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Endothelial dysfunction and inflammation in patients with non-obstructive coronary arteries

Aim	To determine levels of markers for endothelial dysfunction and inflammation, endothelin-1, E-selectin, and tumor necrosis factor α (TNF-α) in patients with ischemic heart disease (IHD) and non-obstructive and obstructive coronary artery (CA) disease.
Material and methods	This study included 32 patients with verified IHD and non-obstructive (main group, n=19) and obstructive (comparison group, n=13) CA disease. Endothelial dysfunction was diagnosed by photoplethysmography and videocapillaroscopy. Serum concentrations of endothelin-1, E-selectin, and TNF- α were measured in all patients.
Results	Patients with non-obstructive CA disease showed a tendency towards more pronounced endothelial dysfunction (alternative stiffness index, 7.8 m/s [6.35; 9.08]; reflection index, 36.95% [23.4; 52.65]; capillary density following reactive hyperemia, 54.33 cap/mm^2 [48.92; 75.83]; capillary density following venous occlusion, 74.33 cap/mm^2 [67.83; 93.00]) compared to the comparison group (alternative stiffness index, 9.05 m/s [7.08; 10.58]; reflection index, 28.25% [23.35; 53.75]; capillary density following reactive hyperemia, 66.83 cap/mm^2 [50.83; 78.67]; capillary density following venous occlusion, 87.0 cap/mm^2 [77.58; 78.67]), although statistically significant differences were not found. Concentration of endothelin-1 was significantly higher in the IHD group with non-obstructive CA disease (0.45 ng/ml [0.28;0.65]) compared to patients with CA atherosclerotic stenosis (0.35 ng/ml [0.25; 0.38], p=0.035). Concentrations of E-selectin did not significantly differ between the groups (main group, 21.1 ng/ml [18.45; 35.03]; comparison group, 28.55 ng/ml [19.08; 35.01], p=0.29). In both groups, concentrations of TNF-α did not exceed the lower threshold of sensitivity (<2.3 pg/ml).
Conclusion	Endothelial dysfunction and increased endothelin-1 in patients with non-obstructive CA disease along with inflammation may additionally contribute to the pathogenesis of IHD in the absence of hemodynamically significant CA stenoses. Too low level of TNFα in both groups prevented us from using it as a diagnostic marker. Further study is needed that would include a greater number of patients and a search for alternative markers.

Keywords	Ischemic heart disease, nonobstructive coronary artery disease; endothelial dysfunction; endothelin-1; photoplethysmography; capillaroscopy
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Introduction

According to the World Health Organization, coronary artery disease (CAD) is one of the top ten causes of death worldwide (2019) [1]. The high prevalence of CAD, significant economic burden, and the associated risk of invasive interventions require the development of new algorithms to diagnose and treat the disease. One such method is to estimate the pre-test probability (PTP) of CAD. The 2019 European Society of Cardiology Guidelines on Chronic Coronary Syndromes focused on the use of a predictive model to estimate PTP of obstructive CAD based on age, sex, and the nature of symptoms [2]. The calculation of PTP based on basic scores produced poor-quality data. This frequently leads to over-diagnosing CAD, when an invasive investigation, such as coronary angiography (CAG), has not confirmed obstructive CAD [3].

In order to determine the probability of CAD objectively, in addition to PTP disease risk factors should be considered (smoking, dyslipidemia, family history, arterial hypertension, and diabetes mellitus) and the results of exercise stress testing. However, these studies were conducted in countries with a low risk of cardiovascular disease [4]. In Russia, according to the Federal Service for State Statistics (Rosstat)

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CAD is the leading cause of death (28.4%) (2018) [5]. Thus, the development of new diagnostic algorithms using specific markers is an emerging priority.

Of all patients with CAD diagnosis, the group with non-obstructive CAD is the least studied. These are patients with typical angina pectoris picture, documented myocardial ischemia (stress echocardiography, myocardial scintigraphy, cardiac magnetic resonance imaging) and without hemodynamically significant coronary stenosis (<50% stenosis). According to CAG, this category includes patients with normal coronary arteries (without angiographic stenosis), minor (angiographic stenosis <30%), and moderate (>30% but <50% stenosis) CAD. The incidence of non-obstructive CAD can reach 50% in chronic and 20% in acute coronary syndrome. Although these patients experience no stenosis, they suffer adverse cardiovascular events [4], such as myocardial infarction with non-obstructive coronary arteries (MINOCA). According to various authors, the rate of MINOCA in this form of CAD is 2.2 to 21.8% [6]. Patients with MINOCA are typically younger, more likely to be female, and less frequently present diabetes mellitus, arterial hypertension, and dyslipidemia This indicates the predominantly pathogenic role of non-atherosclerotic etiological factors such as psychosocial aspects, insulin resistance, and inflammation [7].

The main element of non-obstructive CAD pathophysiology is impaired coronary microcirculation, i.e., so-called coronary microvascular dysfunction (CMD).This covers a wide range of clinical situations in which the structure and function of coronary arteries is impaired, leading to myocardial ischemia without significant coronary stenosis [8]. Several clinical [9] and experimental [10] studies have demonstrated the key role of endothelium dysfunction (ED) in the pathogenesis of CMD.

Recent experimental studies on animal models of non-obstructive CAD have shown that perivascular adipocytes secrete adipokines, such as leptin, resistin, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). These are potent pro-inflammatory molecules which can contribute to the development of inflammatory stress in the endothelium, its functional impairment and reduction of nitric oxide (NO) bioavailability either by direct exposure or via hyperproduction of endothelin-1 [11]. Inflammation stimulates insulin resistance development [12, 13], which also contributes to the suppression of NO synthesis due to signal transmission disruption in the vascular smooth muscle cells [14]. Insulin resistance in patients without diabetes mellitus is a pathogenetic factor and an independent risk factor in cardiovascular diseases [15], including MINOCA, but its role in MINOCA has not been studied yet [16].

Since aggressive atherosclerosis is less common in patients with non-obstructive CAD, there may be mechanisms which cause inflammation and impair endothelial function, thus leading to CMD development. Inflammation can be a link between CMD and atherosclerosis.

This article presents the intermediate results of the study being carried out at Hospital Therapy Department No. 1 of the N.V. Sklifosovskiy Institute of Clinical Medicine, I.M. First Moscow State Medical University. It is planned to include more patients and to perform additional laboratory tests to evaluate the expression of microRNA and IL-1β, IL-6.

Materials and methods

The study is being carried out pursuant to the Declaration of Helsinki in Cardiology Department No. 1 of University Clinical Hospital No. 1 of I.M. Sechenov First Moscow State Medical University (Sechenov University). At this stage, the study includes two groups of CAD patients: non-obstructive (index group, n=19); and obstructive (comparison group, n=13) CAD. Inclusion criteria for the index group were: documented myocardial ischemia; absence of significant coronary stenosis (<50%) according to CAG; and no history of myocardial revascularization (coronary artery bypass grafting, balloon angioplasty, and coronary artery stenting). The comparison group included patients with CAD and obstructive CAD according to CAG.

Patients in both groups were comparable in terms of age and body mass index. Female patients prevailed in the non-obstructive CAD group (Table 1).

There were no significant differences between the groups in terms of the main clinical and anamnestic characteristics (Table 2).

All patients underwent standard laboratory tests and clinical investigations: complete blood count and biochemical blood tests; urinalysis; electrocardiogram; 24-hour blood pressure monitoring and electrocardiogram; echocardiography; chest X-ray; and bicycle exercise test.

Photoplethysmography was used to assess the structural and functional state of large and small vessels (Angioskan-01, Russia). The method is based on the registration of the pulse volume amplitude of blood flow in the microcirculatory vessels using an optocoupler. Photoplethysmographic signal is recor-

ded at rest and after occlusion test (reactive hyperemia test). The endothelial function of microcirculatory vessels is estimated by an increase in the pulse volume amplitude of blood flow. This is determined by the occlusion index which is a ratio of the pulse volume amplitude after the test to the initial amplitude at rest) [17]. A similar method of assessing endothelial dysfunction (ED) is used for peripheral arterial tonometry (PAT). Bonetti et al. showed by means of the endothelial pulse amplitude test (Endo-PAT) that an occlusion index <1.35 shows 80% sensitivity and 85% specificity for coronary ED [18]. The FDA approved this method for the non-invasive evaluation of coronary ED in patients with CAD [19].

The structural condition of large vessels was evaluated using the alternative stiffness index (aSI). This allows an assessment of the elasticity of large vessels (aorta) by means of the pulse wave velocity of propagation from the proximal aorta to the reflection site (normal (reference) values are 5–8 m/sec). The functional state is characterized by phase shift (PS), calculated by pulse wave delay time after the occlusion test on the relevant hand from the pulse wave on the hand on which the test was not performed (normal values >10 msec). The occlusion index (IO; normal values >1.8) and reflection index (RI), are parameters which determine the structural status of small resistive arteries (normal values <30%), in order to evaluate microvascular ED in arterioles.

The capillary bed was evaluated by a capillaroscope (Kapillaroscan-1, Russia). The following indicators were calculated for the capillaries: percentage of capillary recovery (PCR); and percentage of perfused capillaries (PPC). PCR shows the percentage of capillaries out of the maximum amount which are additionally involved after the reactive hyperemia test (normal values 16.5±7.1%). PPC shows what percentage of capillaries out of the maximum possible number are additionally involved after the reactive hyperemia test (normal values 92.5 ± 5.3%). Capillary density at rest (CDr), CD after venous occlusion test (CDvo), and CD after reactive hyperemia test (CDrh) were determined. These values were calculated by counting the number of skin capillaries per area unit (U/mm2). It should be noted that there are no clear standards for CD parameters [21]. Table 3 shows the mean values.

An immunoenzymatic assay was performed in all patients, in order to determine the levels of endothelin-1 (reference values 1–3 pg/mL; EnzoLifeScientific kit, USA) and e-selectin (reference values 0.5–1.5 ng/mL; Technoclon kit, Technozym E-selectin: AgeIISE, Austria). TNF-α was also estimated in all patients.

The data obtained was analyzed using STATISTICA 13.3 software. Descriptive statistics of quantitative indicators are expressed in terms of mean and standard deviation. In non-normal distribution, the median (Me) and interquartile range [Q1; Q3] were used. Pearson's correlation test (normal distribution of variables), Spearman's correlation test (non-normal distribution of variables), and the Mann-Whitney U-test (intergroup comparisons) were used for the correlation analysis of the parameters of interest.

Table 1. Demographic characteristics of the subjects

Patient characteristics	CAD patients with non-obstructive coronary arteries, n = 19	CAD patients with obstructive coronary arteries, n = 13	p
Age, years	64.89±7.61	66.92±7.02	0.446
Male, n (%) Female, n (%)	4 (26.3); 15 (73.7)	9 (69.2); 4 (30.8)	0.04
BMI, kg/m^2	28.14±3.69	30.4±5.91	0.718

BMI, body mass index; CAD, coronary artery disease.

Table 2. Clinical characteristics of the subjects

Clinical and anamnestic characteristics of CAD patients

Patient characteristics	Patients with non-obstructive coronary arteries, n = 19	Patients with obstructive coronary arteries, n = 13	p
Angina pectoris, n (%)	16 (84.2)	9 (69.2)	0.258
Inspiratory dyspnea, n (%), equivalent of angina pectoris	14 (73.7%)	11 (84.6%)	0.933
History of myocardial infarction, n (%)	4 (21)	6 (46.1)	0.270
CHF, n (%)	2 (10.5)	3 (23)	0.589
Hypertensive heart disease, n (%)	18 (94.7)	11 (84.6)	0.39
Stenosing atherosclerosis BCA, n (%)	4 (21)	5 (45.5)	0.459
History of CVA, % (n)	2 (10.5)	2 (15.4)	0.857

BCA, brachiocephalic arteries;
CHF, chronic heart failure; CVA, cerebrovascular accident.

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Table 3. Comparative analysis of the indicators characterizing the structural and functional state of the vascular wall at different levels of the vascular bed

Structural and functional indicators	Patients with non-obstructive coronary arteries, Me [Q1; Q3]	Patients with obstructive coronary arteries, Me [Q1; Q3]	Normal values	p
aSI, m/s	7.8 [6.35; 9.08]	9.05 [7.08; 10.58]	5–8	0.54
RI, %	36.95 [23.4; 52.65]	28.25 [23.35; 53.75]	< 30	0.79
IO	1.5 [1.38; 1.78]	1.4 [1.28; 1.53]	> 1.8	0.3
СФ, ms	5.1 [1.75; 7.75]	6.45 [5.53; 9.03]	> 10	0.67
CD, cap/mm^2	55.5 [48.58; 63.83]	61.33 [52.67; 75.17]	≈ 53 (49 ;57)	0.27
CDrh, cap/mm^2	54.33 [48.92; 75.83]	66.83 [50.83; 78.67]	≈ 59 (56 ;62)	0.62
CDvo, cap/mm^2	74.33 [67.83; 93.00]	87.0 [77.58; 78.67]	≈ 87 (82 ;105)	0.23
PCR, %	16.25 [5.74; 30.36]	5.69 [5.21; 8.31]	16.5 ± 7.1	0.25
PPC, %	70.74 [50.6; 97.28]	71.22 [66.67; 95.49]	92.5 ± 5.3	0.87

aSI, alternative stiffness index; RI, reflection Index; IO, occlusion index, PS, phase shift;
CDr, capillary density at rest, CDrh, capillary density after reactive hyperemia; CDvo, capillary density after venous occlusion;
PCR, percentage of capillary recovery; PPC, percentage of perfused capillaries.

Results

The evaluation of the vascular wall remodeling parameters in the index group detected structural changes in small resistive arteries (RI>30%). Increased stiffness of large vessels (aSI >8 m/sec) was observed in the comparison group. IO was reduced in both groups, i.e., microvascular (small resistive arteries, arterioles) endothelial function was violated, and the functional state of conducting arteries was impaired (PS<10 msec). Capillaroscopy showed that CDvo characterizing structural changes of capillaries and CDrh reflecting their functional state was reduced in the group of CAD with non-obstructive coronary arteries. Capillary dysfunction was observed in both groups (decreased in PPC in the index group and decreased in PCR in the comparison group). The structural and functional analysis of vessels did not show statistically significant differences between the groups. However, many indicators did not correspond to normal values in most subjects (Table 3).

Evaluation of the results obtained showed a statistically significant difference between the levels of endothelin-1 (0.45 [0.28; 0.65] ng/mL) in the group of CAD with non-obstructive coronary arteries when compared to CAD patients with stenotic coronary atherosclerosis (0.35 [0.25; 0.38] ng/mL, p=0.035) (Figure 1). The E-selectin levels were not significantly different in the study groups (21.1 [18.45; 35.03] ng/mL in the index group; and 28.55 [19.08; 35.01] ng/mL in the comparison group; p=0.29). TNF-α did not exceed the lower sensitivity threshold (<2.3 pg/mL) in both groups.

The statistical analysis of CAD patients with non-obstructive coronary arteries detected a moderate positive correlation between endothelin-1 and reflection index (RI; r=0.518; p<0.05). There was no such correlation in the comparison group.

Discussion

Endothelial dysfunction is an independent prognostic factor of adverse cardiovascular events [22]. ED in patients with non-obstructive coronary arteries increases cardiovascular risk, such as the risk of atherosclerosis, and exacerbates the prognosis [23, 24]. According to the ACOVA (Abnormal Coronary VAsomotion in patients with stable angina and unstructured coronary articles) study, in more than 60% of CAD patients with non-obstructive coronary arteries, the acetylcholine test used for the diagnosis of coronary ED [25] causes angina pectoris and significant electrocardiographic changes [26]. Non-invasive peripheral arterial tonometry (PAT; Endo-PAT2000) demonstrated significant impairment of endothelial function in patients with CAD. This was the case especially for those with non-obstructive coronary arteries. The reactive hyperemia (RH) ratio was significantly reduced in this group and may be considered as a prognostic factor of non-obstructive CAD before CAG [27]. However, it should be noted that the study was conducted only in female patients and included a small number of subjects (n=42). The prognostic value of PAT in patients with hemodynamically insignificant coronary stenosis is still unknown [28].

The data obtained using an Angioscan-1 device and video capillaroscopic imaging also demonstrated the trend in the index group towards more pronounced endothelial dysfunction, mainly microcirculatory.

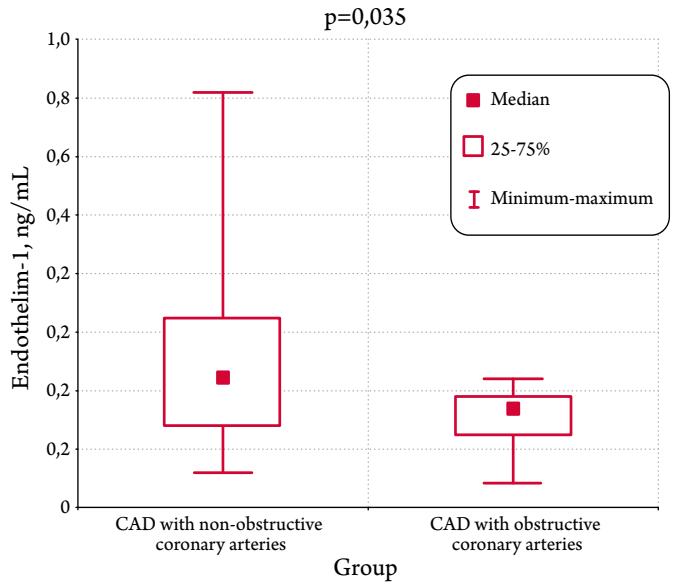
Significantly increased levels of endothelin-1 were detected in the group of patients with non-obstructive CAD when compared with the comparison group. Endothelin-1 produced by the endothelial cells is one of the most potent endogenous vasoconstrictors [29]. In higher concentrations it is known to have pro-inflammatory and proliferative properties [30].

It can be assumed that ED and local inflammation of the vascular wall is an integral part of the CMD pathogenesis in patients with non-obstructive CAD.

The theory of inflammation in the pathogenesis of cardiovascular diseases has been discussed for a number of years. Every year a growing number of extensive studies support the hypothesis of the role of inflammation in the pathogenesis of CAD. The CANTOS (Canakinumab Antiinflammatory thrombosis outcomes Study) study demonstrated that the use of canakinumab (monoclonal anti-IL-1β antibodies) improves prognosis in patients with obstructive CAD [31]. The studies of colchicine COLCOT (Colchicine Cardiovascular Outcomes Trial) and LoDoCo 2 (Low Dose Colchicine 2) also confirm the inflammatory theory of atherosclerosis [32].

In our study, TNF-α was lower than the reference range in all subjects. Thus, it cannot be used as a diagnostic marker in these groups of patients. Elevated endothelin-1 levels, more severe ED in the index group, and the lack of informative value of TNF-α in this situation require further study, while alternative markers of ED and coronary artery inflammation need to be determined. The synthesis of endothelin-1 is regulated at the genome level. Endothelin-1 matrix RNA is activated by inflammatory factors, such as transforming growth factor-beta, TNF α-F, IL, and angiotensin II [33]. Due to the unique hemodynamics physiology, coronary endothelium has five times less endothelial No-synthase and 2.5 times more endothelin-1 matrix RNA expression than the aorta [34]. Thus, microRNA is of great interest as a regulator of gene expression, including encoding pro-inflammatory cytokines and ED markers, by inhibiting the translation of various matrix RNAs [35]. The deep sequencing method allowed about 300 microRNAs to be detected in the heart [36]. Circulating microRNAs involved in the proliferation of intima cells (microRNA-21, microRNA-145, microRNA-221/222), development of atherosclerosis (microRNA-122, microRNA-33), myocardial hypertrophy and fibrosis (microRNA-21,133), and vascular remodeling (microRNA-24, microRNA-126) were identified. Studying expression levels and defining specific microRNAs offers great potential for their future clinical use as biomarkers and treatment targets in CAD.

Figure 1. Endothelin-1 levels (ng/mL) in CAD patients with non-obstructive and obstructive capillary arteries



Conclusion

Analysis of the findings showed that increased expression of endothelin-1 and ED could contribute more to the pathogenesis of CAD with non-obstructive coronary arteries. Further study including more patients will be required, in order to assess endothelin-1, IL-6, IL-1β, and circulating microRNAs. It is planned to include a total of 60 patients (30 individuals per group). Reliable results that prove the role of local vascular wall inflammation in patients with non-obstructive CAD need to be obtained. In the future, we plan to study the expression of circulating microRNAs: microRNA-126, a key regulator maintaining vascular integrity; and microRNA-24, regulating intima hyperplasia and smooth-muscle vessel cell proliferation, associated with inflammation and levels of IL-8, IL-6, TNF-α [37]. Studying the expression levels of circulating microRNAs, which regulate endothelial function and inflammation processes, will provide an insight into the pathogenesis of non-obstructive CAD.

No conflict of interest is reported.

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