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МАКРОФАГИ В ЭПИКАРДИАЛЬНОЙ ЖИРОВОЙ ТКАНИ И СЫВОРОТОЧНЫЙ NT-proBNP У ПАЦИЕНТОВ СО СТАБИЛЬНОЙ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

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Резюме. Ишемическая болезнь сердца (ИБС) является хроническим воспалительным заболеванием, причем дисфункциональная эпикардиальная жировая ткань выступает в роли важного источника воспаления. N-терминальный фрагмент мозгового натрийуретического пептида В-типа (NT-proBNP) является общепризнанным сердечно-сосудистым маркером кардиального происхождения. Причем в последнее время было показано, что провоспалительные стимулы также могут влиять на его секрецию.

Целью исследования стала оценка сывороточной концентрации NT-proBNP в сопоставлении с составом клеток иммунной системы в эпикардиальной жировой ткани (ЭЖТ) и цитокиновым профилем у пациентов с ИБС.

В исследование вошли пациенты со стабильной ИБС и хронической сердечной недостаточностью II-III ФК по классификации Нью-Йоркской кардиологической ассоциации (NYHA) с показаниями для проведения операции аортокоронарного шунтирования (АКШ) (n = 10; в возрасте 59,5 (53,0-65,0) лет; 50% мужчины). Образцы ЭЖТ и подкожной жировой ткани (ПЖТ) получали в ходе планового аортокоронарного шунтирования (АКШ). Для исследования применяли иммуногистохимический метод окрашивания антителами к CD68, CD45, IL-1β и TNFα. Для подсчета клеток использовали световую микроскопию. Подсчет клеток проводился в 10 полях зрения при увеличении 400. Перед проведением оперативного вмешательства у пациентов производили взятие венозной крови утром натощак. Кровь центрифугировали при 1500 g, с последующим аликвотированием образцов сыворотки крови, которые хранились при температуре -40 °C. Концентрации NT-proBNP, IL-1β, IL-6, IL-10, TNFα оценивали в сыворотке методом иммуноферментного анализа (ИФА).

Мы выявили увеличение продукции IL-1β и TNFα в ЭЖТ в сравнении с ПЖТ. Уровень NT-proBNP превышал концентрацию 125 пг/мл у 4 пациентов и коррелировал с содержанием $CD68^+$ макрофагов как в ЭЖТ, так и в ПЖТ ($r_s = 0,762$; $p = 0,010$ и $r_s = 0,835$; $p = 0,003$ соответственно). Концентрация NT-proBNP положительно коррелировала с количеством $CD45^+$ лейкоцитов ($r_s = 0,799$; $p = 0,006$) и $IL\text{-}1\beta^+$ клеток ($r_s = 0,705$; $p = 0,023$) исключительно в ЭЖТ. Среди сывороточных маркеров, NT-proBNP был отрицательно связан с уровнем глюкозы натощак ($r_s = -0,684$; $p = 0,029$), и положительно в сывороточной концентрацией IL-6 ($r_s = 0,891$; $p = 0,001$).

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Увеличение сывороточной концентрации NT-proBNP у пациентов с ИБС соответствует аккумуляции макрофагов в ЭЖТ, что ассоциируется с увеличением продукции IL-1β в ЭЖТ и коррелирует с метаболическими параметрами.

Ключевые слова: макрофаги, эпикардиальная жировая ткань, NT-proBNP, ишемическая болезнь сердца, воспаление

MACROPHAGES IN EPICARDIAL ADIPOSE TISSUE AND SERUM NT-proBNP IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE

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Abstract. Coronary artery disease (CAD) is widely considered a chronic inflammatory disorder, and dysfunction of epicardial adipose tissue could be an important source of the inflammation. Amino-terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) is a known marker of cardiovascular disorders of cardiac origin. Recent studies show that inflammatory stimuli may influence its secretion. Our purpose was to evaluate NT-proBNP serum concentration in relation to immune cell ratios in epicardial adipose tissue (EAT), and cytokine levels in the patients with stable CAD.

Patients with stable CAD and heart failure classified into classes II–III, according to the New York Heart Association (NYHA) scale, scheduled for the coronary artery bypass graft (CABG) surgery, were recruited into the study (n = 10; 59.5 (53.0-65.0) y. o.; 50% males). The EAT and subcutaneous adipose tissue (SAT) specimens were harvested in the course of CABG surgery. Immunostaining with anti-CD68, anti-CD45, anti-IL-1β and anti-TNFα monoclonal antibodies was performed to evaluate cell composition by differential counts *per* ten fields (400 magnification). Fasting venous blood was obtained from patients before CABG. Blood was centrifuged at 1500g, aliquots were collected and stored frozen at -40 °C until final analysis. Concentrations of NT-proBNP, IL-1β, IL-6, IL-10, TNFα were determined in serum samples by enzyme-linked immunosorbent assay (ELISA).

We have found increased production of IL-1β and TNFα cytokines in EAT compared to SAT. Concentrations of NT-proBNP exceeded 125 pg/ml in 4 patients, and correlations between the $CD68^+$ macrophage counts in both EAT and SAT samples ($r_s = 0.762$; $p = 0.010$ and $r_s = 0.835$; $p = 0.003$, respectively). NT-proBNP levels showed positive relations with $CD45^+$ leukocyte counts ($r_s = 0.799$; $p = 0.006$), and with $IL\text{-}1\beta^+$ cell numbers ($r_s = 0.705$; $p = 0.023$) in EAT samples only. As for the serum biomarkers, NT-proBNP levels showed negative correlation with fasting glucose levels ($r_s = -0.684$; $p = 0.029$), and positive correlation with serum IL-6 concentrations ($r_s = 0.891$; $p = 0.001$).

Increased serum concentrations of NT-proBNP in CAD patients correlate with accumulation of macrophages in EAT, which is associated with increased production of IL-1β in EAT and correlates with some metabolic parameters.

Keywords: macrophages, epicardium, adipose tissue, NT-proBNP, coronary artery disease, inflammation

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Introduction

Adipose tissue represents an important source of inflammation in cardiovascular patients. White adipose tissue produces a wide range of adipokines: various cytokines, chemokines and hormones with the potential to regulate the development of inflammation. The balance between inflammatory and anti-inflammatory adipokines skews to the inflammatory side under the development of the dysfunction of adipose tissue observed during obesity. This in turn serves as a stimulus to the enrichment of the adipose tissue with the immune cells, both

of myeloid and lymphoid origin. An observed accumulation of leukocytes aggravates tissue specific and systemic insulin resistance even further [13].

Epicardial adipose tissue (EAT) is positioned in the close proximity to the coronary arteries and has a great potency to impact the heart functioning [8]. Infiltartion of EAT with inflammatory cells (macrophages and $CD8^+$T lymphocytes) increases in coronary artery disease (CAD) patients, while cellular composition of SAD remains unaffected [7].

The family of natriuretic peptides includes atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), secreted from the cardiac atria, ventricles and vascular endothelium, respectively. All the natriuretic peptides are mainly involved in the regulation of work of renal system, increasing glomerular filtration and enhancing diuresis, as well as participate in redistribution of the fluid from the blood vessels into interstitial space. Natriuretic peptides have been proven to be important cardiovascular markers hence they allow to distinguish the presence of the heart failure and predict the incident cardiovascular events [10].

BNP is released from the tissue of cardiac ventricles in the equimolar quantitates with more stable amino–terminal fragment of pro-B-type natriuretic peptide (NT-proBNP) during the pressure or volume overload of the heart [2]. According to the experimental and clinical data NT-proBNP possesses anti-inflammatory properties and increases in acute inflammatory conditions even in the absence of the heart failure and other cardiac disorders [4].

The data on the interconnections between NT-proBNP levels and EAT thickness and volume remain contradictory: the levels of NT-proBNP were directly related to the EAT thickness in patients with acute ischemic stroke and stable CAD [1], while obese heart failure (HF) with preserved ejection fraction (HFpEF) patients were characterized by the lower level of NT-proBNP compared to nonobese HFpEF and healthy individuals despite increased epicardial fat thicknes [12]. Currently there are no data whether NT-proBNP (even though being the most widely used cardiovascular marker) is interconnected to the level of inflammation in EAT.

The aim of the present study was evaluation of NT-proBNP concentration in relation to the immune cellular composition of EAT and cytokine background in patients with stable CAD.

Materials and methods

The study protocol was approved by the local Biomedical Ethics Committee of Cardiology Research Institute (protocol #146 from June 16, 2016). All procedures were performed in accordance with the Helsinki Declaration and principles of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

We have enrolled 10 patients aged 50-68 years with stable CAD and heart failure New York Heart Association (NYHA) class II-III (50% males) who were scheduled for the coronary artery bypass graft (CABG) surgery. All the patients signed an informed consent to participate in the study. Clinical characteristics of patients are represented in Table 1. Exclusion criteria from the study were as following: inflammatory processes of any localization; acute coronary event such as transitory ischemic attack, acute coronary syndrome, and acute myocardial infarction within 6 months before the study; obesity class III and higher (body mass index (BMI) > 35); severe comorbidity (hepatic failure, kidney failure, cancer of any localization); refusal to participate in the study.

Fasting samples of 10 ml of peripheral blood were obtained 2-3 days in advance of the scheduled CABG. Serum samples have been prepared via centrifugation of blood at 1000g for 15 minutes. Enzyme-linked immunosorbent assay (ELISA) was used to determine concentration of the soluble cytokines and hormones in serum: NT-proBNP (Biomedica, Germany),

TABLE 1. CLINICAL CHARACTERISTICS AND LABORATORY MEASUREMENTS OF THE PATIENTS

Parameters	
Gender (m/f)	5/5
Age, years	59.5 (53.0-65.0)
Left ventricular ejection fraction < 40% / < 50% / normal, n (%)	1 (10%) / 2 (20%) /7 (70%)
Body mass index, kg/m²	29.2 (27.4-31.2)
Waist circumference, cm	97.0 (93.0-103.0)
Epicardial adipose tissue thickness, mm	5.6 (5.0-7.4)
Fasting glucose, mM	6.1 (5.7-6.7)
Fasting insulin, μIU/ml	11.9 (7.5-20.7)
HbA1c, %	6.4 (6.0-8.3)

TABLE 2. COUNTS OF ACCUMULATING CELLS IN SUBCUTANEOUS AND EPICARDIAL ADIPOSE TISSUE DEPOTS

Cell phenotype	Subcutaneous adipose tissue	Epicardial adipose tissue	p
$CD45^+$ leukocytes, number of cells	8.0 (6.0-14.0)	6.0 (3.0-18.0)	0.959
$CD68^+$ macrophages, number of cells	10.0 (4.0-14.0)	15.0 (10.0-28.0)	0.285
IL-1β$^+$ cells, number of cells	1.0 (0.0-2.0)	6.0 (3.0-10.0)	0.005
IL-1β in tissue, scores	0 (0-0)	1.0 (1.0-2.0)	0.012
TNF^+ cells, number of cells	9.0 (6.0-14.0)	14.5 (8.0-17.0)	0.047
TNF in tissue, scores	2.0 (1.0-2.0)	2.0 (1.0-2.0)	0.686

IL-1β, IL-6, IL-10, TNFα, high-sensitive C-reactive protein (hsCRP) (Vector-BEST, Russia).

In total 1 cm^3 of EAT and subcutaneous adipose tissue (SAT) was harvested in the course of the scheduled CABG surgery. Samples of SAT and EAT were obtained before connecting of heart-lung machine using sharp scalpel without electrocoagulation. Biopsies were fixed in 10% buffered formalin for 24 hours, were subjected to standard histological wiring, embedded in paraffin, sectioned into 3-5 μm thick slices and applied on Polysine slides (Thermo Scientific, USA). Selected sections were subjected to immunohistochemistry. Obtained specimens were deparaffinized in xylols and alcohols and washed in distilled water. Antigens unmasking was performed in moist incubation chamber at 97 °C in Tris-EDTA buffer (pH = 9.0) for 20 minutes. Slides after unmasking were cooled down up to the room temperature and washed twice in phosphate buffer saline (PBS). Each section was circled with paraffin marker. Endogenous peroxidase blocking solution was applied for 10 minutes followed by washing in PBS 2 times. Protein block was applied for 10 minutes followed by washing in PBS 2 times. Murine anti-human monoclonal antibodies against CD68 (Aglient Dako, Denmark), CD45 (Cell marque, Germany), IL-1β (Abcam, UK) and TNFα (Gene Tex, USA) were applied for 30 minutes followed by washing in PBS 3 times. Horse-reddish peroxidase was added for 15 minutes and washed in PBS 4 times. DAB solution was added for 40 seconds and washed in PBS 4 times. Sections were counterstained with hematoxylin, rehydrated and mounted under the cover glass. Light microscopy (microscope Axio Imeger M2, Zeiss, Germany) was used for analysis. Number of cells was quantified from ten 400 magnified fields. Tissue production of cytokines was evaluated according to the staining intensity and staining area: score 1 corresponded to low staining intensity and staining area up to 30%; score 2 corresponded to medium staining intensity and staining area above 30% but below 60%; score 3 corresponded to intense continuous cytokine staining.

Statistical analysis was performed in Statistica 13.0 software (StatSoft Inc., USA). Shapiro–Wilk criterion was used to assess the normality of the distribution of the data. Continuous variables were presented as median and interquartile range (Me ($Q_{0.25}$-$Q_{0.75}$)). Statistical comparisons were performed using Mann–Whitney test. Calculation of means in sub-groups was performed by k-means cluster analysis. Associations between parameters were evaluated using Spearman correlation coefficient. All statistical hypotheses were accepted according to the achieved significance level $p < 0.05$.

TABLE 3. LEVELS OF NT-proBNP, ADIPOKINES AND CYTOKINES IN BLOOD OF RECRUITED PATIENTS

Parameters	
NT-proBNP, pg/ml	84.48 (34.95-166.72)
IL-1β, pg/ml	0.51 (0.36-0.79)
IL-6, pg/ml	1.94 (0.83-3.18)
TNFα, pg/ml	0.35 (0.28-0.38)
IL-10, pg/ml	3.18 (2.39-3.58)

Results and discussion

Numbers of $CD45^+$ cells and $CD68^+$ macrophages did not differ between SAT and EAT (Table 2). However, we have revealed increased accumulation of IL-1β$^+$ and TNF^+ cells in EAT, compared to SAT in recruited patients, as well as increased scores of tissue expression of IL-1β in EAT (Table 2).

Concentrations of NT-proBNP, serum cytokines and chemokines in the total group of patients are represented in Table 3. Concentrations of NT-proBNP exceeded cut-off value set for the diagnosis of chronic heart failure (125 pg/ml) in 4 patients according to the recent National guidelines [11].

We have revealed positive correlations between serum concentrations of NT-proBNP and counts of $CD68^+$ macrophages both in EAT and SAT ($r_s = 0.762$; $p = 0.010$ and $r_s = 0.835$; $p = 0.003$, respectively). NT-proBNP was positively related to the counts of $CD45^+$ leukocytes ($r_s = 0.799$; $p = 0.006$) and numbers of IL-1β$^+$ cells ($r_s = 0.705$; $p = 0.023$) only in EAT. As for the serum biomarkers, NT-proBNP was negatively related to the level of fasting glucose

(r_s = -0.684; p = 0.029) and positively correlated with the serum IL-6 concentrations (r_s = 0.891; p = 0.001).

The involvement of BNP into pathogenesis of inflammation has been confirmed in multiple studies. Thus, patients with rheumatoid arthritis presented with elevated levels of NT-proBNP even in the absence of the heart failure [14]. Elevation of NT-proBNP was associated with increased mortality in SARS-CoV-2 patients irrespective of the heart failure status [3].

Weak-to-moderate correlation between NT-proBNP and macrophage migration inhibitory factor (MIF) in HFpEF patients demonstrated in the study of Luedike P. et al. (2018) allows to presume that associations observed in our study may be due to the changes in EAT macrophages' chemotaxis [9].

IL-1β may be regarded as a potential cytokine involved in regulation of inflammation in epicardial fat, as we have observed elevation of it in EAT and concentrations of IL-1β correlated with NT-proBNP levels. According to the results of van Tassell B.W. et al. (2018) daily injections of interleukin-1 receptor antagonist to patients with heart failure with preserved ejection fraction was associated with decrease of high-sensitivity CRP and NT-proBNP levels in 4 weeks [15].

Metabolic effects of NT-proBNP have also been appreciated recently. Thus, increase of NT-proBNP levels was associated with the reduction of the risk of diabetes development and HDL, triglycerides and adiponectin were identified as the putative mediators of this effect. Receptors to NPs are found in adipose tissue and they may stimulate lipolysis, promote browning of adipocytes and affect adipokines' release upon binding [5]. According to Heinisch B.B. et al. (2012) BNP has a potency to induce redistribution of glucose in human organism in insulin-independent manner lowering its concentration in the blood [6]. This may explain the inverse correlation between NT-proBNP and fasting glucose observed in our study. Further studies targeting changes of NT-proBNP in diabetes in respect to the development of inflammation in EAT are required.

The limitations of the study include low number of patients being recruited and its descriptive design.

Conclusion

Thus in our study we have shown for the first time, that increased concentrations of NT-proBNP in serum of CAD patients correlate with the accumulation of macrophages in epicardial adipose tissue, which is associated with increased production of proinflammatory cytokine IL-1β and changes of metabolic parameters. Further prospective studies are required to identify the potential consequences of increased NT-proBNP production for the development of cardiovascular and total undesirable events in these patients.

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