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Potent influence of obesity on suppression of plasma B-type natriuretic peptide levels in patients with acute heart failure: An approach using covariance structure analysis

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ABSTRACT

Background: Plasma B-type natriuretic peptide (BNP) levels may vary widely among patients with similar stages of heart failure, in whom obesity might be the only factor reducing plasma BNP levels. We investigated the effect of obesity and body mass index (BMI) on plasma BNP levels using serial measurements before and after treatment (pre- and post-BNP and pre- and post-BMI) in patients with acute heart failure.
Methods: Multiple regression analysis and covariance structure analysis were performed to study the interactions between clinical factors in 372 patients. The pre-BMI was shown as a combination index of obesity and fluid accumulation, whereas the post-BMI was a conventional index of obesity.
Results: There was a significant inverse correlation between BMI and BNP in each condition before and after treatment for heart failure. The direct significant associations of the log pre-BNP with the log post-BNP (β: 0.387), the post-BMI (β: −0.043), and the pre-BMI (β: 0.030) were analyzed by using structural equation modeling. The post-BMI was inversely correlated, but importantly, the pre-BMI was positively correlated, with the log pre-BNP, because the pre-BMI probably entailed an element of fluid accumulation. There were few patients with extremely high levels of pre-BNP among those with high post-BMI, due to suppressed secretion of BNP.
Conclusions: The low plasma BNP levels in true obesity patients with acute heart failure are of concern, because plasma BNP cannot increase in such patients.

1. Introduction

B-type or brain natriuretic peptide (BNP) is one of the natriuretic peptides and is widely used for diagnosis and predicting prognosis in heart failure [1–5]. Although the plasma BNP level is thought to be a good biochemical marker of heart failure, the levels may vary widely among patients in whom the severity of heart failure is clinically in the same range [6]. The wide range of plasma BNP levels may be explained by a number of factors contributing to the secretion of BNP, which differ among individuals and vary according to conditions. Among the factors contributing to plasma BNP levels, ventricular hemodynamic overload significantly stimulates the secretion of BNP; combined ventricular dysfunction and associated body fluid overload are the major stimulating factors [2,3]. Volume overload induced by renal dysfunction is another major contributor to increased plasma BNP levels. Aging and male sex also influence plasma BNP levels [7]. Neurohumoral factors, the renin–angiotensin–aldosterone (RAA) system, endothelin-1, oxidative stress, inflammatory cytokines, and others can increase plasma BNP levels [8–10]. The conditions associated with these factors finely modulate plasma BNP levels according to the individual. In circumstances such as these, it is interesting to note that the above factors are almost all positive regulators of plasma BNP levels; the negative regulatory factors are rare. Fat accumulation/obesity may be the only applicable factor decreasing plasma BNP levels. However, the true impact of obesity on plasma BNP levels has not yet been clarified. It is uncertain whether obesity per se has a major impact on plasma BNP levels.

It is possible that the main cause of the wide range of plasma BNP levels in clinically similar stages of heart failure may be the result of habitus, with obesity or slenderness contributing to the development of heart failure. Plasma BNP levels are likely to increase in slenderness but not in obesity among patients with heart failure. To precisely determine the effect of obesity on plasma BNP levels, it is necessary to identify a suitable marker of fat accumulation/obesity during heart failure.

Body mass index (BMI) is the simplest and best marker of fat accumulation or obesity in general; however, the BMI of a patient with heart failure represents not only fat accumulation/obesity but also body fluid excess due to heart failure, because BMI is calculated as

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body weight (kg) divided by the square of the height (cm). Fluid accumulation due to cardiac dysfunction would further augment cardiac overload and thereafter tends to increase plasma BNP levels, whereas obesity itself decreases plasma BNP levels. Therefore, the BMI before treatment (pre-BMI) was used as a combined index of obesity and fluid accumulation for descriptive purposes in this study, whereas the BMI after treatment (post-BMI) was an index of obesity, as conventionally applied. To the best of our knowledge, no study has focused on the true effect of obesity on plasma BNP levels during the "wet" period by using the BMI during the "dry" period.

Another impediment to this type of analysis is statistical computing intractableness. Theoretically, the secretion of BNP is influenced by many factors at all times. It is thus quite logical to simultaneously include every possible factor including fluid accumulation into the same analysis. It might thus be preferable in this study to use BMI before treatment as a component of the same equation, because it partially represents fluid accumulation. However, the BMI before treatment would surely be confounded with the BMI after treatment, and therefore, multiple regression analysis cannot be applied simultaneously. Furthermore, many other clinical factors related to each other would simultaneously influence plasma BNP levels. Simultaneous comparison of the influence of possible factors affecting plasma BNP levels requires highly technical computing; covariance structure analysis or data-mining technology would be required for this complex statistical analysis.

We investigated the impact of obesity on plasma BNP levels by using a path analysis based on covariance structure analysis in patients admitted to our institution with acute heart failure. Among hemodynamic parameters and blood samples measured serially during treatment, we used two data points: before and after the treatment of acute heart failure.

2. Methods

2.1. Study patients

The study population consisted of 372 consecutive patients hospitalized due to acute heart failure between 2012 and 2014 at Jikei University Hospital. The sampling data included BMI and plasma BNP levels on admission before treatment, and after intensive treatment for acute heart failure. We excluded patients with acute myocardial infarction (AMI), because plasma BNP levels noticeably and rapidly increase during the 24 h after onset of AMI in a monophasic manner, then transiently decrease, possibly followed by another increase two to three days after onset (depending on the degree of ventricular remodeling), thus resulting in a biphasic profile [11]. Patients who required emergency surgery, including coronary artery bypass and noncardiac surgery, during the period between the collection of the first and second plasma BNP samples were also excluded. The study protocol (27–243 [8128]) was approved by the Ethics Committee of The Jikei University School of Medicine, and we complied with the routine ethical regulations of our institution. This is a retrospective study and informed consent could not be obtained from each patient. Instead of obtaining informed consent from each patient, we posted a notice about the study design and contact information at a public location in our institution.

2.2. Diagnosis of acute heart failure

Acute heart failure was diagnosed according to the guidelines for the treatment of acute heart failure published by the Japanese Circulation Society. Patients with heart failure symptoms (New York Heart Association [NYHA] functional class II to IV) underwent several examinations (blood gas analysis, blood sampling, electrocardiogram, plain chest radiography, and echocardiogram), and agreed to be admitted to our hospital.

2.3. Treatment of acute heart failure

The patients were treated with drugs, such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, beta blockers, nitrates, carperitide (human atrial natriuretic peptide), and, if necessary, catecholamines and mechanical support such as respirators, intra-aortic balloon pumping, or percutaneous cardiopulmonary support.

2.4. Blood sampling and measurement of plasma BNP and other levels

We collected data for plasma BNP and other levels. The first sample was obtained immediately after admission and before intensive treatment (pre-BNP). In each case, the second sample was collected when the clinical symptoms of acute heart failure improved and the patient's condition stabilized. Whole blood (5 mL) was collected in tubes containing potassium ethylenediaminetetraacetic acid (EDTA) (1 mg/mL blood). Plasma BNP was measured with a rapid enzyme-linked immunosorbent assay (nonextracted) using an antibody to human BNP (Shionogi Co. Ltd., Tokyo, Japan). Serum biochemical analyses including creatinine (Cr) were performed in a central laboratory in our hospital during the study.

2.5. Echocardiographic examination and other measurements

An echocardiographic examination was performed in all patients by three expert cardiologists, and left ventricular ejection fraction (LVEF) was used as a marker of systolic dysfunction. BMI was calculated on the basis of height and weight on admission and after therapy.

2.6. Statistical analysis

Continuous variables were expressed as the means ± standard deviation (SD) or medians. The correlation between two factors was expressed as Spearman's correlation coefficient and single regression analysis. Multiple regression analysis was performed when multiple values were compared. In the multivariate analysis, natural logarithmic conversion (log) was performed on the BNP values, because they were not normally distributed. A chi-squared analysis was applied for a test for comparison between two groups, if it is necessary. Statistical analyses were performed using SPSS Statistics version 23.0 (SPSS Inc., Chicago, IL, USA), and differences were considered to be statistically significant for P-values < 0.05.

Path analysis was used to investigate the relation between clinical factors in this study population and especially to survey probable causal effects on the plasma BNP levels before the treatment. Path analysis was performed with IBM SPSS AMOS version 23 (Amos Development Corporation, Meadville, PA, USA) [12]. The obtained structural equation models were tested and confirmed at the significance level for P-values < 0.05. The causality model defines some hierarchical regression models between clinical factors and the plasma BNP levels. Paths between variables are drawn from independent to dependent variables with directional arrow for every regression model (arrowhead on one end only). A two-way arrow between two variables indicates the correlation between these two variables. For every regression, the total variance in dependent variable is theorized to be caused either by independent variables of the model or by extraneous variables (e). Each path has a coefficient showing the standardized coefficient of regressing independent variable on dependent variable of the relevant path. The indirect effect was determined by multiplying the path coefficients of intervening variables.