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Risk Stratification in Patients with Coronary Artery Disease: Timeliness of Invasive Interventions

Abstract

Introduction. Coronary artery disease (CAD) remains a top cause of morbidity and mortality nowadays. Current guidelines are used to define timely diagnostic and management strategies for a patient with new angina symptom. According to the guidelines, the main purpose is assessment of the pre-test probability of obstructive CAD. Exercise electrocardiography is the most accessible method with 85-90% specificity and 45-50% sensitivity. Cardiopulmonary exercise testing (CPET) with concomitant monitoring of electrocardiogram, heart rate and blood pressure, expired gas analysis has become widespread among different exercise tests. CPET is an important clinical tool to estimate exercise capacity. In most cases it allows to determine the causes of limited physical activity, evaluate both the blood supply (pulmonary, cardiovascular, haematopoietic systems) and tissue oxygen metabolism (skeletal muscle system) in response to physical exercise. The indications for invasive coronary angiography include: high clinical risk of CAD, symptoms which are refractory to medical therapy, low tolerance to exercise or if revascularization is considered for improvement of prognosis.

The aim. To highlight the need for a combination of non-invasive stress testing (CPET, stress echocardiography) and invasive testing (such as coronary angiography) to develop proper tactics of treating patients with established CAD.

Conclusion. Described clinical case demonstrates preferences of combined different functional non-invasive tests (CPET, stress echocardiography) in a patient with confirmed CAD, who received prognosis modifying therapy and had high exercise tolerance due to regular cardio training. This gave the reason for postponing the repeated ICA to determine the dynamics of the progression of coronary atherosclerosis. However, when an anginal attack occurred and repeated urgent ICA was performed, it became necessary to perform coronary artery bypass grafting and, later, due to the continuation of anginal attacks and the presence of areas of ischemia, stenting of the trunk of the left coronary artery.

Keywords: *cardiopulmonary exercise testing, invasive coronary angiography, stress echocardiography, revascularization.*

Introduction. Coronary artery disease (CAD) remains a top cause of morbidity and mortality nowadays [1]. According to modern guidelines, the strategy of invasive diagnostics in patients with a stable course of the disease is carried out according to special indications. Coronary angiography in chronic coronary syndromes is recommended after non-invasive tests. We present the sequence of tests in this paper. We also want to emphasize using the given clinical case that for physically active patients it is necessary to combine both non-invasive and invasive techniques.

Current guidelines are used to define timely diagnostic and management strategies for a patient with new angina symptom. According to the recommendations, the main purpose is assessment of the pre-test probability (PTP) of obstructive CAD [2]. In patients with PTP <15%, diagnostic testing is recommended after assessment of clinical symptoms, risk factors for cardiovascular disease, resting electrocardiogram (ECG) changes, and data of the cardiac CT calcium score. In patients with high clinical risk of CAD (>15% PTP), symptoms which are refractory to medical therapy or low tolerance to exercise, and data of initial tests (echocardiogram, exercise electrocardiography) that indicate high risk of coronary event, invasive coronary angiography (ICA) should be provided. Invasive confirmation of the haemodynamic significant stenosis is an indication for revascularization. Functional non-invasive tests based on detection of myocardial ischaemia through ECG changes, abnormalities of wall motion through stress echocardiography or cardiac magnetic resonance, or perfusion changes through single-photon emission computed tomography (SPECT), positron emission tomography or contrast cardiac magnetic resonance are used for the diagnosis of obstructive CAD.

Sensitivity and specificity of functional non-invasive tests are shown in Table 1.

Table 1

Characteristics of CAD diagnostic tests [2]

	Characteristics	
	Sensitivity (%)	Specificity (%)
Exercise electrocardiography	45-50	85-90
Exercise stress echocardiography	80-85	80-88
Exercise stress SPECT	73-92	63-87
Dobutamine stress echocardiography	79-83	82-86
Dobutamine stress MRI	79-88	81-91
Vasodilator stress SPECT	90-91	75-84
Vasodilator stress MRI	67-94	61-85
Coronary CTA	95-99	64-83
Vasodilator stress PET	81-97	74-91

CTA, computed tomography angiography; MRI, magnetic resonance imaging; PET, positron emission tomography.

Exercise electrocardiography is the most accessible method with 85-90% specificity and 45-50% sensitivity. The most important predictor of long-term survival is left ventricular (LV) function. Patients with reduced left ventricular ejection fraction (LVEF) <40% belong to the high risk category (annual mortality >3%). The Duke Treadmill Score is used to evaluate the result of an exercise test. This score predicts 5-year mortality and degree of coronary artery disease (https://www.omnicalculator.com/health/duke-score).

Cardiopulmonary exercise testing (CPET) with concomitant monitoring of ECG, heart rate and blood pressure, expired gas analysis has become widespread among different exercise tests. CPET is an important clinical tool to estimate exercise capacity. In most cases it allows to determine the causes of limited physical activity, evaluate both the blood supply (pulmonary, cardiovascular, haematopoietic systems) and tissue oxygen metabolism (skeletal muscle system) in response to physical exercise [3]. Such test is performed using either a bicycle ergometer or a treadmill. The protocol with gradual increase in load is used in both methods. VO2max is the main parameter measured during CPET and it evaluates exercise intolerance more accurately than metabolic equivalents of task (METs) and Watts. The most common indications for CPET include: determining the cause(s) and severity of exertional dyspnea, assessing exercise capacity and estimating prognosis in various disease states (including chronic heart failure), evaluating preoperative and postoperative complication risk (e.g., for thoracic, heart and visceral surgery), early measuring of treatment response (e.g., drugs, rehabilitation), risk stratification of cardiovascular diseases, guiding and monitoring individual physical training in rehabilitation (e.g., cardiac, pulmonary).

According to the data of researches, CPET sensitivity and specificity in the diagnosis of myocardial ischemia are 87% and 74%, respectively [4]. Confirmation of CAD is based on the concept of “ischemic cascade”, according to which signs of left ventricular dysfunction precede ST segment depression and angina. To analyze heart dysfunction induced by physical exercise, main parameters are used: VO2 indicates cardiac output; ΔVO2/ΔWR slope (peak oxygen uptake over work rate) and VO2/HR ratio (O2 pulse) indicate stroke volume. Changes in these parameters are characterized by the fact that, despite the further increase in physical activity, at a certain moment VO2 and O2 pulse stop growing linearly in relation to work, and the curves on the graph flatten out much earlier than in healthy age-matched individuals [5].

The 2019 ESC Guidelines recommend the use of either non-invasive functional imaging of ischaemia or anatomical imaging using coronary CT angiography (CTA) as the initial test for diagnosing CAD [1]. The indications for ICA include: high clinical risk of CAD, symptoms which are refractory to medical therapy, low tolerance to exercise or if revascularization is considered for improvement of prognosis. ICA is necessary in patients with suspected CAD in cases of inconclusive non-invasive testing (level of evidence IIb) and isn't recommended in case of low risk according to its negative results. ICA is contraindicated simply for risk stratification (IIIc). Assessment of event risk is recommended based on clinical evaluation and the result of the diagnostic test. In patients with suspected or newly diagnosed CAD, either stress imaging, coronary CT or exercise electrocardiography are performed for risk stratification. Contrast CTA becomes more widely used nowadays. It is more efficient for patient with PTP of CAD 15-65%. Contrast CTA detects subclinical coronary atherosclerosis, but can also accurately rule out both anatomically and functionally significant CAD. It should be noted that with the increase in PTP of CAD (especially with age), vascular calcification is more common, which can lead to overdiagnosis of stenotic lesions.

ICA dominates among invasive methods in symptomatic patients with expected improvement of functional status or high risk of cardiovascular event. However, for patients who are unable to pass imaging stress tests, have a reduced LVEF <40% and typical angina pectoris, or are employed in certain occupations (pilots), ICA may be useful for the main aim, that is, to rule-in or rule-out CAD.

It is difficult to assess indications and frequency of ICA in patients with confirmed CAD, who despite proper management and negative exercise test have typical angina pectoris.

The aim of this paper was to highlight the need for a combination of non-invasive stress testing (cardiopulmonary exercise testing, stress echocardiography) and invasive stress testing (such as coronary angiography) to develop proper tactics of treating patients with established CAD.

Clinical case. On October 20, 2021 male patient K., 72 years old, was admitted to Kyiv City Oleksandrivska Clinical Hospital with complaints of constringent pain behind sternum, which occurred during the rest, lasted more than 30 min and was unresponsive to nitrates.

The patient suffered from essential hypertension and CAD. In 2010, he underwent ICA, during which 50% stenosis of right coronary artery (RCA) was revealed. Despite no occlusive lesion and absence of the indications for the intervention, the Absorb stent was implanted on the patient's demand. After stenting he had no angina, constantly followed the recommendations for lifestyle modification including 40-60 min cardio exersises three times per week. The patient regularly took aspirin and clopidogrel for 12 month after stenting, then aspirin monotherapy, atorvastatin 20 mg (low density lipoprotein target level of <1.4 mmol/L was achieved), bisoprolol 5 mg, ramipril 5 mg. In 2014, first paroxysm of atrial fibrillation was treated by amiodarone i.v. and then orally, then it was replaced by sotalol. Echocardiography revealed LV hypertrophy, no heart chamber dilatation, preserved LVEF (60%). CPET showed normal VO2 level and no changes on the ECG (risk of coronary insufficiency was low), that's why the patient refused to undergo ICA. Since the CHADS-VASc score was 3 points, aspirin was substituted by rivaroxaban 20 mg (glomerular filtration rate 75 ml/min/1.73 m^2). Another management changes were switching from ramipril to valsartan and addition of eplerenone 25 mg. Throughout the year short paroxysms of atrial fibrillation were recorded on Holter ECG monitoring. Treatment with flecainide, propafenon, and combination of amiodarone plus β-blocker failed to support sinus rhythm. In 2015, it was decided to perform catheter ablation. The patient continued medical treatment and active physical activity. Twice a year exercise test was conducted (with β-blocker withdrawal some days before the test). Conclusion: time of the exercise treadmill test was 9 min 43 sec, treadmill speed 5.1 km/h, treadmill grade 14% (in terms of submaximal test 9 METs). The exercise test was performed against the background of taking medications. Taking into account the gas exchange measurements, the level of the exercise tolerance was moderate (5.9 METs, VO2 20.7 ml/min/kg, 95% predicted). Physical capacity was moderate. Aerobic performance was moderate. Oxygen uptake at the anaerobic threshold (AT) was 15.8 ml/min/kg, 4.51 METs (76% of VO2 peak). The response to exercise was normal. The gas exchange measures of exercise-induced myocardial ischemia (VO2 peak and the O2 pulse) reached their normal predicted value, 94% and 127%, respectively (ΔVO2/ΔWR during treadmill was not calculated). Slowing of the growth of O2 pulse after the AT draws attention and may indirectly demonstrate (without changes of VO2 and ischemic ECG) a lack of coronary flow reserve. The change of gas exchange (VE/VCO2 at the AT 35.8 and V-slope 32.7) with VO2 94% of predicted is most likely due to increased pressure in the pulmonary artery during exercise with mitral valve regurgitation and myocardial hypertrophy of LV. Stage of heart failure according to Weber was B.

The resting ECG: sinus rhythm, regular, incomplete right bundle branch block. ECG after test: no signs of ischemia, rare supraventricular premature complexes. Time of restitution 6 min. Blood pressure (BP) before test 120/80 mmHg, maximum BP 170/90 mmHg, BP after restitution 120/80 mmHg.

On March 25, 2021, without any previous provoking factors, the patient suddenly complained of chest discomfort, dyspnea, blood pressure drop. He was brought to the emergency department of Hospital Quirónsalud Marbella by an ambulance crew. Despite no changes on the resting 12-lead ECG, non-ST-elevation myocardial infarction was diagnosed due to double elevation of troponin level and its raise in 8 hours. Coronary angiogram (03/29/2021) showed multivessel stenosis (Fig. 1): dominant RCA: 90% stenosis, left main coronary artery (LMCA): 70% stenosis of distal part, left anterior descending artery (LAD): moderate stenosis of medium and distal part. Coronary artery bypass grafting (CABG): a.mammaria-LAD, v.Saphena-RCA marginal and proximal left circumflex artery (PLCx) was performed on the same day.

After 5 months, new episode of angina induced the patient to consult the cardiology in Marbella (Spain) again.

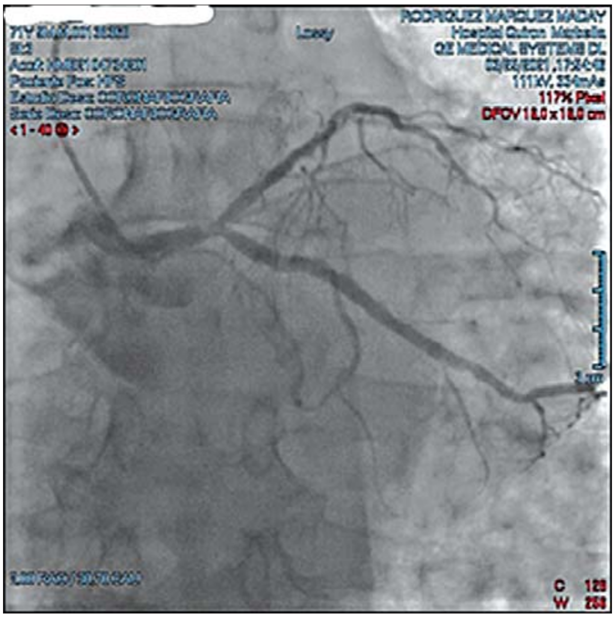

Fig. 1. *Coronary angiography (03/25/2021)*

Transient elevated troponin level was measured; it returned to normal in 2 hours. The resting ECG was without ischemic changes. The patient was instructed to continue medical treatment (atorvastatin 20 mg, valsartan 40 mg, eplerenone 25 mg, rivaroxaban 15 mg, clopidogrel 75 mg).

When the patient came back to Ukraine, angina evaluation was proceeded. Stress echocardiography with dobutamine, conducted on September 20, 2021, revealed ischemic changes. Decreased blood supply to the region vascularizated by left coronary artery or left circumflex artery with high coronary reserve in the area of LAD (Fig. 2, 3, 4, 5, 6) was observed.

Fig. 3. *Result of 5 mg dobutamine stress echocardiography*

Fig. 4. *Result of 10 mg dobutamine stress echocardiography*

Fig. 2. *Stress echocardiography before pharmacology test*

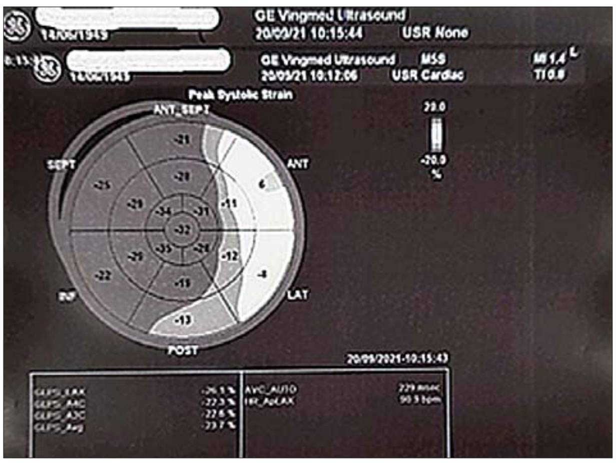

Fig. 5. *Result of 20 mg dobutamine stress echocardiography*

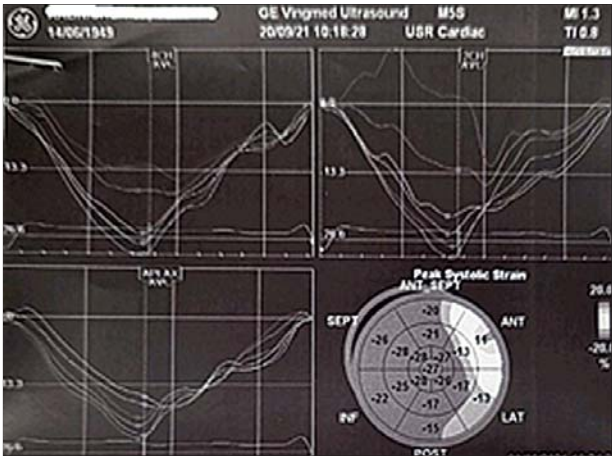

Fig. 6. *Stress echocardiography during restitution period*

Drug therapy was not effective in the prevention of disease progression. Worsening of the patient's condition was observed. On October 20, 2021 he was admitted to the intensive care unit of Kyiv City Oleksandrivska Clinical Hospital with severe angina and dyspnea. On examination, he was noted to have normal jugular vein pulse and no carotid arteries pulsation. The S1 was soft and S2 normally audible; there was soft systolic murmur over the apex. His heart rate was 60 bpm, his BP was 120/80 mmHg. The patient's lungs had no bilateral crackles, respiratory rate was normal with SaO2 98%. He was found to have no hepatomegaly, no ankle edema. ECG showed sinus rhythm, regular, incomplete right bundle branch block. Biochemical test revealed elevated troponin level (30.91 ng/ml, normal level <0.06). The patient's diagnosis was: CAD. Recurrent non-Q-wave myocardial infarction on 10/20/2021. Postinfarction cardiosclerosis (myocardial infarction on 03/25/2021). CABG (a.mammaris-LAD, Ao-RCA, Ao-v.Saphena-PLCx) on 03/29/2021. RCA stenting in 2010. Persistent atrial fibrillation. Catheter ablation in 2015. Stage 2 essential hypertension. Heart failure with preserved ejection fraction (LVEF 47%).

Urgent angiography (10/20/2021) showed 90% LMCA stenosis, LAD is filled through left internal mammary artery, thinning of the distal anastomosis. Right circumflex artery (RCx) is filled through the functioning autovenous shunt. RCA is filled through the functioning autovenous shunt, ONCX 60%. Based on data of angiography and stress echocardiography, stenting of LMCA was decided. It was performed using Xience 3.25815 m on 10/20/2021 (Fig. 7).

Drug treatment included dual antiplatelet therapy (clopidogrel 75 mg and apixaban 2.5 mg BID (using of rivaroxaban was complicated by hemorragical rash), ranolazine 500 mg BID, rosuvastatin 20 mg, valsartan 40 mg, eplerenone 25 mg, trimetazidine 80 mg, bisoprolol 2.5 mg.

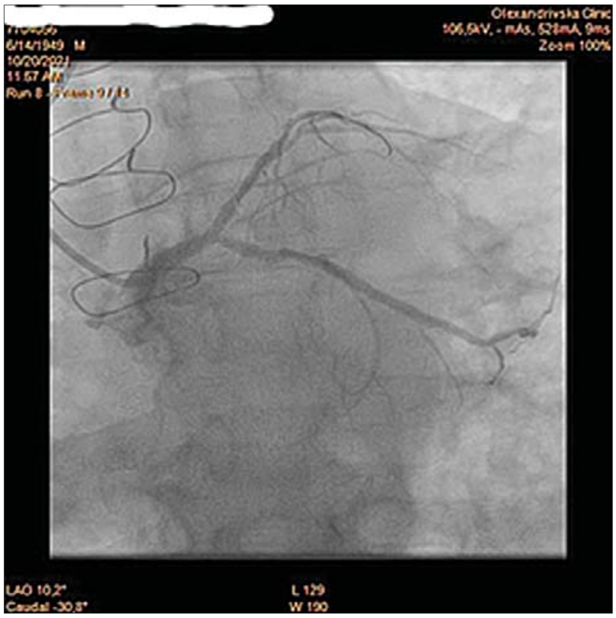

Fig. 7. *View after LMCA stent placement*

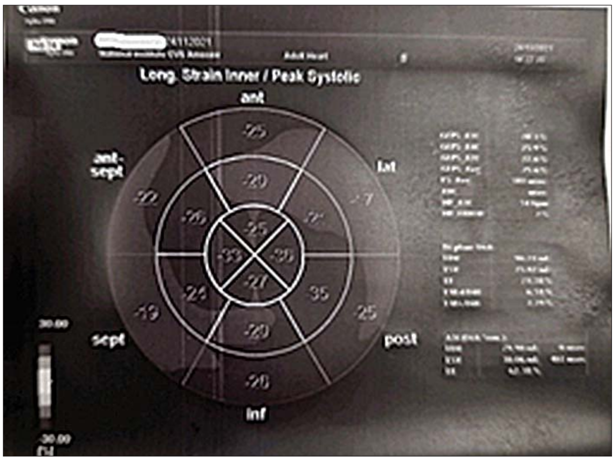

Fig. 8. *Stress echocardiography before pharmacology probe (after LMCA stent placement)*

Stress echocardiography was performed again after one month. Positive changes in LV walls movement (Fig. 8, 9, 10, 11) were observed.

Conclusion. Cardiac rehabilitation is a clinically effective and cost-effective intervention for patients with acute coronary syndrome or heart failure with reduced ejection fraction and after coronary revascularization according to the data of randomized, controlled trials [6]. The importance of quality assurance in cardiac rehabilitation was emphasized in the 2020 position statement of the European Association of Preventive Cardiology (EAPC), the 2017 guidance from the British Association for Cardiovascular Prevention and

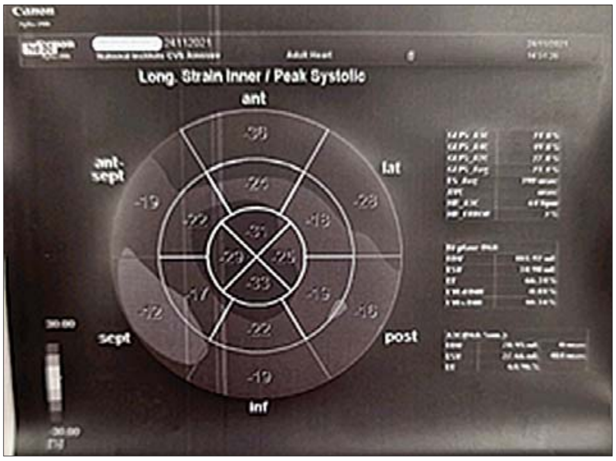

Fig. 9. *Result of 10 mg dobutamine stress echocardiography (after LMCA stent placement)*

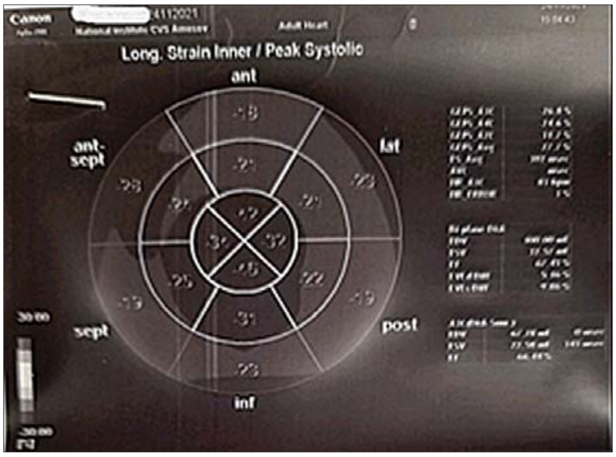

Fig. 10. *Result of 40 mg dobutamine stress echocardiography (after LMCA stent placement)*

Rehabilitation and the 2020 position statement from the Secondary Prevention and Rehabilitation Section of EAPC [7]. CPET with concomitant monitoring of ECG, heart rate and BP, expired gas analysis has become widespread among different exercise tests both to determine exercise tolerance and to choose training programs. In recent years, more studies have found that CPET has an important predictive role in disease prognosis [8]. This test helps to determine the need for invasive interventions, such as coronary angiography, in patients with confirmed CAD [9].

Presented clinical case demonstrates benefit of combined different functional non-invasive tests (CPET, stress echocardiography) in patients with confirmed CAD who receive prognosis modifying therapy, have high exercise tolerance due to regular cardio training (false negative CPET) for timely invasive coronary angiography (repeated, if necessary) in order to prevent myocardial infarction.

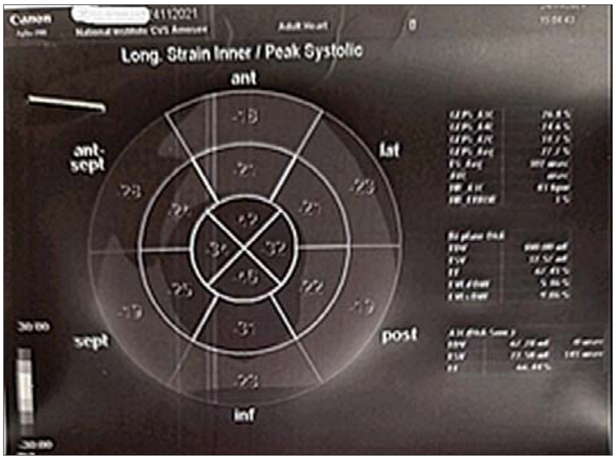

Fig. 11. *Stress echocardiography during restitution period (after LMCA stent placement)*

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Стратифікація ризику у хворих з ішемічною хворобою серця – своєчасність інвазивних втручань

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Резюме

Вступ. Ішемічна хвороба серця (ІХС) сьогодні перебуває на першому місці як за показниками захворюваності, так і смертності. Сучасні клінічні рекомендації використовують для визначення тактики своєчасної діагностики та стратегії лікування пацієнта з новим симптомом стенокардії. Відповідно до рекомендацій основною метою є оцінювання передтестової ймовірності ІХС. Найбільш доступним є навантажувальний ЕКГ-тест із специфічністю 85–90 % і чутливістю 45–50 %. Кардіопульмональний навантажувальний тест (КПНТ) із супутнім моніторингом ЕКГ, частоти серцевих скорочень і артеріального тиску, аналізом виділених газів набув значного поширення серед різних навантажувальних тестів. КПНТ є важливим клінічним інструментом для оцінювання фізичної працездатності, дає змогу в більшості випадків визначити причини обмеження фізичної активності, оцінити як кровопостачання (легенева, серцево-судинна, кровотворна системи), так і кисневий обмін тканин (система скелетних м'язів) у відповідь на фізичні вправи. Показання до інвазивної коронарної ангіографії (ІКА) включають: високий клінічний ризик ІХС, симптоми, резистентні до медикаментозної терапії, низьку толерантність до фізичних навантажень або якщо реваскуляризація розглядається для покращення прогнозу. Інвазивна коронарна ангіографія необхідна пацієнтам із підозрою на ІХС у випадках непереконливого неінвазивного тестування (рівень доказовості IIb) і не рекомендована в разі низького ризику за їхніми негативними результатами.

Мета – наголосити на необхідності поєднання неінвазивного стрес-тестування (кардіопульмональний тест, стрес-ехокардіографія) та інвазивного тестування (коронароангіографія) для розробки тактики лікування пацієнтів із встановленою ІХС.

Висновок. Наведений клінічний випадок демонструє переваги комбінування різних функціональних неінвазивних тестів (КПНТ, стрес-ехокардіографія) у пацієнта з підтвердженою ІХС, який отримував прогноз-модифікуючу терапію, мав високу толерантність до фізичного навантаження внаслідок регулярних кардіотренувань. КПНТ показав високу толерантність до фізичного навантаження, що мало підставу для відтермінування проведення повторної ІКА для визначення динаміки прогресування коронарного атеросклерозу. Однак у разі виникнення ангінозного нападу та проведення повторної ургентної ІКА виникла необхідність проведення аорто-коронарного шунтування та пізніше, внаслідок продовження ангінозних нападів і наявності зон ішемії за даними стрес-ехокардіографії, стентування стовбура лівої коронарної артерії.

Ключові слова: *кардіопульмональний навантажувальний тест, інвазивна коронарографія, стрес-ехокардіографія, реваскуляризація.*

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