Basile et al, 1987; Arieff, 1994). This could be due to several methodological aspects in the previous studies. EEG was analyzed for epochs when the patients were performing mental arithmetic exercises, which could have changed the EEG background activity. The power ratio in previous studies was calculated for 3–7/7–13 Hz, which does not include a significant portion (0.5–3.0 Hz) of the delta band. By including the whole delta frequency band, we found a significant increase in its relative power.

**Table 1**  
EEG changes during hemodialysis, demonstrated by spectral analysis.

Parameter	Start of hemodialysis	End of hemodialysis	p
Total Power [ $\mu V^2$ ]	14.54 (7.17, 20.7)	19.41 (12.98, 39.29)	<b>&lt;0.001*</b>
RP Delta [%]	0.32 $\pm$ 0.14	0.37 $\pm$ 0.19	<b>0.035*</b>
RP Theta [%]	0.14 (0.09, 0.2)	0.12 (0.09, 0.21)	0.967*
RP Alpha [%]	0.24 (0.14, 0.34)	0.2 (0.13, 0.32)	0.146*
RP Beta [%]	0.24 (0.19, 0.38)	0.23 (0.12, 0.32)	0.071*
Power Ratio	0.94 (0.57, 1.6)	1.08 (0.68, 2.04)	<b>0.033*</b>

RP = Relative Power; Power Ratio =  $(\text{Delta} + \text{Theta})/(\text{Alpha} + \text{Beta})$ .  
\* Wilcoxon rank-sum test; + Student t test for paired samples.

**Table 2**

Correlation between the biochemical and clinical parameters of the patients and the spectral EEG changes: significant correlation in univariate and multivariate analysis.

Dependent variable – EEG parameters difference <b>end-start</b> of dialysis	Independent variable–	Univariate analysis		Multivariate linear analysis	
		Coefficient of correlation	p	b (95% confidence interval)	p
Total Power	Age	–0.39	<b>0.003</b>	–1.456 (–2.734; –0.179)	<b>0.026</b>
	Bicarbonate	–0.28	<b>0.041</b>	–	–
	Urea	0.37	<b>0.005</b>	–	–
Delta Relative Power	Total duration of dialysis (months)	0.34	<b>0.011</b>	–	–
	Glycemia	–0.34	<b>0.013</b>	–0.001 (–0.002; 0)	<b>0.036</b>
	BW	–0.31	<b>0.020</b>	–	–
Theta Relative Power	Age	–0.27	<b>0.044</b>	–0.002 (–0.003; 0)	<b>0.030</b>
	Total duration of dialysis (months)	–0.32	<b>0.015</b>	–0.001 (–0.001; 0)	<b>0.011</b>
Alpha Relative Power	Glycemia*	0.38	<b>0.004</b>	–	–
	Body weight	0.29	<b>0.030</b>	–	–
Beta Relative Power	Glycemia	0.27	<b>0.047</b>	0.001 (0; 0.001)	0.047
Power Ratio	Age	–0.28	<b>0.039</b>	–	–
	Glycemia*	–0.34	<b>0.012</b>	–	–
	Urea	0.41	<b>0.002</b>	0.033 (0.008; 0.058)	<b>0.011</b>

\* Nonlinear relationship.

Since 1960', hemodialysis has proven a lifesaving treatment for patients with CKD. However, a paradoxical change in neurological status was noted in some patients, from the early days of hemodialysis. This deterioration consisted of headache, dizziness, nausea, vomiting, muscular cramps, tremor, convulsions, and altered states of consciousness were described as dialysis disequilibrium syndrome (DDS) (Arieff, 1994; Patel et al., 2008; Zepeda-Orozco and Quigley, 2012; Mistry, 2019). These unfavorable changes occurred especially in the first dialysis sessions and appeared when the correction of some biochemical parameters (especially urea) was too rapid. Hence, it was hypothesized that DDS was caused by cerebral edema and increased intracranial pressure, due to difference in osmolality between the rapidly dialyzed serum and the CSF that was lagging behind (Kennedy et al., 1963; Port et al., 1973).

We found that EEG spectral changes induced by hemodialysis were associated with younger age, recent start of hemodialysis therapy and with the level of uremia, which are similar to the risk factors for DSS mentioned above (Arieff, 1994; Patel et al., 2008). In addition, we found that lower glycaemia before hemodialysis was also associated with increase in delta relative power. It is well documented that hypoglycemia causes diffuse EEG slowing and lower glycaemia levels could predispose patients with CKD to the spectral changes during hemodialysis.

When using modern dialysis methods, clinically manifest DDS is a rare phenomenon. Although our patients generally experienced mild symptoms, such as malaise and fatigue at the end of the dialysis sessions, these were not severe and specific enough to be considered as DDS. However, we found significant spectral changes (slowing) after hemodialysis, and these changes were associated with the same risk factors that previously were reported for DSS, suggesting that the spectral changes revealed the pathomechanisms of CNS changes induced by dialysis.

## 5. Conclusions

We found that hemodialysis lead to slowing of the EEG background activity and increase in the relative power in delta frequency band. This is a potential biomarker for quantifying functional changes in the Central Nervous System during hemodialysis.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cnp.2021.03.006>.

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