

# The Role of Cardiac Rhythm Variability and Autonomous Dysfunction in Predicting Aritmias in Oncological Patients Receiving Cardiotoxic Therapy

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**Abstract** The study assessed the prognostic significance of heart rate variability and myocardial repolarization parameters in oncological patients receiving cardiotoxic chemotherapy. It has been established that a pronounced decrease in SDNN and RMSSD, an increase in the LF/HF ratio, and a prolongation of the QTc interval after 2-3 therapy cycles are reliably associated with the development of clinically significant and life-threatening arrhythmias. Patients with low heart rate variability were characterized by a significantly higher frequency of supraventricular and ventricular rhythm disturbances, as well as prolongation of QTc. The obtained data confirm the feasibility of including VSR analysis and QT-parameters dynamics in the cardiological monitoring protocol for early stratification of arrhythmogenic risk and improvement of antitumor treatment safety.

**Keywords** Heart rate variability, Autonomic dysfunction, Heart arrhythmias, QT interval, QT dispersion, Chemotherapy, Cardiotoxicity, Oncological patients, Prognosis, Prevention

## 1. Introduction

Cardio-oncology as an interdisciplinary field has gained particular relevance against the backdrop of increasing cancer patient survival rates and expanding the use of potentially cardiotoxic anti-tumor regimens (anthracyclines, anti-HER2-therapy, tyrosine kinase inhibitors, immune checkpoint inhibitors). Heart rhythm disorders are often considered a frequent and prognostically unfavorable complication that can lead to the modification or discontinuation of antitumor treatment and worsen the outcome [1,2]. The ESC recommendations on cardio-oncology emphasize the need for active monitoring of cardiovascular complications during anti-tumor therapy, including arrhythmias and conduction disorders, using ECG monitoring and individual risk stratification [3].

One of the promising non-invasive tools for early assessment of arrhythmogenic risk is the analysis of heart rate variability (HRV), which reflects the state of vegetative regulation and the balance of sympathetic/parasympathetic effects on the heart. HRV decrease is considered a marker of autonomous dysfunction and unfavorable cardiovascular prognosis, and in oncological patients, it can be formed both due to the tumor process itself and under the influence of

antitumor treatment, inflammatory reactions, anemia, electrolyte imbalances, and drug interactions [4,5]. It has been shown that during chemotherapy, early changes in HRV can be detected according to daily Holter monitoring data, reflecting a decrease in the adaptive capabilities of the cardiovascular system even before the development of pronounced clinical manifestations [6].

Autonomic dysfunction is particularly important during anthracycline therapy, for which changes in HRV indicators have been described, indicating disruption of autonomic regulation even in the early stages of treatment and in patients without a clear decrease in ejection fraction [7,8]. In immuno-oncological therapy, there is also high interest in the problem of arrhythmogenicity: immune-mediated cardiac complications, including myocarditis, are often accompanied by rhythm and conduction disorders, which requires increased vigilance and improvement of early risk detection methods [9].

**The aim of the study** is to assess the role of heart rate variability and autonomic dysfunction indicators in predicting the development of arrhythmias in oncological patients receiving cardiotoxic anti-tumor therapy, with the aim of early stratification of arrhythmogenic risk and substantiation of preventive and monitoring approaches.

## 2. Materials and Methods of Research

The study included patients  $\geq 18$  years old with confirmed oncopathology receiving cardiotoxic chemotherapy. Patients

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were divided into three groups: 1st group - standard management without preventive electrolyte correction; 2nd group - active monitoring and correction of K<sup>+</sup> and Mg<sup>2+</sup> levels before each cycle; 3rd group - combined prevention, including electrolyte correction and cardioprotective therapy ( $\beta$ -blockers, ACEI/ARB). All patients underwent a clinical examination, standard ECG registration with an assessment of the QT/QTc interval, and, if necessary, Holter ECG monitoring, echocardiography, as well as laboratory blood electrolyte levels.

The main endpoints of the study were the frequency of electrolyte imbalance disorders, the frequency of heart arrhythmias, and the dynamics of the QTc interval. Statistical processing of the data was carried out using standard methods of variation statistics; the differences were considered statistically significant at  $p < 0.05$ .

### 3. Research Results

The study assessed changes in autonomic regulation parameters (heart rate variability indicators, HRV) and myocardial repolarization (QTc, QT variance) in patients receiving cardiotoxic chemotherapy. To analyze the prognostic significance of the indicators, patients were divided into subgroups: subgroup A - without clinically significant arrhythmias ( $n=76$ ) and subgroup B - with clinically significant or life-threatening arrhythmias ( $n=36$ ). Additionally, an assessment of the influence of preventive approaches (1-3 groups) on the frequency of arrhythmias was conducted.

Before starting therapy, no statistically significant differences were found between subgroups in SDNN, RMSSD, and LF/HF. After 2-3 cycles of chemotherapy, patients in subgroup B recorded a more pronounced decrease in SDNN and RMSSD, as well as an increase in LF/HF, reflecting increased sympathicotonia (Table 1).

When analyzing heart rate variability (HRV) indicators, no initially statistically significant differences were found

between subgroups A and B: the values of SDNN ( $118.4 \pm 22.7$  vs  $115.9 \pm 24.1$  ms;  $p=0.56$ ), RMSSD ( $27.8 \pm 8.6$  vs  $26.9 \pm 9.1$  ms;  $p=0.62$ ) and LF/HF ( $1.78 \pm 0.62$  vs  $1.86 \pm 0.71$ ;  $p=0.48$ ) were comparable, indicating the same initial level of autonomic heart rate regulation.

After 2-3 cycles of chemotherapy, patients in subgroup B exhibited pronounced signs of autonomic dysfunction: SDNN decreased to  $78.2 \pm 18.9$  ms versus  $104.6 \pm 20.3$  ms in subgroup A ( $p < 0.001$ ), and RMSSD - to  $16.3 \pm 6.8$  ms versus  $24.1 \pm 7.9$  ms ( $p < 0.001$ ), reflecting a significant decrease in overall rhythm variability and parasympathetic activity. At the same time, the LF/HF indicator in subgroup B significantly increased to  $3.12 \pm 0.98$  compared to  $2.06 \pm 0.74$  in subgroup A ( $p < 0.001$ ), indicating an increase in sympathicotonia.

For clinical interpretation, threshold values were used: SDNN  $< 80$  ms and/or RMSSD  $< 20$  ms after 2-3 therapy cycles. In low VSR, the frequency of ventricular arrhythmias and prolongation of QTc was significantly higher (Table 2).

Analysis of the frequency of arrhythmias depending on the level of heart rhythm variability showed significant differences between the groups. In patients with low VSR, supraventricular extrasystole was registered in almost half of the observed patients (47.8%), which was 2 times higher than in patients with preserved VSR (23.1%;  $p=0.006$ ).

Particularly pronounced differences were found in relation to ventricular rhythm disturbances: ventricular extrasystole  $\geq$  Lown II was observed in 32.6% of patients with low VSR and only in 10.3% of patients with preserved VSR ( $p=0.002$ ). Paroxysms of supraventricular tachycardia were also significantly more frequently detected in the group with low VSR (5.1% versus 15.2%;  $p=0.048$ ).

A longer QTc interval of more than 470 ms was recorded in 26.1% of patients with low VSR, which was more than 3 times higher than in the group with preserved VSR (7.7%;  $p=0.005$ ). Clinically significant arrhythmias requiring changes in management tactics or enhanced monitoring were detected in 21.7% of patients with low VSR compared to 6.4% with preserved VSR ( $p=0.010$ ).

**Table 1.** Dynamics of HRV (24-hour Holter) indicators depending on the development of arrhythmias

Indicator	Subgroup A (n=76)	Subgroup B (n=36)	p
SDNN, ms (original)	$118,4 \pm 22,7$	$115,9 \pm 24,1$	0,56
SDNN, ms (2-3 cycles)	$104,6 \pm 20,3$	$78,2 \pm 18,9$	$<0,001$
RMSSD, ms (original)	$27,8 \pm 8,6$	$26,9 \pm 9,1$	0,62
RMSSD, ms (2-3 cycles)	$24,1 \pm 7,9$	$16,3 \pm 6,8$	$<0,001$
LF/HF (original)	$1,78 \pm 0,62$	$1,86 \pm 0,71$	0,48
LF/HF (2-3 cycles)	$2,06 \pm 0,74$	$3,12 \pm 0,98$	$<0,001$

**Table 2.** Frequency of arrhythmias depending on VSR level after 2-3 therapy cycles

Indicator	Low BP (n=46)	Preserved BP (n=78)	p
Supraventricular extrasystole	47,8%	23,1%	0,006
Ventricular extrasystole ( $\geq$ Lown II)	32,6%	10,3%	0,002
Supraventricular tachycardia paroxysms	15,2%	5,1%	0,048
QTc elongation ( $>470$ ms)	26,1%	7,7%	0,005
Clinically significant arrhythmias	21,7%	6,4%	0,010

In the multifactorial model (considering age, gender, therapy type, initial QTc, and electrolytes), SDNN <80 ms and LF/HF >3.0 after 2-3 therapy cycles proved to be independent predictors of clinically significant arrhythmias (Table 3).

**Table 3.** Predictors of clinically significant arrhythmias (logistic regression)

Indicator	OR	95% CI	p
SDNN <80 ms (2-3 cycles)	3,8	1,6–8,9	0,002
RMSSD <20 ms (2-3 cycles)	2,9	1,3–6,6	0,010
LF/HF >3.0 (2-3 cycles)	4,2	1,8–9,7	0,001
QTc >470 ms (after 2-3 cycles)	2,6	1,1–6,0	0,028

The results of single-factor and multi-factor analysis showed that a number of electrophysiological and vegetative indicators after 2-3 cycles of cardiotoxic chemotherapy are independent predictors of the development of clinically significant arrhythmias. The highest risk is associated with a marked decrease in heart rate variability: the SDNN value <80 ms increased the risk of developing arrhythmias by 3.8 times (OR=3.8; 95% CI 1.6-8.9; p=0.002), and RMSSD <20 ms - by 2.9 times (OR=2.9; 95% CI 1.3-6.6; p=0.010).

The strongest prognostic significance was demonstrated by the LF/HF >3.0 autonomic balance indicator, which increased the risk of clinically significant arrhythmias by 4.2 times (OR=4.2; 95% CI 1.8-9.7; p=0.001), which indicates the key role of sympathetic hyperactivation in the formation of the arrhythmogenic substrate.

Furthermore, it was established that the prolongation of the QTc interval beyond 470 ms was also an independent risk factor, increasing the likelihood of developing clinically significant arrhythmias by 2.6 times (OR=2.6; 95% CI 1.1-6.0; p=0.028).

Thus, the combination of reduced heart rate variability and QTc prolongation indicators allows for effective early stratification of arrhythmogenic risk in oncological patients receiving cardiotoxic therapy and justifies the inclusion of HRV analysis in the dynamic cardiotoxic monitoring protocol.

## 4. Conclusions

The conducted research showed that in oncological patients receiving cardiotoxic chemotherapy, the development of arrhythmias is closely related to disorders in vegetative regulation and changes in myocardial repolarization processes.

A pronounced decrease in heart rate variability indicators (SDNN and RMSSD) in combination with an increase in the LF/HF ratio and an increase in the QTc interval after 2-3 therapy cycles is a reliable predictor of clinically significant and life-threatening arrhythmias. Patients with low VSR are characterized by a significantly higher frequency of both supraventricular and ventricular rhythm disturbances, including prolongation of QTc. The obtained results substantiate the need for dynamic monitoring of HRV and QT/QTc parameters, as well as the implementation of preventive measures for early stratification of arrhythmogenic risk and improvement of the safety of antitumor treatment.

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