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Alterations of soluble TWEAK and CD163 concentrations in patients with chronic heart failure

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ABSTRACT

Inflammatory activation plays a pivotal role in chronic heart failure with reduced ejection fraction (HF-REF). A novel mediator from TNF family: soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) along its soluble decoy receptor CD163 (sCD163) recently has been investigated in other cardiovascular pathologies. We aimed to evaluate sTWEAK and sCD163 concentrations in HF-REF patients.

The study enrolled 79 patients with stable HF-REF, EF < 35%. The control population without history of heart failure included two groups: 26 comorbidities matched patients and 27 healthy volunteers. sTWEAK and sCD163 serum concentrations were determined using ELISA kits. Univariate and multivariate analysis was performed to assess variables affecting concentration of sTWEAK and sCD163.

HF-REF patients were characterized by higher sTWEAK (median 374 IQR: 321–429 vs 201 IQR: 145–412 pg/ml, $P = 0.005$), sCD163 (median 744 IQR: 570–1068 vs 584 IQR: 483–665 pg/ml, $P = 0.03$) concentrations and sTWEAK/sCD163 ratio (median 0.53 IQR: 0.32–0.7 vs 0.3 IQR: 0.22–0.37, $P = 0.001$) comparing to healthy volunteers. Comparing to comorbidities matched controls, HF-REF patients had lower sTWEAK levels (median 374 IQR: 321–429 vs 524 IQR: 384–652 pg/ml; $P = 0.002$), while sCD163 and sTWEAK/sCD163 ratio didn't differ. Concentration of sTWEAK in HF-REF was affected by white blood cell count and aspirin intake, while sCD163 by exercise capacity, LV diastolic volume, CRP and presence of arterial hypertension.

Conclusions: HF-REF patients present increased sTWEAK and sCD163 levels as well as sTWEAK/sCD163 ratio when compared to healthy subjects, however CHF itself appears to be associated with down-regulation of sTWEAK.

1. Introduction

Chronic heart failure (CHF) is a common and progressive disease characterized by impaired function of myocardium that may be characterized by a reduction in ejection fraction (heart failure with reduced ejection fraction – HF-REF). Cardiomyocytes loss and pathological remodeling are the crucial factors in the development and progression of this disease [1].

Inflammatory activation is involved in the pathogenesis of CHF. It has been shown, that inflammatory cytokines and their receptors are associated with the unfavorable remodeling and deterioration of CHF symptoms [2,3]. Tumor necrosis factor (TNF) superfamily members play an important role in the inflammatory response [4,5]. One of them is a soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK), which mediates a variety of cellular responses from proliferation to fibrosis and cell death [5–7]. Furthermore, this cytokine has prognostic value in patients with ST-elevation myocardial infarction, where elevated sTWEAK levels predicted an adverse short-term outcome [8]. The same author reported association of decreased concentration of this cytokine with an adverse prognosis in patients with stable CHF in 4-years observation study [9]. Low sTWEAK levels also independently predicted mortality in advanced non-ischemic heart failure (HF), while such effect was not observed in ischemic HF patients [10].

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One of the TWEAK receptors is membrane protein CD163 [11]. CD163 is known as a scavenger receptor expressed by monocytes and macrophages and is involved in the clearance of hemoglobin–haptoglobin (Hb–Hp) complexes, protecting tissues from oxidative damage and inflammation [11]. Because of molecular similarity between Hb–Hp complex and TWEAK, this cytokine has the affinity to the CD163 receptor. TWEAK binding by CD163 leads to neutralization of both molecules, therefore CD163 is considered to be a 'decoy' receptor for sTWEAK [12]. Recently, this receptor was proposed to be a marker specific for subpopulation of monocytes and macrophages exhibiting strong anti-inflammatory properties [11,13]. The CD163 expression is mediated by a variety of pro- and anti-inflammatory factors, e.g. it is up-regulated by interleukin 10 (IL-10) and glucocorticoids [14,15]. Interestingly, interleukin 6 (IL-6), known as a pro-inflammatory cytokine, exerts similar effects on CD163 expression as IL-10 [16]. Pro-inflammatory mediators such as interleukin-1, tumor necrosis factor α (TNF-α) and chemokine CXCL-8 – known as interleukin-8 (IL-8) were found to decrease expression of CD163 [17–19]. Recent studies on cardiovascular disorders demonstrated that sCD163 and the relation of sCD163 to sTWEAK levels can be considered as potential biomarkers of inflammatory activation [20,21]. Furthermore, there is a growing body of evidence suggesting that sTWEAK and its interaction with receptors may contribute to the pathogenesis and progression of HF [7,9].

According to these facts we assume that sTWEAK and sTWEAK/sCD163 ratio might be the mechanism that influences the inflammatory status in CHF patients. Therefore the study aimed at the evaluation of alterations in the levels of sTWEAK and sCD163 in HF-REF patients as potential factors involved in the course of the disease.

2. Materials and methods

2.1. Population

The study enrolled 79 patients with stable chronic heart failure in NYHA class II-III with ejection fraction lower than 35% (heart failure with reduced ejection fraction – HF-REF) diagnosed in echocardiography age 64.7 ± 11.1. The population included 11 (14%) females. The mean body mass index (BMI) was 28.5 ± 4.4 kg/m^2. The etiology of heart failure included dilated [31 (39%) patients] or ischemic cardiomyopathy [48 (61%) patients]. The reference cohort consisted of two groups without history of HF:

1. Control group – 26 volunteers (outpatient) matched for age, sex and body weight, with comorbidities adequate to those observed in the HF-REF patients age 62.7 ± 8.3 years. The group included 5 (19%) females. The mean BMI was 28.4 ± 3.9 kg/m^2.
2. Reference group – 27 healthy volunteers (outpatient) age 53.4 ± 10 years. The group included 7 (26%) females. The mean BMI was 26.5 ± 3 kg/m^2.

All patients underwent the same diagnostic assessment: a medical interview with assessment of NYHA functional class, physical examination, transthoracic echocardiography, cardiopulmonary exercise test (CPET), 6 min walk test with distance assessment (6MWD) and venous blood tests. Patients with active infection were excluded from the study.

2.2. Echocardiography

Two-dimensional echocardiographic measurements included EF assessment according to Simpson's method (bi-plane method), end-diastolic diameter (LVEDD) as well as end-systolic and end-diastolic volume of left ventricle (LVESV and LVEDV respectively). This method was also used to exclude any significant heart abnormalities in the both control groups.

2.3. Cardiopulmonary exercise test

CPET was performed using symptoms limited treadmill exercise test with RAMP protocol. The electrocardiogram was continuously monitored for the heart rate, occurrence of ST segment changes or arrhythmias. Of the numerous parameters, peak oxygen uptake (peak VO_2), peak carbon dioxide exertion (VCO_2), oxygen and carbon dioxide end-tidal pressures ($PetO_2$, $PetCO_2$) and the slope of the VE/VCO_2 relationship from the initiation to peak exercise (VE/VCO_2 slope) were used for analysis.

2.4. Blood samples collection and measurements

Fasting peripheral venous blood samples were obtained from patients with HF-REF and controls. Serum aliquots of 1.5 ml were stored at −80 °C for future analysis. Concentrations of sTWEAK and sCD163 were determined using commercially available ELISA kits (eBioscience, Austria and R&D Systems, USA, respectively) according to the manufacturer instructions. The detection limit was 9.7 pg/ml and 0.177 ng/ml for sTWEAK and sCD163 respectively. All measurements were performed in duplicate and means were taken for further analysis. Blood samples were also analyzed for B-type natriuretic peptide (BNP), C-reactive protein (CRP), hemoglobin, blood count, uric acid and creatinine concentrations. Creatinine clearance (ml/min) was estimated by Cockroft–Gault formula.

2.5. Statistical analysis

The distribution of all variables was verified with Kolmogorov–Smirnov test. The data was expressed as a mean ± standard deviation (SD) unless stated otherwise when median values with interquartile range (IQR) are given. Statistical analysis was performed using Student's *t*-test or Mann–Whitney U test for continuous data depending on distribution and χ^2 test for categorical variables. The analysis of variance (ANOVA) with Fisher post hoc test was used for the three groups analysis. Pearson's correlation coefficient was used to examine the relationship between 2 continuous variables. The univariate and multivariate stepwise regression (we initially included parameters listed in Tables 3 and 4) analyzes were used to identify factors affecting sTWEAK and sCD163 concentrations. $P < 0.05$ was considered statistically significant. A statistical software package Statistica 10 (USA) was used for analysis.

The study complied with the Declaration of Helsinki and was approved by the institutional medical ethics committee. All patients were involved in the study after signing an informed consent for participating in the study, including taking and storage of blood samples.

3. Results

3.1. Clinical characteristics

Clinical characteristics of HF-REF, control and reference groups are presented in Table 1. Most HF-REF patients was in III NYHA functional class (67%, $n = 53$). This group also had limited exercise capacity which was expressed in shortened 6MWD, lower mean peak VO_2 and peak VCO_2 (Table 1). HF-REF group also manifested impairment of gas exchange characterized by elevated VE/VCO_2 slope (Table 1).

Standard laboratory tests' results are summarized in Table 2.