Dynamic Changes in Brain Natriuretic Peptide Concentration in Early Acute Myocardial Infarction and Its Diagnostic Value for Heart Failure (Postprint)

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Abstract

Objective: To investigate the dynamic evolution pattern of brain natriuretic peptide (BNP) concentration in the early stage of acute myocardial infarction (AMI) and the diagnostic value of BNP concentration at each time point for concurrent heart failure. Methods: Patients with AMI who presented to the Department of Cardiology, Guangzhou General Hospital of Guangzhou Military Command from January 1, 2016 to July 31, 2016 and underwent emergency percutaneous coronary intervention (PCI) within 12 h of onset were enrolled. Venous blood BNP concentration was measured at bedside within 1 h after PCI and at 12, 20, 24, and 48 h after onset, and cardiac function diagnosis at each time point was recorded. Patients were divided into a peak BNP elevation group (>400 pg/mL) and a peak BNP roughly normal group ($ $400 pg/mL) based on whether the peak BNP concentration within 48 h exceeded 400 pg/mL. Results: A total of 70 patients were enrolled in this study. BNP exhibited a single-peak pattern of initial increase followed by decrease within 48 h after onset. Friedman M test indicated statistically significant differences in BNP concentration among the five time points (2=141.7, P<0.05). Pairwise comparisons revealed no statistically significant difference in BNP concentration between 20 h and 24 h after onset (2=0.173, P>0.05), while all other pairwise comparisons showed statistical significance (P<0.05). The time to peak was 20-24 h after onset. Compared with the peak BNP roughly normal group (n=47), the peak BNP elevation group (n=23) had older age, lower body mass index, longer reperfusion time, higher proportion of anterior wall myocardial infarction, and higher incidence of pulmonary infection during hospitalization, with all differences being statistically significant (P<0.05). Binary logistic regression showed that age, body mass index, and anterior wall myocardial infarction were independently

associated with elevated peak BNP concentration. ROC curve analysis indicated that BNP concentration within 1 h after PCI had no diagnostic value for heart failure (P>0.05), whereas BNP at 12, 20, 24, and 48 h after onset had diagnostic value for heart failure (P<0.05), with areas under the curve of 0.860, 0.786, 0.768, and 0.863, respectively, and optimal cutoff values of 156.5, 313.7, 240.9, and 285.9 pg/mL, respectively. Conclusion: In the early stage of AMI, BNP shows a single-peak pattern of initial rise followed by decline, peaking at 20-24 h after onset, and the diagnostic value of BNP at different time points after onset for concurrent heart failure varies.

Full Text

Preamble

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Abstract

Objective To explore the dynamic changes in brain natriuretic peptide (BNP) concentration and the diagnostic value of BNP for heart failure at different time points in the early phase of acute myocardial infarction (AMI). **Methods** AMI patients admitted to the Department of Cardiology at Guangzhou General Hospital of Guangzhou Military Command between January 1, 2016 and July 31, 2016, who underwent emergency percutaneous coronary intervention (PCI) within 12 hours of symptom onset, were enrolled. Bedside measurements of venous blood BNP concentration were performed within 1 hour after PCI and at 12, 20, 24, and 48 hours after onset, with cardiac function diagnosis recorded at each time point. Patients were divided into a high peak BNP group (>400 pg/mL) and a normal peak BNP group ($ 400*pg/mL*)*based*on*whether*their*peak*BNP*concentration*within*48*hours*exceeded*400*pg/mL.* ***Results**A*total*of*70*patients*were*enrolled.*BNP*concentration*within*48*hours*after*AMI*onset*showed*a*unim = 141.7, P < 0.05). Pairwise comparisons revealed no significant difference between BNP concentrations at 20 hours and 24 hours (^{2} = 0.173, P > 0.05), while all other pairwise comparisons showed statistical significance (P < 0.05). The peak occurred at 20-24 hours after onset. Compared with the normal peak BNP group (n = 47), the high peak BNP group (n = 23) had significantly older age, lower body mass index (BMI), longer reperfusion time, higher proportion of anterior wall myocardial infarction, and higher incidence of pulmonary infection during hospitalization (P < 0.05). Binary logistic regression showed that age, BMI, and anterior wall myocardial infarction were independently associated with elevated peak BNP concentration. ROC curve analysis indicated that BNP concentration within 1 hour after emergency PCI had no diagnostic value for heart failure (P > 0.05), while BNP concentrations at 12, 20, 24, and 48 hours after onset had significant diagnostic value (P < 0.05),

with areas under the curve of 0.860, 0.786, 0.768, and 0.863, respectively, and optimal cutoff values of 156.5, 313.7, 240.9, and 285.9 pg/mL. **Conclusions** BNP concentration in the early phase of AMI shows a unimodal pattern of initial increase followed by decrease, peaking at 20-24 hours after onset. The diagnostic value of BNP concentrations for heart failure varies across different time points.

Keywords: acute myocardial infarction; percutaneous coronary intervention; brain natriuretic peptide; heart failure

Introduction

The widespread application of emergency percutaneous coronary intervention (PCI) has significantly reduced mortality in patients with acute myocardial infarction (AMI) [1-2]. However, postoperative heart failure (HF) severely compromises the benefits of revascularization [3-4]. Early identification of HF after AMI within an appropriate time window and timely intervention are crucial for improving patient prognosis [5].

Brain natriuretic peptide (BNP) is currently the gold standard blood biomarker for diagnosing acute HF [6]. It is massively synthesized and secreted during myocardial ischemia, increased ventricular volume load, and elevated wall tension [7], and correlates with HF severity, serving as an objective indicator for HF diagnosis and prognosis assessment. Few studies have reported on the pattern of BNP concentration changes in the early phase of AMI and factors influencing peak BNP concentration. Whether early BNP concentration after AMI correlates with HF remains controversial [8], and whether the diagnostic value of BNP concentration for HF at this stage is related to detection timing remains unclear. Therefore, this study aimed to explore the dynamic evolution of early BNP concentration in AMI patients undergoing emergency PCI, identify major factors influencing peak BNP concentration, evaluate the diagnostic value of BNP at different time points for acute HF, and determine the optimal time window and cutoff value for BNP in diagnosing HF after AMI.

1.1 Study Subjects

AMI patients admitted to the Department of Cardiology at Guangzhou General Hospital of Guangzhou Military Command between January 1, 2016 and July 31, 2016, who underwent emergency PCI, were selected as study subjects.

Inclusion criteria: Age $\geq$ 18 years; reperfusion time (symptom onset to balloon dilation) $<$ 12 hours; definite diagnosis of AMI; consent to participate in the study. AMI diagnosis followed the third universal definition of myocardial infarction [9].

Exclusion criteria: Patients with prior myocardial infarction; patients with chronic HF; patients with pulmonary hypertension, cor pulmonale, severe hepatic or renal insufficiency, or cerebrovascular diseases from any cause.

All enrolled patients received standardized secondary prevention therapy for coronary artery disease according to current AMI guidelines, with timely symptomatic treatment for complications such as pulmonary infection, atrial fibrillation, and HF.

1.2.1 General Data

General data including gender, age, body mass index (BMI), medical history (hypertension, diabetes, hyperlipidemia, angina, smoking), reperfusion time (symptom onset to balloon dilation), troponin I, estimated glomerular filtration rate (eGFR), and medication regimens during hospitalization were collected and recorded. eGFR was calculated using the modified MDRD formula [10]: eGFR $[\mathrm{mL}/(\mathrm{min} \cdot 1.73\mathrm{m}^2)] = 186 \times [\text{serum creatinine } (\ \mathrm{mol/L}) \times 0.0113]^{-1 \cdot 154} \times \mathrm{age}^{-0 \cdot 203} \times (0.742 \text{ if female}) \times (1.233 \text{ if Chinese})$.

Clinical cardiac function was assessed at each time point (within 1 hour after PCI, and at 12, 20, 24, and 48 hours after onset) to determine whether HF was present at that time. Diagnosis of acute HF in AMI patients was primarily based on clinical manifestations and physical examination [11]: new typical clinical manifestations of HF (such as fatigue, varying degrees of tachycardia, or gallop rhythm, with moist rales audible in the lower 1/2 lung fields); pulmonary congestion, pulmonary edema, or pleural effusion on chest X-ray; or cardiogenic shock.

1.2.2 BNP Detection

Peripheral venous blood samples were collected within 1 hour after PCI and at 12, 20, 24, and 48 hours after onset. Whole blood BNP concentration was rapidly measured at the bedside (designated as P1-P5) using immunofluorescence assay. Reagents and detection equipment were provided by Shenzhen MicroPoint Biotechnologies Co., Ltd. Vacuum blood collection tubes containing ethylenediaminetetraacetic acid (EDTA) were used as anticoagulants. Samples were tested at room temperature within 2 hours after collection, with results displayed within 15 minutes. The detection range was 5-5000 pg/mL.

1.2.3 Grouping Criteria

Peak BNP concentration for each patient was defined as the highest concentration within 48 hours after onset. Patients were divided into a high peak BNP group (BNP $>$ 400 pg/mL) and a normal peak BNP group (BNP $\leq$ 400 pg/mL) based on whether their peak BNP concentration exceeded 400 pg/mL.

1.3 Statistical Analysis

All data were analyzed using SPSS 20.0 software. Categorical data were expressed as n (%) and compared between groups using ^{2} test. Normally distributed continuous data were expressed as mean $\pm$ standard deviation and

compared using independent samples t-test. Non-normally distributed continuous data were expressed as median (Q1-Q3) and compared using Mann-Whitney U test. Differences in BNP concentrations across different time points were analyzed using Friedman M test. Logistic regression models were used to analyze independent factors associated with elevated peak BNP concentration, with odds ratios (OR) and 95% confidence intervals (CI) calculated. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic value of BNP at each time point for acute HF and to determine optimal cutoff values. $P < 0.05$ was considered statistically significant.

A total of 70 AMI patients meeting inclusion and exclusion criteria were enrolled, including 61 males and 9 females, with mean age 55.7 $\pm$ 12.4 years. Reperfusion time was 6.3 $\pm$ 2.9 hours from symptom onset, and the first BNP sampling time was 7.2 $\pm$ 2.8 hours from onset. There were 40 cases of acute anterior wall myocardial infarction and 30 cases of acute non-anterior wall myocardial infarction. Medical history included angina in 31 patients, hypertension in 22, diabetes in 20, hyperlipidemia in 40, and smoking in 55. Based on peak BNP levels, patients were divided into a high peak BNP group (n = 27) and a normal peak BNP group (n = 43).

2.1 Dynamic Evolution of BNP Concentration After AMI

BNP concentration within 1 hour after PCI (i.e., 7.2 $\pm$ 2.8 hours after onset) was 23.0 (5.0-60.2) pg/mL, then gradually increased to 114.4 (47.3-176.2) pg/mL at 12 hours, 281.0 (161.8-412.7) pg/mL at 20 hours, peaked at 306.5 (181.4-450.4) pg/mL at 24 hours, and subsequently decreased to 189.8 (102.2-380.0) pg/mL at 48 hours. BNP concentration within 48 hours after AMI onset showed an overall unimodal trend of initial increase followed by decrease. Friedman M test indicated statistically significant differences in BNP concentrations across the five time points ($^2 = 141.7$, $P < 0.05$). Pairwise comparisons revealed no significant difference between BNP concentrations at 20 hours and 24 hours ($^2 = 0.173$, $P > 0.05$), while all other pairwise comparisons showed statistical significance ($P < 0.05$). Therefore, BNP reached its peak concentration at 20-24 hours after AMI onset [Figure 1: see original paper].

2.2 Comparison of General Data Between High and Normal Peak BNP Groups

Compared with the normal peak BNP group, the high peak BNP group had significantly older age, lower BMI, longer reperfusion time, higher proportion of anterior wall AMI, and higher incidence of pulmonary infection during hospitalization ($P < 0.05$). No statistically significant differences were observed between groups in gender, eGFR, troponin I, AMI type, medical history (hypertension, diabetes, hyperlipidemia, angina, smoking), incidence of atrial fibrillation during hospitalization, or concomitant medications (digitalis, dopamine, β-blockers, ACEI/ARB) ($P > 0.05$,).

2.3 Factors Influencing Elevated Peak BNP

Binary logistic regression (forward method) analysis identified age (OR: 1.088, 95% CI: 1.026-1.153, P = 0.005), BMI (OR: 0.733, 95% CI: 0.579-0.929, P = 0.01), and anterior wall myocardial infarction (OR: 3.616, 95% CI: 1.005-13.016, P = 0.049) as independent influencing factors for elevated peak BNP concentration.

2.4 ROC Curve Analysis of BNP Diagnostic Value for HF at Each Time Point

ROC curve analysis showed that BNP concentration measured within 1 hour after PCI had no diagnostic value for HF at that time ($P > 0.05$). BNP concentrations at 12, 20, 24, and 48 hours after onset had diagnostic value for HF, with areas under the curve (AUC) all above 0.768 ($P < 0.001$). The optimal cutoff values for diagnosing HF at these time points were 156.50, 313.71, 240.91, and 285.89 pg/mL, respectively, with sensitivity above 75.0% and specificity above 50.0% for all time points ().

Discussion

Myocardial ischemia and necrosis after AMI lead to weakened contractility and decreased compliance, resulting in myocardial stretch, increased heart rate, and increased atrial and ventricular volume and wall tension load, which trigger explosive synthesis and secretion of BNP. Therefore, detecting BNP concentration after AMI has important clinical implications [12]. However, if tested too early, BNP may not have risen yet, increasing testing frequency and reducing efficiency. If tested too late, patients may already have clinical symptoms, delaying intervention, affecting prognosis, and increasing medical costs. Exploring the dynamic evolution of early BNP concentration after emergency PCI, factors influencing peak BNP concentration, and the diagnostic value of BNP at different time points for acute HF can improve BNP detection efficiency and provide evidence for early HF identification and timely initiation of anti-HF therapy.

This study found that BNP concentration increased slowly from AMI onset to within 1 hour after PCI, then accelerated, with the fastest increase between 12-20 hours, followed by slowed elevation between 20-24 hours, peaking at 24 hours and then gradually decreasing. This trend may be related to the unique synthesis and secretion mechanism of BNP after AMI. Previous studies have confirmed that only small amounts of BNP exist in normal individuals, stored as BNP precursor (proBNP) in atrial secretory granules, with circulating BNP stable below 10 pg/mL [13]. In early AMI, the increase in BNP mainly results from rapid cleavage and release of small amounts of proBNP from atrial secretory granules. Later, mainly due to uncoordinated contraction between infarcted and non-infarcted areas after myocardial necrosis, left ventricular end-diastolic pressure increases, stimulating massive synthesis and release of BNP from ventricles [14]. Therefore, BNP concentration elevation after AMI shows an initial slow

followed by rapid increase. Jin et al. [15] measured plasma BNP concentrations at 2, 4, 6, and 24 hours after onset in 40 AMI patients and found that BNP concentration increased with time, peaking at 24 hours (489.9 ± 244.73 pg/mL). Morita et al. [16] dynamically measured BNP concentrations within 7 days in 50 AMI patients and found two patterns: unimodal pattern peaking at 20.3 ± 1.5 hours (244 ± 45 pg/mL) and bimodal pattern with first peak at 19.5 ± 1.4 hours (382 ± 43 pg/mL) and second peak at day 5 ± 1 (416 ± 68 pg/mL). The time to peak in these studies is consistent with our findings, but peak concentrations differ, possibly due to variations in PCI treatment rates, study populations, and BNP detection methods. However, compared with Morita' s study, we only measured BNP within 48 hours, so whether a second peak occurs at 7 days or later remains unclear and warrants further investigation. The dynamic BNP curve suggests that BNP peaks at 20-24 hours after onset in AMI patients undergoing emergency PCI, and testing BNP within this time window may better reflect actual cardiac function and improve diagnostic efficiency.

When investigating factors influencing peak BNP concentration in early AMI, we found that advanced age and low BMI affected peak BNP. No similar studies have been reported previously, as most research focused on factors influencing baseline BNP concentration in normal or HF populations. Hamada and Harada et al. [17-18] respectively found that with increasing age in normal populations and those with decreased cardiac function, ventricular compliance decreases and cardiac reserve deteriorates, leading to elevated baseline BNP levels. Additionally, multiple studies [19-20] have shown an inverse correlation between BMI or obesity and plasma BNP concentration. Some scholars [21] believe this is because obese individuals have more adipose tissue, and natriuretic peptide receptors are distributed on adipocyte surfaces, resulting in higher natriuretic peptide receptor concentrations and faster BNP clearance, thus lower BNP levels. These studies demonstrate that elderly and low BMI patients have higher baseline BNP concentrations. Our study further demonstrates that advanced age and low BMI also affect the peak BNP concentration after AMI. Whether they influence peak BNP by affecting baseline BNP values or by influencing the magnitude of BNP elevation remains unknown and requires further investigation. Our study also found that anterior wall myocardial infarction affects peak BNP, possibly because the anterior wall plays a key role in cardiac pumping [22]. After anterior wall myocardial infarction, changes in wall mechanical tension are more pronounced than in inferior wall infarction, stimulating greater synthesis and secretion of BNP from ventricular myocytes. Therefore, BNP concentration is significantly higher in anterior wall AMI patients than in non-anterior wall AMI patients. Consequently, even with relatively good cardiac function, elderly, thin patients with anterior wall myocardial infarction may have relatively high BNP concentrations, while in young, obese patients with non-anterior wall myocardial infarction, HF should not be excluded based solely on non-elevated BNP to avoid missed diagnosis.

ROC curve analysis in this study revealed that BNP at 12, 20, 24, and 48 hours after onset could diagnose HF at those times, with different optimal cut-

off values, while BNP within 1 hour after PCI had no diagnostic value for HF. The mechanism of BNP elevation after AMI involves increased left ventricular end-diastolic pressure and atrial pressure after cardiac contractile function impairment, stimulating residual ischemic and hypoxic myocytes at the border between infarcted and non-infarcted areas to synthesize and secrete BNP [23]. This is a compensatory indicator of cardiac function that appears secondary to hemodynamic changes. Therefore, using BNP for early HF diagnosis in the ultra-early phase of AMI may have low diagnostic efficacy [24] and is prone to missed diagnosis. Clinicians should primarily rely on clinical evidence, closely observing symptoms and signs to assess cardiac function to avoid misdiagnosis or missed diagnosis. Moreover, since BNP shows dynamic evolution after AMI [25] and varies at different time points, clinical diagnosis of HF should combine clinical manifestations with reference to different cutoff values at different time points to accurately assess true cardiac function.

This study has limitations: the number of included cases was small; all enrolled patients received standard medical therapy, which may affect plasma BNP levels; and more accurate cardiac function assessment methods such as echocardiography and right heart catheterization were not performed at each time point in this study.

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Note: Figure translations are in progress. See original paper for figures.