Relationships between glomerular filtration rate and HRV/EEG parameters

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Abstract

Background. Sympathetic outflow may be capable of selectively increasing or decreasing glomerular capillary pressure and hence glomerular filtration rate (GFR) by differentially activating separate populations of renal nerves. Sympathetic outflow to the kidney is regulated by major cortical, brainstem and medullary areas. The purpose of this study is to find out the relationship between GFR and HRV/EEG parameters as markers of the neural regulation of the kidney.

Materials and Methods. The object of observations were 10 men aged 37-69 years without clinical diagnosis tested twice with 7-days interval. The rate of glomerular filtration was calculated according to endogenous creatinine clearance and the Cockcroft & Gault formula. The state of the autonomic nervous system was assessed by the HRV method. Simultaneosly qEEG recorded.

Results. For the sample as a whole, a weak (r=0.396; p>0.05) correlation was found between HRV-marker of sympathetic tone and GFR. However, two clusters of individuals can be distinguished: with a strong correlation (r=0.852; n=12) and its complete absence (n=8). The qEEG method revealed neural structures generating delta and theta rhythms that upregulate GFR, and generating beta rhythm that downregulate GFR. The regression model, which includes 16 EEG parameters, allows estimating GFR with a standard error of 3,4 mL/min.

Conclusion. Glomerular filtration rate is subject to the modulatory regulatory influence of the nervous system and can be estimated with high accuracy by EEG parameters.

INTRODUCTION

The renal nerves constrict the renal vasculature causing decreases in renal blood flow (RBF) and glomerular filtration rate (GFR). Whether renal hemodynamics are influenced by changes in renal nerve activity within the physiological range is a matter of debate. Denton et al [3] have identified two morphologically distinct populations of nerves within the kidney, which are differentially distributed to the renal afferent and efferent arterioles. TYPE I nerves almost exclusively innervate the afferent arteriole whereas TYPE II nerves are distributed equally on the afferent and efferent arterioles. Authors have also demonstrated that TYPE II nerves are immuno-reactive for neuropeptide Y while TYPE I nerves are not. This led them to hypothesise that in the kidney, distinct populations of nerves innervate specific effector tissues and that these nerves may be selectively activated, setting the basis for the differential neural control of GFR. In physiological studies, authors demonstrated that differential changes in glomerular capillary pressure occurred in response to graded reflex activation of the renal nerves, compatible with their hypothesis. Thus, sympathetic outflow may be capable of selectively increasing or decreasing glomerular capillary pressure and hence GFR by differentially activating separate populations of renal nerves. This has important implications for our understanding of the neural control of body fluid balance in health and disease.

Sympathetic outflow to the kidney is regulated by major cortical, brainstem and medullary areas [4,8].

The purpose of this study is to find out the relationship between GFR and HRV/EEG parameters as markers of the neural regulation of the kidney.

MATERIALS AND METHODS

The object of observations were 10 men aged 37-69 years and weight 75-100 kg without clinical diagnosis, tested twice with 7-days interval. Daily urine was collected on the eve, in which determined the concentration of creatinine (by Jaffe's color reaction by Popper's method [5]). Next day creatinine determined in serum. The rate of glomerular filtration was

calculated according to endogenous creatinine clearance and the Cockcroft DW & Gault MH [2] formula.

To assess the parameters of heart rate variability (HRV), recorded electrocardiogram during 7 min in II lead (hardware-software complex "CardioLab+HRV" produced by "KhAI-Medica", Kharkiv, Ukraine). For further analyses the following parameters HRV were selected. Temporal parameters (Time Domain Methods): heart rate (HR), the standard deviation of all NN intervals (SDNN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD), the percent of interval differences of successive NN intervals greater than 50 ms (pNN_{50}), triangular index (TNN). Spectral parameters (Frequency Domain Methods): power spectral density (PSD) bands of HRV: high-frequency (HF, range $0,4 \div 0,15$ Hz), low-frequency (LF, range $0,15 \div 0,04$ Hz), very low-frequency (VLF, range $0,04 \div 0,015$ Hz) and ultralow-frequency (ULF, range $0,015 \div 0,003$ Hz). We calculated classical indexes: LF/HF, LFnu=100%•LF/(LF+HF), Centralization Index (VLF+LF)/HF [1,6].

Simultaneosly qEEG recorded at rest a hardware-software complex "NeuroCom Standard" (KhAI Medica, Kharkiv, Ukraine) monopolar in 16 loci (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2) by 10-20 international system, with the reference electrodes A and Ref on the earlobes. Two minutes after the eyes had been closed, 25 sec of artifact free EEG data were collected by computer. Among the options considered the average EEG amplitude (μV), average frequency (Hz), frequency deviation (Hz), index (%), absolute (μV^2/Hz) and relative (%) PSD of basic rhythms: β ($35 \div 13$ Hz), α ($13 \div 8$ Hz), θ ($8 \div 4$ Hz) and δ ($4 \div 0,5$ Hz) in all loci, according to the instructions of the device.

We calculated also for HRV and each locus of EEG the Entropy (h) of normalized PSD using Popovych's IL [10]:

$$hEEG = - [PSD\alpha \cdot \log_2 PSD\alpha + PSD\beta \cdot \log_2 PSD\beta + PSD\theta \cdot \log_2 PSD\theta + PSD\delta \cdot \log_2 PSD\delta]/\log_2 4;$$

$$hHRV = - [PSDHF \cdot \log_2 PSDHF + PSDLF \cdot \log_2 PSDLF + PSDVLF \cdot \log_2 PSDVLF + PSDULF \cdot \log_2 PSDULF]/\log_2 4.$$

For statistical analysis used the software package "Microsoft Excell" and "Statistica 6.4 StatSoft Inc" (Tulsa, OK, USA).

RESULTS

The screening revealed only a weak linear correlation between GFR and PSD LFnu as a marker of sympathetic tone (Fig. 1). However, the sample can be divided into two clusters. In the larger cluster (n=12) there is a strong direct correlation, but in the smaller cluster (n=8) it is completely absent.

GF = 63,4 + 0,646*LFnu
Correlation: r = 0,396

$y = 2,26x - 59,4$
$R^2 = 0,727$

$y = 0,023x + 105,5$
$R^2 = 0,004$
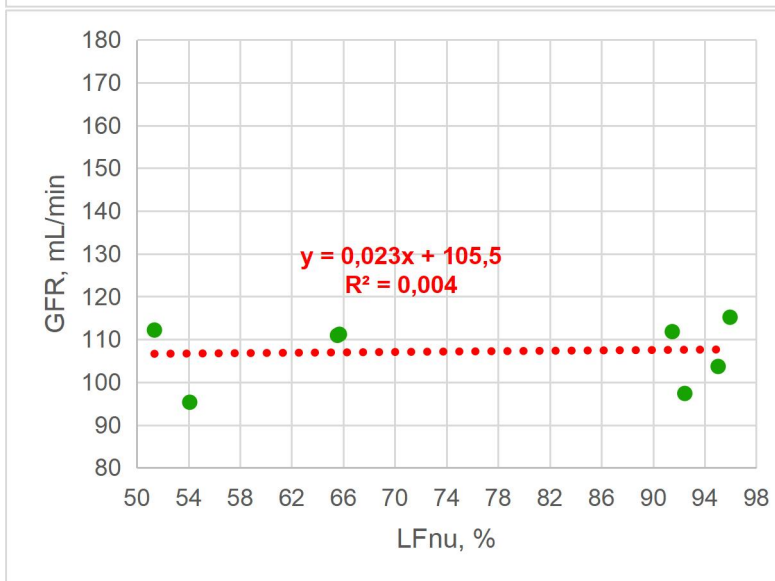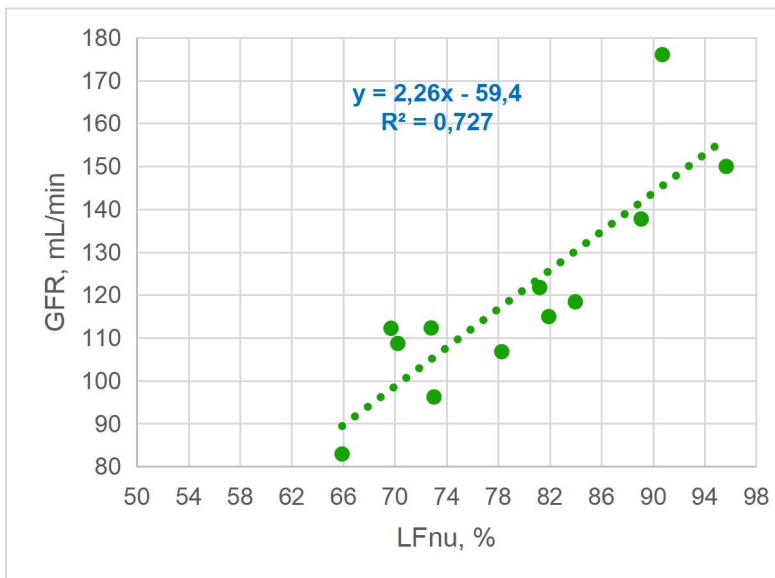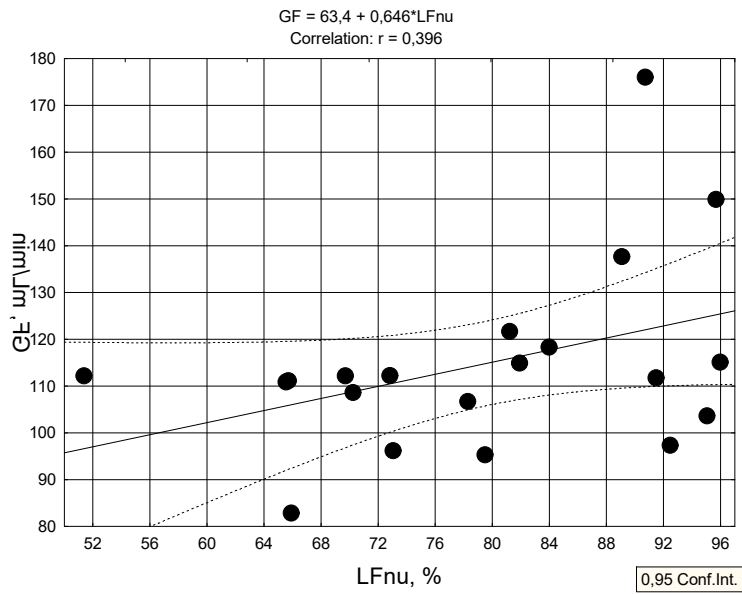
Fig. 1. Scatterplot of correlation between LFnu HRV (X-line) and glomerular filtration rate (Y-line)

The lack of correlation is consistent with the concept of the graded response of the 3 renal neuroeffectors to graded increases in the frequency of renal sympathetic nerve stimulation. At the lower frequency range, there is stimulation of renin secretion rate (RSR), without effects on urinary sodium excretion ($U_{Na}V$), RBF, or GFR. At slightly higher frequencies, there is stimulation of RSR and decrease in $U_{Na}V$, without effects on RBF, or GFR [4]. However, our data contradicts another provision of the stated concept that at higher frequencies, there is stimulation of RSR and a decrease in $U_{Na}V$ and renal vasoconstriction, with decreased RBF and GFR [4]. Apparently, in this situation, there is an increase in cardiac output and RBF caused by the sympathetic influence.

Contrary to the expectation that arose from previous studies [10,11,12], this study did not reveal a significant relationship between LFnu and EEG parameters (Fig. 2).
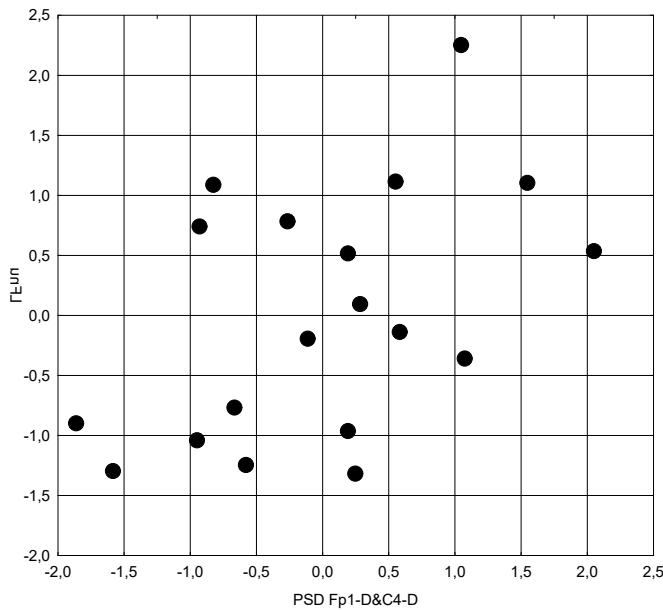
R=0,479; R^2=0,230; χ$^2_{(2)}$=4,2; p=0,124; Λ Prime=0,770
Fig. 2. Scatterplot of canonical correlation between PSD Fp1-δ and C4-δ EEG (X-line) and LFnu HRV (Y-line)

Screening revealed significant relationships between GFR and a number of EEG parameters. The strongest positive correlation was with PSD Fp1-δ (Fig. 3), and negative – with PSD C3-β (Fig. 4).
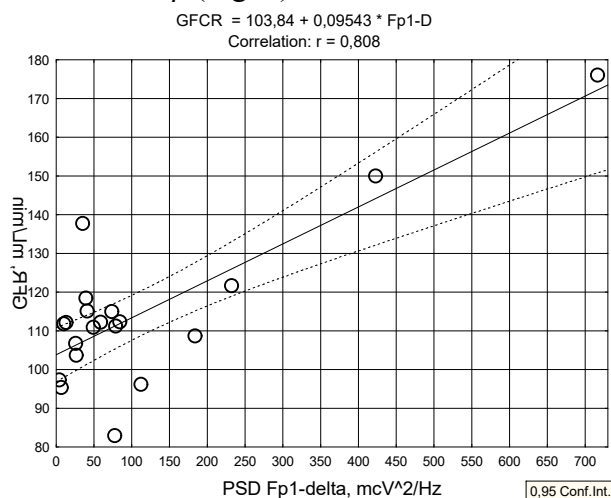

Fig. 3. Scatterplot of correlation between PSD Fp1-δ (X-line) and glomerular filtration rate (Y-line)

GFR = 141,90 - 1,121*C3-B%
Correlation: r = -0,580
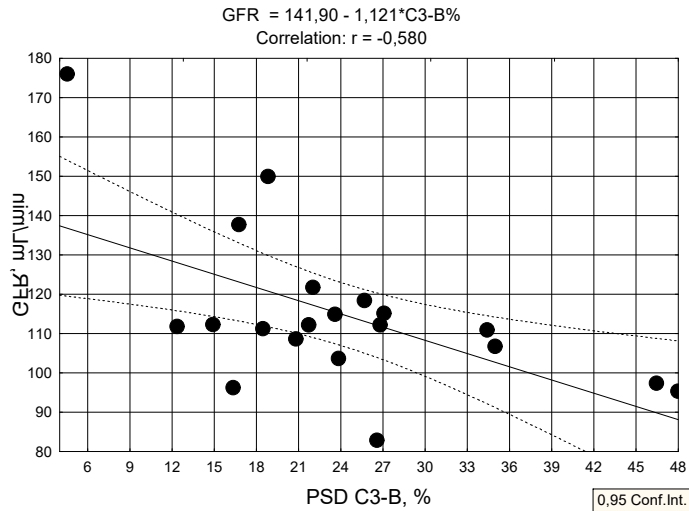
Fig. 4. Scatterplot of correlation between PSD C3-β (X-line) and glomerular filtration rate (Y-line)

In general, were revealed neural structures generating delta and theta rhythms that upregulate GFR, and generating beta rhythm that downregulate GFR. Another downregulating factor was entropy (Table 4).

Table 4. Regression Summary for GFR

$R=0,998$; $R^2=0,996$; Adjusted $R^2=0,972$; $F_{(16,3)}=42$; $p=0,005$; SE of estimate: 3,4 mL/min

N=20		Beta	St. Err. of Beta	B	St. Err. of B	$t_{(3)}$	p-level
Variables	r		Intercpt	163,3	15,1	10,8	0,002
PSD Fp1-δ, µV²/Hz	**0,81**	-0,479	0,270	-0,057	0,032	-1,77	0,175
PSD Fp1-δ, %	**0,60**	2,743	0,378	2,372	0,327	7,26	0,005
PSD T4-θ, µV²/Hz	**0,72**	2,090	0,213	1,701	0,173	9,81	0,002
PSD C4-δ, µV²/Hz	**0,69**	-2,176	0,207	-0,141	0,013	-10,5	0,002
PSD C4-δ, %	**0,47**	1,826	0,170	1,589	0,148	10,7	0,002
PSD F8-δ, µV²/Hz	**0,61**	1,462	0,149	0,102	0,010	9,81	0,002
PSD C4-θ, µV²/Hz	**0,60**	-1,594	0,251	-1,058	0,167	-6,34	0,008
PSD T4-δ, µV²/Hz	**0,50**	0,330	0,137	0,033	0,014	2,41	0,095
PSD T4-δ, %	**0,48**	-4,818	0,540	-4,871	0,546	-8,92	0,003
PSD F4-θ, µV²/Hz	**0,47**	1,381	0,232	1,386	0,233	5,95	0,009
PSD C3-θ, µV²/Hz	**0,46**	0,495	0,139	0,336	0,094	3,56	0,038
PSD C3-β, %	**-0,58**	-0,686	0,130	-1,326	0,252	-5,27	0,013
PSD Fp1-β, %	**-0,53**	2,674	0,303	3,703	0,420	8,81	0,003
PSD T4-β, %	**-0,51**	-2,613	0,371	-3,969	0,564	-7,04	0,006
PSD T3-β, %	**-0,46**	0,432	0,163	0,524	0,198	2,66	0,077
PSD Fp1 Entropy	**-0,55**	-0,144	0,079	-22,21	12,19	-1,82	0,166

Taken together, these neural structures account for 97.2% of GFR (Table 4 and Fig. 5).
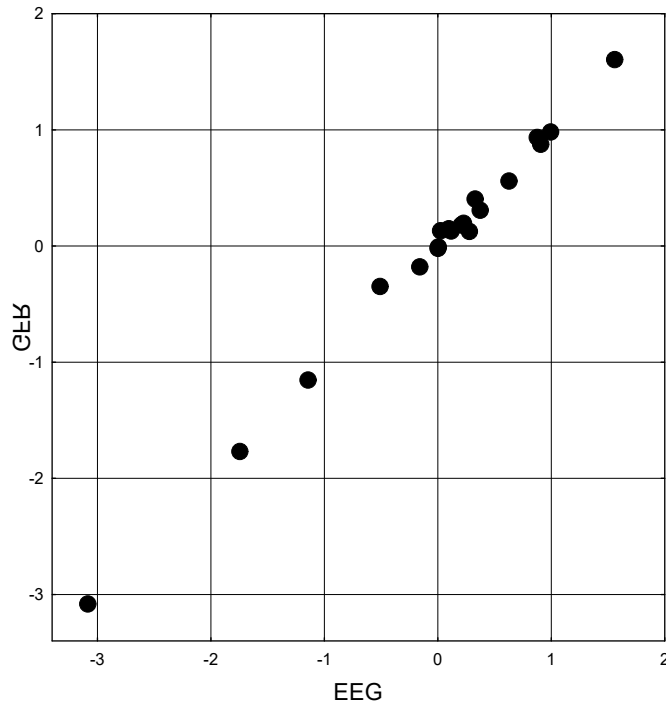
R=0,998; R²=0,996; $\chi^2_{(16)}$=54; p<10⁻⁵; Λ Prime=0,004
Fig. 5. Scatterplot of canonical correlation between EEG parameters (X-line) and glomerular filtration rate (Y-line)

DISCUSSION

The relationship between EEG parameters and glomerular filtration rate (GFR) has been a subject of recent research interest. The findings suggest a strong correlation between EEG parameters and GFR, indicating a significant influence of the nervous system on glomerular filtration. This correlation has led to the development of a regression model that allows for the non-invasive estimation of GFR with high accuracy, which could have important clinical implications. Specifically, neural structures generating delta and theta rhythms have been identified to upregulate GFR, while those generating beta rhythm downregulate GFR [14].

Studies have explored various aspects related to kidney function and GFR. For instance, research has investigated the impact of baseline GFR on subsequent changes in GFR in patients with chronic kidney disease (CKD). The relationship between kidney size parameters, such as cortical and medullary thickness, and GFR among living kidney donors has been examined. The correlation between kidney size on computed tomography and GFR, creatinine, and HbA1C in patients with diabetes and/or chronic kidney disease has been explored [15,16,17].

The use of EEG as an adjunctive neuropsychological assessment in clinics for individuals with chronic stroke has been recommended, especially for those who may have difficulty with conventional assessments [18]. Studies have investigated the association between brain natriuretic peptide (BNP) levels in acute heart failure and their relationship with GFR, highlighting BNP as a popular biomarker for acute heart failure [19].

The research on the correlation between EEG parameters and GFR sheds light on the intricate relationship between the nervous system and kidney function. Understanding these connections can have significant implications for clinical practice, especially in the diagnosis and management of conditions affecting kidney health.

The study on the relationship between EEG parameters and glomerular filtration rate (GFR) sheds light on the neural regulation of kidney function. While the results partially confirm the concept of a graded response of renal neuroeffectors to neural stimulation, they also suggest more complex relationships. The lack of a strong correlation between LFnu HRV and GFR for the entire sample challenges previous assumptions about the influence of the sympathetic system on GFR [20]. This discrepancy highlights the need for further research to elucidate the intricate interplay between neural activity and kidney function.

Recent studies have explored the mechanisms underlying neural entrainment and oscillatory responses in various brain regions. Investigations into deep brain stimulation have revealed resonant beta-band evoked oscillations in the pallidum of Parkinson's disease patients, providing insights into neural dynamics in pathological conditions [21]. Studies on brain responses to different types of current stimulation, such as interferential current and alternating current stimulation, have offered valuable information on brainwide activation patterns and neural network responses [22].

The exploration of neural stimulation techniques, such as vagus nerve stimulation and renal nerve stimulation, for modulating neural activity for therapeutic purposes has been ongoing [23,24]. These studies underscore the significance of understanding neural responses to stimulation in optimizing treatment strategies for conditions like epilepsy and hypertension.

The evolving research on neural responses to stimulation contributes valuable insights into the intricate interplay between neural activity and physiological processes. By delving into the neural correlates of various stimulation modalities, researchers can advance our comprehension of neural regulation and potentially identify novel therapeutic approaches for neurological and renal disorders.

The LFnu-GFR correlation analysis revealed the presence of two clusters, suggesting the existence of different GFR regulation mechanisms among individuals [25].

This complexity underscores the intricate regulatory processes influencing glomerular filtration rate. The impact of delta and theta brainwave rhythms on GFR may implicate subcortical structures in kidney function regulation [26]. These slower brainwave frequencies appear to significantly modulate kidney function. The negative correlation between beta rhythm and GFR may indicate the inhibitory role of the cerebral cortex on glomerular filtration [27]. This emphasizes the complex interplay between neural activity and kidney function regulation.

Research has explored the dynamics of brain rhythms and their implications for various physiological and cognitive processes. For example, studies on the temporal and spatial propagation of EEG signals have provided insights into brain activity dynamics, particularly in conditions like childhood absence epilepsy [28]. Investigations into resting-state brain rhythms have illuminated how these oscillations influence cognitive functions such as vocabulary acquisition [29]. The effects of closed-loop ultrasound stimulation on neural oscillations has highlighted the modulatory potential of external stimuli on brainwave patterns [30].

Understanding the intricate relationships between different brainwave frequencies and their effects on physiological processes like kidney function is essential for advancing our understanding of neural regulation mechanisms. By delving into the nuances of neural oscillations and their associations with physiological parameters, researchers can uncover novel insights into the complex interplay between neural activity and organ function. This variability underscores the complexity of processes influencing glomerular filtration rate. The influence of delta and theta brainwave rhythms on GFR may point to the involvement of subcortical structures in kidney function regulation [31,32]. These slower brainwave frequencies seem to significantly impact kidney function. The negative correlation between beta rhythm and GFR may reflect the inhibitory role of the cerebral cortex on glomerular

filtration [33]. This negative relationship highlights the intricate interplay between neural activity and kidney function regulation.

Understanding the complex relationships between heart rate variability (HRV) parameters and neural activity can offer valuable insights into the regulatory mechanisms affecting physiological processes like kidney function. Exploring the connections between different brainwave frequencies and HRV metrics can lead to a deeper comprehension of the interaction between neural activity and organ function regulation.

The developed method of estimating GFR based on EEG parameters may provide an alternative to invasive methods of assessing kidney function. This innovation could offer a non-invasive and potentially more accessible approach to monitoring kidney health [34].

Understanding the neural regulation of GFR could lead to new therapeutic strategies in kidney diseases. Insights gained from studying the neural influences on kidney function may pave the way for novel treatment modalities targeting the neural pathways involved in renal regulation [35].

Monitoring EEG parameters could potentially serve for early detection of kidney function disorders. By leveraging EEG technology for regular monitoring, healthcare providers may be able to detect changes in neural activity that could signal early signs of kidney dysfunction, enabling timely intervention and management [36].

Directions for Future Research: 1. Conduct studies on a larger and more diverse group, including individuals with kidney diseases, to enhance the generalizability of the results Phakdeekitcharoen et al. [37,38]. 2. Investigate how the relationships between EEG and GFR change in various pathological states and under the influence of treatment to understand the dynamics of neural regulation in kidney diseases [39,40]. 3. Conduct longitudinal studies to assess whether changes in EEG precede alterations in GFR, providing insights into the predictive value of neural activity for kidney function [41,42]. 4. Explore the physiological mechanisms underlying the observed correlations between EEG parameters and GFR to deepen the understanding of the neural regulation of kidney function [43,44].

The study discussed in the scientific article highlights the significant relationship between EEG parameters and glomerular filtration rate (GFR), indicating a profound influence of the nervous system on kidney function. The research introduces a regression model that enables the accurate estimation of GFR non-invasively, which holds crucial implications for clinical practice. It identifies neural structures responsible for generating delta and theta rhythms that enhance GFR and those producing beta rhythm that diminish GFR [45].

The references selected to support this discussion include studies on chronic kidney disease (CKD), renal insufficiency, and kidney function. These references provide insights into the complexities of kidney diseases, the impact of baseline GFR on subsequent changes in GFR, and the correlation between kidney size, biochemical parameters, and GFR estimation formulas in various patient populations [46,47,48]. Studies on living kidney donors, renal hemodynamics, and kidney transplantation shed light on the importance of assessing parameters like kidney size and GFR in clinical settings [49,50,51].

Research on pediatric kidney transplant recipients, neuroendocrine tumors, and metabolic syndrome in patients with lupus nephritis offers valuable information on monitoring GFR, arterial stiffness, and the relationship between specific diseases and kidney function [52,53,54]. These references collectively contribute to the understanding of the intricate interplay between neural activity, kidney function, and various health conditions, emphasizing the significance of accurate GFR estimation and its clinical implications.

To address the concern regarding the lack of a control group with impaired kidney function in the study, it is essential to consider references that discuss chronic kidney disease (CKD) and its impact on glomerular filtration rate (GFR). One relevant reference is the study

by [55], which focuses on evaluating thyroid hormone levels and lipid profiles in CKD patients and establishing their correlation with disease severity. This reference provides insights into the pathophysiological processes associated with poor kidney function and decreased GFR in CKD patients.

The work [56], which delves into modeling the glomerular filtration barrier and the development of proteinuria, a common early pathological characteristic in chronic kidney diseases like diabetes and hypertension. Understanding the mechanisms leading to proteinuria is crucial in comprehending the progression of kidney diseases and their impact on GFR.

The study [57] investigates kidney function impairment in men with primary infertility, highlighting the association between kidney function and infertility status. This reference sheds light on the potential implications of kidney function abnormalities in specific patient populations and emphasizes the importance of considering kidney health in various clinical contexts. Explore the relationship between kidney function, CKD, and associated pathologies, researchers can gain a more comprehensive understanding of the implications of impaired kidney function on GFR and its relevance in pathological conditions.

To address the concern about potential confounding factors such as age, gender, and comorbidities not being accounted for in the study, it is crucial to consider references that discuss the impact of these factors on disease severity and outcomes. One relevant reference is the study [58], which examines the correlation of pre-existing comorbidities with disease severity in individuals infected with the SARS-COV-2 virus. This reference highlights the importance of considering comorbidities in assessing disease severity, emphasizing the need to account for such factors in research studies.

The work [59], which conducts a meta-analysis on the impact of comorbidities and complications, along with age, gender, obesity, and smoking history, on the severity of COVID-19. This study underscores the significance of demographic characteristics and comorbidities in influencing disease outcomes, providing valuable insights into the interplay of these factors.

The study [60] explores biometric covariates and outcomes in COVID-19 patients, highlighting older age, male gender, and an increased number of comorbidities as risk factors for poor outcomes. Understanding how these factors contribute to disease progression is essential for comprehensive research and accurate interpretation of study results. The influence of age, gender, and comorbidities on disease severity and outcomes, researchers can enhance the validity and reliability of their findings by accounting for these important confounding factors.

The study's limitation of a relatively small number of subjects (n=10) impacting the generalizability of the results can be addressed by referencing studies that discuss the importance of sample size determination and its implications on research outcomes. One relevant reference is the work [61], which discusses the importance of small samples in medical research and how intensive efforts to control confounders and obtain accurate data can lead to more truthful results with a small sample size. This reference underscores the significance of meticulous control and accurate data collection even with limited sample sizes.

The study [62], which explores how science journalists evaluate psychology research based on factors like sample size, representativeness, p-values, and researcher prestige. This study demonstrates the impact of sample size on the perception and evaluation of research findings, highlighting the need for careful consideration of sample size in research design and reporting. Delve into the implications of small sample sizes on research outcomes and validity, researchers can acknowledge and address the limitations associated with limited sample sizes, thereby enhancing the credibility and applicability of their study results.

The study presents new evidence on the neural regulation of glomerular filtration, highlighting the intricate relationship between the nervous system and kidney function. By

establishing a connection between EEG parameters and glomerular filtration rate (GFR), the research provides valuable insights into the neural mechanisms impacting kidney function. This understanding contributes to the broader knowledge of the physiological processes governing urinary system function [63].

The study introduces a regression model based on EEG parameters as a non-invasive tool for accurately assessing GFR. This innovative approach shows significant promise for clinical applications, offering a reliable method for estimating kidney function without invasive procedures. The use of EEG data to predict GFR represents a notable advancement in nephrology and creates opportunities for enhanced patient care and management [64].

The results of the study underscore the significance of integrating research on the nervous system and kidney function to improve our understanding of urinary system physiology and pathophysiology. By bridging neuroscience and nephrology, the findings emphasize the interconnected nature of these systems and stress the importance of considering neural influences on kidney health. This holistic approach enriches our comprehension of kidney diseases and their management [65].

The study's findings advance our understanding of the neural regulation of glomerular filtration and introduce a promising avenue for non-invasive GFR assessment. By promoting the integration of research on the nervous system and kidney function, the study contributes to a comprehensive understanding of urinary system physiology and pathophysiology, ultimately enhancing clinical practices and patient outcomes.

CONCLUSIONS

1. A weak linear correlation was found between GFR and sympathetic tone markers (LFnu) in HRV. However, the sample could be divided into two clusters, one showing a strong correlation and the other no correlation. The study revealed neural structures generating delta and theta rhythms that positively influence GFR and beta rhythms that negatively impact GFR. Additionally, entropy was identified as a downregulating factor for GFR. The neural structures identified accounted for 97.2% of GFR variance.

2. The regression model, which includes 16 EEG parameters, allows estimating GFR with a standard error of 3,4 mL/min. Such accuracy is not much inferior to that when calculating GFR according to the Cockcroft & Gault formula [13].

3. Determination of GFR is used to assess the functional reserve of the kidneys [7] and the effectiveness of treatment of patients with kidney diseases [9,10]. We hope that our proposed formula will be used as an alternative non-invasive method of estimating GFR.

4. The study provides new evidence for complex neural regulation of glomerular filtration. The developed regression model based on EEG parameters is a promising tool for non-invasive assessment of GFR. The results highlight the importance of integrating research on the nervous system and kidney function in understanding the physiology and pathophysiology of the urinary system.

5. The study explores the relationship between glomerular filtration rate (GFR) and HRV/EEG parameters as indicators of kidney neural regulation. The sympathetic outflow to the kidney is controlled by various brain areas, affecting GFR. The research involved 10 men, and GFR was calculated using creatinine clearance. HRV and qEEG methods were used to assess the autonomic nervous system. A weak correlation was found between HRV and GFR for the sample, but two distinct clusters emerged with varying correlations. qEEG identified neural structures influencing GFR positively and negatively, allowing for accurate GFR estimation.

6. The renal nerves play a crucial role in regulating renal blood flow and GFR. Different populations of nerves within the kidney can selectively influence GFR through sympathetic outflow. The study aimed to understand the neural control of GFR by examining the

relationship between GFR and HRV/EEG parameters. The research involved physiological studies to demonstrate the differential effects of renal nerve activation on GFR. The findings suggest that sympathetic outflow can modulate GFR by activating specific neural pathways within the kidney.

7. The study included 10 men without clinical diagnoses, and GFR was calculated using creatinine clearance. HRV parameters were assessed to understand sympathetic tone, and qEEG was used to identify neural structures influencing GFR. The results showed a weak linear correlation between GFR and sympathetic tone, with two distinct clusters of individuals. Significant relationships were found between GFR and various EEG parameters, indicating neural structures that upregulate or downregulate GFR. The regression model incorporating EEG parameters allowed for precise GFR estimation.

ACKNOWLEDGMENT

ACCORDANCE TO ETHICS STANDARDS

Tests in patients are conducted in accordance with positions of Helsinki Declaration 1975, revised and complemented in 2002, and directive of National Committee on ethics of scientific researches. During realization of tests from all parent of participants the informed consent is got and used all measures for providing of anonymity of participants.

For all authors any conflict of interests is absent.

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