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Transient Increase in Plasma Brain (B-Type) Natriuretic Peptide after Percutaneous Transluminal Coronary Angioplasty

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Summary

Background: Brain (B-type) natriuretic peptide (BNP) is known to be secreted predominantly from the myocardium. Brain natriuretic peptide plasma concentrations have been shown to be markedly increased in patients with acute myocardial infarction; however, plasma BNP response during episodes of myocardial ischemia has not been established.

Hypothesis: This study was designed to examine plasma BNP in patients with transient myocardial ischemia induced by inflation of a percutaneous transluminal coronary angioplasty (PTCA) balloon.

Methods: Thirty consecutive patients (26 men and 4 women; mean age 61 years) who underwent PTCA, and another 49 patients (39 men and 10 women; mean age 63 years) who underwent diagnostic coronary angiography were enrolled in this study. Serum BNP concentrations were assayed in all patients.

Results: Plasma BNP was increased significantly with a peak concentration of 66.1 ± 65.2 pg/ml 24 h after PTCA. Coronary angiography did not cause plasma BNP increase (immediately before 30.4 ± 29.0 pg/ml, 24 h after 33.7 ± 30.6 pg/ml). No significant differences were present in hemodynamic parameters measured immediately before and 24 h after PTCA.

Conclusion: Plasma BNP is increased by transient myocardial ischemia induced by PTCA.

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Introduction

Brain (B-type) natriuretic peptide (BNP), a second member of the natriuretic peptide family, has been isolated from porcine brain and has a remarkably similar sequence homology to atrial natriuretic peptide.[1] Since its discovery, BNP secretion and its physiologic activity have been gradually elucidated. Circulating BNP is believed to be a sensitive marker of ventricular overload, since BNP is synthesized and secreted primarily by myocardium during a period of increased work.[2,3] Several studies have shown plasma BNP elevations in patients with heart failure or ventricular hypertrophy.[4–7] Brain natriuretic peptide acts as an acutely responsive "emergency" cardiac hormone against ventricular overload.[8–10] Plasma BNP increases in the acute phase of myocardial infarction, which results in a rapid increase in ventricular load.[11–14] However, the response of plasma BNP in patients with angina pectoris, a condition characterized by transient myocardial ischemia, has not been established. Percutaneous transluminal coronary angioplasty (PTCA) is used widely for the treatment of ischemic heart disease, and transient myocardial ischemia is induced during inflation of the PTCA balloon. The present study was designed to examine plasma concentrations of BNP over a period of 4 days in patients undergoing PTCA in order to assess the response to transient myocardial ischemia.

Methods

Study Patients

Thirty consecutive patients (26 men 4 women, age range 32–79, mean age 61 ± 11 years), who underwent PTCA for angina pectoris, were included in this study. Percutaneous transluminal coronary angioplasty was performed to the left anterior descending artery in 14 patients, the left circumflex artery in 3 patients, and the right coronary artery in 7 patients. In six patients, the procedure was performed simultaneously in

two vessels. Left ventricular end-diastolic pressure in these 30 patients was 9.4 ± 4.4 mmHg (range 2–17 mmHg). The collateral circulation could be detected in only five patients undergoing PTCA during diagnostic coronary angiogram. Thirteen patients (43%) who underwent PTCA had a history of hypertension. A group of 49 patients (39 men and 10 women, age range 17–78, mean age 63 ± 11 years) who underwent diagnostic coronary angiography for angina pectoris served as controls. Twenty-one patients (43%) who underwent diagnostic coronary angiogram had a history of hypertension. Patients with renal failure, left bundle-branch block, permanent pacemaker, severe valvular disease, cardiomyopathy, any form of congenital heart disease, or change in medication during the study were excluded. This protocol was approved by the hospital ethics committee. All patients signed an informed consent prior to participating in the study.

Angioplasty Procedure

All patients were given ticlopidine and aspirin at a dose of 100 mg and 81 mg, respectively, twice daily from Day 2 before PTCA to 1 month after PTCA. Other cardiac medications, including calcium-channel blockers, angiotensin-converting enzyme inhibitors, nicorandil, and isosorbide dinitrate were administered at the discretion of the physician. During PTCA, dextran (100 ml/h) and isosorbide dinitrate (0.5–1.0 μg/kg/min) were infused intravenously following the administration of heparin (100 U/kg). A PTCA balloon, selected to match the diameter of the target vessel determined during coronary angiography, was inflated between 110 and 660 s until an adequate clinical result was obtained. Chest pain or discomfort and ST-segment change of ≥ 0.1 mV in ≥ two leads on standard electrocardiogram (ECG) were observed in all of the study patients. An average of 280 ml of iomeprol contrast medium (iode 400 mg/ml) was used.

Hemodynamic Study

A Swan-Ganz catheter was inserted via the femoral vein prior to PTCA and removed after 24 h. Right atrial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, and cardiac index were recorded. Cardiac index was measured in triplicate by thermodilution technique. Heart rate was monitored by continuous ECG. Arterial pressure was measured using a brachial cuff. All hemodynamic parameters were measured immediately before and 24 h after PTCA in all patients.

Coronary Angiography Procedure

After intravenous heparin (3000 U), baseline hemodynamic measurements and left ventriculography were performed using standard techniques. Coronary angiography was recorded in multiple angulated projections after an intracoronary administration of isosorbide dinitrate (5 mg) to visualize coronary artery stenosis. Abdominal aortography also was performed in 27 patients to evaluate aortoiliac atherosclerotic disease. An average of 180 ml of iomeprol was used as contrast medium.

Blood Sampling

Blood sampling was performed at 7:00 A.M. on the day of PTCA after an overnight fast, with the patient in the supine position, with samples obtained immediately before and after PTCA, and 4, 8, 12, 24, 36, 48, 72, and 96 h after the procedure. In the control patients who underwent diagnostic coronary angiography without PTCA, blood samples were obtained immediately before and 24 h after angiography. Blood samples were collected in ethylene diamine tetraacetic acid (EDTA)-coated tubes containing 500 IU/ml aprotinine, immediately centrifuged at 4°C, and then stored at −80°C until analysis.

Measurement of Brain Natriuretic Peptide

The plasma concentration of BNP was measured with specific radioimmunoassay using a monoclonal antibody which recognizes the ring structure of human BNP. Plasma BNP concentration was measured in 0.1 ml of plasma without an extraction procedure using a highly sensitive immunoradiometric assay (IRMA) (Shionoria BNP, Shionogi, Osaka, Japan), as reported previously.[4, 5, 15, 16] The minimum detectable human BNP is 1 pg/ml in this assay, and the degree of cross reactivity with human atrial natriuretic peptide is < 0.001% on a molar basis. The intra- and interassay variations were both < 10% in this assay system.

Statistical Analysis

Plasma BNP concentrations were compared over the time course using two-ways analysis of variance (ANOVA) repeated measure with Scheffe's test. Plasma concentrations of BNP in the three coronary artery groups or two groups (patients who underwent PTCA to one vessel or simultaneously to two vessels) were compared using two-way ANOVA repeated measure. Hemodynamic parameters in patients undergoing PTCA and plasma BNP concentrations in patients undergoing diagnostic coronary angiography were compared using the paired Student's *t*- test. All values are expressed as mean ± standard deviation (SD) unless otherwise indicated. Statistical significance was determined at $p < 0.05$.

Results

Percutaneous transluminal coronary angioplasty was successful in all patients, with no significant increase in plasma creatine phosphokinase measured 24 h after PTCA. Plasma BNP increased significantly from 28.4 ± 25.8 pg/ml immediately prior to PTCA to a peak level of 66.1 ± 65.2 pg/ml 24 h after PTCA (Fig. 1). Between the three groups undergoing PTCA, no significant difference existed to the left anterior descending artery, left circumflex artery, or right coronary artery. The respective plasma BNP concentrations were 30.9 ± 28.6, 32.4 ± 41.6, and 25.5 ± 21.3 pg/ml immediately before PTCA, and the peak levels were 65.7 ± 70.7, 63.4 ± 78.8, and 80.1 ±

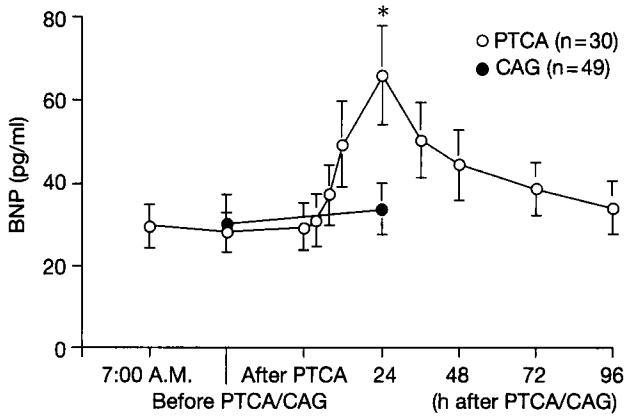

FIG. 1 The time course of plasma brain natriuretic peptide (BNP) in patients undergoing angioplasty (PTCA) or diagnostic coronary angiography (CAG). Plasma BNP increased and reached a peak level 24 h after PTCA. Coronary angiography did not affect the plasma BNP concentration. Values are expressed as mean ± standard error of the mean (SEM). * $p < 0.05$ compared with values immediately before PTCA.

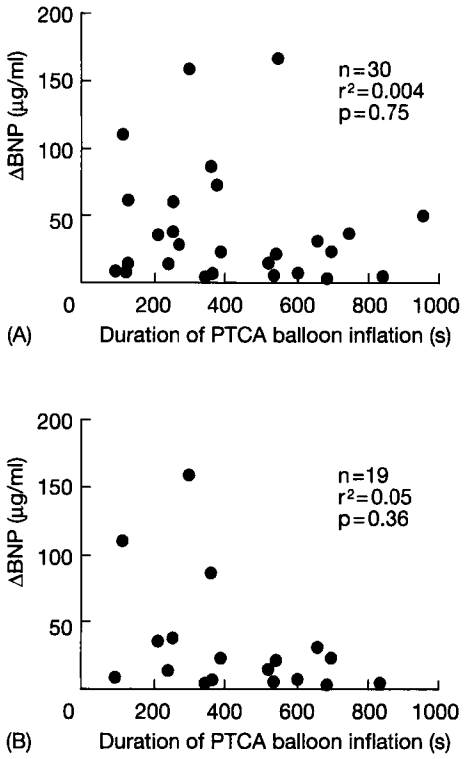

FIG. 2 Correlation between the magnitude of the increase in plasma brain natriuretic peptide (BNP) and duration of angioplasty (PTCA) balloon inflation. (A) Scatterplot in all patients undergoing PTCA (n = 30); (B) subgroup of patients undergoing PTCA to the proximal left anterior descending artery (n = 19). There was no significant correlation between plasma BNP concentrations and balloon inflation time in both groups. ΔBNP = the magnitude of the increase in BNP measured immediately before and 24 h after PTCA.

75.3 pg/ml 24 h after PTCA. Plasma BNP in the 24 patients undergoing single-vessel PTCA and the 6 patients undergoing double-vessels PTCA were 31.5 ± 30.3 and 22.7 ± 21.2 pg/ml immediately before PTCA, and peaked at 69.7 ± 69.9 and 51.7 ± 42.8 pg/ml, respectively, 24 h after PTCA. The differences between these groups were not significant. No significant correlation was found between the magnitude of the plasma BNP elevations and the duration of the PTCA balloon inflation in any patient, or in the subgroup of patients undergoing PTCA to the proximal left anterior descending artery (Fig. 2). Plasma BNP measured immediately before and 24 h after the procedure did not differ significantly in the control patients undergoing only diagnostic coronary angiography (Fig. 1). No significant changes were present in the hemodymanic parameters obtained immediately before and 24 h after PTCA (Table I).

Discussion

Several previous studies have shown that plasma BNP increases in various types of heart disease, such as in acute myocardial infarction. Although some of these studies have described plasma BNP elevations in patients with angina pectoris, it remains unclear whether the plasma BNP concentration increases in response to transient myocardial ischemia, as some investigators have found an increase after transient myocardial ischemia, while others have not.[17–20] The present study demonstrates that transient myocardial ischemia caused by PTCA leads to transient increases in plasma BNP, which peak 24 h after PTCA. Prior studies have revealed that plasma BNP increased proportional to pulmonary capillary wedge pressure.[21, 22] We measured hemodymanic parameters, such as pulmonary capillary wedge pressure, immediately prior to and 24 h after PTCA when peak BNP concentrations were detected, and we found no significant differences between these two times. This suggests that the transient increase in plasma BNP after PTCA is not due to hemodynamic change. Percutaneous transluminal coronary angioplasty was not performed at the

TABLE I Hemodynamic parameters immediately before and 24 h after percutaneous transluminal coronary angioplasty (PTCA)

Hemodynamic parameters	Before PTCA	24 h after PTCA	p Value
Systolic blood pressure (mmHg)	125 ± 15	123 ± 26	0.68
Diastolic blood pressure (mmHg)	69 ± 8	67 ± 9	0.28
Heart rate (beats/min)	71 ± 10	70 ± 9	0.87
Pulmonary capillary wedge pressure (mmHg)	8 ± 4	9 ± 3	0.50
Systolic pulmonary arterial pressure (mmHg)	23 ± 7	23 ± 7	0.84
Right atrial pressure (mmHg)	5 ± 3	6 ± 3	0.51
Cardiac index (l/min/m²)	3.0 ± 0.6	3.4 ± 0.7	0.13

same time of day in our study. Since previous studies have shown no circadian variation in plasma BNP,[23] we excluded any effect of the timing of PTCA by measuring plasma BNP early in the morning on the day of PTCA as well as immediately before the procedure (i.e., after completion of preparations such as guiding catheter insertion). Plasma BNP did not change between these two times, suggesting that the timing of PTCA had no effect on the results. Since previous studies observed a 1.2-fold increase in plasma BNP after left heart catheterization in patients with coronary artery disease,[24] we sought to exclude any effect of the procedures employed during PTCA, including arterial puncture and catheter insertion, heparin and nitrates administration, and infusion of contrast medium in the coronary artery. We measured plasma BNP concentrations in controls before and after coronary angiography, which employs these procedures similar to PTCA. Plasma BNP did not change significantly with coronary angiography, indicating that the cardiac catheterization procedure itself has no effect on plasma BNP. The major difference between the groups undergoing PTCA and coronary angiography was the transient ischemia caused by the PTCA balloon; thus, the temporary increase in plasma BNP after PTCA must be attributed solely to this transient ischemia. These results indicate that plasma BNP may potentially play a role as an index of recent myocardial ischemia in patients with angina pectoris.

In the present study, no significant difference in plasma BNP was observed between the three subgroups undergoing PTCA, namely, the left anterior descending artery, left circumflex artery, or right coronary artery, or between the two groups treated with either single- or double-vessel PTCA. These results demonstrate that the plasma BNP increase is not affected by the area or volume of ischemic myocardium perfused by the target coronary artery. Measurement of ventricular tissue BNP concentrations in a rat coronary artery ligation model have shown a 5-fold increase 24 h after ligation. This increase was similar in both ischemic and nonischemic tissue, and increased tissue BNP levels were observed in the right ventricle as well,[25] suggesting that plasma BNP elevations result not only from secretion in ischemic myocardium, but from release of BNP from the entire ventricle including nonischemic myocardium. This may explain why the area and volume of ischemic myocardium by PTCA balloon inflation had no effect on plasma BNP elevations in the present study. We found no correlation between the magnitude of the increase in plasma BNP and the duration of myocardial ischemia produced by PTCA balloon inflation. The severity of myocardial ischemia depends on the duration of myocardial ischemia and the imbalance between myocardial oxygen supply and demand.[26] Myocardial oxygen demand is determined by heart rate, contractility, and systolic wall tension.[26] The blood flow supplied by collateral circulation during PTCA balloon inflation also influences the severity of myocardial ischemia;[27, 28] thus, the severity of ischemia is multifactorial. Although the duration of ischemia is one of the many determinants of severity in myocardial ischemia, we observed no correlation between the magnitude of the increase in plasma BNP and the duration of myocardial ischemia.

The present study demonstrates that plasma BNP increases during transient myocardial ischemia, but the mechanism involved remains unclear. Several studies have shown that BNP synthesis and secretion are stimulated by stretching of the ventricular myocardium.[29–31] It has been shown that even transient ischemia of the ventricular myocardium results in reduced wall motion and extension of the ischemic region. The extension of ischemia may be responsible for the elevations in plasma BNP. Hypoxia has also been reported to increase ventricular BNP secretion,[32] suggesting that myocardial ischemia may elicit plasma BNP elevation. However, ventricular wall stretching and myocardial hypoxia cannot explain increases in tissue BNP in nonischemic myocardium.[25] Further study is necessary to elucidate the mechanisms responsible for the increases in plasma BNP produced by transient myocardial ischemia.

Conclusion

The present study demonstrates that plasma BNP increased and peaked 24 h after transient myocardial ischemia caused by PTCA; however, the mechanism involved remains unclear. Plasma BNP may potentially play a role as an index of recent myocardial ischemia in patients with angina pectoris.

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