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Egypt J Neurol Psychiatry Neurosurg (2023) 59:107
https://doi.org/10.1186/s41983-023-00704-9

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH

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Identification of small diameter nerve fiber damage in hemodialysis patients' hands using the cutaneous silent period

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Abstract

Background The arteriovenous fistula is the most effective vascular access option for hemodialysis patients. An important and largely unreported concern detected at follow-up is the complaints of tingling or numbness in the hands of those patients. Furthermore, the cutaneous silent period qualifies as a straightforward evaluation of small nerve fiber function. This study aims to evaluate the function of small-diameter nerve fibers in the hands of patients undergoing continuous hemodialysis (HD) on the side with the arteriovenous fistula (AVF) and on the contralateral side.

Results A cross-sectional study of 40 randomly chosen patients with chronic kidney disease on regular hemodialysis three times weekly the cutaneous silent period (CSP) was recorded on the hand with and without AV fistula. The cutaneous silent period (CSP) CSP was elicited by electrical square pulse stimulation using standard bipolar electrodes. The average cutaneous silent period onset and end latencies demonstrated significant prolongation in the hemodialysis patient group (arteriovenous fistula and non-arteriovenous fistula) compared with the control group. Correlation between cutaneous silent period with hemodialysis duration and adequacy of hemodialysis (KT\V). There was a statistically negative correlation observed between cutaneous silent period onset latency on the arteriovenous side and a positive correlation with KT\V on non-arteriovenous fistula. side.

Conclusions Hemodialysis patients recommended to undergo regular neurophysiological testing to check for small nerve fiber affection. In particular, measuring the cutaneous Silent period that provides a quick and noninvasive way to rule out small A-delta nerve malfunction. In addition, less nerve injury results from hemodialysis's increased efficiency.

Keywords Cutaneous silent period, Arteriovenous fistula, Hemodialysis

Introduction

Worldwide, by 2030, more than 5 million individuals are anticipated to have end-stage renal disease, a doubling of the current state [1]. In addition to having a higher mortality rate, those who get maintenance dialysis experience additional symptoms and have lower health-related quality of life (HRQOL) than the general population [2]. Uremic neuropathy is a factor in the lower HRQOL in dialysis patients [3].

Patients with chronic kidney disease (CKD) may develop polyneuropathy as a result of glomerulonephritis, diabetes, hypertension, or a multi-system concomitant disorder. It is generally known that individuals with CKD have a high prevalence of uremic polyneuropathy (UP), which ranges from 60% to 100%. The signs and symptoms of UP start at the foot distally, proceed slowly

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up the legs, and are symmetrical. Typically, patients have sensory symptoms, such as leg cramps, numbness, paresthesia, pain, and prickling. A small percentage of individuals express discomfort, pain, and hyperalgesia in their feet. Reports of restless legs are common [4].

An arteriovenous fistula is the greatest selection for vascular access in patients who need hemodialysis. However, A serious issue that usually goes unreported at follow-up is feelings of tingling or numbness in the hand [5].

Uremic polyneuropathy still significantly limits the quality of life for uremic patients despite adequate dialysis and transplant programs. Ischemic monomeric neuropathy and mononeuropathies linked to arteriovenous (AV) fistulas are very frequently described in CKD [4].

Only large-diameter myelinated fibers are evaluated in routine neurophysiological nerve conduction studies (NCS) and are unable to identify impairment in small-diameter nerve fibers by this method. While pain, hyperalgesia, and dysesthesia are symptoms of malfunction in small-diameter nerve fibers, paresthesia and numbness accompanying with UP frequently represent damage of large-diameter fibers [6].

The cutaneous silent period (CSP) empowers a simple evaluation of small nerve fiber function. A-delta nerve fibers that are thinly myelinated are excited by a noxious cutaneous stimulus on the fingertips, which temporarily suppresses voluntary muscle movement. Fingertip stimulation by high-intensity electrical stimulus affects both big and small-diameter fibers, eliciting complex excitatory and inhibitory responses that may partially overlap in a given muscle. The inhibition of muscular activation is referred to as a spinal inhibitory reflex [7]. The evaluation of the function of small-diameter nerve fibers is greatly aided by CSP, a supplemental approach to traditional NCS. However, it is uncommon for neurophysiological units to perform quantitative sensory testing on small and unmyelinated nerve fibers [8].

The goal of the present work was to evaluate the function of small-diameter nerve fibers in the hands of patients undergoing continuous hemodialysis (HD) on the side with the arteriovenous fistula (AVF) and on the contralateral side.

Methods

A cross-sectional study was conducted on 40 CKD patients receiving routine, three-times-per-week hemodialysis sessions at Al-Azhar University Hospital, internal medicine department, hemodialysis unite, new damietta, Egypt. A control group of 40 healthy individuals with similar gender and age distributions is also included in the study.

Hemodialysis technique: was performed three times per week, the dialysis session was 4 h in duration, using conventional heparin. Vascular access was through the arterio-venous fistula. The dialyzer used was a high flux poly-sulphone with a membrane surface area suitable for each patient The blood flow rate was 300–350 ml/min with a dialysate flow rate of 500 ml/min. Ultrafiltration varied rendering to the patient's actual weight. Bicarbonate was the buffer used throughout the study for all patients.

Inclusion criteria

Patients on maintenance hemodialysis, Patients older than 18 years, Both gender, Hemodialysis for more than 3 months.

Exclusion criteria

Individuals with illnesses that could lead to the development of polyneuropathies, such as diabetes, hypothyroidism, vitamin B12 deficiency, and alcoholics, patients with previously nonfunction AVF in the other arm of the functioning AVF, patients with permcath, and temporary catheters as vascular access, people with psychiatric illnesses, systemic inflammatory and malignant diseases, and patients taking medications that could affect their peripheral nerves, and patients who refused to participate in the study.

All included persons submitted the following: history including the duration of HD and the cause of ESKD, clinical examination including examination of arteriovenous fistula, Routine blood investigations, including CBC, blood urea, serum creatinine, parathormone, calcium, and adequacy of hemodialysis (Kt/V) was assessed using the urea kinetics index (Kt/V urea), which is a function of dialyzer urea clearance, treatment time, and urea distribution volume.

Equilibrated Kt/V formula:

$$\text{Dugirdas}: \text{kt}/v = -\ln\left(\frac{\text{postBUN}}{\text{preBUN} - .03}\right) + \left(\left(4 - 3.5 \times \frac{\text{postBUN}}{\text{preBUN}}\right) \times \frac{\text{UF}}{\text{weight}}\right)$$

where K is the effective clearance of urea, t is the duration of the session, and V is the volume of urea distribution. UF is ultrafiltration (weight loss), W is post-dialysis weight (dry weight), T is duration of the dialysis session.

When Kt/V is greater than or equal to 1.2, dialysis is regarded as efficient. The absolute minimum that must be maintained at all times is that. Any readings outside of that range signify an inadequate response to hemodialysis therapy.

The cutaneous silent period (CSP): The neurophysiological study was performed at neurophysiology unite

of neurology department, Al-Azhar University Hospital, New Damietta, Egypt. The neurophysiological parameters were verified on the hand with AV fistula and contralateral hand. The cutaneous silent period (CSP) was provoked by electrical square pulse stimulation using standard bipolar electrodes.

The cutaneous silent period (CSP) was produced by electrical stimulations on the tip of digit II by the bipolar electrodes. (80–100 mA intensity, 0.5 ms duration, 250 ms sweeps, 30 and 10,000 Hz filters). The recording was positioned on the muscle belly of the abductor pollicis brevis. A minimum of four distinct responses were occurred to determine CSP parameters. The onset latency was documented at the beginning of voluntary muscle activity inhibition, and the late latency at the start of new muscle activity. The change among the latencies designates the duration of CSP. All participants sat in a comfortable chair in a quiet room.

Statistical analysis

The statistics were prepared, arranged, and statistically analyzed using a statistical package for social science (SPSS) version 18 (SPSS Inc., USA, Chicago, Illinois). Numerical data existed as mean ± SD (standard deviation), while categorical data were offered as frequency and percent. *P* value < 0.05 was considered significant for the interpretation of results. Comparison between groups was done by independent samples (t) test for two means and one-way analysis of variance for more than two means with the least significant differences, the comparison was done by ANOVA with post hoc test Turkey Multinomial logistic regression and stepwise linear regression analysis.

Results

This study included 40 patients with chronic kidney disease on maintenance hemodialysis, the average age was (51.0 ± 10.9) years and males were 22 (55%) and females were 18 (45%) and 40 healthy persons as a control group the mean age (47.05 ± 10.5), 21 (52.5%) male and [19 (47.5%)] female with no statistically significant difference between both groups regarding age and sex. The co-morbid conditions in the hemodialysis group were 36 (90%) hypertension, 2 (5%) chronic hepatitis c, 8 (20%) cardiovascular disease, and 1 (2.5%) hyperparathyroidism. As regards to etiology of end-stage renal disease hypertension 36 (90%), (2.5%) contrast nephropathy, 3 (7.5%) glomerulonephritis, 3 (7.5%) post-transplantation rejection, 1 (2.5%) polycystic kidney disease and 2 (5.0%) with unknown etiology.

When hemodialysis patients (AVF and non-AVF) were comparable to the control group, the mean CSP onset and end latencies showed a significant prolongation. However, when comparable to the control group, hemodialysis patients (AVF and non-AVF) showed no any significant variations in the length of CSP (Table 1).

Correlation between CSP with hemodialysis duration and KT\V. There was a statistically negative correlation between CSP onset latency on the AVF side and a positive correlation with KT\V on non AVF side. In addition, there was a statistically negative correlation between CSP end latency and HD duration on the AVF and non-AVF sides. There is a statistically negative correlation observed between CSP duration with HD duration on the AVF side and other side (Table 2).

The stepwise linear regression analysis of the possible predictors of hemodialysis duration as a dependent variable and other possible independent predictors. AVF CSP duration was a significant negative predictor for longer

Table 2 Correlation between CSP and hemodialysis duration and KT\V

Hand side	AVF		Non AVF	
	HD duration	KT\V	HD duration	KT\V
CSP onset latency				
Pearson Correlation	− 0.356*	0.194	− 0.263	0.402*
Sig. (two-tailed)	0.024	0.230	0.101	0.010
CSP end				
Pearson Correlation	− 0.392*	− 0.181	− 0.396	0.289
Sig. (two-tailed)	0.012	0.263	0.011	0.070
CSP duration				
Pearson Correlation	− 0.413*	0.186	− 0.378*	0.132
Sig. (two-tailed)	0.008	0.250	0.016	0.418

CSP Cutaneous silent period, *KT\V* adequacy of hemodialysis, *AVF* arteriovenous fistula

*statistically significant

Table 1 Cutaneous silent period onset, end latencies and duration (CSP) (mean ± SD)

Characteristics	Patients AV	Patients non-AV	Control	ANOVA^{+}
CSP onset latency (ms)	89.6 ± 11.6$^{\beta}$	88.3 ± 8.8$^{\beta}$	54.1 ± 8.0	*P* < 0.001*
CSP end latency (ms)	146 ± 2.3$^{\beta}$	144.3 ± 15.6$^{\beta}$	120.7 ± 9.4	*P* < 0.001*
CSP duration (ms)	58.5 ± 9.4	60.7 ± 9.4	61.3 ± 9.1	*P* = 0.391

CSP Cutaneous silent period, *AV* arteriovenous fistula, *statistically significant, $^{\beta}$significant to controls, $^{+}$post hoc Tukey

Table 3 CSP parameters as predictors of hemodialysis duration

Model	Beta coefficients	*t*	Sig.
(Constant)		0.075	0.941
AVF CSP onset latency	− 0.147	− 0.728	0.475
non AVF CSP onset latency	− 0.128	− 0.555	0.585
AVF CSP end	0.168	0.723	0.478
non AVF CSP end	0.677	1.175	0.253
AVF CSP duration	− 2.141	− 3.618	0.002
non AVF CSP duration	1.716	2.749	0.012

CSP Cutaneous silent period, *AVF* arteriovenous fistula

Table 4 CSP parameters as predictors of Kt\v

Model	Beta coefficients	*t*	Sig.
AVF CSP onset latency	− 0.257	− 0.659	0.517
non AVF CSP onset latency	0.019	0.042	0.967
AVF CSP end	0.200	0.444	0.662
non AVF CSP end	− 0.821	− 0.738	0.469
AVF CSP duration	0.877	0.766	0.452
non AVF CSP duration	0.059	0.049	0.961

CSP Cutaneous silent period, *AVF* arteriovenous fistula

hemodialysis duration. Conversely, non-AVF CSP length had a strong positive prediction of longer hemodialysis duration (Table 3).

The stepwise linear regression analysis of the possible predictors of hemodialysis duration as a dependent variable and other possible independent predictors. CSP end had no significant prediction of longer Kt\v (Table 4).

Discussion

forty randomly selected CKD patients undergoing continuous hemodialysis are included in this a cross-sectional study along with 40 healthy volunteers who are harmonized for age and gender. The goal of the present work was to evaluate the function of small-diameter nerve fibers in the hands of patients undergoing continuous hemodialysis (HD) on the side with the arteriovenous fistula (AVF) and on the contralateral side.

The majority of hemodialysis (HD) patients exhibit symptoms of uraemic neuropathy, a condition for which there was no known treatment. Although the exact origin of uraemic neuropathy is unknown, continuous exposure to intermediate molecules or other solutes such as potassium may be a contributing factor [9]. Dialysis patients who have uremic peripheral neuropathy have an underappreciated clinical symptom that significantly lowers their quality of life.

The majority of patients receiving continuous hemodialysis have an increase in clinical and neurophysiological manifestations of polyneuropathy despite advancements in dialysis technology [10]. Morbidity due to uremic neuropathy is anticipated to rise along with the number of dialysis patients, the percentage of patients who also have diabetes, and the length of the kidney transplant waiting list [9]. Large, fast-conducting nerve fibers in the lower leg, which are usually affected by accelerated uremic neuropathy and have been found to considerably improve after dialysis, are the focus of the majority of electrophysiological research [11].

A good method for primarily identifying the function of A delta fibers is CSP estimation. CSP latency measures the synaptic delay that accompanied an inhibitory spinal response as well as conduction from A-delta afferents to efferent motor axons [12].

The results of this study showed the average CSP onset and end latencies were significantly prolonged in the hemodialysis patient group (AVF and non-AVF) when compared with the control group, but the duration of CSP showed no significant differences among hemodialysis patients (AVF and non-AVF) when compared with the control group. This is similar to a study by Denislic and colleagues 2015 [6] who demonstrated that the hemodialysis patients' mean CSP onset latency was considerably longer than that of the control group (control group confidence interval was 51.2–64.1 ms; healthy versus AV besides the healthy versus non-AV, $p < 0.0001$). A similar association was detected for CSP end latencies. Measurement of CSP duration and muscular activity inhibition failed to distinguish between the groups. In contrast to our study, there was a study by Kayacan and colleagues (2011) [13] of twenty patients who demonstrated persistent shortening of CSP duration, a sign of thin fiber uremic neuropathy.

A chief step in the progress of the prolongation of the onset of CSP latency may be the ischemic aspect owing to the A–V fistula [14] Some authors propose the existence of severe carpal tunnel syndrome accompanying polyneuropathy in hemodialysis patients [15]. There is an excessive probability that the small unmyelinated nerve fibers stay extra sensitive to ischemia than the large myelinated fibers [16].

This study demonstrates the correlation between CSP with hemodialysis duration and KT\V. There is a statistically negative correlation was detected between CSP onset latency on the AVF side and a positive correlation with KT\V on non AVF side. In addition, there was a statistically negative correlation noted between CSP end and HD duration on the AVF and non-AVF side. There was a statistically negative correlation observed between CSP duration with HD duration on the AVF side and other side (Table 2).

The stepwise linear regression analysis of the possible predictors of hemodialysis duration as a dependent

variable and other possible independent predictors. AVF CSP duration was a significant negative predictor for longer hemodialysis duration. Conversely, the non-AVF CSP duration had a strong positive prediction of longer hemodialysis duration (Table 3).the stepwise linear regression analysis of the possible predictors of hemodialysis duration as a dependent variable and other possible independent predictors (Table 4) These signify that the duration of CKD influences the level of nerve fiber damage

A study by Tirić-Čampara and colleagues [16] included 35 healthy volunteers and 38 consecutive hemodialysis patients. The results of the study established that in patients with A–V fistulas, a significant prolongation of the onset CSP latency was attained (p<0.001); however, CSP's duration remained unchanged. And concluded that in patients undergoing hemodialysis, the significant impairment of small nerve fibers was documented. The evaluation of small nerve fibers helps to determine how well the peripheral nervous system functions as a whole.

Conclusion

Hemodialysis patients should undergo regular neurophysiological testing to check for small nerve fiber affection. In particular, measuring the cutaneous Silent period provides a quick and noninvasive way to rule out small A-delta nerve malfunction. In addition, less nerve injury results from hemodialysis's increased efficiency.

Abbreviations

AVF	Arteriovenous fistula
CKD	Chronic kidney disease
CSP	Cutaneous silent period
HD	Hemodialysis
HRQOL	Health-related quality of life
KT/V	Adequacy of hemodialysis
UP	Uremic polyneuropathy
UF	Ultrafiltration

Acknowledgements

Not applicable.

Author contributions

AS contributed to the research idea, methodology, data collection, analysis and data interpretations, general supervision of the research group, writing of the manuscript, drafting and revising the manuscript. HA contributed of data collection, data analysis, data interpretations, writing of the manuscript, drafting and revising the manuscript. All authors read and approved the final manuscript.

Funding

No funding sources for this research had been declared (financial or non-financial). Funding was provided by the researchers.

Availability of data and materials

Findings on which the conclusions of the manuscript rely are summarized in the manuscript. For further inquiries, please contact the corresponding author.

Declarations

Ethics approval and consent to participate

The study was accepted by the local Ethics committee of Damietta Faculty of Medicine Al-Azhar University. Registration Number: DFM-IRB 00012367-22-02-007. Issuing and Expiration Date: 17-2-2022 valid until 16/02/2024, The research is acceptable according to the guidelines and declaration of Helsinki and the committee standard operating procedure guidelines. Damietta Faculty of Medicine IRB, Al-Azhar University, Egypt. Before contributing to the study, the process was explained to each person, and verbal and written consent was provided by each person of the contributors, and was accepted by the ethical committee as the study practice does not obstruct any medical circumstances and has no effects on the health of contributors.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Received: 13 May 2023 Accepted: 4 July 2023
Published online: 07 August 2023

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