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ORIGINAL ARTICLE

Prognostic Value of Plasma Ghrelin in Predicting the Outcome of Patients with Chronic Heart Failure

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Background and Aims. Ghrelin is an endogenous ligand of the growth hormone (GH) secretagogue receptor and is closely associated with chronic heart failure (CHF). We undertook this study to investigate the relevance of ghrelin in CHF prognosis.

Methods. A total of 145 in-patients with CHF in NYHA class II, III or IV despite optimized therapy were prospectively included in the study, grouped according to NYHA class and compared with 55 healthy control subjects. Ghrelin and N-terminal pro-B-type natriuretic peptide (Nt pro-BNP) were measured in plasma by ELISA. Echocardiographic information was also measured, including left atrial dimension, left ventricular end-diastolic diameter, LV volume and left ventricular ejection fraction (LVEF). Patients were followed for 2 years or until major adverse cardiac events.

Results. Plasma ghrelin levels were significantly lower in patients with CHF than in control subjects ($p = 0.014$). In addition, plasma ghrelin levels differed significantly with the severity of CHF. Notably, survival analysis showed that high ghrelin levels were an indicator of a favorable prognosis for CHF. Our results also showed that ghrelin correlated inversely with plasma Nt pro-BNP levels ($r = -0.562$, $p < 0.001$) and positively with LVEF ($r = 0.620$, $p < 0.001$) in patients with CHF. Furthermore, multivariate analysis showed that ghrelin levels were independently associated with adverse cardiac events (hazard ratio: 0.72; 95% CI: 0.64–0.81, $p = 0.03$).

Conclusions. Ghrelin is a new biomarker of CHF severity as well as a new prognostic predictor for patients with CHF. Future experimental and clinical studies are warranted to evaluate ghrelin as a novel prognostic tool and for its therapeutic potential in patients with CHF.

Key Words: Chronic heart failure, Cardiovascular active peptide, Ghrelin, Prognosis.

Introduction

Chronic heart failure (CHF) is a prevalent and morbid chronic illness. According to the European Society of Cardiology and the American Heart Association, CHF affects approximately 15 million Europeans and >5 million Americans (1,2). In the Chinese population, 2 million persons have had a myocardial infarction, 4.2 million have heart failure, 5 million have pulmonary heart disease, 2.5 million have rheumatic heart disease, and 2 million have congenital heart disease (3). This morbid illness carries a very poor prognosis and leads to frequent hospitalizations or deaths. Repeated hospitalization for CHF is a heavy burden to both the patient and the healthcare system. About 3 million Chinese persons die from cardiovascular disease annually, which accounts for 41% of deaths from any cause and is the leading cause of death in China. The increase in mortality in rural residents is greater than that in urban citizens (3). For years, investigators have strived to take measures to reduce hospitalization and mortality rates of CHF patients. Despite these efforts, recent reports indicated that re-hospitalization and mortality rates remain persistently high without any improvement over the past several years. Thus, this issue is obviously worth more attention.

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Ghrelin, a 28-amino acid peptide, was first reported by Kojima in rat and human stomachs in 1999 (4). As the endogenous ligand of the growth hormone secretagogue receptor (GHS-R), ghrelin was initially identified as a strong stimulant for the release of growth hormone (GH) (5). Interestingly, ghrelin and its receptors widely exist in the cardiovascular system. Iglesias et al. observed the expression of ghrelin mRNA in a cultured HL-1 cell line by RT-PCR, the expression of ghrelin peptide in HL-1 and human cardiomyocytes by immunohistochemistry, and in the culture medium of these cells by radioimmunoassay (6), suggesting that ghrelin may exert paracrine/autocrine effects in the cardiovascular system. Increasing evidence has demonstrated that ghrelin is closely associated with CHF. In healthy volunteers and patients with CHF, ghrelin can reduce peripheral vascular resistance, resulting in an increase in cardiac index and stroke volume index (7,8). Ghrelin can also improve ventricular remodeling (9,10), reduce cardiac injury induced by ischemia/reperfusion (I/R) (11) and isoprenaline (12), and reduce infarct size (13). *In vitro*, ghrelin reduces inotropism (14,15) and lusitropism (15) and protects cardiomyocytes from apoptosis (16). In addition, GH is indispensable for the maintenance of heart structure and function. Thus, ghrelin has an indirect cardioprotective effect.

Based on these findings, we speculated that ghrelin levels might change before or after heart failure. The fluctuation of ghrelin is likely to correlate with the prognosis of CHF and we decided to investigate the hypothesis that ghrelin acts as a prognostic marker for CHF. This may occur in relation to N-terminal pro-B-type natriuretic peptide (Nt pro-BNP), a marker already used to predict the readmission rates of CHF patients (17). Echocardiographic parameters such as left ventricular ejection fraction (LVEF) are also important when considering CHF patients' prognosis, with some suggestion that LVEF may also predict CHF outcome (18). An additional prognostic marker would make it easier to target the treatment for CHF and should help improving patients' outcome.

At present, no data are available concerning the prognostic value of ghrelin in patients with CHF. Therefore, the aim of this study was to investigate the prognostic value of ghrelin in diagnosing CHF.

Patients and Methods

Study Design

In this prospective cohort study, correlation of plasma ghrelin with CHF prognosis was estimated by measuring the incidence of major adverse cardiac events (e.g., death from all causes, CHF-related death and readmission for CHF and malignant arrhythmia according to dynamic electrocardiogram), which was evaluated by direct clinical examination from an outpatient visit every month, an inpatient visit every 6 months, using a follow-up form and phone calls once a month, or by direct interrogation of the patients' relatives.

Patients

One hundred and forty-five patients with CHF (83 males and 62 females, mean age 69.6 ± 23.8 years, range 31–82 years) in the Weifang People's Hospital between January and July 2009 were included in this study. Included patients were diagnosed with CHF for at least 1 year and were persistently in New York Heart Association classification (NYHA) class II, III or IV despite optimized medical therapy. Patients with acute heart failure were excluded. Patients were divided into three subgroups by NYHA class. Patients with one or more of the following conditions were excluded: a) the presence of active infection or gastric ulcer; b) recent antineoplastic therapy such as chemotherapy, radiation therapy or surgery; c) other primary cachectic states such as thyroid disease or severe liver disease; and d) chronic renal impairment. Clinical follow-up was performed for 2 years or until occurrence of major adverse cardiac events, with a mean of 384 ± 254 days. All patients received optimal pharmacological treatments for CHF tailored to their specific condition to optimize their survival. In addition, patients also received treatments required by their comorbidities (hypertension, diabetes, etc), according to the guidelines for CHF in adults (19).

This study included 55 healthy control subjects (30 males and 25 females, mean age 67.1 ± 19.5, range 35–80 years). Healthy control subjects were recruited from healthy hospital personnel without recent body weight loss or gain; they had no acute or chronic diseases and no regular medication.

This study was approved by the ethics committee of the Weifang People's Hospital, Weifang (China) and was conducted in accordance with good clinical practice guidelines and in line with the Declaration of Helsinki. All participants provided written informed consent.

Measurements

Sampling and Experimental Methods

Blood samples were taken from patients with CHF from the antecubital vein between 7:00 AM and 8:00 AM on the day of admission before medication, after overnight fasting because plasma ghrelin levels have been shown to be altered by food intake (20). The blood was immediately transferred into a chilled glass tube containing Na_2EDTA (1 mg/mL) and aprotinin (500 U/mL), then immediately centrifuged at 1500 g for 15 min at 4°C. Plasma samples were frozen and stored at −70°C and were extracted before assay. Ghrelin plasma levels were measured using an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions (Phoenix Biotech, Beijing, China). No significant cross-reactivity with other proteins was observed. Intra-assay variation of ghrelin