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Translational

The impact of an inverse correlation between plasma B-type natriuretic peptide levels and insulin resistance on the diabetic condition in patients with heart failure

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ABSTRACT

Background. A diabetic state is causally related to heart failure (HF); therefore, there should be a close correlation between the severity of diabetes and HF. However, a direct relationship between these conditions has rarely been reported and remains unclear. This study was designed to precisely examine this relationship, taking into consideration the possible association between natriuretic peptide (NP) levels and insulin resistance.

Material and methods. We examined various hemodynamic parameters and simultaneously performed blood biochemical analyses of consecutive patients who underwent cardiac catheterization at our institution (n = 840).

Results. Simple regression analyses showed that hemoglobin A1c (HbA1c) levels were not significantly changed by the left ventricular end-diastolic pressure (LVEDP) and left ventricular ejection fraction (LVEF), which were correlated with a low cardiac index. Rather, there was a negative correlation between the HbA1c levels and plasma BNP levels as a marker of HF. A multivariate analysis showed no correlations between the HbA1c levels and cardiac functional parameters (LVEDP, LVEF or the plasma BNP levels), suggesting that the trend toward high HbA1c levels in HF cases is likely to be limited for unknown reasons. To search for an explanation of this finding, we examined the potential biological interactions between BNP and insulin resistance. A multivariate analysis revealed that

Abbreviations: AF, atrial fibrillation; ANOVA, one-way analysis of variance; ANP, A-type natriuretic peptide; BMI, body mass index; BNP, B-type natriuretic peptide; CAPD, continuous ambulatory peritoneal; cGK, c-GMP-dependent protein kinase; c-GMP, cyclic guanosine monophosphate; CI, cardiac index; CSA, coronary spastic angina; DBP, diastolic blood pressure; HD, hemodialysis; HIF-1α, hypoxia-inducible factor; HF, heart failure; HOMA-IR, homeostasis model assessment-insulin resistance; HTN, hypertension; IHD, ischemic heart disease; IRI, immunoreactive insulin; Log BNP, logarithmic BNP; Log HOMA-IR, logarithmic HOMA-IR; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; NEP, endopeptidase; NP, natriuretic peptide; RAAS, renin–angiotensin aldosterone system; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SBP, systolic blood pressure; s-Cr, serum creatinine.

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the plasma BNP levels were positively correlated with age, creatinine levels and LVEDP and inversely correlated with the male gender, body mass index and HOMA-IR (homeostasis model assessment-insulin resistance) ($P < 0.001$, respectively), but not HbA1c levels. This analysis indicated a close correlation between plasma BNP levels and insulin effectiveness in HF.

Conclusions. HF and diabetes tend to worsen with each other; however, the appearance of an association between them was likely blunted due to the considerable effect of NP in counteracting insulin resistance, even during the metabolically harmful condition of HF.

1. Introduction

Diabetes is often associated with hypertension, ischemic heart disease (IHD) and chronic kidney disease, all of which are major risk factors for heart failure (HF) [1]. The presence of diabetes markedly increases the likelihood of HF and results in worse outcomes for patients with HF [2,3]. Furthermore, the Framingham Study firmly established an epidemiological link between diabetes and HF [4], and similar findings have since been noted in a number of other studies [5,6]. Therefore, there is no doubt that diabetes is a critical risk factor for HF in the future. Conversely, the onset of HF is an independent risk factor for developing or worsening diabetes [7].

The pathophysiology of HF is complex and includes a variety of underlying mechanisms. Among these elements, neurohumoral factors, such as the renin–angiotensin aldosterone system (RAAS), sympathetic nervous system and others, deeply contribute to the pathophysiology of HF [8]. Oxidative stress is also important for the progression of cardiac remodeling, which leads to HF. Many studies have recognized that remodeling stimuli, such as mechanical strain and the level of tumor necrosis factor-α, may increase the formation of reactive oxygen species (ROS) in the myocardium [9,10]. On the other hand, the pathophysiology of diabetes is also very complicated, although some of its underlying mechanisms appear to be similar to those of HF. For example, the RAAS, sympathetic nervous system and oxidative stress also each contribute to the pathogenesis of diabetes [11]. Furthermore, cardiac function subsequently deteriorates as a result of increased atherosclerosis and myocardial damage caused by diabetic microangiopathy. Therefore, it is reasonable to speculate that diabetes is associated with the deterioration of HF.

To the best of our knowledge, few reports have shown a close correlation between the HbA1c level and the current degree of HF as evaluated by hemodynamic and other parameters. We suppose that this may be a paradox of the relationship between diabetes and HF in that the relationship between diabetes and the future onset of HF may be different from the relationship between diabetes and the current degree of HF. Importantly, this information would be useful to resolve various questions pertaining to the association between energy metabolism and HF, and there may be compensatory mechanism(s) involved in the pathophysiology of HF that could potentially rescue metabolic abnormalities, including glucose intolerance and reduced lipid catabolic activity.

A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), also known as atrial and brain natriuretic peptides, respectively, are cardiac hormones with a wide range of potent biological effects, including vasodilation, natriuresis and inhibition of the RAAS and sympathetic nervous system. BNP is selectively secreted from the ventricles, and the magnitude of this secretion varies as a function of the severity of HF [12]. We and others have previously shown that ANP and BNP are anti-inflammatory hormones; the infusion of human ANP (carperitide) is useful for improving hemodynamics as well as inhibiting ROS production in patients with HF [13]. Furthermore, an important report using BNP transgenic mice revealed that BNP is a metabolic regulator by demonstrating that the natriuretic peptide (NP)/cyclic guanosine monophosphate (c-GMP)-dependent protein kinase (cGK) cascade promotes muscle mitochondrial biogenesis and lipid oxidation, thus preventing obesity and glucose intolerance [14]. However, the effects of NP on energy metabolism have not yet been clearly proven or elucidated in humans because the only disease related to high NP levels is HF, and many other humoral factors associated with HF may cause the deterioration of glucose and catabolic lipid metabolism. Hence, the favorable actions of NP on energy metabolism may be hidden or outstripped by these other factors.

We continue to believe in the pluripotency of endogenous NP secreted from the failing heart and herein hypothesize that NP counteracts both hemodynamic deterioration and the development of metabolic abnormalities in HF. In this study, we examined the possible hidden actions of NP, especially on glucose metabolism, in patients with cardiovascular disease using common indicators, including hemoglobin A1c (HbA1c) levels, homeostasis model assessment-insulin resistance (HOMA-IR) as a marker of insulin resistance, body mass index (BMI) and plasma BNP levels.

2. Material and Methods

2.1. Study Patients

The study population consisted of 840 consecutive patients admitted to the Jikei University Hospital from February 2012 to July 2014 in whom left heart catheterization, including hemodynamic measurements, coronary angiography (n = 840) and left ventriculography (n = 797), and blood sampling tests of the plasma BNP level were performed and reviewed. The insulin and serum glucose levels were also measured in each patient. Among them, right heart catheterization with a Swan–Ganz catheter was performed in addition to left heart catheterization (n = 218). Individuals requiring an urgent catheter intervention for acute coronary syndrome were excluded from this study because the plasma BNP level rapidly and considerably changes within the acute phase of acute myocardial infarction [15]. We also excluded patients with type 1 diabetes mellitus and those receiving insulin therapy. The subjects' baseline characteristics, including clinical parameters and biochemical data, were collected retrospectively from their medical records, and the