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Heart rate variability in children with chronic pyelonephritis and I–III stages of chronic kidney disease

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Abstract. ***Background.*** *Assessment of heart rate variability allows us to get an idea about the functional state of the autonomic nervous system and to identify changes in autonomic homeostasis in children. The purpose was to study the features of vegetative regulation in children with chronic pyelonephritis at the initial stages of chronic kidney disease by analyzing heart rate variability.* ***Materials and methods.*** *There were surveyed 94 children aged 6–17 years without exacerbation of chronic pyelonephritis with CKD stage I–III. There was conducted daily monitoring of ECG, followed by mathematical processing.* ***Results.*** *Analysis of the statistical characteristics of the Z-scores of the time analysis indicators revealed a significant decrease in the standard (root-mean-square) deviations of the RR interval in patients of all groups with a significant decrease in this indicator in children with CKD stage III. A significant decrease in RMSSD values was demonstrated in patients with CKD stage III, and patients with CKD stages I to III demonstrated pNN50 decline. In a spectral analysis, patients showed a significant increase in the total power of the spectrum of heart rate variability of TP and its domains (VLF, LF), sympathetic-parasympathetic ratio of LF to HF and decrease of HF.* ***Conclusions.*** *76.6 % of children with chronic pyelonephritis and CKD stage I–III presented with the vegetative imbalance. With the progression of CKD, the autonomic imbalance exacerbated, as evidenced by the presence of correlations between the glomerular filtration rate and findings of time (SDNN, pNN50) and spectral (TP, LF, HF) analysis of heart rate variability. The revealed changes suggest the expected development of cardiovascular disorders even before the appearance of significant changes in the central hemodynamics.*

Keywords: *heart rate variability; children; chronic pyelonephritis; chronic kidney disease*

Introduction

Cardiovascular pathology leads to the death in the majority cases both in adults and children with chronic kidney disease (CKD) [1, 2]. However, in children and adolescents with CKD, cardiovascular complications usually have subclinical course, starting developing already at the early stages [3, 4]. With the progression of CKD, the importance of the sympathetic nervous system increases, which activity is accompanied by the increase of cardiovascular risks [5]. Damage and disorder of the structures of the autonomic nervous system leads to morphological rearrangements of the cardiovascular system associated with the release of mediators, hormones, biologically active substances, which, in turn, enhance the autonomic imbalance and provoke the development of a number of biochemical and immune shifts in the body [6]. At present, the most informative non-invasive method for quantitative assessment of the autonomic regulation of heart rate is the study of heart rate variability (HRV), which gives an opportunity to get an idea of the functional state of the CNS and to identify changes in vegetative homeostasis in children. In scientific publications, information on the results of HRV study in adult patients with terminal stage of chronic renal failure [7–9], as well as the effect of hemodialysis on the parameters of the CNS in this cohort of patients [10, 11] were highlighted. There are no enough data on the state of functional reserves of autonomic regulation, neurohumoral regulation of the heart, the ratio between sympathetic and parasympathe-

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tic parts of the autonomic nervous system in children with CKD [12, 13].

Purpose: to study the peculiarities of autonomic regulation in children with chronic pyelonephritis at the initial stages of CKD by analyzing the heart rate variability.

Materials and methods

There were examined 94 children aged from 6 to 17 years (41 boys and 53 girls) with chronic pyelonephritis with CKD stage I–III. The control group consisted of 78 virtually healthy children of the corresponding age. The patients were divided into groups depending on the stage of chronic kidney disease: the first group included 47 children with CKD stage I (GFR > 90 ml/min), the second group — 30 patients with CKD stage II (GFR from 60 to 90 ml/min), the third group — 17 patients with CKD stage III (GFR from 30 to 59 ml/min).

The planned clinical trial was approved by the Bioethics Committee of Dnipropetrovsk Medical Academy of the Ministry of Health of Ukraine and conducted in accordance with the guidelines of the Helsinki Declaration (1975). All participants and/or their parents were fully informed about the methods and scope of the study and provided written informed consent to participate.

The criteria for inclusion of patients in the study were following: the presence of the voluntary informed consent of a child and his/her parents to participate in the clinical study; age of patients from 6 years to 17 years 11 months 29 days; presence of verified diagnosis of chronic pyelonephritis; the absence of clinical and laboratory signs of exacerbation of chronic pyelonephritis. The criteria for exclusion of patients from the study were: refusal of a child or his/her parents to participate in a clinical trial; the presence of congenital heart disease or other primary cardiac diseases, acute infections.

All patients and children of the control group underwent daily ECG monitoring using the software-hardware complex Cardiotechnika-04-AD-1 (Inkart, St. Petersburg, Russia). The dynamic series of cardiac intervals detected during cardiointervalographic study were processed using the mathematical analysis of HRV. The HRV assessment was conducted in time and spectral analysis regimes in accordance with the International Standards of Measurement, Physiological Interpretation and Clinical Use developed by the European Society of Cardiology and North American Society of Pacing and Electrophysiology.

For time analysis of HRV, the following parameters were used: SDNN (ms) — standard (square root) RR deviation, SDNN index (ms) — average 5 minute standard deviation throughout the recording, SDANN (ms) — RMS deviation calculated on the basis of RR intervals, which were averaged over every 5 minutes of the recording, RMSSD (ms) — mean square deviation of inter-interval differences (activity of parasympathetic influences), pNN50 (%) — share of adjacent RR intervals, inter-interval differences between which exceed 50 ms of spectral power (ms^2). The decrease in the values of time parameters of heart rate variability was interpreted as an enhancement of sympathetic effects, the increase — as the activation of parasympathetic ones.

Spectral analysis was carried out by means of a fast Fourier transform with the calculation of the total power of the spectrum — TP (ms^2) and its three components in the following frequency band: very low frequencies (VLF) (0.003–0.04 Hz), which characterizes the degree of connection of autonomous segmentary levels of blood circulation regulation with suprasegmentary; the power of the low frequency (LF) spectrum (0.04–0.15 Hz), which mainly reflects the activity of the sympathetic part of the autonomic nervous system; the power of the high frequency (HF) spectrum (0.15–0.4 Hz), which characterizes the influence of the parasympathetic part; as well as the sympatho-parasympathetic index of the LF/HF — the index reflecting the balance of the sympathetic and parasympathetic parts.

The results were statistically processed using the Statistica 8.0 program. The verification of the distribution according to the Gauss's law was carried out using the Shapiro-Wilk test. Given that most of the samples did not conform to the Gauss's law, the results were presented as median (Me) and interquartile range (Q25; Q75). Due to the age and gender dependence of heart rate variability in children, Z-estimates were used in order to compare with the corresponding normative parameters. The Z-estimate was the degree of deviation from the arithmetic mean of the statutory indicator for this age group expressed in terms of the standard deviation of the same series, or by the formula: $Z = (X - Xn) / Sx$, where X — the value of the obtained indicator in the examined child, Xn — the arithmetic mean of the normative indicator in this age group, S — the standard deviation of the arithmetic mean of the statutory indicator. Mann-Whitney criterion was used to compare the groups. A correlation and one-factor dispersion analysis was performed to determine the relationship between the indicators. The difference between values was considered statistically verisimilar at the level of significance criterion — $p < 0.05$.

Results

In children with chronic pyelonephritis and CKD stage I–III, when compared with statutory indicators, the unidirectional nature of changes in the time indices (SDNN, RMSSD, pNN50) (Table 1) and spectral analysis (TP, LF, HF, LF/HF) of HRV was recorded (Table 2).

Analysis of the statistical characteristics of Z-estimates of time analysis indicators revealed a probable decrease in SDNN levels in patients in all groups with the most significant decrease in this indicator in children with CKD stage III. A sharp decline in SDNN (greater than 3 S) was observed in 4.26 % of patients with CKD stage I, 13.3 % of patients with CKD stage II and in 35.3 % of patients with CKD stage III. The levels of RMSSD and pNN50, which are indicators of activity of the parasympathetic chain of vegetative regulation, also tended to decrease. However, the probable decrease in comparison with the control group was demonstrated for RMSSD in patients with CKD stage III, and for pNN50 — in patients with CKD stage I and III.

Describing the general tendencies of changes in the parameters of the spectral analysis of HRV, it can be noted that for patients with CKD stages I–III as compared with the control group, there is a verisimilar gradual increase in the

total power of HRV spectrum and its domain LF. At the same time, with the progression of CKD, a probable decrease in the power of the high-frequency spectrum was recorded. The degree of changes in the power of HRV spectrum had probable group differences both for the low-frequency component (H = 23.22; p = 0.0001) and for high-frequency component (H = 14.45; p = 0.0023).

A significant decrease in the power of the high-frequency component against the background of low-frequency levels has led to a statistically significant increase in the ratio of LF/HF in patients with CKD stages I–III, as compared to healthy subjects, without any intergroup differences (H = 1.67; p = 0.8725).

Additionally, Spearman correlation analysis revealed likely correlations between the levels of glomerular filtration rate and HRV indices, namely, GFR and SDNN (r = +0.564; p = 0.023), GFR and pNN50 (r = +0.492; p = 0.037), GFR and TP, LF, HF (r = –0.591, p = 0.030; r = –0.662, p = 0.012; r = +0.627, p = 0.018, respectively).

Discussion

In our study in children with chronic pyelonephritis and CKD stages I–III, reliable shifts in both total HRV and domains were determined, which according to the present data is a complication of CKD, and not the initial state [14]. Probable changes in the SDNN, TP, LF and HF indices in the examined patients during the day reflect the decrease in the total effect of autonomous blood circulation regulation, associated with the increase of sympathetic regulation, which inhibits the activity of the autonomous circuit. The indicated signs of autonomous dysregulation are intensified by the presence of a possible decrease in the parameters characterizing the activity of the parasympathetic chain of vegetative regulation, namely: RMSSD in patients with GFR below 60 ml/min and pNN50 in all groups of patients with CKD. Reduced power of the high frequency component resulted in a statistically significant increase in LF/HF ratio in children with CKD in all groups as compared with healthy subjects without group differences. The increase in this indicator is also a reflection of vegetative imbalance toward hypersympathicotonia. The indicated shifts in the regulation of the autonomous circuit have been confirmed by the studies performed both among the adult contingent [15] and in the pediatric population [12, 16].

The power of the very low-frequency component of HRV spectrum of VLF characterizes the activity of the sympathetic part of the autonomic nervous system [17, 18]. However, in this case we are talking about more complex influences of the supra-segmentary level of regulation, since the amplitude of this domain is closely related to the

Table 1. Z-estimate of time characteristics of heart rate variability in children with chronic pyelonephritis and chronic kidney disease, Me (Lq; Uq)

Indicators		Groups of examined patients			p
		1st (n = 47)	2nd (n = 30)	3rd (n = 17)	
SDNN, ms	24 hours	–1.37* (–2.08; –0.68)	–1.42* (–2.36; –0.94)	–2.68* (–3.24; –1.62)	p_{1-2} = 0.4121 p_{1-3} = 0.0232 p_{2-3} = 0.062
	Day	–1.43* (–2.15; –0.77)	–1.45* (–2.43; –0.97)	–2.78* (–3.24; –1.62)	p_{1-2} = 0.4651 p_{1-3} = 0.0273 p_{2-3} = 0.057
	Night	–1.22 (–1.78; –0.62)	–1.39* (–2.29; –0.92)	–2.44* (–2.86; –1.43)	p_{1-2} = 0.5465 p_{1-3} = 0.0329 p_{2-3} = 0.075
RMSDD, ms	24 hours	–0.97 (–1.54; –0.65)	–0.49 (–1.07; –0.48)	–1.40* (–1.76; –0.95)	p_{1-2} = 0.0355 p_{1-3} = 0.3791 p_{2-3} = 0.0371
	Day	–0.69 (–1.27; –0.49)	–0.42 (–0.92; –0.37)	–1.22* (–1.56; –0.88)	p_{1-2} = 0.0365 p_{1-3} = 0.4564 p_{2-3} = 0.0291
	Night	–1.09 (–1.69; –0.77)	–0.57 (–1.23; –0.55)	–1.49* (–1.77; –0.98)	p_{1-2} = 0.0321 p_{1-3} = 0.4427 p_{2-3} = 0.0251
pNN50, %	24 hours	–2.80* (–3.66; –1.14)	–0.99 (–3.54; 0.11)	–3.50* (–3.72; –2.63)	p_{1-2} = 0.0730 p_{1-3} = 0.4123 p_{2-3} = 0.0348
	Day	–2.78* (–3.56; –1.11)	–0.69 (–3.44; 0.56)	–3.45* (–3.65; –2.68)	p_{1-2} = 0.0643 p_{1-3} = 0.2734 p_{2-3} = 0.0345
	Night	–2.84* (–3.73; –1.17)	–1.63* (–3.62; –0.41)	–3.54* (–3.76; –2.59)	p_{1-2} = 0.0881 p_{1-3} = 0.4536 p_{2-3} = 0.0443

Note: * — statistically significant difference with the indicators of the control group.

psycho-emotional stress and functional state of the cerebral cortex, and the power of VLF fluctuations is a sensitive indicator of metabolic process control. That is, VLF reflects the effect of higher autonomic centers on the cardiovascular subcortical center, the state of neurohumoral and metabolic regulation levels and can be used as a marker for the relationship between the segmentary levels of blood flow regulation with supra-segmentary ones [19–21]. The increase in the level of VLF, which indicates high power compensatory mechanisms and can lead to disruption of the adaptive reserves of the organism was recorded in 21.3 % of patients with CKD stage I, in 20.0 % of children with CKD stage II and in 11.8 % of patients with CKD stage III. Reduction in the power of the VLF spectrum, which confirms the depletion of the energy reserves of the body, was recorded at night and was typical for 61.7 % of patients with CKD stage I,

Table 2. Z-estimate of spectral characteristics of heart rate variability in children with chronic pyelonephritis and chronic kidney disease, Me (Lq; Uq)

Indicators		Groups of examined patients			p
		1st (n = 47)	2nd (n = 30)	3rd (n = 17)	
TP, ms²	24 hours	0.89 (–0.67; 1.47)	1.45 (0.22; 1.65)	3.46* (1.53; 5.07)	$p_{1–2}$ = 0.3426 $p_{1–3}$ = 0.0478 $p_{2–3}$ = 0.0345
	Day	0.92 (–0.19; 1.65)	1.42 (–0.14; 2.09)	4.87* (2.72; 6.03)	$p_{1–2}$ = 0.5126 $p_{1–3}$ = 0.0212 $p_{2–3}$ = 0.0127
	Night	–0.11 (–0.31; 1.45)	1.22 (–0.25; 2.31)	7.56* (2.25; 11.29)	$p_{1–2}$ = 0.3159 $p_{1–3}$ = 0.0006 $p_{2–3}$ = 0.0031
VLF, ms²	24 hours	3.34* (2.37; 3.72)	2.77* (0.47; 4.27)	4.14* (2.61; 4.99)	$p_{1–2}$ = 0.0886 $p_{1–3}$ = 0.0743 $p_{2–3}$ = 0.0498
	Day	3.98* (2.59; 4.56)	2.93* (0.88; 3.87)	4.54* (2.55; 4.86)	$p_{1–2}$ = 0.0182 $p_{1–3}$ = 0.0053 $p_{2–3}$ = 0.0533
	Night	0.59 (0.26; 1.27)	2.61* (0.30; 3.54)	3.89* (2.02; 4.56)	$p_{1–2}$ = 0.0617 $p_{1–3}$ = 0.5927 $p_{2–3}$ = 0.0087
LF, ms²	24 hours	2.55* (1.79; 2.79)	1.91* (1.33; 3.51)	5.11* (3.67; 7.94)	$p_{1–2}$ = 0.0794 $p_{1–3}$ = 0.0019 $p_{2–3}$ = 0.0000
	Day	1.88* (1.76; 2.41)	1.69* (1.43; 2.47)	6.46* (3.32; 7.29)	$p_{1–2}$ = 0.3311 $p_{1–3}$ = 0.0012 $p_{2–3}$ = 0.0000
	Night	1.46 (–0.65; 1.59)	2.86* (1.77; 3.35)	4.21* (3.23; 6.17)	$p_{1–2}$ = 0.0145 $p_{1–3}$ = 0.0009 $p_{2–3}$ = 0.0002
HF, ms²	24 hours	–0.60 (–1.21; –0.46)	–3.20* (–9.61; 0.68)	–12.72* (–14.41; –9.05)	$p_{1–2}$ = 0.0365 $p_{1–3}$ = 0.0241 $p_{2–3}$ = 0.0025
	Day	–9.64* (–10.98; –6.12)	–6.36* (–9.46; 0.47)	–12.69* (–13.79; –9.12)	$p_{1–2}$ = 0.0312 $p_{1–3}$ = 0.0160 $p_{2–3}$ = 0.0015
	Night	1.23 (–1.21; 1.25)	–6.12* (–9.61; 0.55)	–12.81* (–14.56; –9.18)	$p_{1–2}$ = 0.0312 $p_{1–3}$ = 0.0160 $p_{2–3}$ = 0.0015
LF/HF	24 hours	1.34 (–0.7; 3.53)	1.80* (–0.47; 5.12)	2.62* (0.7; 10.10)	$p_{1–2}$ = 0.3625 $p_{1–3}$ = 0.0042 $p_{2–3}$ = 0.0635
	Day	3.37* (2.01; 5.47)	1.86* (–0.45; 4.92)	2.66* (0.88; 10.16)	$p_{1–2}$ = 0.4133 $p_{1–3}$ = 0.8332 $p_{2–3}$ = 0.2345
	Night	1.21 (0.85; 2.76)	1.69* (–0.50; 5.23)	2.60* (0.66; 9.97)	$p_{1–2}$ = 0.3112 $p_{1–3}$ = 0.0720 $p_{2–3}$ = 0.3052

Note: * — statistically significant difference with the indicators of the control group.

70.0 % of patients with CKD stage II, and 76.5 % of children with CKD stage III.

The results of our study suggest that in children with chronic pyelonephritis changes in total HRV occur gradually during CKD progression, rather in the decrease of renal function, which is confirmed by the presence of probable correlations between GFR and the main indicators of HRV. This assumption is also evidenced in studies conducted among adult patients with CKD of IV–V stages [15, 22], and in a cohort of pediatric patients [12, 16]. At the same time, it was found that by the levels of most indicators of both time and spectral analysis of HRV, there is no probable difference between patients with CKD stage I and II. This is likely to be due to the fact that the overwhelming majority of patients with GFR below 90 ml/min received angiotensin converting enzyme inhibitors as a component of renonoprotective therapy for a long time, which, according to modern ideas, contribute to the normalization of total HRV [23–25].

Conclusions

1. In 76.6 % of children with chronic pyelonephritis and CKD of I–III stages, vegetative imbalance is detected, which manifests in HRV (growth of TP, LF, LF/HF and reduced SDNN, RMSSD, pNN50, HF). These changes reflect the shift of vago-sympathetic balance toward weakening of the parasympathetic and domination of the tone of the sympathetic part of the nervous system.

2. Gradual loss of renal functions, which occurs during CKD progression, exacerbates autonomic imbalance, which is confirmed by the presence of probable correlations between the integral index of renal function (GFR) and findings of time (SDNN, pNN50) and spectral (TP, LF, HF) analysis of HRV.

3. The autonomic imbalance with the weakening of the parasympathetic and domination of the sympathetic tone of the nervous system obviously leads to the weakening of the overall adaptive capacities of the organism and demonstrates expected development of cardiovascular disorders even before the appearance of significant changes of central hemodynamics.

Conflicts of interests. Author declares the absence of any conflicts of interests that might be construed to influence the results or interpretation of their manuscript.

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Варіабельність серцевого ритму в дітей із хронічним пієлонефритом і хронічною хворобою нирок I–III стадії

Резюме. Актуальність. Оцінка варіабельності серцевого ритму дає можливість отримати уявлення щодо функціонального стану вегетативної нервової системи та ідентифікувати зміни вегетативного гомеостазу в дітей. **Мета роботи:** вивчити особливості вегетативної регуляції в дітей із хронічним пієлонефритом на початкових стадіях хронічної хвороби нирок (ХХН) шляхом аналізу варіабельності серцевого ритму. **Матеріали та методи.** Обстежено 94 дитини віком від 6 до 17 років поза загостренням хронічного пієлонефриту з ХХН I–III стадії. Проводилось добове моніторування електрокардіограми з подальшою математичною обробкою. **Результати.** Аналіз статистичних характеристик Z-оцінок показників часового аналізу виявив вірогідне зниження значень стандартного (середньоквадратичного) відхилення інтервалу RR у хворих усіх груп із суттєвим зменшенням цього показника в дітей із ХХН III стадії. Вірогідне зменшення показника активності парасимпатичних впливів RMSSD продемонстрували хворі з ХХН III стадії, а показника pNN50 — пацієнти з I та III стадією ХХН. При спектральному аналізі у хворих виявлено вірогідне збільшення загальної потужності спектра варіабельності серцевого ритму (TP) і його доменів (VLF, LF), симпато-парасимпатичного співвідношення LF/HF та зниження потужності високочастотного спектра (HF). **Висновки.** У 76,6 % дітей із хронічним пієлонефритом та ХХН I–III стадії відзначається порушення вегетативного балансу. Із прогресуванням ХХН вегетативний дисбаланс поглиблюється, що підтверджується наявністю вірогідних кореляцій між швидкістю клубочкової фільтрації та показниками часового (SDNN, pNN50) і спектрального (TP, LF, HF) аналізу варіабельності серцевого ритму. Виявлені зміни свідчать про очікуване формування кардіоваскулярних порушень ще до появи значущих змін центральної гемодинаміки.

Ключові слова: варіабельність серцевого ритму; діти; хронічний пієлонефрит; хронічна хвороба нирок

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Вариабельность сердечного ритма у детей с хроническим пиелонефритом и хронической болезнью почек I–III стадии

Резюме. Актуальность. Оценка вариабельности сердечного ритма дает возможность получить представление о функциональном состоянии вегетативной нервной системы и идентифицировать изменения вегетативного гомеостаза у детей. **Цель работы:** изучить особенности вегетативной регуляции у детей с хроническим пиелонефритом на начальных стадиях хронической болезни почек (ХБП) путем анализа вариабельности сердечного ритма. **Материалы и методы.** Обследовано 94 ребенка в возрасте от 6 до 17 лет вне обострения хронического пиелонефрита с ХБП I–III стадии. Проводилось суточное мониторирование электрокардиограммы с последующей математической обработкой. **Результаты.** Анализ статистических характеристик Z-оценок показателей временного анализа выявил достоверное снижение значений стандартного (среднеквадратического) отклонения интервала RR у больных всех групп с существенным уменьшением этого показателя у детей с ХБП III стадии. Достоверное уменьшение показателя RMSSD продемонстрировали больные с ХБП III стадии, а показателя pNN50 — пациенты с I и III стадией ХБП. При спектральном анализе у больных выявлено достоверное увеличение общей мощности спектра вариабельности сердечного ритма (TP) и его доменов (VLF, LF), симпато-парасимпатического соотношения LF/HF и снижение мощности высокочастотного спектра (HF). **Выводы.** У 76,6 % детей с хроническим пиелонефритом и ХБП I–III стадии отмечается нарушение вегетативного баланса. С прогрессированием ХБП вегетативный дисбаланс усугубляется, что подтверждается наличием корреляций между скоростью клубочковой фильтрации и показателями временного (SDNN, pNN50) и спектрального (TP, LF, HF) анализа вариабельности сердечного ритма. Выявленные изменения свидетельствуют об ожидаемом формировании кардиоваскулярных нарушений еще до появления значимых изменений центральной гемодинамики.

Ключевые слова: вариабельность сердечного ритма; дети; хронический пиелонефрит; хроническая болезнь почек