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Pattern of circulating microparticles in chronic heart failure patients with metabolic syndrome: Relevance to neurohumoral and inflammatory activation

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ABSTRACT

Background: The role of pattern of circulating endothelial cell-, platelet-, and monocyte-derived microparticles in metabolic syndrome (MetS) patients with chronic heart failure (CHF) is not still understood.
The aim of the study was to investigate a pattern of circulating MPs in MetS patients with CHF in relation to neurohumoral and inflammatory activation.
Methods: The study retrospectively involved 101 patients with MetS (54 subjects with CHF and 47 patients without CHF) without documented coronary artery stenosis >50% at least of one artery and 35 healthy volunteers. Biomarkers were measured at baseline of the study. Circulating MPs were phenotyped by flow cytometry technique.
Results: The results of the study have shown that numerous of the circulating platelet-derived and monocyte-derived MPs in subjects with MetS (with or without CHF) were insufficiently distinguished from the level obtained in healthy volunteers. We found an elevated level of CD31+/annexin V+ MPs in association with a lower level of CD62E+ MPs. All these led to decreased CD62E+ to CD31+/annexin V+ ratio among patients with MetS in comparison with healthy volunteers, as well as in MetS patients with CHF compared with those who did not demonstrated CHF. Therefore, we found that biomarkers of biomechanical stress (NT-proBNP) and inflammation (hs-CRP, osteoprotegerin) remain statistically significant predictors for decreased CD62E+ to CD31+/annexin V+ ratio in MetS patients with CHF.
In conclusion, decreased CD62E+ to CD31+/annexin V+ ratio reflected impaired immune phenotype of MPs may be discuss surrogate marker of CHF development in MetS population.

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1. Introduction

The traditionally recognized metabolic syndrome (MetS) is defined as risk factor clustering related to the development of type 2 diabetes mellitus (T2DM) and cardiovascular disease [1]. MetS includes abdominal obesity, insulin resistance, dyslipidemia, and elevated blood pressure and associates with other co-morbidities including the prothrombotic and proinflammatory states [2]. Accumulating evidences have been shown that MetS is a powerful risk factor for cardiovascular disease (CVD) event, as well as all-cause and CVD mortality in total population [3–5]. The underlying pathophysiological mechanisms resulting in the MetS, i.e. insulin resistance (IR), associate with activation of neurohumoral mechanisms, immunity, cytokine production, systemic pro-inflammatory response, and oxidative stress [6–8]. All these factors may affect the development of CVD through inducing endothelial dysfunction [9–10] and microvascular inflammation [11].

Recent studies have shown a controversial role of MetS in patients at high risk of chronic heart failure (CHF) and in subjects with documented CHF. Although MetS associates with cardiovascular risk factors and CVD outcomes [12–15], prognostic impact of MetS on CHF progression is not fully confirmed and widely discussed [16,17]. Therefore, it is still unclear whether MetS may induce development and progression of cardiac failure through imbalance between endothelial injuries and repair [18,19]. Probably microparticles (MPs) corresponding to cell-to-cell cooperation, immunity, tissue reparation, and vascular function, are key factors that coordinate microvascular integrity and function [20].

Extracellular microparticles are microvesicles with sizes ranging between 50 and 1000 nm released from the plasma membrane of a wide variety of cells, including endothelial cells, mononuclear cells, and platelets, by specific (cytokine stimulation, apoptotic agents, mononuclear

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cooperation, coagulation, etc.) and non-specific (shear stress) stimuli [21]. Circulating endothelial-derived microparticles (EMPs) depending on their origin (apoptotic-derived or activated endothelial cell production) are capable of transferring biological information (regulating peptides, hormones) or even genetic material, as well as proteins and lipid components, from one cell to another without direct cell-to-cell contact to maintain cell homeostasis [22,23]. EMPs derived from activated endothelial cells may have pro-angiogenic and cardio-protective properties [24]. In opposite, apoptotic EMPs that originated from damaged endothelial cells are discussed as marker of endothelial cell injury and vascular aging [25].

Platelet-derived microparticles (PMPs) are a heterogeneous population of microvesicles that are secreted from chemokine and cytokine activated platelets. PMPs that mediate multiple cellular responses predominantly affected protein and lipid metabolism, coagulation and inflammation [26]. Elevated PMPs show a relation to clinical outcomes and mortality in several patient populations [27].

Numerous studies have shown that monocyte-derived microparticles (MMPs) are realized from activated and/or apoptotic monocytes in response to various stimuli, i.e. antigen stimulation, growth factors, inflammatory interleukins, and chemokines and cytokines [28–30]. Elevated levels of circulating MMPs are documented in almost all thrombotic diseases, infective, rheumatic and autoimmune diseases, stroke, myocardial infarction, atrial fibrillation, as well as in metabolic, ischemic/hypoxic states, and critical conditions [31–33]. However, the significance of MPs in MetS patients as an inductor of development and progression of CHF remains controversial. An example of this controversy is that it is still unknown if circulating MPs found in peripheral blood cause injury of the endothelium and worsening of CHF whether they are the result of disease progression in response to endothelial dysfunction and vascular dysintegrity [34,35]. The aim of the study was to investigate the pattern of circulating endothelial cell-, platelet-, and monocyte-derived MPs in MetS patients with CHF in relation to neurohumoral and inflammatory activation.

2. Methods

The study retrospectively evolved 101 patients with MetS (54 subjects with CHF and 47 patients without CHF) without documented coronary artery stenosis >50% at least of one artery and 35 healthy volunteers who were examined between February 2013 and November 2013. The study was approved by the local ethics committee of the State Medical University, Zaporozhye, Ukraine. The study was performed in conformity with the Declaration of Helsinki. All the patients have given their informed written consent for participation in the study.

MetS was diagnosed based on the National Cholesterol Education Program Adult Treatment Panel III criteria [36]. Patients were enrolled in the MetS cohort when at least three of the following components were defined: waist circumference ≥90 cm or ≥80 cm in men and women respectively; high density lipoprotein (HDL) cholesterol <1.03 mmol/L or <1.3 mmol/L in men and women respectively; triglycerides ≥1.7 mmol/L; blood pressure ≥130/85 mm Hg or current exposure of antihypertensive drugs; and fasting plasma glucose ≥5.6 mmol/L. Subjects with defined T2DM or treatment with oral antidiabetic agents or insulin were not enrolled in the study. Current smoking was defined as consumption of one cigarette daily for three months. Anthropometric measurements were made using standard procedures.

2.1. Methods for visualization of coronary arteries

Contrast-enhanced multispiral computed tomography angiography has been performed for all the patients with dysmetabolic disorder prior to their inclusion in the study on Optima CT660 scanner (GE Healthcare, USA) using non-ionic contrast Omnipaque (Amersham Health, Ireland) [37]. Subjects with atherosclerotic lesions >50% of diameter at least of one coronary artery were excluded for further enrollment in the study.

2.2. Transthoracic echocardiography

Transthoracic echocardiography was performed according to a conventional procedure on ultrasound scanner ACUSON (SIEMENS, Germany) in B-mode and Tissue Doppler Imaging with phased probe of 2.5–5 MHz. Left ventricular (LV) end-diastolic and end-systolic volumes, LV ejection fraction (LVEF) were measured by modified Simpson's method [38].

2.3. Calculation of glomerular filtration rate

Glomerular filtration rate (GFR) was calculated with the CKD-EPI formula [39].

2.4. Measurement of circulating biomarkers

To determine circulating biomarkers, blood samples were collected at baseline in the morning (at 7–8 a.m.) into cooled silicone test tubes wherein 2 mL of 5% Trilon B solution was added. Then they were centrifuged upon permanent cooling at 6000 rpm for 3 min. Plasma was collected and refrigerated immediately to be stored at a temperature −70 °C. Serum N-terminal brain natriuretic peptide (NT-proBNP), adiponectin, RANKL and osteoprotegerin (OPG) were measured by high-sensitive enzyme-linked immunosorbent assays using commercial kits (R&D Systems GmbH, Wiesbaden-Nordenstadt, Germany) according to the manufacturers' recommendations. The inter-assay coefficients of variation were as follows: NT-proBNP: 4.5%, adiponectin: 5%, RANKL: 7.0%; OPG: 8.2%.

High-sensitive C-reactive protein (hs-CRP) was measured by commercially available standard kit (R&D Systems GmbH, Wiesbaden-Nordenstadt, Germany). The intra-assay and inter-assay coefficients of variation were <5%.

Fasting insulin level was measured by a double-antibody sandwich immunoassay (Elecsys 1010 analyzer, F. Hoffmann-La Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficients of variation were <5%. The lower detection limit of insulin level was 1.39 pmol/L.

Insulin resistance was assessed by the homeostasis model assessment for insulin resistance (HOMA-IR) [40] using the following formula:

$$\text{HOMA-IR (mmol/L} \times \mu\text{U/mL)} = \text{fasting glucose (mmol/L)} \times \text{fasting insulin (}\mu\text{U/mL)}/22.5.$$

Concentrations of total cholesterol (TC), cholesterol of low-density lipoproteins (LDL-C) and cholesterol of high-density lipoproteins (HDL-C) were measured by enzymatic method.

2.5. Assay of circulating endothelial-derived microparticles

Circulating MPs were isolated from 5 ml of venous citrated blood drawn from the fistula-free arm. To prevent contamination of samples platelet-free plasma (PFP) was separated from whole blood. PFP was centrifugated at 20,500 × rpm for 30 min. MP pellets were washed with DMEM (supplemented with 10 μg/mL of polymyxin B, 100 UI of streptomycin, and 100 U/ml of penicillin) and centrifuged again (20,500 rpm for 30 min). The obtained supernatant was extracted, and MP pellets were re-suspended into the remaining 200 μL of supernatant. PFP, MPs, and supernatant were diluted five-, 10-, and five-fold in PBS, respectively.

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