Cytokine 111 (2018) 13–19

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

NT-proBNP and CA 125 levels are associated with increased pro-inflammatory cytokines in coronary sinus serum of patients with chronic heart failure

Adina Elena Stanciu[a,*], Marcel Marian Stanciu[b], Radu Gabriel Vatasescu[c]

[a] Institute of Oncology Bucharest, Department of Carcinogenesis and Molecular Biology, 252 Fundeni, 022338 Bucharest, Romania
[b] University Politehnica of Bucharest, Electrical Engineering Faculty, 313 Splaiul Independentei, 060042 Bucharest, Romania
[c] Clinic Emergency Hospital Bucharest, Department of Cardiology, 8 Calea Floreasca, 014461 Bucharest, Romania

ARTICLE INFO

Keywords:
Heart failure
Coronary sinus
NT-proBNP
CA 125
Cytokines
Inflammation

ABSTRACT

Purpose: Heart failure (HF) is considered to be a complex syndrome associated with neurohormonal and cytokine activation, that contribute to its progression. There are evidences which showed that, carbohydrate antigen 125 (CA 125), a tumor marker widely used for ovarian cancer therapy monitoring, was significantly elevated in HF patients. We hypothesized that inflammatory stimuli may be responsible for amino-terminal fragment of the prohormone B-type natriuretic peptide (NT-proBNP) and CA-125 production and release in chronic HF (CHF). We aimed to measure the levels of NT-proBNP, CA 125, pro-anti-inflammatory cytokines (IL-6, IL-1β, IL-8, TNF-α and IL-4), from peripheral venous (PV) and coronary sinus (CS) blood samples, in patients with CHF and to assess their correlation with echocardiographic indices.

Methods: We enrolled 32 subjects (20M/12F) with CHF (III-IV NYHA functional class) who were to undergo cardiac resynchronization therapy (CRT) device implantation and 30 healthy controls (18M/12F). Two blood samples, from PV and CS, were collected at the time of CRT for each CHF patient. Serum levels of biomarkers were measured by ELISA. Cardiac function was assessed echocardiographically.

Results: All investigated biomarkers were significantly higher in CHF patients than in non-CHF controls ($P < 0.001$). There were positive correlations between biomarkers concentrations in PV and CS (r between 0.54 and 0.98, all $P < 0.003$). NT-proBNP, IL-6 and IL-1β levels were 17%, 86% and 36% higher in CS than in PV, these increases being very well correlated each other, while CA 125 levels were 86% higher in PV than in CS. Moreover, CS NT-proBNP, CS IL-6 and CS IL-1β serum concentrations were inversely related to the echocardiographically determined left ventricular ejection fraction (LVEF) ($r = -0.61$, $P < 0.001$; $r = -0.71$, $P < 0.001$ and $r = -0.48$, $P = 0.005$, respectively). A positive relationship was found between CA 125 and IL-1β ($r = 0.51$, $P = 0.003$) in CS serum and between CA 125 and IL-6 ($r = 0.43$, $P = 0.015$), TNF-α ($r = 0.46$, $P = 0.008$) in PV serum. CA 125 concentrations were closely related to NT-proBNP both in CS ($r = 0.46$, $P = 0.008$) and PV ($r = 0.52$, $P = 0.002$).

Conclusions: CS sampling of NT-proBNP, CA 125 and pro-anti-inflammatory cytokines provides an additional insight into the possible mechanisms by which these biomarkers lead to left ventricular remodeling. Our results clearly suggest that serum NT-proBNP and CA 125 levels not only in PV, but also in CS of patients with CHF, may be dependent on inflammation as a consequence of cytokine network activation.

1. Introduction

Chronic heart failure (CHF) is a global pandemic affecting at least 26 million people worldwide and is increasing in prevalence [1]. HF progression is associated with left ventricular (LV) remodeling, which manifests as gradual increases in LV volumes [end-diastolic volume

Abbreviations: CA 125, carbohydrate antigen 125; CRT, cardiac resynchronization therapy; CS, coronary sinus; CHF, chronic heart failure; IL, interleukin; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left-ventricular end-systolic volume; NT-proBNP, amino-terminal fragment of the prohormone B-type natriuretic peptide; NYHA class, New York Heart Association class; PV, peripheral venous; SD, standard deviation; TNF-α, tumor necrosis factor-alpha

* Corresponding author at: Institute of Oncology Bucharest, Department of Carcinogenesis and Molecular Biology, 252 Fundeni, 022338 Bucharest, Romania.
E-mail address: adinaelenastanciu@yahoo.com (A.E. Stanciu).

https://doi.org/10.1016/j.cyto.2018.07.037
Received 1 March 2018; Received in revised form 4 July 2018; Accepted 31 July 2018
1043-4666/ © 2018 Elsevier Ltd. All rights reserved.

(LVEDV), end-systolic volume (LVESV)], wall thinning and a continuous decline in LV ejection fraction (LVEF). The process of cardiac remodeling is triggered by the alterations of many mediators such as hemodynamic load, neurohumoral factors, cytokines (tumor necrosis factor-alpha [TNF-α], interleukins IL-1β, IL-6, IL-8), enzymes, oxidative stress, ion channels and mechanical stress. Structural studies have elucidated the mechanisms by which tissue inhibitors of matrix metalloproteinases selectively inhibit different groups of matrix metalloproteinase leading to extracellular matrix remodeling in many diseases [2–4]. B-type natriuretic peptide (BNP), particularly its amino-terminal fragment (NT-proBNP), has emerged as powerful biomarker of cardiovascular risk in patients with HF [5]. By comparison, NT-proBNP has a longer half-life than BNP, higher stability and lower intra-patient variability [5,6]. It is well established that some biomarkers from the field of oncology, such as carbohydrate antigens 19-9 (CA 19-9) and 125 (CA 125), tissue polypeptide specific antigen (TPS), cromogranin A and B could be of interest in HF management [7–10]. Of all these cancer biomarkers, CA 125, a tumor marker widely used for ovarian cancer therapy monitoring, has been designated as having a real potential role in HF [10]. Previous studies have found that CA 125 could be produced by mesothelial cells as a consequence of mechanical stress such as fluid overload/serosal effusions and/or inflammation, but the precise mechanisms leading to CA 125 elevation in HF are still unknown. We hypothesized that inflammatory stimuli may be responsible for NT-proBNP and CA 125 production and release.

Unfortunately, the biomarkers levels measured from the peripheral circulation may not reflect intracoronary levels. Studies using blood samples, from both peripheral and cardiac microcirculation, may provide a better insight into HF pathophysiology. Therefore, we decided to collect both peripheral venous (PV) and coronary sinus (CS) blood samples from the same patients at the time of cardiac resynchronization therapy (CRT) device implantation. CRT is an effective treatment in moderate to severe drug-refractory HF, that may induce LV reverse remodeling in a significant proportion of the patients. CS sampling may offer enhanced sensitivity or specificity for coronary events, from assessments of the local intracardiac milieau to a lack of dilution effects [11].

The present study was designed to measure the levels of NT-proBNP, CA 125, pro-anti-inflammatory cytokines (IL-6, IL-1β, IL-8, TNF-α and IL-4), from peripheral venous and coronary sinus blood samples, in patients with CHF, during CRT, and to assess their correlation with echocardiographic indices.

2. Materials and methods

2.1. Patients and study protocol

We prospectively enrolled 32 consecutive patients with CHF, wide QRS and NYHA functional class III or IV (20M/12F, age 60 ± 10 years, 32 left-bundle branch block - LBBB, 15 ischemic, baseline mean LVEF 20.9 ± 5.5%), who were to undergo biventricular pacemaker/defibrillator placement for CRT in Clinic Emergency Hospital Bucharest. CRT was indicated in accordance with current recommendations, namely NYHA functional class ≥ III despite adequate pharmacotherapy, LVEF ≤ 35% and prolonged QRS duration ≥ 120 ms. This initial cohort was chosen as biomarkers could be measured from CS blood, at the time of the CRT implant, without additional risk to the subjects. Subjects with recent acute coronary syndrome, atrial fibrillation, antecedents of neoplasia [12], diabetes, thyroid dysfunction, pulmonary, hepatic, or renal impairment, as well as those with surgery in the 6 months prior to the implant were excluded. Since serum cytokines may be elevated due to acute or chronic infections and inflammation, these conditions have also been excluded from this study. All patients had stable symptoms for at least 3 months at the time of evaluation. In order to minimize the effect of medication, patients receiving antibiotic or anti-inflammatory agents were not included in the study. For each enrolled subject, a detailed medical and drug history was obtained. All patients underwent physical examination and routine laboratory tests. HF symptoms and functional capacity were evaluated using NYHA functional class, Minnesota Living with Heart Failure Questionnaire (MLHFQ) and 6-minutes' walk test (6-MWT).

A number of 30 healthy subjects (18M/12F, age 57 ± 7 years) were randomly selected from the individuals who volunteered for general routine health evaluation and underwent echocardiography. None of the controls had any cardiovascular disease, history of hypertension, malignancy, diabetes, thyroid dysfunction, pulmonary, hepatic, or renal impairment and infections or inflammatory signs at the time of evaluation. All physical and laboratory examination parameters were normal. The control subjects did not undergo cardiac catheterization.

The study conforms to the principles outlined in the Declaration of Helsinki and was approved by the Clinic Emergency Hospital Bucharest ethics committee. Enrolled patients and volunteers signed an informed consent.

2.2. Echocardiographic measurement

All patients and volunteers underwent standard transthoracic 2D and color Doppler echocardiography with a commercially available system (Vingmed Vivid 7, General Electric-Vingmed, Milwaukee, Wisconsin, USA). Images were obtained in the parasternal (long- and short-axis) and apical (2-, 3-, and 4-chamber) views using a 3.5 MHz transducer (16 cm depth). LVEDV, LVESV and LVEF were measured in the apical two- and four-chamber views using the biplane Simpson's formula. Digital routine gray-scale 2D cine-loops from 3 consecutive beats (with gain settings adjusted to optimize endocardial definition) were obtained at end-expiratory apnea from mid-LV short-axis view at the papillary muscle level. LV dyssynchrony criteria were also included: septal-to-posterior wall motion delay in short axis view with M mode > 130 ms, the presence of the septal flash and speckle tracking radial strain septal to posterior wall peak-to-peak delay ≥ 130 ms.

2.3. Biomarker measurements

In all CHF patients there have been collected two blood samples, from periphery and CS, within 15 min of each other during the index CRT implant procedure. CS is the main cardiac vein and it has become a clinically important structure especially through its role in providing access for biventricular pacemaker placement [11]. Cannulation of the CS has allowed the access to blood sampling. PV blood was drawn from one of the upper extremity veins. In volunteers, blood specimens were drawn by venipuncture. All blood samples were collected in Vacuette® polyethylene terephthalate glycol clot activator tubes (Greiner Bio-One). The serum samples were obtained by clotting (30 min, room temperature) and centrifugation (15 min at 1000*g* and 4 °C) and then were aliquoted into labeled cryo-vials and frozen at −80 °C for a variable period of maximum 12 months. NT-proBNP (amino acids 1–76) is a very useful biomarker for HF. The Study Group on Biomarkers in Cardiology (ESC Working Group on the Acute Cardiac Care), has reported a very good stability of this peptide for at least one year at −80 °C [5]. However, we investigated the stability of NT-proBNP. Storage at −80 °C for 12 months resulted in NT-proBNP concentrations decreasing between 0.4% and 1.2% compared with samples thawed after 24 h storage.

Serum concentrations of NT-proBNP, CA 125, IL-6, IL-1β, IL-8, TNF-α and IL-4 were measured using commercially available quantitative enzyme-linked immunosorbent assay (ELISA) kits (NT-proBNP from Biomedica Gruppe; CanAg CA 125 from Fujirebio Diagnostics, INC; Human IL-6, IL-1β, IL-8, TNF-α and IL-4 Quantikine from R&D Systems, Inc., Minneapolis, MN, USA).

The precision (intra-assay variation) was tested by 8 measurements of 3 different samples of known concentrations in 1 assay. The reproducibility (inter-assay variation) for the same 3 samples was tested 8

Download English Version:

https://daneshyari.com/en/article/8628661

Download Persian Version:

https://daneshyari.com/article/8628661

Daneshyari.com