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Elevation of carbohydrate antigen 125 in chronic heart failure may be caused by mechanical extension of mesothelial cells from serous cavity effusion

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ABSTRACT

Objectives: The practical application of elevated carbohydrate antigen 125 (CA125) to predict clinical outcome in chronic heart failure (CHF) is under debate. The mechanism for this CA125 elevation remains unknown. We hypothesize that mechanical stress on mesothelial cells initiates CA125 synthesis.

Design and methods: A total of 191 patients suffering from edema and/or dyspnea were enrolled. 109 patients were diagnosed as CHF, and 82 patients without CHF were assigned as control group. Echocardiography, CA125, N-terminal pro-brain natriuretic peptide (NT-proBNP), and other biochemical parameters were measured. All enrolled patients underwent heart function classification.

Results: Patients with serous cavity effusion (SCE) demonstrated higher serum CA125 than patients without SCE (82.91 (61.90–103.92) vs. 44.98 (29.66–60.30) U/mL, $P < 0.001$). In the absence of SCE, CA125 levels in CHF patients were slightly higher than non-CHF patients (52.37 (34.85–69.90) vs. 35.15 (23.81–46.49) U/mL, $P = 0.017$). Additionally, compared with non-CHF patients, CHF patients had higher levels of high-sensitivity C-reactive protein (hsCRP) and lower superoxide dismutase (SOD). In all enrolled patients, CA125 levels were negatively correlated with SOD concentrations ($r = -0.567$, $P < 0.001$), and positively correlated with hsCRP levels ($r = 0.608$, $P < 0.001$). Receiver operating characteristic curve analysis showed that CA125 was better in predicting SCE than NT-proBNP, while NT-proBNP was more suitable for predicting CHF than CA125. The in vitro study demonstrated that MUC16, the CA125 coding gene, was up-regulated by mechanical stretch on human mesothelial cell line (MeT-5A).

Conclusions: CA125 elevation in CHF was associated with SCE. Mechanical extension of mesothelial cells from SCE plays an important role in CA125 increase.

Introduction

Carbohydrate antigen 125 (CA125) has been served as the most frequently used biomarker for ovarian cancer detection and predicting patients' prognosis after treatment since it was firstly described [1,2]. It may also elevate in other cancers and some relatively benign conditions [3,4]. Interestingly, elevation of CA125 has also been documented in patients with chronic heart failure (CHF) [5–7]. However, the practical application of elevated CA125 in CHF is still under debate. Further research is required for demonstrating the mechanisms for CA125 elevation in patients with CHF.

CA125 is a high-molecular-weight soluble glycoprotein encoded by the MUC16 gene in humans [8]. It is synthesized by mesothelial cells,

Abbreviations: AAO, ascending aorta; A/G, albumin/globulin ratio; ALB, albumin; AOR, aortic root; AUC, areas under the curve; CA125, carbohydrate antigen 125; CHF, chronic heart failure; DBP, diastolic blood pressure; GLB, globulin; hsCRP, high-sensitivity C-reactive protein; IVSd, interventricular septum depth; LA, left atrium; LVDd, left ventricular diastolic dimension; LVEF, left ventricular ejection fraction; LVPWd, left ventricular posterior wall depth; MeT-5A, human mesothelial cell line; M/F, male/female; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association classes; ROC, receiver operator characteristic; RT-PCR, reverse transcription polymerase chain reaction; RVDd, right ventricular diastolic dimension; SBP, systolic blood pressure; SCE, serous cavity effusion; SOD, superoxide dismutase; TP, total protein.

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such as pericardium, pleura, peritoneum and Müllerian epithelium in response to various stimuli, including mechanical stress, oxidative stress and inflammation [3,4,7,9]. Under the condition of serous cavity effusion (SCE), the production of CA125 synthesized by mesothelial cells may be influenced by mechanical extension. We previously raised the hypothesis that SCE and inflammatory stimuli might initiate CA125 synthesis in CHF [10]. Meanwhile, Miñana G et al. has found that SCE and systemic inflammatory activity are interrelated pathways and that CA125 might be a surrogate for both processes [11]. Nevertheless, the clinical significance of CA125 remains unclear.

In this study, we evaluated the potential clinical application of CA125 elevation in patients with cardiovascular disease. In addition, we further explored the CA125 synthesis on human mesothelial cell line (MeT-5A) with mechanical stress.

Materials and methods

Ethics statement

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University. Informed written consent was obtained from each participant.

Study population and data collection

Total 216 patients who had cardiovascular diseases with edema and/or dyspnea and were admitted between January 2008 and July 2012 to the cardiology department of Sun Yat-sen Memorial Hospital for hospitalizations with or without a history of CHF were screened for possible enrollment into this study. Patients who were diagnosed as acute coronary syndrome, neoplastic disease, cirrhotic hepatic disease, acute or chronic inflammatory disease, severe chronic renal failure, infectious disease, nephrotic syndrome,and ovary disease/gynecological disease were excluded from the analysis. In addition, anyone who had been receiving treatment with steroids, cyclosporine, methotrexate or other immunosuppressive agents was also excluded. Total 191 patients (53% male and 47% female; median age 72 years old) were included into final analysis. In all enrolled patients, 57% patients were diagnosed as CHF, and 34% patients were in the presence of SCE. A flow chart of patient enrollment and characteristics was presented Fig. 1.

Demographic, clinical, and physical examination for each patient were recorded. These included age, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate.

Measurement of serum CA125, N-terminal pro-brain natriuretic peptide (NT-proBNP) and superoxide dismutase (SOD)

Blood samples were collected into EDTA tubes at room temperature. Serum CA125 levels were determined with the immunoassay kits (CA125 AXSYM, Abbott immunoenzymatic kit, Abbott Laboratories, Abbott Park, IL). The upper normal limit of CA125 is 35 U/mL. Serum NT-proBNP levels were measured with the electrochemiluminescence immunoassay (Elecsys® proBNP assay, Roche Diagnostics Corporation; Indianapolis, Ind). Plasma and erythrocyte SOD activity was estimated using an assay kit (Cayman Chemical, Ann Arbor, MI, USA), and the absorbance at 450 nm was measured with a Wallac Victor 2 multilabel counter (Perkin Elmer Life Sciences, Turka, Finland) [12].

Biochemical test of blood samples

Laboratory parameters including high-sensitivity C-reactive protein (hsCRP), total protein (TP), albumin (ALB), and globulin (GLB) were measured using blood samples drawn by venipuncture after at least 10 h of overnight fasting. Serum samples were measured by a standardized and certified program using automatic biochemical analyzer (7170A, HITACHI, Japan).

Echocardiographic evaluation

All patients underwent echocardiography within 4 h of admission to assess cardiac function. The echocardiographic examination was carried out on a 2-dimensional Doppler (Vivid 3®, GE VingMed Ultrasound; Haifa, Israel) using a 2.5-MHz transducer. Echocardiographic parameters included left ventricular ejection fraction (LVEF), aortic root (AOR), ascending aorta (AO), left atrium (LA), right ventricular diastolic dimension (RVDd), interventricular septum depth (IVSd), left ventricular diastolic dimension (LVDd), and left ventricular posterior wall depth (LVPWd) were measured.

SCE evaluation

Patients underwent chest radiography,chest ultrasound and abdominal ultrasound. Written informed consent was obtained from each

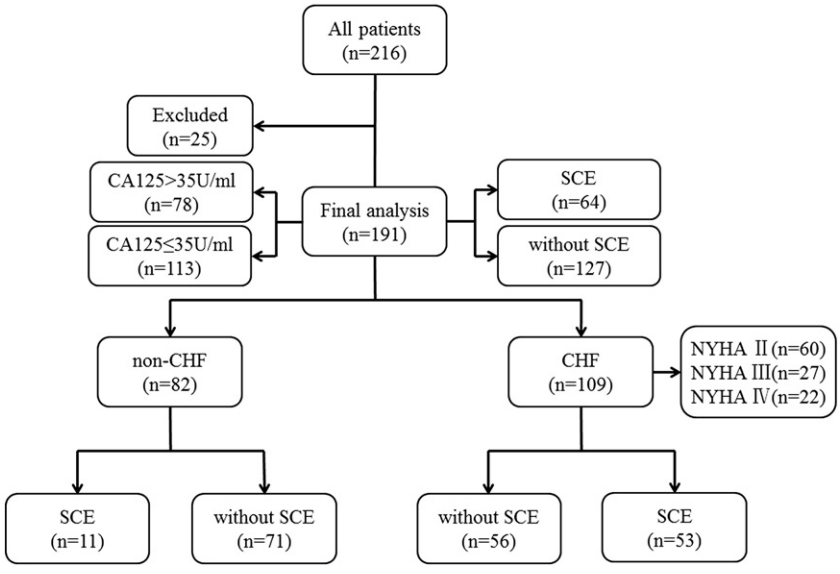

Fig. 1. Flow chart of patient characteristics. CA125, carbohydrate antigen 125; CHF, chronic heart failure; NYHA, New York Heart Association classes; SCE, serous cavity effusion.