CASE STUDY

CONTENTS 🔼

Case of early uncomplicated multivascular nonobstructive coronary atherosclerosis in young male: novel aspects of noninvasive diagnostic

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ABSTRACT

This clinical report demonstrates the case of nonobstructive coronary artery disease in a 38-year-old male with the only complaint of an episodical increase in blood pressure. A combination of risk factors raised the suspicion of nonobstructive coronary artery disease. It was substantiated by the modified stress test which consists of electrocardiography, echocardiography, laser Doppler flowmetry, pulse oxymetry, capnometry, lactate measurement, and blood pressure monitoring while cycling. Only afterward, the patient passed over coronary computed tomography angiography, which confirmed the suspected diagnosis precisely. Based on the current case, we aimed to increase the awareness of physicians about nonobstructive coronary artery disease and propose an algorithm for nonobstructive coronary atherosclerosis screening.

KEY WORDS: case report, ischemia with nonobstructive coronary artery disease, atherosclerosis screening, stress echocardiography, endothelial dysfunction

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INTRODUCTION

Ischemia with nonobstructive coronary artery disease (INOCA) has become widespread condition that affects approximately 3-4 million individuals annually. It is defined as less than 50% epicardial coronary artery (CA) stenosis on angiography. A large number of such patients have an asymptomatic course or with atypical pain syndrome and, often, shortness of breath during physical exertion as the only symptom. Unless earlier INOCA was believed to be among benign disorders, upto-date data demonstrate it is associated with serious cardiovascular outcomes (major adverse cardiovascular events), recurrent hospitalization, additional medical procedures, decline in quality of life, satisfaction with medical care, and mortality especially in patients of older age, with diabetes, hypertension, smoking. Of note, the risk of myocardial infarction and death in patients with 3 non-obstructive CAs is similar to single-vessel coronary obstruction [1].

INOCA occurrence is tightly associated with microvascular dysfunction [2]. Quiet often, it is manifested by dysfunction of endothelium-dependent vasodilatation of arterioles, associated with insufficient amount of synthesized NO or its non-absorption [3]. However, limited attention is paid to the impact of oxygen, carbon dioxide, and lactate on coronary flow including microvascular [4]. Coronary angiography is the principal method of INO-CA diagnosis confirmation [1]. However, it is demonstrated that the effectiveness of computer tomography (CT) as a non-invasive method is not worse than that of invasive angiography [5]. Nevertheless, the cost-effectiveness of both procedures is assessed with questionable results of the patients' risk stratification regarding the necessity of every procedure [6]. Therefore, the non-invasive algorithm of nonobstructive atherosclerosis detection remains one of the most urgent problem [7].

Thus, in this case, we presented the patient with early uncomplicated multivascular nonobstructive coronary atherosclerosis with the establishment of the preliminary diagnosis before providing CT. For this purpose, we applied above-mentioned regularities of microvasculature to improve the technique of stress echocardiography to identify patients with nonobstructive coronary atherosclerosis.

CASE REPORT

PATIENT INFORMATION

Male patient P., 38 years old, visited a cardiologist on an outpatient basis with complaints of episodically increased blood pressure (BP) and with the diary of BP and heart rate (HR) which he kept for 10 days before cardiologist visiting

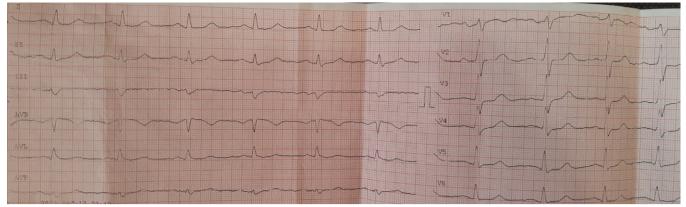


Fig. 1. 12-channel ECG of the patient.

following the recommendations of his colleagues: BP (mmHg) – HR (bpm); 171/122 – 85; 107/73 – 87; 110/75 – 91; 170/112 – 89; 140/109 – 88; 172/114 – 83; 134/99 – 94; 141/97 – 77; 127/94 – 94; 149/100 – 101.

No other complaints, including any discomfort in the heart region, palpitation, or dyspnoe, were mentioned.

HISTORY OF PRESENT ILLNESS

From the anamnesis, the history of such disorders has lasted for not more than 2–3 weeks. The patient associated BP dysregulation with stressful periods at work.

PERSONAL HISTORY

No therapeutical disorders, traumas, surgeries, or allergic reactions were registered. The patient denied harmful habits and any history of medicine intake.

OBJECTIVELY

The general condition is satisfactory with hypersthenic body habitus type and body mass index – 29.8 kg/m². The skin and visible mucous membranes are clean. The left border of the relative dullness of the heart is shifted 0.5 cm outward from the left midclavicular line while percussion at the 5th intercostal space. Heart tones are muffled, and regular. No murmurs while auscultation of the heart. Pulse 92 bpm, rhythmic, with satisfactory properties. BP – 180/120 mm Hg. No pathological findings were noticed during the physical examination of the lungs, and abdomen. No peripheral edema.

DIAGNOSTIC ASSESSMENT

On the ECG (Fig. 1), sinus regular rhythm was registered, the horizontal position of the electrical heart axis, negative Sokolov-Lyon criteria, and mild diffuse changes of the myocardium with possible signs of hypoxic changes of left ventricular (LV). No other peculiarities. The patient underwent two-dimensional transthoracic echocardiography (Toshiba Artida, SSH-880CV) (Table 1). The wall thickness and ejection fraction (EF=56%) were normal. Mild enlargement of LV volumes. S-shape interventricular septum. Signs of diastolic dysfunction of LV (type I, impairment of LV relaxation) were also confirmed with pulse wave tissue Doppler imaging. Slightly increased stiffness of left and right CAs. No changes in the local contractility of LV were noticed.

However, while 2D Speckle tracking echocardiography (Toshiba Artida), a significant reduction of global longitudinal strain and local deformation of the myocardium were observed in the 4-chamber view in the apical-lateral and medial-lateral segments, and the 3-chamber view in the apical-lateral and medial-posterior segments (Fig. 2A, B, C).

Consequently, we provided more profound investigations of the patient.

The results of laboratory assessments are aggregated in Table 2. Data of complete blood count with blood differential rate, levels of thyrotropic hormone, triiodothyronine, thyroxine, C-reactive protein, creatinine, uric acid, potassium, magnesium, homocysteine, D-dimer are within normal reference ranges. Dyslipidemia and hyperglycemia are noticed.

Carotid ultrasound registered hemodynamically insufficient local hyperechoic plaque with regular contour along the posterior wall of common carotid arteries bifurcation from the left side (stenosis 44% of diameter and 31% of surface) (Fig. 3A, B).

All collected information hinted to suspect initial non-obstructive atherosclerosis of CAs in the patient. So, the patient passed stress test following modified protocol (Table 3), particularly in addition to ECG registration during bicycling, EchoCG before and after cycling (Table. 4), BP control before the test, after each stage and at 1', 3', 5' of restitution, such parameters as SaO₂ (Fig. 4), etCO₂ and lactate were measured as well as Laser Doppler Flowmetry (LDF) was performed before and after stress test (Fig. 5A, B).

LDF-gram before physical exertion demonstrated endothelial dysfunction with the trend of arteriolospasm even without normalization of microcirculation. Four minutes after deflation, improvement in the constant

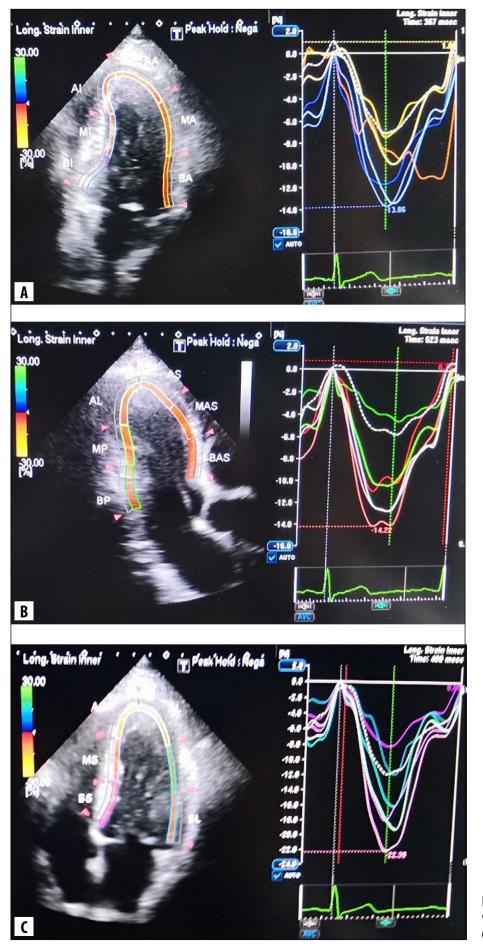


Fig. 2.A) 2D Speckle tracking. 2-chamber view; B) 2D Speckle tracking. 3-chamber view: C) 2D Speckle tracking. 4-chamber view.

Table 1. EchoCG data of the patient at rest

Parameter	Result	Reference range
Diameter of aorta, mm		20-37
Aortic valve opening, mm		17-25
Left atrial diameter, mm	41.2 *	20-40
Interventricular septum thickness at end diastole, mm		6-11
Left ventricular posterior wall thickness at end diastole, mm		6-11
Anterior wall of right ventricular, mm		< 5
Right ventricular dimension at end diastole, mm	30	9-30
Right atrial diameter, mm	34	20-40
Ejection fraction, %	56	> 55
End-diastolic volume, mL	162.2 *	51-160
End-systolic volume, mL	85.1	14-70
Stroke volume, mL	92.1	30-100
E/ A (peak velocity of early diastolic transmitral flow (m/ s)/ peak velocity of late transmitral flow (m/ s)		1.5-1.6
Deceleration time of early diastolic transmitral flow, ms		160-220
Isovolumic relaxation time, ms	96	60-100
Peak velocity of diastolic flow, cm/ s	71.3	62-80
Pulmonary artery systolic pressure	25.8	<30

Notes: * - out of reference ranges.

Table 2. Laboratory data of the patient

Parameter	Result	Reference range
 Lipidogram		
Cholesterol, mmol/l	5.56 *	<5.2
Triglycerides, mmol/l	2.05 *	<1.7
High density lipoproteins, mmol/l	0.97 *	>1.00
Low density lipoproteins, mmol/l	4.14 *	<3.0
Very low density lipoproteins, mmol/l	0.94	0.26-1.00
Serum glucose, mmol/l	6.4 *	4.11-5.89
Glycated hemoglobin, %	5.7 *	4.5-5.6

Notes: * - out of reference ranges.

component of microcirculation (M=3.60 PPU vs M=4.74 PPU), as well as the variable component of mictocirculation (absence of arteriolospasm on the LDF-gram after stress test with the increase in area under the curve of post-ischemic reactive hyperemia (430 PPU vs 740 PPU) were noticed.

Hence, the stress test was positive. The patient fulfilled 86% of the targeted workload with 87% of targeted HR which indicates high tolerance to physical exertion. Initial atherosclerosis may be suspected in the distal segment of the left anterior descending artery or circumflex artery.

Based on complaints, anamnesis, physical examination, and results of all above-presented laboratory and instrumental investigation we established the diagnosis: Arterial hypertension, I stage, grade 1-2, mild risk (SCORE scale). Coronary artery disease: INOCA (non-obstructive coronary atherosclerosis)? Heart failure I. To establish the diagnosis precisely the patient was directed to coronary CT angiography. It was visualized combined atherosclerotic plaques in left anterior descending artery, circumflex artery. and right coronary artery, stenosing the vessels up to 25%, 20% and 35%, respectively.

Thus, preliminary diagnosis was confirmed and we established final diagnosis: Arterial hypertension, I stage, grade 1-2, mild risk (SCORE scale). Coronary artery disease: INOCA (multivascular non-obstructive coronary atherosclerosis: left anterior descending artery 25%, circumflex artery 20%, right coronary artery 35%). Heart failure I.

THERAPEUTIC INTERVENTION

It was prescribed nebivolol 5 mg once a day, perindopril 5 mg once a day, rosuvastatin 10 mg once a day, L-arginine 1

Stage	Initial (0)	1	2	3	Restitution	Rest
Workload, W	0	50	100	150	30	0
Time, min:s	3:00	3:00	3:00	1:00	3:00	5:00
HR, bpm	67	111	131	142	90	65
BP, mm Hg	120/75	130/80	160/80	190/90	140/75	120/75
ECG	sinus regular rhythm, mild diffuse myocardial changes	-//-	-//-	Upsloping depression up to 0.9 mm in V ₅₋₆	As initial	As initial
EchoCG	Normokinesis of all segments in long-axis, short axis, 2Ch-, 4Ch-views	-//-	-//-	Mild hypokinesis in 4Ch-view (apical-lateral segment) and in 2Ch-view (apical-anterior segment)	As initial	As initia
RR, 1/min.	15-20	-	-	18-20	-	15-18
SpO2	95	95	95	96	96	95
etCO2	3.3-3.4	-	-	3.5-3.6	-	3.3
Lactate	1.3	-	-	-	-	7.0
Complaints	-	-	Dyspnoe	Dyspnoe, fatigue in the muscles of legs	Dyspnoe	-

Table 3 The	nrotocol of r	nodified stress	test of the	natient
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Notes: 2Ch – 2-chamber, 4Ch – 4-chamber.

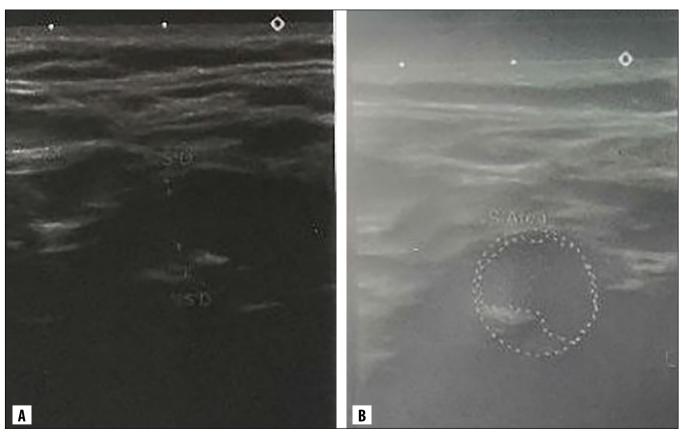


Fig. 3. A) Carotid ultrasound. Common carotid artery; B) Carotid ultrasound. Bifurcation.

spoon 3 times a day, acetylsalicylic acid 75 mg once a day, mild physical activity (walking) regularly.

Despite the fact that the patient had a low pre-test probability of coronary artery disease based on his age, the absence of bad habits (non-smoker), and the typical angina attacks, we took into account other important risk factors for atherosclerosis, namely: the presence of atherosclerotic plaques in the brachiocephalic arteries, hyperlipidemia, an elevated level of glycated hemoglobin and blood glucose, arterial hypertension and increased body mass index. These

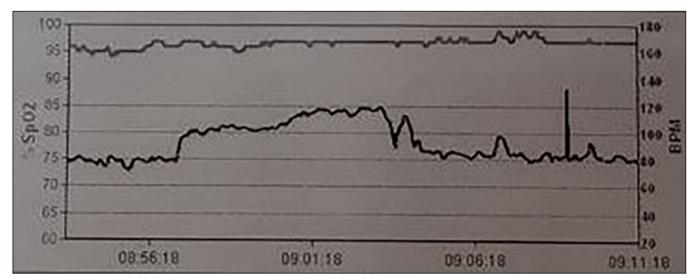
Table. 4. EchoCG before and after stress test

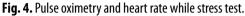
Before stress test	Echography views	After stress test
- Andre H	Long-axis view	- Andrew
hunn	Short-axis view	
	2-chamber view	No. of the second se
- Andrew	4-chamber view	H-h-h-h

important risk factors arose suspicion regarding non-obstructive coronary atherosclerosis [1].

Despite the absence of ischemia on the ECG and changes in the regional myocardial contractility according to the standard echocardiogram, the use of the 2d Spackle tracking option, namely, the determination of the longitudinal deformation of the myocardium, allowed us to be more confident in making this diagnosis [8]. In Fig. 3 from the longitudinal strain of the patient is significantly reduced (the reference point is less than 15%) in all coronary artery basins (at least in two adjacent segments). These changes may indicate a violation of perfusion in the subendocardial layer of the left ventricle. The occurrence of a decrease in longitudinal strain in two adjacent segments is linked to the damage of a specific coronary artery [8]. In observed patient it can be suspected multiple vascular damage. To confirm this assumption, we performed modified stress echocardiography on both patients.

From Table 3, the patient cycled 150 W for 1 min, while he did not reach the submaximal HR (88%). The test was stopped due to severe shortness of breath and weakness in the leg muscles. In the course of load steps, single ventricular extrasystoles appeared already at 50 W, and at 100 W, they were joined by supraventricular ones, at 150 W, depression of the ST segment by 0.9 mm appeared in leads V5-6. The graph of SpO2 did not change during all stages and corresponded to the norm. According to etCO2, the initial level was 3.5% at the peak of the load, it fluctuated from 3.8 to





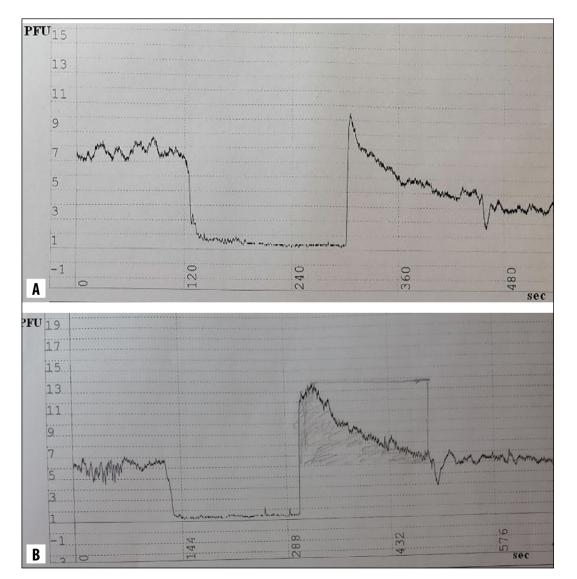


Fig. 5.A) LDF-grams of the patient before stress test; B) LDF-grams of the patient after stress test.

3.5%, and returned to the initial during the restitution period. According to lactate before exercise, it was 1.25 mmol/l, and during the restitution period it increased to 7 mmol/l. When hypoxemia occurs (the partial pressure of oxygen in the blood decreases), an increase in hydrogen ions, CO_2 and lactate is observed, causing dilation of arterioles, which leads

to an increase in the number of functioning capillaries of the myocardium [9] The same metabolites are formed while myocardial ischemia. At the same time the metabolism of the ischemic myocardium switches from the cycle of tricarboxylic acids to aerobic, and with aggravating of ischemia even to anaerobic glycolysis. At the same time, the level of CO2 decreases and the amount of lactate in the blood increases progressively. But the number of ATP molecules synthesized by the myocardium significantly decrease [10-12].

In turns of the echocardiography data, there was mild hypokinesis in the apical anterior and apical lateral segments at the peak of the load, which corresponds to the lesion of the distal segment left anterior descending artery or circumflex artery. Thus, it can be concluded that the usual stress echocardiography with a visual assessment of regional myocardial contractility has disadvantages due to the subjective assessment that depends on the experience of the operator [13]. However, when analyzing additional options, it is possible to slightly increase the diagnostic value of stress echo for the diagnosis of initial coronary atherosclerosis.

Regarding etCO2 analysis, its increase at the peak of physical exertion may indicate still aerobic glycolysis in the myocardium. Nevertheless, initial coronary atherosclerosis can be suspected especially when lactate has crossed the lactate (anaerobic) threshold of 4 mmol/l. The stenosing coronary atherosclerosis with the transition of the myocardium metabolism to anaerobic glycolysis is diagnosed if the level of etCO2 on the peak of physical exertion has become lower than the initial level, whereas the lactate level is high [14. In addition, such combination may arise the suspicion about the deterioration of the microcirculation of the myocardium due to the spasm of arterioles. Thus. Observed patient is more likely to have initial atherosclerosis according to the results of modified stress EchoCG, eventhough the ECG changes are questionable. Furthermore, we suspected initial nonobstructive atherosclerosis which was confirmed by results of coronary computed tomography angiography with the trend toward arteriolospasm [16]. The results of LDF also suggested the possibility of vasospasm [17].

The prescribed treatment following the wholistic management of the patient taking into account multiple pleiotropic effects of drugs (nebivolol with vasodilation effect [18] and L-arginine with combination of vasodilation and endothelium protection effects [19], rosuvastatin [20], perindopril [21], and acetylsalicylic acid [22]).

CONCLUSIONS

physicians should be aware of INOCA as clinal picture of the latter is divorce and non-specific. The diagnostic at early stages with further appropriate treatment prevents progression of disease including complications. Proposed algorithm of modified stress test may be a promising method for initial atherosclerosis screening in the patients with suspicion of INOCA before coronary computed tomography angiography or coronary angiography.

Informed Consent and Ethical Approval. The patient gave written consent to participate in current observation after the explanation of the purpose and allowed to publish the results of the later with depersonalized data.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Dear Colleagues!

We are pleased to invite you to participate in the International Scientific and Practical Conferencec

"Second Scientific Readings in Memory of Professor D. O. Alpern: Current Issues in Pathological Physiology".

This event will be held in a mixed (online-offline) format on May 8-9, 2025, at the Kharkiv National Medical University.

We welcome representatives from scientific institutions, higher education institutions, young scientists, graduate students, and healthcare professionals to join us at the conference.

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During the conference, a competition for scientific works titled "*Pathology Through the Eyes of Young Scientists*" will be held among higher education students and young scientists. The winners will be announced on May 9, 2025. The participant of the competition, whose scientific work will take the first place, will have the opportunity to publish the article for free in a foreign journal of ALUNA Publishing House (Warsaw, Poland). To participate in the competition, you must register by April 30, 2025, by following the link (<u>https://forms.gle/WkEWdMDHkd76p49z7</u>) and send your research to the e-mail of the organizing committee.

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