

Research Article

Clinical Features, Course and Indicators of Endothelial Function and Systemic Immune-Inflammatory Response in Patients with Chronic Coronary Artery Disease Depending on Affected Coronary Artery Number

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Abstract

In Ukraine, cardiovascular diseases are the leading cause of morbidity and rank second among primary diseases. Nowadays the most common cardiovascular disease is coronary artery disease that accounts for 33.7% of total cardiovascular pathology cases.

The objective of the research was to study clinical manifestations and indicators of endothelial function and immune-inflammatory response in the patients with coronary artery disease, heart failure with preserved left ventricular ejection fraction depending on affected coronary artery number.

Materials and methods. The study included 62 patients with chronic coronary artery disease, heart failure with preserved left ventricular ejection fraction who underwent coronary artery stenting. Among the examined patients, males prevailed – 52 (83.9%) individuals. All the patients were randomized according to the number of the affected coronary arteries and divided into two groups. Clinical manifestations were studied; the patients' quality of life was assessed; the functional state of the myocardium was determined according to the six-minute walk test; the indicators of endothelial dysfunction were analyzed by endothelin-I level; the indicators of immune inflammatory response were analyzed by serum levels of C-reactive protein and tumor necrosis factor.

Results. In the examined patients, the clinical course did not depend on the number of the affected coronary arteries; however, to reduce the incidence of cardiac pain, the patients with multivessel coronary artery disease received 2 ± 0.1 extra nitroglycerin tablets.

Conclusions. Quality of life and physical well-being were better in the patients with single-vessel coronary artery disease ($p < 0.05$). Myocardial functional reserves were lower in the patients with multivessel coronary artery disease ($p < 0.05$), while the intensity of immune inflammation and endothelial dysfunction reduced in case of multivessel coronary artery disease that confirmed a strong correlation between the indicators of tumor necrosis factor and endothelin-I.

Keywords

coronary artery disease; stable angina; coronary arteries; endothelial dysfunction; immune-inflammatory activation

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Problem statement and analysis of the latest research

According to research studies, over the past decade, there has been a tendency for an increase in cardiovascular disease incidence. Cardiovascular diseases account for approximately 40% of all deaths in most European countries. In Ukraine, they account for 63.0% of the total mortality [5].

In most developed countries, coronary artery disease (CAD) is one of the leading causes of morbidity, temporary and permanent disability, as well as mortality [2, 9]. The clinical course of CAD is accompanied by anginal attacks, low exercise tolerance, limited self-care activities, decreased psycho-emotional well-being that impair quality of life (QoL) in the patients [10, 14]. The World Health Organization defines "Quality of Life" as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns [7, 17]. In modern medicine, the term "health-related quality of life" (HRQoL) is most commonly used. When assessing HRQoL, the patient's complaints associated with the disease are considered that allows determining the effect of the disease and treatment on the patient's psychological, emotional and social status [16].

According to most researchers, alongside with stress factor and impaired lipid metabolism, immune inflammatory response which results in endothelial dysfunction (ED) leading to acute coronary events plays a significant role in CAD development as well. According to research studies, a high level of inflammatory markers, namely C-reactive protein (CRP) in healthy individuals serves as a risk factor for developing future cardiovascular accidents [1, 15]. Among the patients with unstable angina, elevated CRP level was observed in 70% of the cases. Immune activation in the vessel wall, regardless of CAD etiology, was found to be maintained by a number of mechanisms including cytokine hyperproduction, increase in autoantibody concentration and impairment of cell-mediated immunity [11, 12]. Among cytokines, tumor necrosis factor- α (TNF- α) plays an important role [13].

ED limits vasodilator reserves, contributes to increased risk of blood clotting, thrombosis, systemic embolism, activation of immunocompetent cells and mediators of cytokine cascade that initiate systemic inflammatory response [6]. ED plays a certain role in the initiation and progression of atherosclerotic plaques and myocardial ischemia, as well as in left ventricular (LV) remodeling and progression of CAD and heart failure. Studies have demonstrated that the clinical condition of the patients with CAD often correlated with overproduction of endothelin-1 (ET-1) [8].

The objective of the research was to study clinical manifestations and indicators of endothelial function and immune-inflammatory response in the patients with chronic CAD, heart failure with preserved LV ejection fraction (EF) depending on affected coronary artery (CA) number; to study dynamics of cardiac pain and to assess QoL in the patients with chronic CAD, heart failure with preserved LVEF depending on affected CA number; to analyze exercise tolerance in the patients with chronic CAD and to determine the interdependent relationship between systemic immune inflammatory response, ED and the number of the affected CA.

1. Materials and Methods

The study included 62 patients with chronic CAD, heart failure with preserved LVEF who underwent CA stenting. The study was carried out in the Cardiology Center of Ivano-Frankivsk Central City Hospital; regular medical check-ups were carried out in municipal polyclinics. Among the examined patients, males prevailed – 52 (83.9%) individuals. The average age was 61.2 ± 1.2 years. The control group included 15 (12 males and 3 females) apparently healthy individuals with the average age of 60 ± 0.7 years. All the patients were randomized according to the number of the affected CA, the results of coronary angiography (CAG), the type of treatment. Among 62 patients, single-vessel coronary artery disease (CAD) was diagnosed in 16 patients, while two-vessel or multivessel CAD was found in 46 patients. In 54 (87.1%) patients, second-degree

or third-degree arterial hypertension stage II-III was observed.

All the patient underwent CAG. The indications for CAG included chronic coronary insufficiency (previous myocardial infarction), heart failure with preserved LVEF, primary angina, unstable (progressive) angina, post-infarction angina, CAG for verification of CAD diagnosis [3]. There were used the Infinix CC-i/FPD angiographs manufactured by Toshiba Medical Systems Corporation (Japan). CAG procedures were performed via radial artery access.

All the patients underwent a complete clinical examination in accordance with the Unified Clinical Protocol of Primary, Secondary (Specialized) and Tertiary (Highly Specialized) Medical Care approved by the Order of Ministry of Health of Ukraine of March 02, 2016, No 152 "Chronic Coronary Artery Disease" (updated September 23, 2016, No 994), the recommendations of the European Society of Cardiology (ESC) "ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012" and the guidelines of the Ukrainian Heart Failure Association (2017).

During clinical examination, the incidence and symptoms of cardiac pain and a weekly dose of nitroglycerin were considered. To assess QoL, there was used a HRQoL questionnaire for patients with heart failure – the Minnesota Living with Heart Failure Questionnaire (MLHFQ) that concerns a variety of physical aspects of the patient's life as well as emotional and social factors, the need for treatment (Rector TS et al., 1987). The MLHFQ contains 21 questions specific to heart failure rated on a scale from 0 (very high QoL) to 105 (very low QoL).

To assess New York Heart Association (NYHA) FC of CAD in cardiac patients, the six-minute walk test (6 MWT) was used. The 6 MWT entails measurement of distance walked over a span of 6 minutes. The patient was offered to walk as far as possible for 6 minutes at the rate of one step per second.

Serum concentration of ET-1 was determined by means of two-step enzyme-linked immunosorbent assay (ELISA) using commercial ELISA kit

BI-20052 Endothelin (Biomedica, Austria), serum level of TNF- α was measured by means of reagent kit "ProCon TNF- α " (Protein Contour, Russian Federation), respectively using an analyzer Stat-Fax 210200 (Awareness Technology, Inc, USA). Serum level of CRP was determined by a latex agglutination test using reagent kit "Granum" (Ukraine) according to the method proposed by the manufacturer.

To objectively assess the reliability of the research results, variational statistical analysis of the results obtained was conducted on a Pentium II PC using the Statistica 8.0 software package and Microsoft Excel statistical functions.

2. Results and Discussion

Single-vessel CAD confirmed by CAG was found in 16 (25.8%) patients, while multivessel CAD was observed in 46 (74.2%) patients – there were 34 (73.9%) patients with two-vessel CAD and 12 (26.1%) patients with three-vessel CAD.

According to CAG, 120 CA were affected. In general, the anterior interventricular branch (AIB) of the left coronary artery (LCA), the AIB of the right coronary artery (RCA) and the left circumflex artery (LCX) were most commonly affected – in 48 (40.0%), 33 (27.5%), 29 (24.2%) cases, respectively; the diagonal branch (DB) of the LCA and intermediate CA were rarely affected – in 7 (5.8%) and 3 (2.5%) cases, respectively (Fig. 1).

After analysis of the cases with single-vessel CAD, the AIB of the LCA was found to be affected in 50.0% of the cases, the RCA – in 31.3% of the cases and the LCX – in 18.7% of the cases.

Multivessel CAD was usually accompanied by damage to the AIB of the LCA in combination with damage to the LCX in 34.8% of the patients; damage to the AIB of the LCA in combination with damage to the RCA in 21.7% of the patients; damage to the RCA in combination with damage to the LCX in 13.1% of the patients; damage to the AIB of the LCA in combination with damage to the DB of the LCA in 4.3% of the cases; damage to the AIB of the LCA in combination with damage to the RCA and the LCX in 8.7% of the cases;

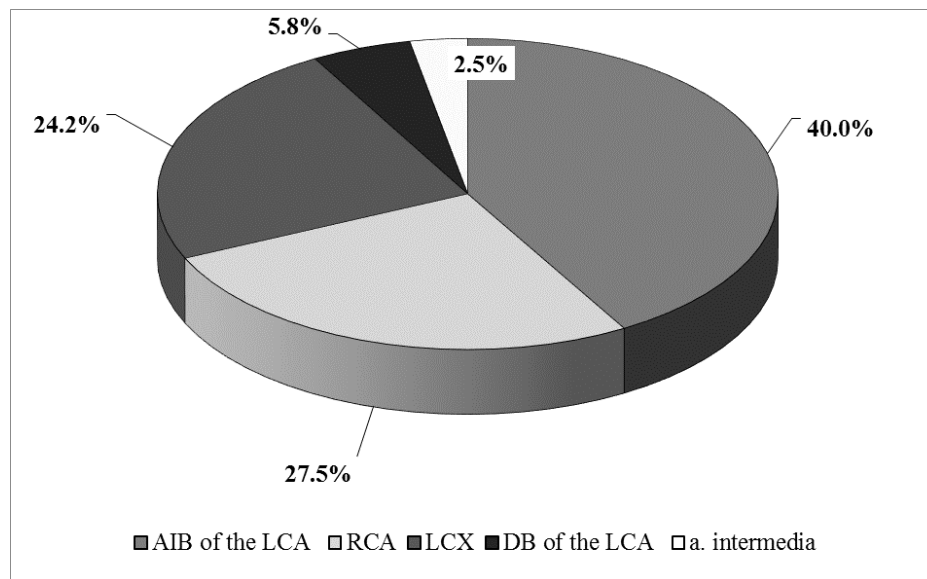


Figure 1. Structure of CA damage in the patients with chronic CAD, heart failure with preserved LVEF

damage to the AIB of the LCA in combination with damage to the RCA and the DB of the LCA in 10.9% of the patients; damage to the AIB of the LCA in combination with damage to the RCA and the intermediate CA in 6.5% of the patients.

Among 62 patients suffering from heart failure with preserved LVEF, single-vessel CAD was diagnosed in 25.8% of the cases, while multivessel CAD was found in 74.2% of the cases. After CAG, all the patients were divided according to the number of the affected CA. Heart failure with preserved LVEF was diagnosed in 25.8% of the patients with single-vessel CAD and 74.2% of the patients with multivessel CAD.

The analysis of the clinical course of the disease showed that anginal attack manifested itself as pain syndrome, namely burning pain in 66.1% of the patients, squeezing pain in 21.0% of the patients, stabbing pain in 12.9% of the patients. Retrosternal pain was accompanied by pressure sensation in 69.1% of the cases, shortness of breath – in 64.5% of the cases, nausea – in 29.4% of the cases, vomiting – in 12.9% of the cases, palpitation – in 85.5% of the cases, dizziness – in 72.6% of the cases. Pain radiation to the left shoulder, arm, jaw, neck and face was observed in all the patients.

The patients with single-vessel CAD additionally received nitroglycerin at a dose of 11.8 ± 0.35

Table 1. Results of QoL assessment in the patients with chronic CAD, heart failure with preserved LVEF depending on affected CA number according to the MLHFQ, points, ($M \pm m$).

Affected coronary artery number	Patients, n = 62
Single-vessel CAD, n = 16	$40.3 \pm 0.94^*$
Multivessel CAD, n = 46	62.1 ± 1.37

Note: * - statistically significant difference between single-vessel and multivessel CAD, $p < 0.001$.

tablets per week, while in the patients with multivessel CAD, the dose of nitroglycerin increased to 13.9 ± 0.24 tablets per week ($p < 0.001$). Thus, the dose of nitroglycerin depended on the number of CA affected.

According to the MLHFQ, in the patients with multivessel CAD, QoL was 35.1% lower as compared to the patients with single-vessel CAD ($p < 0.001$) (Table 1).

According to the results of assessing different aspects of QoL by means of the MLHFQ, in the patients with multivessel CAD, the physical MLHFQ score was 35.1% higher as compared to the patients with single-vessel CAD ($p < 0.001$) and the emotional MLHFQ score was 13.6% higher

Table 2. Results of assessing various QoL aspects in the patients with chronic CAD, heart failure with preserved LVEF depending on affected CA number according to the MLHFQ, points, (M±m).

QoL aspect	Patients, n = 62	
	Single-vessel CAD, n = 16	Multivessel CAD, n = 46
Physical	15.5±0.24	23.9±0.63*
Emotional	12.1±0.24	14.0±0.38*
Social	3.9±0.19	5.3±0.11*
Therapeutic	10.2±0.15	12.9±0.29*

Note: * - statistically significant difference between single-vessel and multivessel CAD, $p < 0.001$.

as compared to the patients with single-vessel CAD ($p < 0.001$). By social aspect, in the patients with multivessel CAD, the MLHFQ score was 26.4% higher as compared to the patients with single-vessel CAD ($p < 0.001$). In the patients with multivessel CAD, the therapeutic aspect was 20.9% higher as compared to the patients with single-vessel CAD ($p < 0.001$) (Table 2).

To analyze exercise tolerance, the 6 MWT was used. Its results showed that before treatment, the median distance walked was 200 m; the test had to be interrupted due to the deterioration of the patient's condition. According to the functional test, half of the patients walked more than 200 m. Reduced exercise tolerance was observed in all the patients. Thus, the patients with single-vessel CAD walked 251.5 ± 8.41 m, while the patients with multivessel CAD walked 219.2 ± 10.58 m ($p < 0.05$). In healthy individuals, the 6 MWT distance was 558.7 ± 2.41 m, that exceeded that in the patients with single-vessel CAD and multivessel CAD by 2.2. and 2.5 times, respectively ($p < 0.001$) (Fig. 2).

The analysis of ED as an independent risk marker of unfavorable clinical course of cardiovascular disease deserves special attention. In the patients with single-vessel CAD, serum concentration of ET-1 was 1.6 times higher as compared to healthy individuals and 1.7 times higher as compared to the

patients with multivessel CAD ($p < 0.001$). A significant difference in the indicators of ET-1 was observed depending on the number of the affected CA. In the patients with multivessel CAD, the indicator of ET-1 exceeded this indicator in the patients with single-vessel CAD by 8.6% ($p < 0.05$).

There was determined a strong correlation between inflammatory processes and damage to the vessel wall. TNF which is activated in cell apoptosis alters vascular endothelium through the enhancement of low-density lipoprotein (LDL) peroxidation that results in the increased production of free radicals with cytotoxic effect. During the patients' examination, TNF- α activity was found to depend on the number of the affected CA. In single-vessel CAD, TNF- α level exceeded normal limits by 4.2 times, while in multivessel CAD, TNF- α level exceeded normal limits by 4.9 times ($p < 0.001$). In the patients with multivessel CAD, TNF- α production was 14.4% higher as compared to the patients with single-vessel CAD.

In the patients with single-vessel CAD, the level of systemic inflammation marker, namely CRP was 3.6 times higher than that in healthy individuals; in the patients with multivessel CAD, it was 4.9 times higher as compared to healthy individuals ($p < 0.001$). The increase in serum CRP level depended on the number of the affected CA. Thus, in the patients with multivessel CAD, serum CRP level exceeded that in the patients with single-vessel CAD by 26.4% ($p < 0.05$) (Table 3).

Since immune inflammation plays an important role in the formation of ED and acute coronary events, we have studied the interdependent relationship between the main components of immune inflammation, namely TNF- α and ET-1 as a marker of endothelial abnormalities depending on the number of the affected CA. In the patients suffering from heart failure with preserved LVEF in case of one-vessel and multivessel CAD, a strong correlation between these indicators was determined ($r = 0.92$, $p < 0.001$ and $r = 0.93$, $p < 0.001$) (Fig. 3, Fig. 4).

Chronic CAD is a disease deserving special attention since late diagnosis and irrational treatment may result in serious cardiovascular events such as myocardial infarction, heart rhythm dis-

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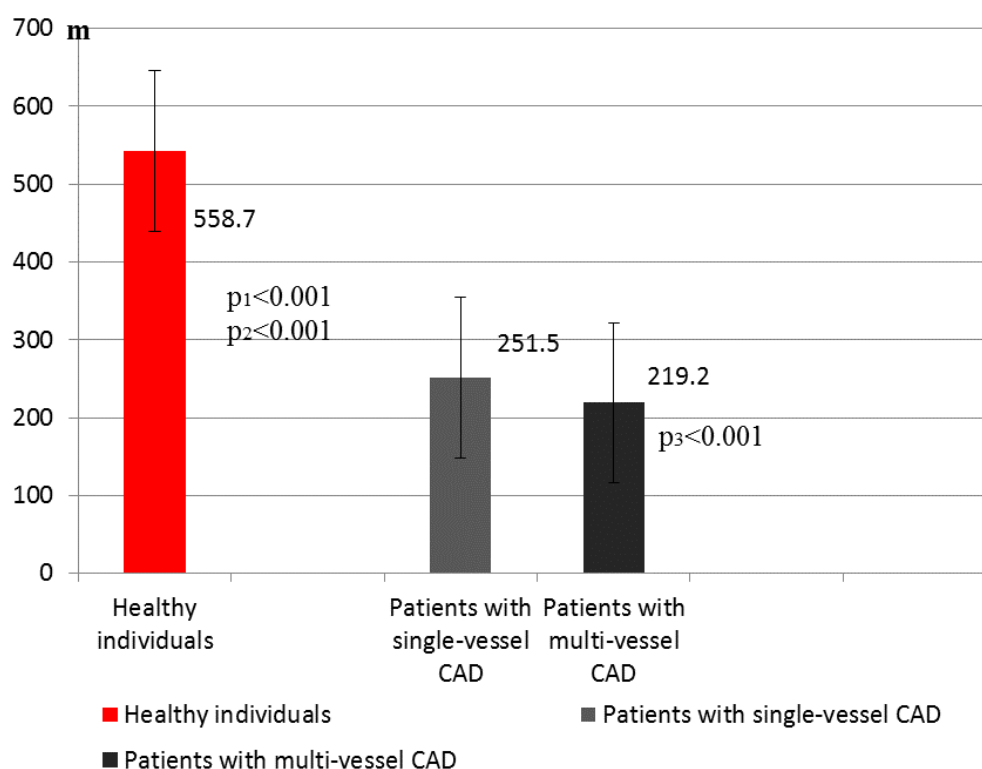


Figure 2. A 6 MWT distance depending on the number of the affected CA.

Notes:

p₁, p₂ – statistical significance of difference in the indicator between healthy individuals and patients with single-vessel and multivessel CAD;

p₃ – statistical significance of difference in the indicator between the patients with single-vessel CAD and those with multivessel CAD.

Table 3. Characteristics of ED and systemic immune-inflammatory activity in the patients with chronic CAD, heart failure with preserved LVEF, (M±m).

Indicators	Healthy individuals, n = 15 1	Patients, n = 62	
		Single-vessel CAD, n = 16 2	Multivessel CAD, n = 46 3
ET-1, ng/l	5.4±0.24	8.5±0.19 p ₁₋₂ <0.001	9.3±0.21 p ₁₋₃ <0.001 p ₂₋₃ <0.05
TNF-α, pg/ml	25.6±2.37	108.1±3.58 p ₁₋₂ <0.001	126.3±4.82 p ₁₋₃ <0.001 p ₂₋₃ <0.05
CRP, g/l	2.4±0.18	8.7±0.42 p ₁₋₂ <0.001	11.0±0.91 p ₁₋₃ <0.001 p ₂₋₃ <0.01

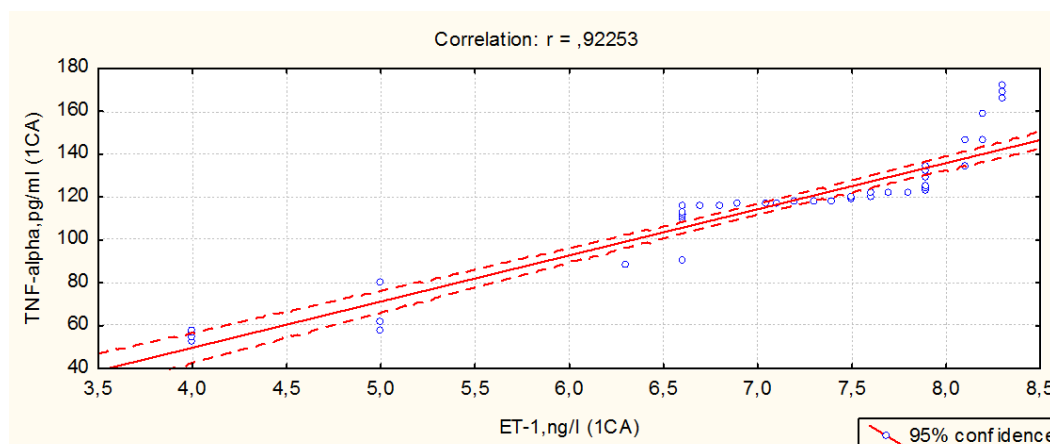


Figure 3. Correlation between TNF-alpha and ET-1 in the patients with chronic CAD, heart failure with preserved LVEF, single-vessel CAD.

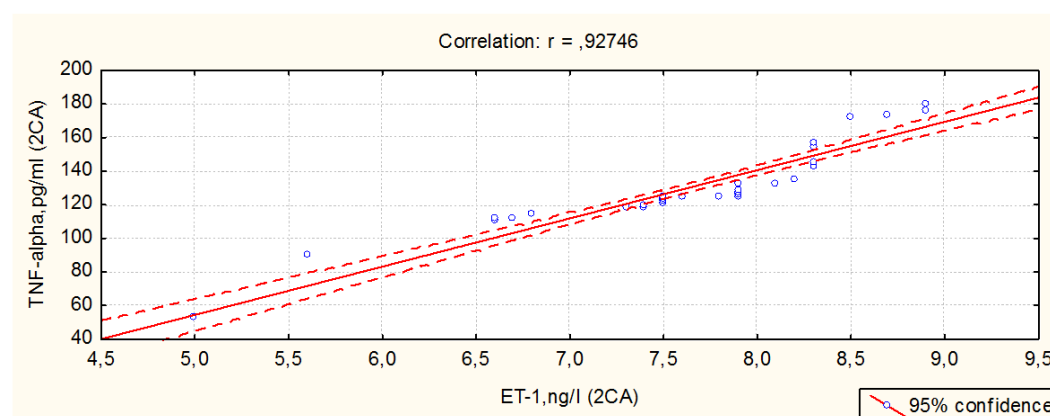


Figure 4. Correlation between TNF-alpha and ET-1 in the patients with chronic CAD, heart failure with preserved LVEF, multivessel CAD.

orders, CAD destabilization and increase in FC and chronic heart failure decompensation which, in turn, are associated with a high risk of fatal outcomes. The question of an individual approach and rational treatment of a particular patient considering the pathogenesis, clinical course and progression of this pathology remains open. Therefore, the study of the dynamics of the indicators of clinical condition, immunological processes and ED of chronic CAD, heart failure with preserved LVEF in the patients undergoing high-quality combination treatment, namely myocardial revascularization and standard long-term pharmacotherapy with the addition of f-channel inhibitor of the sinoatrial node of

cardiac conduction system is promising.

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