

State of nonspecific adaptive mechanisms of the body, assessed by heart rate variability, in patients with acute coronary syndrome depending on its type and outcome

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The problem of acute coronary syndrome (ACS) remains relevant. Despite obvious progress in treatment, the medium and longterm prognosis remains unfavorable. Patients with ACS belong to the veryhighrisk category for

complications, which necessitates the search for additional markers of adverse longterm outcomes.

Aim—to study the state of nonspecific adaptive mechanisms (NAM) of the body using heart rate variability (HRV)

parameters in patients with ACS and to compare these data with disease outcomes.

Materials and methods. This open prospective study included 151 patients with ACS (122 men, 29 women), median age 62.0 [55.0; 69.0] years, divided into 3 groups: Group 1—ACS with persistent STsegment elevation; Group 2—ACS without STsegment elevation who underwent percutaneous coronary intervention; Group 3—ACS without STsegment elevation managed conservatively. The state of NAM was assessed by HRV parameters on admission. Longterm outcomes were evaluated by telephone interview 1 year after hospitalization. The primary endpoint was hospitalization for any form of ACS and/or allcause death within 1 year.

Results. In patients with ACS without STsegment elevation who received only conservative treatment and in patients with unstable angina, heart rate was lower compared to patients with ACS without STsegment elevation who underwent percutaneous coronary intervention. No statistically significant relationship was found between HRV parameters and ACS outcome. Cluster analysis identified 4 clusters with different regulatory features: Cluster 1 was characterized by maximal reduction in HRV; Cluster 2—pronounced centralization of heart rate regulation; Cluster 3—predominance of autonomic loop regulation over central; Cluster 4—predominance of vasomotor cen-

ter activity. In Clusters 1 and 2, with the greatest strain on NAM, a higher number of hospitalizations for ACS and deaths were observed during the 1 year followup.

Conclusion. Cluster analysis allows identification of ACS patients with different degrees of NAM strain. Greater NAM strain is characteristic of patients with myocardial infarction and is associated with an unfavorable prognosis during 1 year followup, while the association of patient status in the identified clusters with prognosis is stronger than that of individual HRV parameters.

Keywords: heart rate variability, state of nonspecific adaptive mechanisms of the body, acute coronary syndrome, cluster analysis, prognosis.

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Introduction

Acute forms of coronary heart disease contribute significantly to mortality from circulatory system diseases, which remain the leading cause of disability and death in industrialised countries [1]. The accuracy of current prognostic tools for longterm outcomes is limited; therefore, the search for new predictive methods remains relevant [2, 3].

Adaptation is a universal property of living matter that accompanies any pathological process. The state of nonspecific adaptive mechanisms (NAM) dynamically changes during the course of the disease, manifesting as alterations in heart rate variability (HRV) parameters. The universal nature of these processes allows them to be used as markers of disease progression and outcome, in addition to traditional clinical, laboratory, and instrumental characteristics. Cardiointervalography (CIG) is an accessible, noninvasive method for assessing the state of NAM via HRV parameters, widely used in clinical practice [4–6].

The physiological interpretation and prognostic significance of HRV parameters in acute coronary syndrome (ACS) have long been recognised and are undisputed [6–8]. However, in the vast majority of studies, this interpretation is limited to the balance between sympathetic and parasympathetic activity of the autonomic nervous system; the parameters are considered individually and are characterised by limited sensitivity and specificity [6, 7].

Cluster analysis, as a mathematical method that allows formal classification of heterogeneous groups, is widely and successfully used in biomedical research [5]. In our previous work, we demonstrated the heterogeneity of the group of patients with nonSTsegment elevation ACS (NSTEMACS), which can be assessed using cluster analysis. The indicators of patients in the identified homogeneous groups correlate better with prognosis than individual HRV parameters in groups formed by formal clinical criteria [9, 10].

Aim—to assess the state of NAM in patients with ACS based on HRV parameters and to correlate these data with the longterm outcome of ACS.

Material and methods

This openlabel prospective study was conducted at the emergency cardiology departments of City Clinical Hospital No. 11, Rostov Region, during 2017–2019, and at the Regional Clinical Hospital, Rostov Region, in 2024, in compliance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. All patients provided written informed consent.

Inclusion criteria: both sexes, age 40–80 years; diagnosis of ACS on admission; predominantly sinus rhythm; signed voluntary informed consent. Exclusion criteria: any form of acute heart failure and decompensated chronic heart failure; rhythm and conduction disturbances; respiratory failure; presence of oncological or any other severe acute or chronic diseases that could distort the study results.

A total of 151 patients with ACS were examined (122 men, 29 women), median age 62.0 [55.0; 69.0] years. The control group comprised 30 practically healthy individuals, matched for sex and age. Examination and treatment of patients were carried out according to the clinical guidelines in force at the time of the study [11, 12]. Group 1 included 29 patients with persistent STsegment elevation who underwent primary percutaneous coronary intervention (PCI). Group 2 included 30 patients with NSTEMACS who underwent primary PCI, and Group 3 consisted of 92 patients with NSTEMACS managed conservatively. Cardiointervalography (CIG) was performed on the first day in the morning, after 15 minutes of adaptation in the supine position, using the hardwaresoftware complex “Varicard 2.51” (Ramena Ltd., Russia) and Iskim software version 6.0, based on 5minute ECG recordings. The following parameters were analysed: heart rate (HR), standard deviation of normal RR intervals (SDNN), stress index (SI), spectral power of the oscillatory process of the envelope curve of the RR interval series (in highfrequency (HF), lowfrequency (LF), and very lowfrequency (VLF) bands), and total spectral power (TP).

The activity of NAM was characterised by the balance between autonomic and central regulatory circuits. Predominance of the autonomic circuit was considered as decreased NAM activity, while pre-

dominance of the central circuit was regarded as increased NAM activity. HR was considered an integral, general indicator of regulatory influences on heart rhythm, with its increase reflecting NAM stress. SDNN was evaluated as a characteristic of autonomic regulation activity, assuming that the main contribution to its value comes from respiratory arrhythmia; its increase reflects predominance of the autonomic circuit, and its decrease—predominance of the central circuit. SI, calculated by geometric methods, characterises the state of NAM in the opposite way to SDNN: its increase indicates predominance of the central circuit, and its decrease—predominance of the autonomic circuit. Spectral parameters were interpreted as the influence on heart rhythm of periodic activity of the respiratory (HF), vasomotor (LF), and higher hypothalamic integrative autonomic (VLF) centres. Predominance of HF was assessed as greater autonomic activity and lower NAM stress; LF and VLF predominance indicated greater central regulation and, consequently, higher NAM stress. The greater the prevalence of wave influences in the VLF range, the higher the activity of the central regulatory circuit. TP, calculated as the sum of HF, LF, and VLF, was considered a characteristic of the combined influence of periodic modulating processes on heart rhythm, analogous to SDNN but excluding nonperiodic processes. Longterm prognosis was assessed via telephone interviews and medical records (outpatient cards, electronic records). Endpoints: hospitalisation for any form of ACS and allcause death within 1 year.

Statistical analysis

Statistical data processing was performed using Statistica 6.0 (StatSoft Inc., USA). Normality of distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Since the studied parameters showed a nonnormal distribution, data are presented as Me [Q25; Q75], where Me is the median, and Q25 and Q75 are the lower and upper quartiles, respectively. Statistical significance of differences was determined using the Mann–Whitney, Kruskal–Wallis, Pearson χ^2 , and Fisher’s exact tests. Differences were considered statistically significant at $p < 0.05$. To identify homogeneous subgroups, exploratory analysis was performed using hierarchical classification with nearestneighbour clustering and Euclidean distance as the measure. Final clusters were formed using the kmeans method.

Table 1. HRV parameters in the control group and patients with ACS (Me [Q25;Q75])

Parameter	Control group, n = 30	Patients with ACS, n = 151	Significance level, p
HR, bpm	68.0 [64.0;71.0]	68 [58.0;77.0]	0.886820
SDNN, ms	40.0 [34.0;44.0]	24.0 [17.0;37.0]	0.000001
SI, y.e.	162.0 [122.0;189.0]	367.0 [153.0;896.0]	0.000013
HF, %	24.3 [19.3;29.7]	23.7 [14.9;38.3]	0.907843
LF, %	33.8 [26.5;39.1]	34.6 [24.5;43.7]	0.588434
VLF, %	41.8 [33.3;48.5]	35.2 [23.2;54.7]	0.183345
TP, ms ²	940.0 [673.0;1284.0]	454.0 [193.0;1046.0]	0.001485

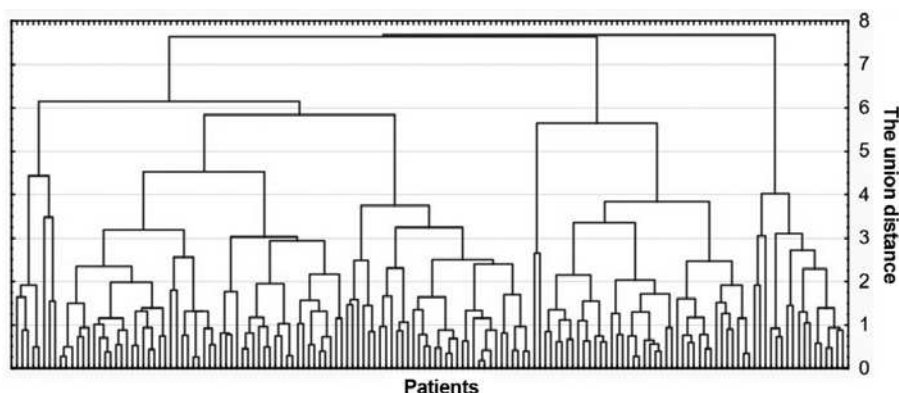


Fig. 1. Distribution of patients in exploratory cluster analysis

Ethical approval. The study protocol was approved by the Ethics Committee upon approval of the dissertation research topic.

Results

In patients with ACS, SDNN and TP were significantly reduced, and SI was elevated, indicating NAM stress (Table 1). The ratio of wave components (HF, LF, VLF) remained within normal limits. Notably, there was

considerable dispersion of parameters, reflecting the heterogeneity of HRV indicators in ACS patients.

After exploratory analysis of the studied HRV parameters (Fig. 1) using kmeans clustering, four clusters were formed, providing adequate comparison group sizes.

In Cluster 1, SI was elevated, SDNN and TP were reduced—the most pronounced among all clusters (Table 2). Among spectral parameters, vasomotor

Table 2. HRV parameters by cluster (Me [Q25;Q75])

Parameter	Cluster 1, n = 34	Cluster 2, n = 43	Cluster 3, n = 38	Cluster 4, n = 36
HR ¹ , bpm	75.0 [70.0; 83.0]	77.0 [69.0; 86.0]	59.5 [55.0; 64.0]	61.0 [56.5; 67.0]
SDNN ² , ms	16.5 [13.0; 22.0]	21.0 [15.0; 28.0]	27.0 [22.0; 37.0]	41.5 [35.7; 57.0]
SI ³ , y.e.	1002.5 [541.0; 1489.0]	594.0 [325.0; 1597.0]	295.0 [155.0; 506.0]	131.5 [63.0; 175.5]
HF ⁴ , %	24.9 [15.8; 32.2]	15.1 [7.4; 21.5]	44.6 [39.7; 53.0]	18.9 [14.6; 26.1]
LF ⁵ , %	46.5 [39.5; 52.9]	23.4 [16.6; 28.0]	28.5 [24.9; 35.1]	43.7 [39.1; 50.0]
VLF ⁶ , %	28.0 [22.0; 37.1]	60.1 [54.7; 65.8]	24.1 [19.3; 30.9]	35.8 [23.1; 45.5]
TP ⁷ , ms ²	192.0 [109.0; 393.0]	321.0 [122.0; 633.0]	474.0 [322.0; 811.0]	1442.0 [953.5; 2139.0]

Note. Statistically significant differences ($p < 0.05$) between comparison groups:

¹—Clusters 1 and 2 vs. Clusters 3 and 4 ($p < 0.000001$).

²—Control vs. Cluster 1 ($p < 0.000001$), Cluster 2 ($p < 0.000001$), Cluster 3 ($p = 0.006842$); Cluster 1 vs. Cluster 3 ($p = 0.000227$), Cluster 4 ($p < 0.000001$); Cluster 2 vs. Cluster 4 ($p < 0.000001$).

³—Control vs. Clusters 1 and 2 ($p < 0.000001$); Cluster 1 vs. Cluster 3 ($p = 0.000101$), Cluster 4 ($p < 0.000001$); Cluster 2 vs. Cluster 4 ($p < 0.000001$); Cluster 3 vs. Cluster 4 ($p = 0.001382$).

⁴—Control vs. Cluster 4 ($p = 0.000004$); Cluster 1 vs. Cluster 2 ($p = 0.008165$), Cluster 3 ($p = 0.000002$); Cluster 3 vs. Clusters 2 and 4 ($p < 0.000001$).

⁵—Control vs. Cluster 1 ($p = 0.000843$), Cluster 2 ($p = 0.002333$), Cluster 4 ($p = 0.004088$); Cluster 1 vs. Cluster 2 ($p < 0.000001$), Cluster 3 ($p = 0.000006$); Cluster 2 vs. Cluster 4 ($p < 0.000001$); Cluster 3 vs. Cluster 4 ($p = 0.000001$).

⁶—Control vs. Cluster 2 ($p = 0.000060$), Cluster 3 ($p = 0.000355$); Cluster 1 vs. Cluster 2 ($p < 0.000001$); Cluster 2 vs. Clusters 3 and 4 ($p < 0.000001$).

⁷—Control vs. Cluster 1 ($p < 0.000001$), Cluster 2 ($p = 0.000225$); Cluster 1 vs. Cluster 3 ($p = 0.006402$), Cluster 4 ($p < 0.000001$); Cluster 2 vs. Cluster 4 ($p < 0.000001$); Cluster 3 vs. Cluster 4 ($p = 0.006402$).

Table 3. Distribution of clusters by type of ACS

Cluster	Group 1, n = 29 STEMI	Group 2, n = 30 NSTEMACS with PCI	3 rpyhna, n = 92 NSTEMACS without PCI
Cluster 1 ¹	7 [24.1%]	8 [26.7%]	19 [20.7%]
Cluster 2 ¹	13 [44.8%]	11 [36.7%]	19 [20.7%]
Cluster 3 ¹	4 [13.8%]	4 [13.3%]	30 [32.6%]
Cluster 4 ¹	5 [17.2%]	7 [23.3%]	24 [26.1%]
1+2 Clusters ²	20 [69.0%]	19 [63.3%]	38 [41.3%]
3+4 Clusters ²	9 [31.0%]	11 [36.7%]	54 [58.7%]

Note. Statistically significant differences ($p < 0.05$) between comparison groups:

¹— $\chi^2 = 11.7249$, $p = 0.068394$;

²— $\chi^2 = 9.03232$, $p = 0.010931$; Group 1 vs. Group 3: $\chi^2 = 6.76$, $p = 0.0093$; Group 2 vs. Group 3: $\chi^2 = 4.41$, $p = 0.0357$.

Table 4. Distribution of clusters by final clinical diagnosis

Cluster	Qwave MI, n = 34	NonQwave MI, n = 47	Unstable angina, n = 70
Cluster 1 ¹	8 [23.5%]	14 [41.2%]	12 [35.3%]
Cluster 2 ¹	15 [34.9%]	11 [25.6%]	17 [39.5%]
Cluster 3 ¹	6 [15.8%]	10 [26.3%]	22 [57.9%]
Cluster 4 ¹	5 [13.9%]	12 [33.3%]	19 [52.8%]
1+2 Clusters ²	21 [63.6%]	18 [58.1%]	17 [29.8%]
3+4 Clusters ²	23 [29.9%]	25 [32.5%]	29 [37.7%]

Note. Statistically significant differences ($p < 0.05$) between comparison groups:

¹— $\chi^2 = 2.43$, $p = 0.487894$;

²— $\chi^2 = 6.43$, $p = 0.040218$.

centre activity (LF) predominated. In Cluster 2, reductions in SDNN and TP were less pronounced than in Cluster 1, with elevated SI and predominance of verylowfrequency periodic influences over high and lowfrequency ones (centralisation of regulation) [4]. In Clusters 1 and 2, HR was higher than in Clusters 3 and 4, but did not differ from the control group. This pattern reflects marked NAM stress in patients of Clusters 1 and 2 [4]. In Cluster 3, SDNN reduction was less than in Clusters 1 and 2, with HF predominance in the spectral parameters due to decreased LF and VLF. In Cluster 4, HF was reduced and LF elevated, indicating more pronounced NAM stress than in Cluster 3, but less than in Clusters 1 and 2. These HRV changes suggest lower NAM stress in patients of Clusters 3 and 4 compared with Clusters 1 and 2.

When comparing HRV parameters according to the type of ACS, a statistically significant difference was found for HR: Group 1—78 [69.0; 85.0], Group 2—73.0 [64.0; 85.0], Group 3—66 [58.0; 75.0] per minute, $p < 0.0001$. Significant differences between Groups 1 and 3 ($p = 0.000024$) and between Groups 2 and 3 ($p = 0.002222$) indicate lower NAM stress in Group 3. Patients in Group 1 more frequently exhibited pronounced NAM stress than those in Group 3, with a statistically significant difference when clusters were combined (Table 3).

In Group 1, 28 patients (93.1%) developed Qwave myocardial infarction (MI), and one patient (6.9%) had nonQwave MI. In Group 2: one patient (3.3%) had Qwave MI, 16 (53.3%) had nonQwave MI, and 13 (43.3%) had unstable angina (UA). In Group 3: 6 patients (6.5%) were diagnosed with Qwave MI, 29 (31.5%) with nonQwave MI, and 57 (62.0%) with UA.

When comparing HRV parameters according to the final clinical diagnosis, a statistically significant difference was found for HR. For Qwave MI—77.0 [66.0; 85.0], nonQwave MI—69.0 [60.0; 80.0], UA—64.0 [57.0; 72.0] per minute, $p = 0.0013$; significant difference between Qwave MI and UA, $p = 0.000975$. Thus, MI was associated with pronounced NAM stress (Table 4).

One year after discharge, contact was lost with 5 patients, 4 died, and 49 were rehospitalised for ACS. Due to the small number of endpoints, they were combined into a composite endpoint (CEP)—allcause death or hospitalisation for ACS. At 1 year, CEP was registered in 7 patients (25.9%) of Group 1, 13 (43.3%) of Group 2, and 34 (37.1%) of Group 3. No statistically significant differences were found between groups.

Among patients with Qwave MI, CEP occurred in 9 (29.0%), in nonQwave MI—in 22 (47.8%), and in UA—in 22 (31.9%). No significant differences were obtained.

Table 5. Distribution of clusters and longterm outcome of ACS

Cluster	No CEP, n = 93	CEP present, n = 53
Cluster 1 ¹	18 (19.4 %)	14 (26.4 %)
Cluster 2 ¹	20 (21.5 %)	20 (37.7 %)
Cluster 3 ¹	28 (30.1 %)	10 (18.9 %)
Cluster 4 ¹	27 (29.0 %)	9 (17.0 %)
1+2 Clusters ²	38 (40.9 %)	34 (64.2 %)
3+4 Clusters ²	55 (56.1 %)	19 (35.8 %)

Note. Statistically significant differences ($p < 0.05$) between comparison groups:

¹— $\chi^2 = 7.64$, $p = 0.054045$;

²— $\chi^2 = 7.33$, $p = 0.006793$.

When comparing HRV parameters according to longterm outcome, no statistically significant differences were found.

The association between longterm outcome and the NAM state variant identified by cluster analysis is presented in Table 5. Pronounced NAM stress in Clusters 1 and 2, as opposed to Clusters 3 and 4, was associated with a negative prognosis—hospitalisation for ACS or death.

Discussion

Patients with ACS constitute a heterogeneous group in terms of clinical presentation, management strategy, and outcomes. Coronary revascularisation is the key intervention determining prognosis in ACS; however, objective difficulties—such as low population density in some regions, long transport times, limited availability of endovascular surgery, and late patient presentation—often lead to a conservative approach. In 2023, PCI was performed in 75.7% of patients with STsegment elevation ACS and in only 39.1% of patients with NSTEMACS, highlighting the ongoing relevance of conservative management and the need for accurate assessment of course and prognosis in these patients [1].

HRV parameters have long been studied for prognostic assessment in MI. Recent metaanalyses and systematic reviews emphasise the limited predictive accuracy of individual HRV indices, difficulties in comparing parameters across studies, and wide variability in values during the first 24 hours of ACS [6, 7]. In 2025, Yang X. et al. developed a risk stratification system incorporating HRV parameters alongside clinical and laboratory data, which demonstrated good pre-

dictive ability for major cardiovascular events such as death, unplanned revascularisation, recurrent MI, or hospitalisation for UA [9]. In the study by Pukkila T. et al., the prognostic value of HRV parameters decreased after adjustment for the GRACE score and left ventricular ejection fraction, while Wang N. et al. found no predictive value for HRV parameters [13, 14].

We attempted to address this problem by identifying groups of patients with a specific, stable combination of HRV parameters on the first day of hospitalisation using cluster analysis. These combinations have a physiological interpretation through the concept of NAM. The obtained variants of NAM states show a clear relationship with disease outcomes, including longterm prognosis. This pattern holds across different types of ACS and approaches to reperfusion therapy. Among all HRV parameters, only HR differed significantly between the compared groups, reflecting the sum of regulatory influences and thus being more sensitive but less specific. Importantly, the NAM states in ACS are not limited to simple sympathetic or parasympathetic predominance, nor can they be described by deviations of any single HRV parameter. The association between NAM state and prognosis emerges when detailed variants of NAM state are identified using multiple HRV parameters.

Conclusion

Among all HRV parameters, significant differences between different ACS variants were found only for HR. Cluster analysis of HRV parameters, as a formal mathematical method, performed on the first day of hospitalisation in patients with ACS, irrespective of its type or revascularisation approach, allows the identification of subgroups with clearly defined characteristics of the state of nonspecific adaptive mechanisms. These states unambiguously characterise the degree of NAM stress. The most pronounced NAM stress, as identified by cluster analysis, was demonstrated in patients with MI who developed the composite endpoint, providing an additional tool for assessing longterm prognosis in ACS.

Conflict of interest: none declared.

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