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# Prognostic factors of left ventricle function deterioration in patients with coronary disease and normal results of echocardiographic examination in a 2-year observation — prospective cohort study

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**Abstract: Introduction:** Coronary disease is one of the strongest risk factors of developing heart failure. Identification of the predictive factors of left ventricle (LV) function deterioration in patients with stable angina pectoris and normal systolic function of LV, is a challenge for clinicians.

**Objective:** Identification of prognostic factors: clinical, echocardiographic, biochemical (NT-proBNP, hsCRP) and spirometric of left ventricle function deterioration in patients with coronary disease and normal results of baseline echocardiographic examination in a 2-year observation.

**Patients and methods:** The study group comprised of 32 patients with stable angina pectoris and normal heart function, aged  $50.9 \pm 4$  years; 23 men (71.8%). At baseline we performed echocardiography, cardiopulmonary exercise testing and determined serum levels of B-type natriuretic peptide and C-reactive protein. 24 months later we performed echocardiography and cardiopulmonary exercise testing.

**Results:** Patients with stable angina pectoris and normal LV function are at risk of developing the impairment of LV function. Diastolic dysfunctions of LV are a crucial element of the whole clinical picture. 53.1% developed of LV diastolic dysfunction: 37% isovolumetric relaxation disorders and 15% pseudonormalization. The analysis of the tests carried out after a 2-year observation indicated a relation-

ship between developing diastolic dysfunction of LV and the presence of type II diabetes ( $p = 0.01$ ). Peak oxygen consumption ( $VO_{2peak}$ ) at baseline was significantly lower in patients who developed diastolic dysfunction of LV after 2 years ( $p = 0.03$ ).

**C o n c l u s i o n s:** The predictors of LV diastolic function deterioration in a 2-year observation in this group of patients include type II diabetes and peak oxygen consumption  $VO_{2peak}$ .

**Key words:** dysfunction of left ventricle, patients with stable angina pectoris, prognostic factors of left ventricle dysfunction.

## Introduction

Coronary disease is one of the strongest risk factors of developing heart failure [1]. Diagnosing cardiac dysfunction in the asymptomatic stages allows to implement early treatment and impede the progression of heart muscle dysfunction [2]. Asymptomatic impairment of left ventricle function develops in approximately 62% of adults [3–6].

According to a number of studies, increased NT-proBNP (N-terminal-pro B-type Natriuretic Peptide) plays a crucial role in the detection of left ventricle dysfunction [7, 8]. Few reports indicated that the analysis of CRP concentration and its altered level in time allows to predict the progression of heart failure and establish the prognosis [9]. This refers to considerably low CRP values (3–10 mg/L) [10]. Therefore, reliable high sensitivity tests for CRP (hsCRP) have been compiled [10].

Identification of the predictive factors of heart function deterioration in the group of patients with increased risk of developing heart failure, including patients with stable angina pectoris and normal systolic function of left ventricle, is a challenge for clinicians. It will allow to select patients requiring more frequent check-ups and modification of pharmacological treatment to prevent or delay the development of clinically evident heart failure. The study involved an attempt to establish factors determining left ventricle function deterioration in patients with stable angina pectoris without left ventricle dysfunction.

## Objective

Identification of prognostic factors: clinical, echocardiographic, biochemical (NT-proBNP, hsCRP) and spiroergometric of left ventricle function deterioration in patients with coronary disease and normal results of baseline echocardiographic examination in a 2-year observation.

## Patients and methods

The study group comprised 32 patients with coronary disease and normal heart function hospitalized in the Department of Coronary Disease, John Paul II Specialist Hospital in Krakow, aged from 39 to 55 years (mean  $50.9 \pm 4$  years). Men constituted 71.8% of the group ( $n = 23$ ).

Inclusion criteria were: age between 30 and 60 years, diagnosed coronary disease confirmed with coronarography or exertion scintigraphy, good conditions for echocardiographic examination and patient's consent for the test.

Exclusion criteria were: clinical signs of heart failure, impaired function of left ventricle, past myocardial infarction, evident signs of heart failure, valvular defects, cardiomyopathy, unsuccessful normalization of arterial pressure within 2 previous years, organ changes in course of diabetes, renal failure, thyroid disorders, cancer, liver diseases considerably impairing its function and pregnancy.

The following were analyzed both at baseline and after 2 years of observation: clinical status (interview with the evaluation of the severity of angina pectoris and physical examination, presence of atherosclerotic risk factors), rest 12-lead electrocardiogram, resting transthoracic echocardiogram and the results of spiroergometric test. On inclusion to the study, the concentrations of NT-proBNP and CRP in the serum were tested. At that point patients were treated pharmacologically according to recommendations. Laboratory tests were performed in the laboratory in John Paul II Specialist Hospital in Kraków. The protocol of the study was approved by the Bioethics Committee of the Jagiellonian University in Kraków (KBET/7B/2005).

The patients were tested for changes in systolic and diastolic heart function after 2 years. The study included the identification of prognostic factors in a 2-year observation: clinical factors, particular echocardiographic and spiroergometric parameters and NT-proBNP.

### Transthoracic resting echocardiogram

Standard views were analyzed: parasternal long axis, parasternal short axis, four-chamber view and two-chamber view. Also, local speed of mitral annulus movement was evaluated with the use of spectrum technique of tissue testing with Doppler method (TDE/DTI). The inflow profile in pulmonary veins and local speed of mitral annulus movement were examined with Doppler tissue method.

The volume of left ventricle and ejection fraction were measured with biplane Simpson's method. End-diastolic parameters were measured in the picture registered on the peak R wave of QRS complex in ECG. Measurements of each parasternal and apical view were carried out. Statistical analysis included approximate values of those measurements.

The analysis included the following non-invasive indicators of increased end-diastolic pressure: ratio of early mitral flow velocity to mitral annulus movement in TDI ( $E/E'$ ) as well as the ratio of maximal velocity of early mitral inflow to the velocity of early inflow propagation ( $E/V_p$ ). The measurements were carried out according to the guidelines of American Echocardiographic Society.

The profile of left ventricular mitral inflow was evaluated based on diagnostic criteria of diastolic failure by the European Cardiology Society and the classification of the Canadian Cardiology Society.

### Spiroergometric test result

Spiroergometric tests were carried out according to the modified Bruce's protocol with the use of treadmill. The following parameters were analyzed:  $VO_{2\max}$ ,  $VCO_2$ , AT and  $VE/VCO_2$ .

Also, the analysis of developing systolic and diastolic dysfunction of left ventricle was performed as well as the relationship between the following echocardiographic, spiroergometric and biochemical parameters: hemodynamic state marker NT-proBNP and CRP inflammatory marker was examined.

Based on the outcomes of echocardiographic tests — baseline ( $E_1$ ) and after 2 years ( $E_2$ ), the evaluation of changes in the baseline LV filling profile and systolic function in terms of trends in changes in the LV filling profile and systolic function in time interval between  $E_1$  and  $E_2$  tests was carried out.

Next, the relationship between the trends in changes in LV filling profile and age, accompanying disorders and particular echocardiographic and biochemical parameters was analyzed in order to determine prognostic factors of LV systolic and diastolic function deterioration. Certain outcomes of this analysis had been previously presented in two publications [11, 12].

### Statistical analysis

Statistical analysis was performed with STATISTICA 8 statistical software by StatSoft Inc. (2008). The obtained data were presented in form of tables including distribution parameters:  $\bar{x}$  — arithmetic mean, SD — standard deviation, min — minimal value and max — maximal value. The charts present comparisons of test outcomes.

The following methods were applied in the statistical analysis:

t-Student test for independent tests in comparison with quantity variables and for repetitive tests in the comparison of 2 groups, multifactor variance analysis (ANOVA) to examine the relationship of systolic function, mitral inflow profile and

spiroergometric test parameters with the analyzed quantity variables and for repetitive tests in case of comparing 2 subsequent tests, Chi2 independence test to analyze the relationship between mitral inflow profile and the analyzed quality variables.

Test results with significance less or equal 0.05 ( $p \leq 0.05$ ) were considered statistically significant.

## Results

### General characteristics of patients

The study group consisted of 32 patients with coronary disease and normal LV systolic and diastolic function aged from 39 to 55 years (mean  $50.9 \pm 4$  years). Men constituted 71.8% of the group ( $n = 23$ ).

Arterial hypertension was found in 29 (90%) patients, lipid disorders in 23 individuals (71.8%) while type II diabetes in 6 patients (0.19%). Metabolic syndrome was diagnosed in 4 individuals (12.5%), addiction to tobacco was found in 18 patients (56%) while contributory family history in 21 patients (66%). Mean body mass index was  $28.17 \pm 4.4$  kg/m<sup>2</sup>. Pain symptoms related to coronary disease class II according to CCS were found in 53% of patients, class I in 43% of patients while class III only in one individual.

Tables 1 and 2 present clinical characteristics of the patients including atherosclerosis risk factors.

**Table 1.** Characteristics of the patients.

Examined parameters	Male n (%)	Age (years) x ± SD	BMI (kg/m <sup>2</sup> ) x ± SD
Examined group n = 32	23 (71.8%)	50.9 ± 4	28.17 ± 4.4

Data are expressed as mean ± standard deviation.

Abbreviations: BMI — body mass index.

**Table 2.** Atherosclerosis risk factors in the examined patients.

Risk factors of atherosclerosis	Arterial hypertension n (%)	Diabetes type 2 n (%)	Smoking n (%)	Hypercholesterolaemia n (%)	Metabolic syndrome n (%)	CAD in family history
Examined group n = 32	29 (90%)	6 (18.7%)	18 (56%)	23 (71.8%)	4 (12.5%)	21 (66%)

Abbreviations: CAD — Coronary Artery Disease.

Table 3 presents echocardiographic parameters in the examined patients.

**Table 3.** Echocardiographic parameters in the examined patients.

Echocardiographic parameters	$x \pm SD$
EF (%)	$62.00 \pm 5.3$
DT (ms)	$207.90 \pm 47.0$
E/A	$1.18 \pm 0.3$
E/E'	$3.40 \pm 0.8$
E/Vp	$1.26 \pm 0.3$
Vp (cm/s)	$65.00 \pm 20.0$
LA (mm)	$36.50 \pm 3.8$
LA area (cm <sup>2</sup> )	$17.60 \pm 2.3$
LVEDD (mm)	$50.70 \pm 5.6$
LVMAS (g)	$190.80 \pm 62.6$
LVMi (g/m <sup>2</sup> )	$96.80 \pm 30.8$

Abbreviations: A — the peak late mitral flow velocity, DT — deceleration time, E — the peak early mitral flow velocity, E' — the peak early diastolic myocardial tissue velocity, EF — ejection fraction, LA — left atrium, LA<sub>area</sub> — left atrial area, LVEDD — left ventricle end-diastolic diameter, LVMAS — left ventricle mass, LVMi — left ventricle mass index, Vp — early diastolic flow propagation velocity.

### Biochemical tests

NT-proBNP in the examined group ranged from 8.928 to 155.4 pg/ml, mean  $49.26 \pm 35.4$  pg/ml. High sensitivity C-reactive protein values (hsCRP) ranged from 0.45 to 20.31 mg/l, mean  $3.13 \pm 3.92$  mg/l.

**Table 4.** NT-proBNP values in the examined group and hsCRP.

Examined marker	x	SD	min	max	p
NT-proBNP (pg/ml)	49.3	35.4	8.90	155.4	NS
hsCRP (mg/l)	4.4	8.5	0.45	45.8	NS

Abbreviations: hsCRP — high-sensitivity, C — Reactive Protein, NT-proBNP — N-terminal-proB-type Natriuretic Peptide.

Results of baseline spiroergometric test are presented in Table 5.

In patients at baseline peak oxygen (V<sub>O2</sub> peak) uptake was 18.8–42.4 ml/kg/min, mean  $28.8 \pm 6.0$  ml/kg/min. The volume of CO<sub>2</sub> ranged between 0.64 do 3.4 l/min, mean  $2.09 \pm 0.76$  l/min. Anaerobic threshold ranged between 15 and 23 ml/kg/min,

**Table 5.** Results of spirometric test at baseline in the examined group.

Spirometric parameters	Examined patients x ± SD	Patients with diabetes type 2 x ± SD
VO <sub>2 peak</sub> (ml/kg/min)	28.80 ± 6.00	25.8 ± 3.0
VCO <sub>2</sub> (l/min)	2.09 ± 0.76	2.3 ± 0.7
AT	18.00 ± 2.50	13.0 ± 3.0
VE/VCO <sub>2</sub>	28.80 ± 4.90	30.0 ± 3.0
VE max	67.90 ± 20.00	74.7 ± 20.0
HR peak exercise (n/min)	131.00 ± 19.00	134.5 ± 18.3

Abbreviations: AT — anaerobic threshold, HR — heart rate, VE — ventilatory equivalent, VE/VCO<sub>2</sub> — ventilatory equivalent of carbon dioxide, VO<sub>2 peak</sub> — oxygen uptake at the peak exercise.

mean 18 ± 2.5 ml/kg/min. Maximal ventilation was from 36.1 to 102.4, mean 67.9 ± 20 ml/min. Ventilatory equivalent of CO<sub>2</sub> ranged from 24 to 44, mean 28.8 ± 4.9. Respiratory quotient was 0.72–1.26, mean 0.99 ± 0.13. Peak exercise heart rate was 90–168, mean 131 ± 19 beats per minute.

### Changes in the function of LV in patients in a 2-year observation

According to the analysis of LV function changes, LV systolic and diastolic function remained unchanged in 15 individuals (46.9%) out of 32 patients. 17 patients (53.1%) developed disorders of LV diastolic function: isovolumetric relaxation disorders in 12 patients (37%) and pseudonormalization in 5 patients (15%).

### Prognostic factors of LV filling profile deterioration in patients with stable angina and normal heart function in a 2-year observation

The comparison of test results performed at baseline and after a 2-year observation are presented in Table 6.

**Table 6.** Comparison of significantly different parameters of spirometric tests in patients with and without LV function deterioration after 2 years.

Spirometric parameters x ± SD	Examined group		P
	without deteriorating LV function n = 15	with deteriorating LV function n = 17	
VO <sub>2 peak 1</sub> (ml/kg/min)	31.3 ± 6.6	26.7 ± 4.5	0.03
VO <sub>2 peak 2</sub> (ml/kg/min)	31 ± 6.3	24.8 ± 6	0.03

Abbreviations: LV — left ventricle, VO<sub>2 peak</sub> — oxygen uptake at the peak exercise.

Peak oxygen consumption ( $VO_{2\text{ peak}}$ ) at baseline was significantly lower in the group with diastolic dysfunction compared to patients with normal function of left ventricle and ranged between to 18.8 and 31.7, mean  $26.7 \pm 4.5$  ml/kg/min ( $p = 0.03$ ). These results has been presented previously [12].

The analysis of the tests carried out after a 2-year observation indicated a relationship between developing diastolic dysfunction and the presence of type II diabetes ( $p = 0.01$ ). Diastolic dysfunction of LV occurred in all patients with type 2 diabetes after a 2-year observation: isovolumetric relaxation disorders developed in 4 patients and pseudonormalization in 2 patients. Table 7 presents echocardiographic parameters in patients with diabetes type 2 assessed at the start of the trial and after 2 years.

**Table 7.** Echocardiographic parameters in patients with diabetes type 2 in first examination and after 2 years.

Echocardiographic parameters $\bar{x} \pm SD$	Examined patients with diabetes type 2 In the 1st Echo	Examined patients with diabetes type 2 After 2 years
EF (%)	$63.00 \pm 4.40$	$66.00 \pm 7.50$
DT (ms)	$203.00 \pm 31.40$	$265.20 \pm 41.60$
E/A	$1.26 \pm 1.36$	$0.54 \pm 0.17$
E/E'	$4.00 \pm 1.09$	$6.30 \pm 4.10$
E/Vp	$1.24 \pm 0.27$	$1.47 \pm 0.46$
Vp (cm/s)	$63.00 \pm 9.70$	$43.60 \pm 18.15$
LV mass/BSA( $g/m^2$ )	$98.70 \pm 27.00$	$111.40 \pm 43.40$

Abbreviations: BSA — body surface area, LVMI — left ventricle, others — see Table 3.

No significant relationship between diastolic function deterioration and age ( $p = 0.56$ ), arterial hypertension ( $p = 0.27$ ), addiction to smoking cigarettes (0.7), lipid disorders ( $p = 0.86$ ) BMI ( $p = 0.2$ ) or positive family history ( $p = 0.5$ ) was observed.

No significant relationship between LV function deterioration after 2 years and the baseline level of NT-proBNP or hsCRP was found. Table 8 presents baseline NT-proBNP and hsCRP values in patients whose LV function remained unchanged and those with LV function deterioration.

According to the analysis of spiroergometric parameters after a 2-year observation, there is a relationship between  $VO_{2\text{ peak } 2}$  and a change in normal profile of left ventricle filling and impaired filling ( $p = 0.015$ ). No such relationship in case of other analyzed parameters of spiroergometric test was found:  $AT_2$  ( $p = 0.6$ ),  $VE/CO_{2\text{ peak } 2}$  ( $p = 0.22$ ) and  $RQ_2$  ( $p = 0.6$ ), as described in the previous publication [12].



**Table 8.** Biochemical tests in patients with and without deterioration of LV function.

Biochemical marker	Group A		P
	without LV function deteriorating	with LV function deteriorating	
NT-proBNP	43.9 ± 32.9	53.90 ± 37.80	NS
hsCRP	2.0 ± 1.8	6.56 ± 11.28	NS

Abbreviations: hsCRP — high-sensitivity, C — Reactive Protein, NT-proBNP — N-terminal-proB-type Natriuretic Peptide.

## Discussion

Coronary disease, as an etiologic factor, is related to poor prognosis in patients with heart failure [13, 14]. Early latent stage of the disease ought to be taken into consideration in the natural course of heart failure development since it is crucial for the implementation of screening test program in groups of patients at risk of developing a full-blown heart failure [15]. The outcomes of own study as well as research by other authors prove that patients with stable angina pectoris without impaired heart function are highly at risk of developing heart failure. Diastolic dysfunction of left ventricle is a crucial element of the whole clinical picture in these patients.

Literature reports emphasize the role of the following factors predisposing to the development of heart failure: older age, female gender, diabetes, obesity, arterial hypertension and the enlargement of left ventricle [16]. According to this study, type II diabetes in patients with normal heart function at baseline significantly influenced the deterioration of left ventricle diastolic function in a 2-year observation ( $p = 0.01$ ). This is related to an unfavorable impact of metabolic disturbances on vascular walls and heart muscle. Both own research and literature data indicate that patients with stable angina pectoris and the accompanying type II diabetes ought to periodically undergo control echocardiographic examination to assess early impairment of left ventricle function [17].

Prognostic values of the analyzed echocardiographic, biochemical and spirometric parameters in a 2-year observation in patients with stable angina pectoris and normal LV function were determined.

Echocardiography is considered the best method to detect asymptomatic heart dysfunction [18]. According to current guidelines, Doppler two-dimension echocardiography is a test of the highest prognostic value [19]. The study also included the analysis of echocardiography results in the aspect of the development of left ventricle dysfunction.

Patients with angina and normal LV function are at risk of developing LV diastolic dysfunction despite the treatment. The profile of disturbed relaxation is a common type of left ventricle diastolic dysfunction in these individuals.

This work included the analysis of the parameters of spiroergometric test which is a gold standard in the assessment of physical fitness [20].

The impairment of heart function involves numerous changes in neurohormonal system which are compensation mechanisms. They lead to balancing the decreased cardiac output and stroke volume. Initial compensation mechanisms (activation of renin-angiotensin-aldosterone system, stimulation of vasopressin production, increased sympathetic activation) stop working after a while and give undesirable effects — blood vessel constriction and heart dilation. Increased pressure in heart chambers leads to increased activity of the natriuretic and vasodilating substances (e.g. NT-proBNP). This balance may be disturbed at physical exertion, which can cause circulatory system decompensation. According to literature, both peak oxygen consumption and increased respiratory response to exertion are acknowledged prognostic parameters [21, 22].

This work indicated that baseline peak oxygen consumption ( $VO_{2\text{ peak}}$ ) in patients without LV dysfunction was significantly lower in the individuals who after 2 years developed diastolic dysfunction compared to the patients whose left ventricle function remained normal ( $26.7 \pm 4.5$  ml/kg/min vs  $31.3 \pm 6.6$ ;  $p = 0.03$ ). Therefore,  $VO_{2\text{ peak}}$  shows a prognostic value in the monitoring of diastolic dysfunction of left ventricle.

According to the observation, NT-proBNP fails to identify patients whose LV function may deteriorate after 2 years.

The outcomes of the study indicated a high prognostic value of the exercise spiroergometric test in the identification of patients, which allows to select of the individuals particularly susceptible to developing LV dysfunction. High prognostic value of  $VO_{2\text{ peak}}$  in monitoring the development of LV diastolic function impairment was proved.

According to the conducted research, stable angina pectoris is significantly related to the risk of developing left ventricle diastolic dysfunction. Periodic control echocardiographic tests and spiroergometric test carried out despite lack of visible signs of heart failure, especially in type II diabetes patients, are vital in the detection of such risk.

## Conclusions

Patients with stable angina pectoris and normal LV function are at risk of developing the impairment of heart function. Diastolic dysfunctions of left ventricle are a crucial element of the whole clinical picture. Type II diabetes leads to left ventricle diastolic dysfunction in a 2-year observation.

According to own study and literature data, the predictors of LV diastolic function deterioration in a 2-year observation in this group of patients include type II diabetes and peak oxygen consumption  $VO_{2\text{ peak}}$ .

## Conflict of interest

None declared.

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