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3.2 Ecg digitization in the differentiation of acute coronary syndrome and rare cardiological pathologies. Clinical examples

Cardiovascular diseases occupy leading positions in morbidity and are the primary cause of death worldwide [77]. A total of 658,000 cases of myocardial infarction (MI) are recorded annually in the United States, with the average age of MI onset being 65.6 years for men and 72 years for women [78]. Considering the significant burden of MI and its fatal and disabling consequences, overdiagnosis and inappropriate treatment strategies are common. It has been established that acute coronary syndrome (ACS) is more often misdiagnosed in women—approximately in 5% of cases compared to 3% in men [79]. Since the time to treatment initiation is considered one of the main determinants of ACS outcomes, it is advisable to use additional technological innovations in the emergency department, which can also help differentiate rare cardiac pathologies from ACS. After the first contact with a patient, an electrocardiogram (ECG) must be performed and interpreted within the first 10 minutes; the median reporting time by a specialist is 2 minutes 51 seconds [77], whereas diagnosis using a smartphone with a single lead is a promising approach for rapid triage of patients with ST-segment elevation myocardial infarction (STEMI), enabling timely primary percutaneous coronary intervention (PCI) [80]. Rapid ECG acquisition with STEMI/NSTEMI differentiation and subsequent PCI reduces mortality from 9% to 7% for STEMI and from 6.5% to 4.9% for NSTEMI [81]. Thorough history-taking and ECG interpretation before determining biomarkers allows exclusion of ACS in 9.4% of patients, while simultaneously stratifying the remaining individuals - this is a promising tool for prehospital triage.

According to ECG changes detected in individuals with ACS, it is recommended to divide them into two working groups:

1. Patients with acute chest pain and persistent ST-segment elevation.
2. Patients with acute chest pain but without persistent ST-segment elevation.

In patients with persistent ST-segment elevation, STEMI should be suspected. In such cases, important ECG findings include new J-point elevation in at least two

contiguous leads of ≥2.5 mm in men under 40 years, ≥2 mm in men aged ≥40 years, or ≥1.5 mm in women regardless of age in leads V2–V3 and/or ≥1 mm in other leads (excluding patients with left ventricular hypertrophy or left bundle branch block). It is crucial to promptly identify patients with STEMI, as the best treatment strategy is to perform PCI as quickly as possible. Studies have confirmed that, with equal delays, PCI is superior to fibrinolysis in reducing mortality, non-fatal recurrent MI, and stroke. A study by K. Champasri et al. reported significantly higher in-hospital mortality in STEMI patients who underwent PCI with a delay of more than 90 minutes (HR=1.5 [95% CI, 1.0–2.1, p=0.046]). However, if a patient seeks medical care more than 12 hours after symptom onset, fibrinolysis should be considered as part of a pharmaco-invasive treatment strategy for STEMI.

In more than 30% of patients with NSTEMI, characteristic abnormal ECG changes are recorded (e.g., ST-segment depression, transient ST-segment elevation, or T-wave abnormalities). When establishing NSTEMI, immediate PCI is considered only for patients at very high risk, while low-risk patients are offered a selective invasive approach and pharmacotherapy.

In the study by T. Lindow et al., the diagnostic significance of ECG criteria in emergency medical settings for STEMI patients was found to be low: the sensitivity of standard ECG markers was 17%, specificity 98%, and predictive value 12%, while extended ECG criteria had sensitivity of 30%, specificity 94%, and predictive value 8%. Research into new ECG markers dates back to the 1960s. The methodology for evaluating and determining the clinical significance of T-wave symmetry was first studied by Ph. Jr. Langner and has progressed significantly with the development of computer technologies. Later, studies by I.A. Chaikovskyi and colleagues established the relationship between ACS treatment effectiveness and changes in T-wave symmetry in phase space.

Based on the "Smart-ECG" medical software developed by the university department (copyright certificate No. 73687 from 05.09.2017), additional diagnostic markers of the first derivative of the T wave (maximum speed ratio, MSR) can be determined, and changes in repolarization phase phenomena can be analyzed using

quantitative assessment of the ST segment (height of ST-segment slope after one second of recording – STH, mm). The indicators of differentiated ECG change in opposite directions depending on whether repolarization phase disturbances are primary or secondary. If ST-segment and T-wave changes are not associated with depolarization abnormalities (QRS changes), they are classified as primary repolarization abnormalities (seen in IHD, myocarditis). In cases where ST-segment and T-wave changes result from abnormal depolarization, they are classified as secondary repolarization abnormalities (such as in left ventricular hypertrophy).

Analysis of ST-segment direction also has important diagnostic value. Normally, the ST segment lies on the isoelectric line; however, in ischemic myocardial changes, a lesion zone develops, creating a potential difference between healthy and damaged tissue. For example, ST elevation in STEMI results in the appearance of a transmural voltage gradient due to disturbances in action potential formation in the epicardium. These changes increase the ST-segment slope height (STH), and the degree of elevation correlates with the severity of ischemic injury and the extent of myocardial damage. The study of new markers through digital ECG technologies may become a leading tool for expanding clinical and diagnostic capabilities, improving understanding of myocardial pathophysiological processes, enabling faster and more accurate disease identification, and improving healthcare delivery overall.

Considering similar ECG findings and the clinical picture at the patient's initial presentation, Brugada syndrome (BrS) and Fabry disease are of particular interest in terms of differential diagnosis. BrS is a genetically determined arrhythmogenic disorder with an autosomal dominant inheritance pattern, associated with a risk of sudden cardiac death. Most mutations are related to the SCN5A gene and cause typical abnormal ECG changes—ST-segment elevation in leads V1–V3, right bundle branch block, and a predisposition to ventricular fibrillation (VF). In BrS, the ECG shows a downward-sloping ST elevation, in contrast to STEMI, where the elevation is “convex” or upward-sloping (“downsloping ST elevation” vs “upsloping and convex ST elevation”).

Brugada syndrome (BrS) is a rare hereditary arrhythmogenic cardiac disorder associated with sudden cardiac death (SCD). The incidence of arrhythmic events (sustained ventricular tachycardia (VT), ventricular fibrillation (VF), or SCD) in BrS is 7.7% in patients with a history of SCD, 1.9% in those with syncope, and 0.5% in asymptomatic patients. Most mutations are related to the SCN5A gene and cause the classic abnormal electrocardiographic (ECG) changes—ST-segment elevation in leads V1–V3, right bundle branch block, and predisposition to VF. BrS is characterized by syncope of unclear origin, paroxysms of polymorphic VT that resolve spontaneously, and severe sleep-related breathing disturbances; however, sometimes the ECG abnormalities typical of this syndrome occur without accompanying clinical signs.

BrS is most often identified in patients in their third or fourth decade of life (mean age 42 ± 15 years), but some "atypical" cases are diagnosed in patients ranging from 2 days to 87 years old. There are certain epidemiological patterns— in Thailand, the prevalence of BrS exceeds that in North America by 146 times and that in Europe by 37 times. Type 1 BrS is characterized by a coved-type ST-segment elevation of at least 2 mm with T-wave inversion. In type 2, after initial ST-segment depression, the segment transitions into a positive T wave ("saddleback" pattern).

Since BrS is a genetically determined disorder, screening examinations of all family members are mandatory. ST-segment changes on ECG should be taken into account in the differential diagnosis of causes of ST-segment elevation: acute coronary syndrome with ST elevation (STEMI), early repolarization syndrome, pericarditis, Takotsubo cardiomyopathy, hyperkalemia, and others. In BrS, the characteristic finding is a downward-sloping ST elevation, in contrast to STEMI where it is "convex" or upward-sloping ("downsloping ST elevation" vs "upsloping and convex ST elevation").

The only effective method for treating VT, VF, and SCD in BrS is implantation of an automatic cardioverter-defibrillator. The effectiveness of conservative therapy aimed at reducing the frequency of VT and SCD has not been proven, although quinidine may be used to treat "electrical storms"; however, there is no evidence supporting its ability to reduce SCD. Thirty percent of patients who are not implanted

with an automatic cardioverter-defibrillator die within three years after the first onset of symptoms.

According to the 2016 J-Wave Syndrome Consensus (HRS/EHRA/APHRS/SOLAECE), a diagnostic assessment system for Brugada syndrome (Shanghai Brugada Scoring System, SBSS) was proposed. It incorporates ECG findings, genetic results, clinical characteristics, and family history. It has been noted that an increase in the score is associated with a higher incidence of VT and VF, while malignant arrhythmias are not observed in patients with a score <3.5. Patients with a high total score typically present with severe symptoms, a family history of sudden death, and positive genetic testing. Based on the scoring system, BrS can be classified as "probable" and/or "definite," "possible," or "nondiagnostic," corresponding to ≥3.5, 2–3, and <2 points respectively.

Fabry disease belongs to the group of rare lysosomal storage disorders and is associated with insufficient production or a complete absence of alpha-galactosidase A [84]. The disease is characterized by multiorgan involvement due to irreversible fibrosis and ultimately leads to patient death from cardiovascular, cerebrovascular complications, or renal failure. The disease most often begins after the age of 10 and manifests as painful crises, whose main features include burning pain in the palms and soles, paresthesias, hypohidrosis, and low-grade fever. A full clinical picture is typically observed 2–3 years after disease onset and includes: skin involvement—symmetrical angiokeratomas; renal involvement—proteinuria, hematuria, cylindruria with possible progression to chronic kidney disease; cardiovascular involvement—left ventricular hypertrophy (LVH), anginal pain; ocular involvement—corneal dystrophic changes; and nervous system involvement—chronic cerebrovascular insufficiency.

Cardiovascular changes in Fabry disease arise both from the direct effects of accumulated Gb3 in the heart and blood vessels—leading to LVH and fibrosis—and from secondary arterial hypertension that develops in the presence of renal pathology. Accumulation of Gb3 in the cells of the conduction system, endothelial cells, valve fibroblasts, and vascular smooth muscle cells results in characteristic clinical

manifestations such as LVH, right ventricular hypertrophy, conduction abnormalities, valvular dysfunction, and the development of microvascular angina [85].

The aim of the study is to identify ECG markers for differentiating acute coronary syndrome from Brugada syndrome and Fabry disease using clinical case examples and ECG digitalization with the software-diagnostic system “Smart ECG”.

Our study was conducted at the Chernivtsi Regional Clinical Cardiology Center. All patients provided written informed consent to participate in the research and to allow the use of their personal data in accordance with current legal regulations and the provisions of the Declaration of Helsinki (1975, 1983).

ECG digitalization was performed using the “Smart ECG” software (certificate of copyright registration No. 73687 from 05.09.2017). Changes in the differentiated T wave were assessed by constructing the first derivative of the T wave and calculating the maximum speed ratio (MSR). The first derivative was constructed based on mathematical calculations using the following equation:

$$Y'_x = \lim_{\Delta x \to 0} \frac{\Delta y}{\Delta x}$$

lim - the limit, **Δy** - the increment of the function, **Δx** - the increment of the argument

The MSR value was defined as the ratio of the second phase of the T wave (V2) to the first phase of the T wave (V1) (Fig. 1). The MSR index was assessed in the ischemic zone—that is, in the lead with a pathologically altered T wave—whereas hypertrophic changes of the left ventricle (LV) were analyzed in lead V2.

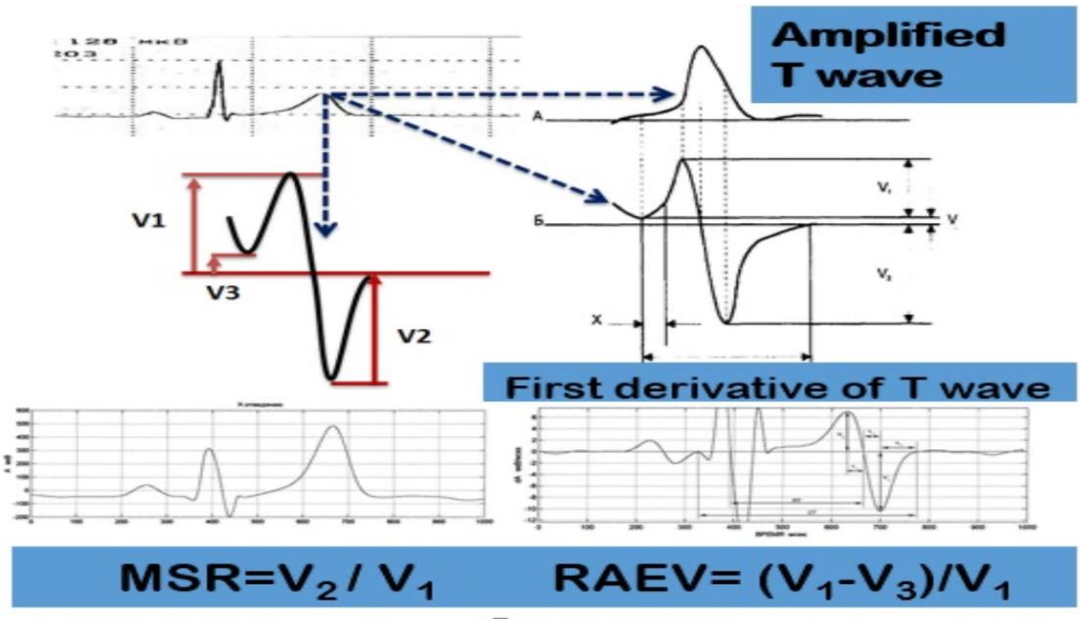

Fig. 1 Principle of constructing the first derivative and the differentiated T wave [made by the authors]

The slope of the ST segment ('ST slope') was analyzed, which included assessing the direction of the ST segment after the J point and calculating the height of its slope 1 second after recording (STH, mm), as shown in Fig. 2.

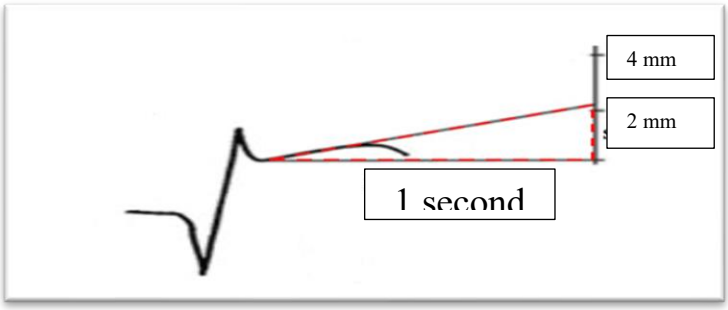

Fig. 2 Principle of assessing the height of the ST-segment slope [made by the authors]

We analyzed clinical cases of patients with Fabry disease and Brugada syndrome, determining the differentiated ECG parameter —the maximum speed ratio (MSR)—and assessing the height of the continued direction of the ST-segment slope (STH, mm).

Clinical Case 1

Patient A. was admitted to the cardiology center's emergency department with complaints of acute constricting chest pain. The ECG showed ST-segment elevation (Fig. 3), so the patient was referred to the intensive care unit with a diagnosis of ACS. Troponin levels were measured—no elevation was detected. A rapid change of the ECG was observed: after the initial ST-segment depression, the segment transitioned into a positive T wave ("saddleback" pattern—saddleback type), which is a marker of Brugada syndrome type 2. However, ST elevation may also indicate ACS, therefore digitalization of the ECG using "Smart ECG" is relevant.

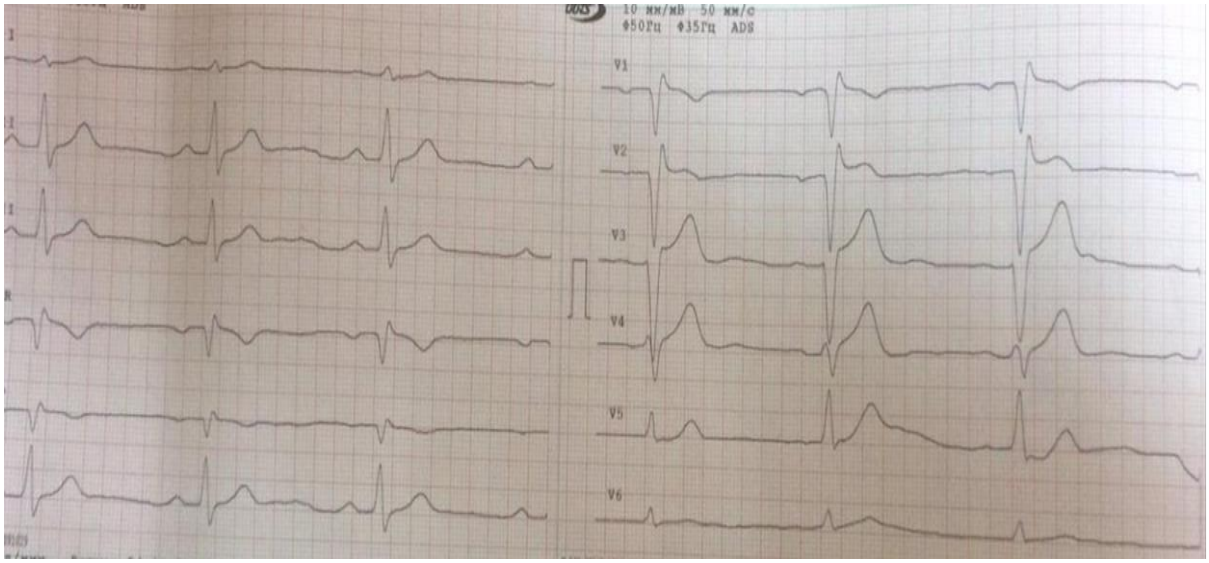

Fig. 3 ECG of the patient on admission [made by the authors]

Using the 'Smart-ECG' medical software, the MSR values obtained from differentiated ECGs and the STH values obtained from digitized ECGs were assessed in leads I, II, III, and V1–V6 (Table 1).

Table 1. Digitized ECG parameters

Lead	MSR	STH, mm
I	1,727	0,3
II	2,088	0,67
III	2,013	0,6
V1	0,582	0,73
V2	3,667	0,57
V3	3,240	1,61
V4	2,007	2,06
V5	1,311	1,06
V6	1,343	0,68

The results obtained from the digitized ECG indicated the absence of ischemic changes. The RMV values were more characteristic of left ventricular hypertrophic changes in most leads, while in leads V5 and V6 the MSR parameter approached values typical of chronic coronary syndrome, and in lead V1—of acute coronary syndrome. However, this was due to a negative T wave, which is a normal variant and therefore does not indicate acute ischemia.

A rapid normalization of the standard ECG, negative troponin test results, and satisfactory overall condition of the patient were noted. The results of the digitized ECG also confirmed the absence of acute ischemic injury. The patient did not undergo further examination or treatment, as she left the hospital of her own will and refused complete diagnostics and therapy. The reasons for discontinuing the hospital stay were rapid improvement of her condition and personal circumstances.

Brugada syndrome is a rare heart disease characterized by ventricular tachyarrhythmia and an increased risk of sudden cardiac death. The diagnostic program includes a family history, ECG recording, thorough medical history taking (respiratory disturbances, dizziness, seizures, ventricular tachyarrhythmias, cardiac arrest), completion of the Shanghai scoring system, genetic testing for the SCN5A gene

mutation, and assessment of ischemia markers (to exclude other pathologies). ECG digitalization expands the diagnostic toolkit, and in the presented clinical case—together with a negative troponin test, positive ECG dynamics, and improvement in the patient's condition—it allowed differentiation between acute coronary syndrome and Brugada syndrome type 2.

Clinical Case 2

Patient B. sought medical attention due to worsening condition and complaints of chest pain, burning pain in the feet and hands, abdominal rash, moderate headache, and general weakness. The patient was hospitalized in the intensive care unit (ICU).

Medical history: The first clinical manifestations appeared at the age of 7–8 as a rash on the lateral surface of the abdomen and groin, followed by discomfort in the distal extremities (numbness, pain) with fever up to febrile levels and elevated blood pressure (BP) of 140–150/90–100 mmHg. At the age of 16, the patient's condition significantly worsened due to the progression of neurological symptoms. An acute cerebrovascular accident was diagnosed (with recurrence at age 36). At age 18, a comprehensive examination revealed proteinuria, and at age 35 the patient noted hearing deterioration. At age 40, cysts of both kidneys, bilateral hydronephrosis, and chronic pyelonephritis in remission were diagnosed. At age 42, chronic kidney disease stage II was identified.

According to the previous examination:

Echocardiography (EchoCG):

Left ventricular ejection fraction (LVEF) – 52%.

Concentric LV hypertrophy with normal LV filling pressure (interventricular septum 13 mm; LV wall – 12 mm). Myocardial LV function is satisfactory.

24-hour Holter ECG monitoring:

Atrial extrasystolic arrhythmia.

Cardiology consultation:

Arterial hypertension stage II, grade 2, risk 4.

Atrial extrasystolic arrhythmia.

Heart failure stage IIA with preserved LVEF (52%), functional class II.

Brain MRI:

Findings may correspond to involvement of the corticospinal tract; pineal gland cyst.

Chest CT:

Signs of emphysematous lung changes and diffuse pneumofibrosis.

DNA testing for Fabry disease:

A hemizygous variant p.(Gly138Arg) in exon 3 of the *GLA* gene was detected. The mutation is pathogenic (class I).

Enzyme testing:

Alpha-galactosidase activity – 2.5 nmol/h/mg (normal = 15.3 nmol/h/mg), i.e. below normal.

Lyso-Gb3 in blood:

55.3 ng/mL (normal = 1.8 ng/mL), i.e. above normal.

Based on the clinical history and additional test results, the patient was diagnosed with a hereditary metabolic disorder from the group of lysosomal storage diseases—Fabry disease, X-linked inheritance type.

A standard ECG was performed. It was noted that in leads II, III, and aVF there was upsloping ST-segment depression up to 1.5 mm in leads III and aVF and up to 0.5 mm in lead II. Upsloping ST-segment elevation was also recorded in chest leads V1–V4, increasing from 0.5 mm in V1, 0.7 mm in V2, to 1.3–1.5 mm in V3 and V4, respectively.

Signs of right atrial and left ventricular hypertrophy were documented (Fig. 4).

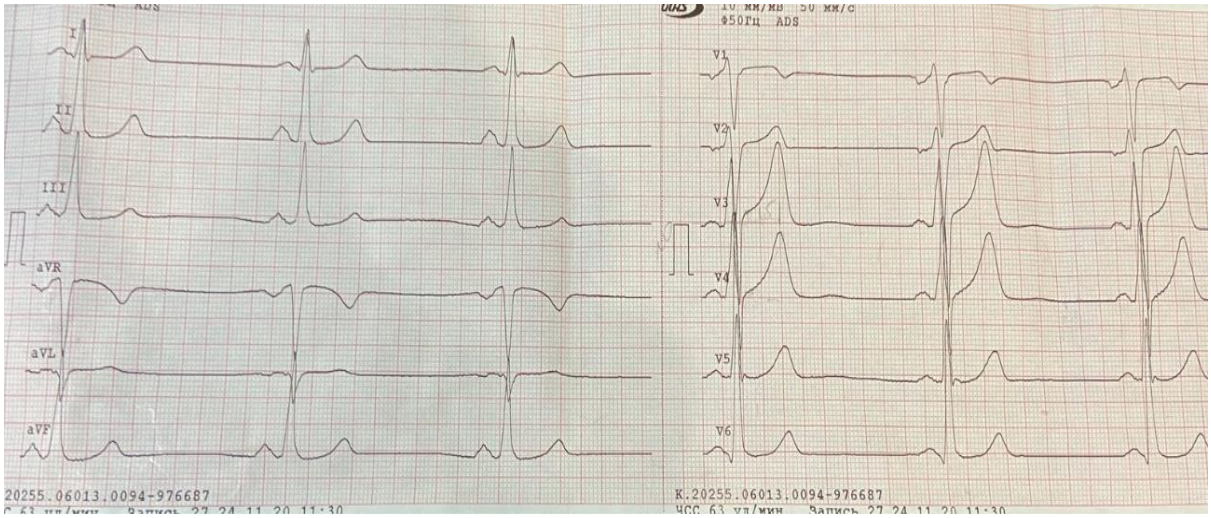

Fig. 4 ECG of patient B before alpha-galactosidase infusion [made by the authors]

During ECG differentiation, it was established that the MSR values did not confirm an ischemic nature of the T-wave changes and were more characteristic of LV hypertrophy. In leads II, III, and aVF, the MSR values were 5.16, 3.66, and 2.87, respectively, while in chest leads V2–V4 they were 5.7, 7.26, and 5.37, respectively.

Similarly, analysis of the "ST slope" changes showed that the ST-segment depression in leads II, III, and aVF had a "benign" upsloping pattern: STH in II, III, and aVF was 0.76, 0.86, and 0.87 mm, respectively.

Likewise, ST-segment changes in leads V2–V4 did not indicate acute myocardial ischemia and also exhibited a "benign" upsloping pattern: 1.18, 2.41, and 3.86 mm, respectively.

Since the patient had a prior diagnosis of Fabry disease, an infusion of alpha-galactosidase ("Replagal") 7.0 mL + 100.0 mL of 0.9% sodium chloride was administered intravenously. Before the infusion, the patient received 1.0 mL of Suprastin and 8 mg of dexamethasone IV. The recommended ongoing medications were Aspirin Cardio 100 mg, ramipril 2.5 mg, and carbamazepine 200 mg in 2–4 doses.

After administration of the drug, the patient experienced improvement in well-being and stabilization of blood pressure (120/75 mmHg). The ECG changes after treatment were also noteworthy (Fig. 5).

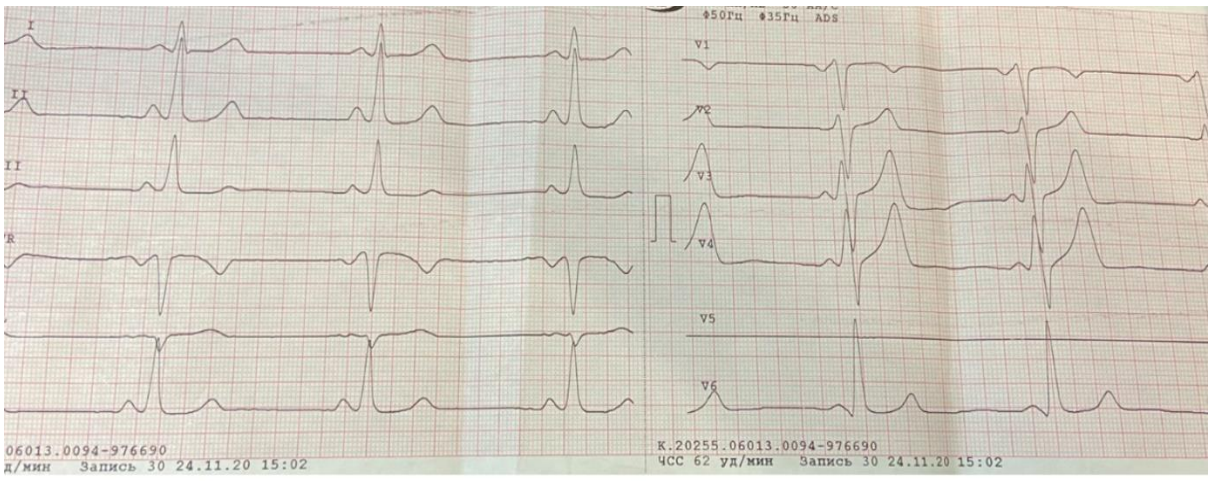

Fig. 5 ECG of patient B after the administered treatment [made by the authors]

The ECG changes involved a reduction in ST-segment depression in leads II, III, and aVF, as well as ST-segment elevation in V2–V4. Similar changes were observed

in RMV values: in leads II, III, and aVF, the values decreased to 2.1, 1.77, and 1.8, respectively; in V2–V4, MSR decreased to 2.69, 2.13, and 2.38, respectively, approaching reference values typical for LV hypertrophy.

This clinical case demonstrates that the manifestations of Fabry disease are associated with involvement of multiple organ systems, which can be identified through analysis of ECG, echocardiography, MRI, DNA testing, enzyme diagnostics, and other methods. Digital ECG processing revealed characteristic ECG features in a patient with a confirmed diagnosis of Fabry disease and confirmed the “non-ischemic” nature of these changes, consistent with current understanding of the pathology.

Thus, ECG digitalization in the differentiation of acute coronary syndrome and rare cardiac pathologies is an accessible and highly informative diagnostic tool.