

## Effects of Brain (B-Type) Natriuretic Peptide on Coronary Artery Diameter and Coronary Hemodynamic Variables in Humans: Comparison With Effects on Systemic Hemodynamic Variables

KEN OKUMURA, MD, HIROFUMI YASUE, MD, HIROMI FUJII, MD, KIYOTAKA KUGIYAMA, MD, KOZABURO MATSUYAMA, MD, MICHIIRO YOSHIMURA, MD, MICHIHISA JOUGASAKI, MD, KOICHI KIKUTA, MD, HIDEJI KATO, MD, HIDENORI TANAKA, MD, HITOSHI SUMIDA, MD, KAZUWA NAKAO, MD\*

Kumamoto and Kyoto, Japan

**Objectives.** This study attempted to clarify the effects of human brain (B-type) natriuretic peptide on coronary artery diameter and coronary vascular resistance in humans.

**Background.** Brain natriuretic peptide induces vasodilation in systemic circulation by activating particulate guanylate cyclase of the vascular smooth muscle.

**Methods.** In 13 patients with normal coronary arteries and left ventricular function, brain natriuretic peptide was infused at 0.5 µg/kg body weight per min for 4 min into the left main coronary artery (six patients, Group A) or into the pulmonary artery (seven patients, Group B). Systemic hemodynamic variables and coronary sinus blood flow were measured before and after the infusion. The lumen diameter of the left coronary artery was quantitatively measured.

**Results.** In both groups, brain natriuretic peptide significantly increased heart rate and decreased mean arterial pressure. Rate-pressure product remained unchanged in both groups. Brain natriuretic peptide decreased systemic vascular resistance index

significantly in both groups (both  $p < 0.01$  vs. baseline), and there was no difference in the effect between the groups. Brain natriuretic peptide decreased coronary vascular resistance in Group A ( $p < 0.01$  vs. baseline) but did not affect coronary vascular resistance in Group B ( $p < 0.01$  vs. Group A). The lumen diameters of the proximal and distal segments of the left coronary artery were increased significantly after brain natriuretic peptide in both groups. After infusion of brain natriuretic peptide, mean plasma level of brain natriuretic peptide in the coronary sinus increased from 36 to 130,411 pg/ml in Group A and from 64 to 12,329 pg/ml in Group B.

**Conclusions.** Brain natriuretic peptide shows a vasodilator effect on the coronary artery system in humans. However, the effect does not appear uniformly but is seen preferentially in the epicardial coronary artery. The sensitivity of the coronary resistance vessels to brain natriuretic peptide is low compared with that of the resistance vessels of the systemic circulation.

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Brain (B-type) natriuretic peptide was first isolated from a porcine brain (1) and subsequently from the hearts of pigs (2) and rats (3,4) and has been shown to form a peptide family with atrial (A-type) natriuretic peptide (5). We recently isolated human brain natriuretic peptide from the human atrium, determined its amino acid sequence (6), established a specific radioimmunoassay for human brain natriuretic peptide (5,7) and demonstrated that brain natriuretic peptide is secreted predominantly from the left ventricle (2-5,7,8). Brain natriuretic peptide has been shown to stimulate cyclic guanylate monophosphate production (9-11) by activating predomi-

nantly the atrial natriuretic peptide-A receptor that couples to particulate guanylate cyclase (12). We have shown (5,7,8) that the plasma levels of brain natriuretic peptide are markedly increased in patients with congestive heart failure, as are the plasma levels of atrial natriuretic peptide, and surpass atrial natriuretic peptide levels in severe cases. We have also shown (13) that the plasma levels of brain natriuretic peptide are increased in patients with acute myocardial infarction. Thus, brain natriuretic peptide may be involved in the regulation of blood pressure and fluid volume, as is atrial natriuretic peptide.

Besides its diuretic and natriuretic effects and inhibitory effect on the renin-angiotensin-aldosterone system (14-17), atrial natriuretic peptide induces vasorelaxation in a variety of organ systems and animal species (18,19). We (20) and other investigators (21) have shown that atrial natriuretic peptide infusion improves left ventricular function by reducing both preload and afterload in patients with congestive heart failure. Chu et al. (22) showed that atrial natriuretic peptide causes marked sustained dilation in the proximal coronary artery of

From the Division of Cardiology, Kumamoto University School of Medicine, Kumamoto, Japan; and \*Second Division, Department of Medicine, Kyoto University School of Medicine, Kyoto, Japan. This study was supported in part by Grant-in-Aid for Scientific Research B-03454257 from the Ministry of Education and Culture and a grant from the Smoking Research Foundation, Tokyo, Japan.

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Address for correspondence: Dr. Ken Okumura, Division of Cardiology, Kumamoto University School of Medicine, Honjo 1-1-1, Kumamoto, 860 Japan.

humans. Lai et al. (23) recently demonstrated a beneficial effect of atrial natriuretic peptide on exercise-induced myocardial ischemia in patients with stable effort angina. We recently reported (24) that atrial natriuretic peptide infusion prevented coronary spasm induced by hyperventilation in patients with variant angina.

In contrast to these vigorous investigations on the effects of atrial natriuretic peptide on systemic and coronary vasculatures, only a few studies on the vasodilator effect of brain natriuretic peptide have been reported (11,25-27). We recently demonstrated (26) that the infusion of human brain natriuretic peptide decreases both preload and afterload to the left ventricle and improves left ventricular function in patients with congestive heart failure. However, the effect of brain natriuretic peptide on the coronary artery system of humans has never been reported.

In the present study, human brain natriuretic peptide was infused into the left main coronary artery of patients with normal coronary arteriograms and normal left ventricular function, and its effects on the coronary artery diameter, coronary vascular resistance and systemic hemodynamic variables were examined. Furthermore, the same dose of the peptide was infused into the pulmonary artery in another group of the patients to clarify whether brain natriuretic peptide administered into systemic circulation shows its effects on the coronary vasculature as it does on the peripheral resistance vessels of systemic circulation.

## Methods

**Study patients.** This study included 13 (4 men, 9 women; mean age 54 years, range 34 to 65) patients who underwent coronary angiographic examination for an atypical chest pain syndrome (12 patients) or an electrocardiographic (ECG) abnormality (T wave inversion in the precordial leads [1 patient]). These patients were found to have no angiographic stenosis  $\geq 25\%$  of the lumen diameter in any coronary artery segments. None of the patients had typical anginal pain at rest or on exertion. Maximal exercise stress test results according to the Bruce standard protocol were negative in all patients. Hyperventilation test results for provoking coronary spasm were negative for myocardial ischemia in all patients. Intracoronary injection of acetylcholine was performed in an attempt to provoke coronary spasm in all patients before the study (28,29). Neither chest pain nor ischemic ST segment changes appeared, and coronary arteriography showed no evidence of coronary spasm in any of the patients.

None of the patients had diabetes mellitus. Two patients had hypertension, with systolic blood pressure  $>160$  but  $<180$  mm Hg and diastolic pressure  $<100$  mm Hg at admission. No patient had a serum cholesterol level  $>250$  mg/dl. Four patients had a history of smoking. Echocardiography revealed normal left ventricular wall motion and normal wall thickness in all patients. Right- and left-sided cardiac catheterizations showed normal hemodynamic data in all patients, and mean ( $\pm$ SD) left ventricular ejection fraction was  $78.5 \pm 6.8\%$ .

None of the patients had congestive heart failure or allergy. All drugs were withdrawn at least 3 days before the study. Written informed consent was obtained from all patients before the study. The study protocol was in agreement with the guidelines approved by the ethics committee at our institution.

**Synthetic human brain natriuretic peptide.** Human brain natriuretic peptide was purchased from Peptide Institute (Minoh, Japan). Its homogeneity was confirmed by reverse-phase, high performance liquid chromatography and amino acid analysis. The human brain natriuretic peptide was dissolved in saline solution with 10% lactose and sterilized by passage through a 0.22- $\mu$ m Millipore filter. The chemical nature and content of brain natriuretic peptide in vials were verified by high performance liquid chromatography and radioimmunoassay.

**Cardiac catheterization and angiographic study.** The study was performed in the morning while the patients were in the fasting state. A 7F thermodilution coronary blood flow catheter (CCS-7U-90B, Webster) was positioned in the coronary sinus by way of the antecubital vein. The catheter position was determined by injection of a small volume of contrast medium (Hexabrix 320), and a stable catheter position was confirmed by fluoroscopy during the procedure. Coronary arteriography was performed with the Sones technique. The left coronary artery was filmed in the right anterior oblique projection and the right coronary artery in the left anterior oblique projection. Relations among the focal spot, the patient and the height of the image tube were kept constant throughout the study. Three ECG leads (I, aVF and  $V_3$ ) and arterial pressure were continuously monitored on an oscilloscope during the study.

Coronary sinus blood flow was determined by the injection of nonheparinized normal saline solution through the thermodilution catheter with a constant-infusion pump at a rate of 36 ml/min and calculated with the use of a Thermo Flow RF (Good Man) (30). The flow curve was recorded on oscillographic paper along with three ECG leads and arterial pressure.

**Study protocol.** After the baseline measurements of coronary sinus blood flow, pulmonary artery, right atrial and aortic pressures and cardiac output (with a thermodilution technique), and after a control arteriogram of the left coronary artery, brain natriuretic peptide solution was infused at 0.5  $\mu$ g/kg body weight per min for 4 min into the left coronary artery (six patients, Group A) or into the pulmonary artery (seven patients, Group B). The infusion rate was 2 ml/min. Coronary sinus blood flow was measured just before termination of the infusion of brain natriuretic peptide, and the blood samples were obtained from the coronary sinus and femoral vein. The left coronary arteriogram was taken just after termination of brain natriuretic peptide infusion, and pressures and cardiac output were measured. Measurements of coronary sinus blood flow and hemodynamic variables, left coronary arteriography and blood sampling from the femoral vein were repeated at 5, 10 and 20 min after termination of the infusion of brain natriuretic peptide. Isosorbide dinitrate (1 mg) was

**Table 1.** Changes in Systemic Hemodynamic Variables After Brain Natriuretic Peptide Infusion Into the Coronary and Pulmonary Arteries

	Baseline	Time After BNP Infusion (min)			
		0	5	10	20
Infusion Into Coronary Artery (Group A)					
Heart rate (beats/min)	73 ± 11	84 ± 13*	88 ± 17*	88 ± 14*	84 ± 11*
Mean arterial pressure (mm Hg)	105 ± 7	95 ± 10*	94 ± 8*	96 ± 9*	99 ± 9
Rate-pressure product (mm Hg·beats/min)	10,152 ± 1,585	10,448 ± 1,699	10,738 ± 2,023	10,666 ± 1,850	10,427 ± 1,274
Mean pulmonary artery pressure (mm Hg)	14 ± 3	13 ± 3	13 ± 4	13 ± 2	12 ± 2†
Cardiac index (liters/min per m <sup>2</sup> )	3.2 ± 0.5	3.9 ± 0.7*	3.9 ± 0.8*	3.7 ± 1.0*	3.5 ± 0.8
Systemic vascular resistance index (dynes·s·cm <sup>-5</sup> ·m <sup>2</sup> )	2,587 ± 353	1,865 ± 332*	1,866 ± 335*	2,037 ± 552*	2,244 ± 575†
Infusion Into Pulmonary Artery (Group B)					
Heart rate (beats/min)	69 ± 12	74 ± 14†	80 ± 17*	82 ± 15*	79 ± 16†
Mean arterial pressure (mm Hg)	101 ± 12	96 ± 12†	88 ± 8*	88 ± 11*	89 ± 11*
Rate-pressure product (mm Hg·beats/min)	10,255 ± 1,560	10,137 ± 1,739	10,074 ± 2,146	9,967 ± 1,752	9,846 ± 2,314
Mean pulmonary artery pressure (mm Hg)	13 ± 4	10 ± 4*	10 ± 4*	10 ± 5*	10 ± 4*
Cardiac index (liters/min per m <sup>2</sup> )	3.0 ± 0.5	3.5 ± 0.5*	3.5 ± 0.4*	3.3 ± 0.4†	3.3 ± 0.4†
Systemic vascular resistance index (dynes·s·cm <sup>-5</sup> ·m <sup>2</sup> )	2,587 ± 329	2,126 ± 332*	1,934 ± 95*	1,993 ± 274*	2,030 ± 272*

\*p < 0.01, †p < 0.05 versus baseline. Data are mean value ± SD. BNP = brain (B-type) natriuretic peptide.

finally injected into the left coronary artery, and the coronary arteriogram was taken from multiple projections.

**Quantitative coronary angiography.** Measurement of the lumen diameter of the left coronary artery was performed quantitatively with the use of a computer-assisted coronary angiography analysis system. End-diastolic cine films were videodigitized and stored in the cardiac image analysis system (Cardio 500, Kontron Instruments). Automated contour detection was performed by a geometric edge differentiation technique similar to the method described by Reiber et al. (31), and the technique was validated in our previous study (32). Analysis of intraobserver and interobserver variability for the measurement of the coronary artery diameter with this system showed high reproducibility ( $r = 0.99$ , SEE 0.05 mm,  $p < 0.001$  and  $r = 0.99$ , SEE 0.04 mm,  $p < 0.001$ , respectively).

The lumen diameters were measured at the proximal and distal segments of the left anterior descending and circumflex coronary arteries (the length of each segment was ~1 cm). The measurement was performed for the arteriogram at baseline, those at 0, 5, 10 and 20 min after brain natriuretic peptide and that after isosorbide dinitrate.

**Measurement of plasma concentration of brain natriuretic peptide.** Plasma concentration of brain natriuretic peptide was measured with a specific radioimmunoassay by using monoclonal antibody that recognized the ring structure of human brain natriuretic peptide, and the minimal detectable quantity of human brain natriuretic peptide was 1 pg/tube as previously reported (5,7). The cross-reactivity with alpha-human atrial natriuretic peptide was <0.005% on a molar basis. The intra-assay and interassay coefficients of variation were 8.4% and 6.4%, respectively.

**Calculation and data analysis.** Coronary vascular resistance (mm Hg·min liter) was calculated as (Mean aortic blood pressure - Right atrial pressure) × 1000/Coronary sinus blood flow; systemic vascular resistance index (dynes·s·cm<sup>-5</sup>·m<sup>2</sup>) as

(Mean arterial pressure - Right atrial pressure) × 80/Cardiac index; and rate-pressure product (mm Hg·beats/min) as Heart rate × Systolic blood pressure.

All data are shown as mean value ± 1 SD. The lumen diameters of the left anterior descending and circumflex coronary arteries were averaged for each of the proximal and distal segments. When serial changes in the systemic and coronary hemodynamic variables, the lumen diameters of the proximal and distal segments of the left coronary artery and the plasma levels of brain natriuretic peptide (expressed as logarithms) in the femoral vein and coronary sinus after infusion of brain natriuretic peptide were compared within a group, one-way analysis of variance for repeated measures followed by the Fisher protected least-significant-difference multiple-comparison test was used. Percent changes in systemic and coronary hemodynamic variables and lumen diameters of the left coronary artery from the baseline values after brain natriuretic peptide were compared between groups using two-way analysis of variance for repeated measures. A  $p$  value <0.05 was considered statistically significant.

## Results

**Effects on systemic hemodynamic variables.** In both groups, the infusion of brain natriuretic peptide resulted in a significant increase in heart rate, a significant decrease in mean arterial pressure, a significant increase in cardiac index and a significant decrease in systemic vascular resistance index (Table 1). These effects of brain natriuretic peptide continued for >10 min in both groups. Rate-pressure product remained unchanged after brain natriuretic peptide in both groups. Mean pulmonary artery pressure decreased significantly at 20 min after brain natriuretic peptide in Group A, whereas it decreased immediately after the infusion in Group B.

**Table 2.** Changes in Coronary Hemodynamic Variables After Brain Natriuretic Peptide Infusion Into the Coronary and Pulmonary Arteries

	Baseline	Time After BNP Infusion (min)			
		0	5	10	20
Infusion Into Coronary Artery (Group A)					
Coronary sinus blood flow (ml/min)	90 ± 26	104 ± 36	112 ± 36*	105 ± 44	99 ± 42
Coronary vascular resistance (mm Hg·min/liter)	1,268 ± 405	991 ± 370†	916 ± 311*	1,052 ± 450†	1,166 ± 560
Infusion Into Pulmonary Artery (Group B)					
Coronary sinus blood flow (ml/min)	111 ± 46	98 ± 25†	88 ± 26*	91 ± 29*	87 ± 30*
Coronary vascular resistance (mm Hg·min/liter)	1,087 ± 440	1,070 ± 358	1,113 ± 346	1,133 ± 435	1,153 ± 333

\*p < 0.01, †p < 0.05 versus baseline. Data presented are mean value ± SD. BNP = brain (B-type) natriuretic peptide.

**Effects on coronary hemodynamic variables.** In Group A, coronary sinus blood flow increased significantly at 5 min after the infusion of brain natriuretic peptide, and coronary vascular resistance decreased significantly immediately after the infusion (Table 2). The effect on the latter continued for >10 min after the infusion. In contrast, coronary sinus blood flow decreased significantly, and coronary vascular resistance remained unchanged after brain natriuretic peptide in Group B.

**Effects on coronary artery diameters.** The baseline lumen diameter of the proximal segment of the left coronary artery was 3.1 ± 0.4 mm in Group A and 3.1 ± 0.6 mm in Group B. In Group A, the diameter increased to 3.4 ± 0.4 mm immediately after the infusion of brain natriuretic peptide (p < 0.001) and increased further to 3.6 ± 0.4 mm at 10 min after the infusion (Fig. 1). In Group B, the diameter increased to

3.5 ± 0.6 mm at 5 min after brain natriuretic peptide (p < 0.001). After isosorbide dinitrate, the diameter increased further in Group B but not in Group A. A similar observation was made in the distal segment. The baseline diameter was 1.4 ± 0.4 mm in Group A and 1.4 ± 0.2 mm in Group B. In Group A, the diameter increased to 1.6 ± 0.4 mm immediately after brain natriuretic peptide (p < 0.001), whereas in Group B, it increased to 1.7 ± 0.3 mm at 5 min after brain natriuretic peptide (p < 0.001).

**Changes in plasma concentration.** The infusion of brain natriuretic peptide resulted in an immediate and marked increase in the plasma concentrations in the femoral vein and coronary sinus in both groups (Table 3). The concentration in the coronary sinus in Group A was ~10 times higher than that in Group B.

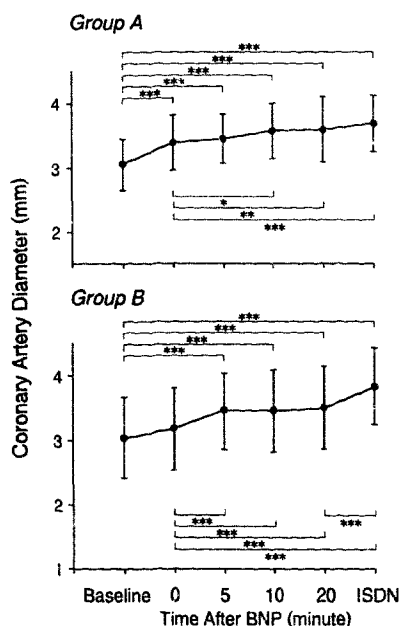
**Comparison of the effects between Groups A and B.** None of the baseline variables differed between the two groups. None of the percent changes in the heart rate, mean arterial pressure, cardiac index and lumen diameters of the proximal and distal segments of the left coronary artery from baseline after the infusion of brain natriuretic peptide was different between the groups. There was a significant difference in the change in the mean pulmonary artery pressure between the two groups (p = 0.0167).

There was a significant difference in the change in coronary sinus blood flow after brain natriuretic peptide between the two groups (p = 0.0023). Figure 2 shows the time course of the percent changes from the baseline in systemic vascular resistance index and coronary vascular resistance after brain natriuretic peptide for both groups. There was no statistical difference in the change in systemic vascular resistance index between the groups. However, a significant difference was noted in the change in coronary vascular resistance between the two groups (p = 0.0046).

## Discussion

Brain natriuretic peptide, first isolated from a porcine brain (1) and subsequently from the hearts of pigs (2) and rats (3,4), is secreted predominantly from the ventricles in humans (2-5,7,8) and forms a natriuretic peptide family with atrial natriuretic peptide (5). We and the other investigators (5,7,8)

**Figure 1.** Time course of the effects of brain natriuretic peptide (BNP) infused into the left main coronary artery (Group A) or the pulmonary artery (Group B) and intracoronary isosorbide dinitrate (ISDN) on the lumen diameter of the proximal segment of the left coronary artery. See text for discussion. \*p < 0.05. \*\*p < 0.01. \*\*\*p < 0.001.



**Table 3.** Changes in Plasma Brain Natriuretic Peptide Concentration After Infusion Into Coronary and Pulmonary Arteries

Sampling Site	Baseline	Time After BNP Infusion (min)			
		0	5	10	20
Infusion Into Coronary Artery (Group A)					
Femoral vein (pg/ml)	14 ± 11	6,704 ± 1,886*	3,503 ± 828*	2,209 ± 1,035*	919 ± 244
Coronary sinus (pg/ml)	36 ± 43	130,411 ± 52,084*			
Infusion Into Pulmonary Artery (Group B)					
Femoral vein (pg/ml)	25 ± 15	10,261 ± 2,838*	4,501 ± 1,437*	2,389 ± 678†	1,016 ± 344
Coronary sinus (pg/ml)	64 ± 45	12,329 ± 2,731*			

\*p &lt; 0.01, †p &lt; 0.05 versus baseline. Data presented are mean value ± SD. BNP = brain (B-type) natriuretic peptide.

have shown that the plasma levels of brain natriuretic peptide are markedly increased in patients with congestive heart failure, as are the plasma levels of atrial natriuretic peptide. We have also shown (13) that the plasma levels of brain natriuretic peptide are increased in patients with acute myocardial infarction. Thus, brain natriuretic peptide seems to be involved in the regulation of blood pressure and fluid volume, as is atrial natriuretic peptide (14-17).

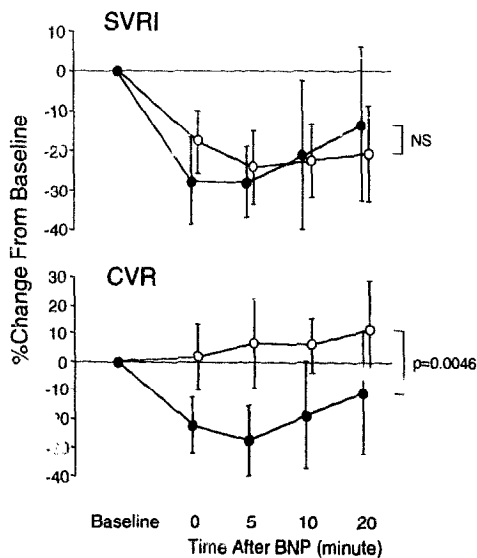
Brain natriuretic peptide stimulates cyclic guanylate monophosphate production (9-11), predominantly by activating the atrial natriuretic peptide-A receptor that couples to particulate guanylate cyclase (12) and thereby induces vasorelaxation. The biologic action of brain natriuretic peptide was shown to be species specific, unlike atrial natriuretic peptide: Human brain natriuretic peptide shows much less vasodilative effect on the

rat thoracic aorta than rat brain natriuretic peptide and rat atrial natriuretic peptide while showing more potent vasodilation in the porcine coronary artery than the other peptides (25). It was also reported (11) that human brain natriuretic peptide showed lower cyclic guanylate monophosphate accumulation in the rat vascular smooth muscle and less vasorelaxant activity in the rat aorta than rat and porcine brain natriuretic peptides despite its high binding affinity to the rat vascular smooth muscle. We examined the effects of human brain natriuretic peptide on systemic hemodynamic variables, renal function and plasma hormone levels in patients with congestive heart failure and in control subjects and demonstrated that brain natriuretic peptide significantly decreased systemic vascular resistance and significantly increased both diuresis and natriuresis (26). Human brain natriuretic peptide may have similar vasodilative effects on the coronary artery system of humans, but such data have not been reported previously.

**Vasodilator effect of brain natriuretic peptide on the epicardial coronary artery.** The results of this study showed that the lumen diameters of both proximal and distal segments of the epicardial coronary artery increased significantly after the infusion of brain natriuretic peptide into the left coronary and pulmonary arteries. Because the rate-pressure product, a marker of myocardial oxygen consumption rate, remained unchanged after brain natriuretic peptide in both groups, and, furthermore, coronary blood flow rather decreased after brain natriuretic peptide in Group B, the epicardial coronary artery dilation seen after brain natriuretic peptide was a result of its primary vasodilator effect, presumably through the production of cyclic guanylate monophosphate (9-12).

As indicated by the time course of the effect of brain natriuretic peptide (Fig. 1), the lumen diameter change was not maximal at the time immediately after the infusion (i.e., at the time when the plasma concentration of brain natriuretic peptide was the highest), and the diameter further increased with time after cessation of the infusion. In Group A, the maximal vasodilation was obtained at 10 to 20 min after the infusion because isosorbide dinitrate showed no further dilator effect. Thus, the vasodilator effect of brain natriuretic peptide on the epicardial coronary artery not only was sustained for at least 20 min but enhanced with time after the infusion. After

**Figure 2.** Time course of the percent changes from baseline in systemic vascular resistance index (SVRI) and coronary vascular resistance (CVR) after brain natriuretic peptide (BNP) infusion into the left main coronary artery (Group A, closed circles) or the pulmonary artery (Group B, open circles). There was no difference in the change in systemic vascular resistance index between the two groups, whereas a significant difference was noted in the change in coronary vascular resistance ( $p = 0.0046$  by two-way analysis of variance).



the infusion of atrial or brain natriuretic peptide, the plasma level of cyclic guanylate monophosphate was shown to increase and reach its peak ~5 min later than the peak of the plasma level of atrial or brain natriuretic peptide (22,24,26). Furthermore, it was sustained at higher levels even after the plasma level of atrial or brain natriuretic peptide returned to the baseline value. Such delayed and sustained elevation of the cyclic guanylate monophosphate level after brain natriuretic peptide may account for the time course of the effect of brain natriuretic peptide.

It has been shown that atrial natriuretic peptide induces vasorelaxation in a variety of organ systems and animal species (18,19). Chu et al. (22) administered atrial natriuretic peptide in humans as a bolus (2.5 µg/kg) and demonstrated that atrial natriuretic peptide induced marked, sustained dilation in the proximal coronary artery and brief minor change in coronary blood flow. Lai et al. (23) recently demonstrated beneficial effects of atrial natriuretic peptide on exercise-induced myocardial ischemia in patients with stable effort angina through improvement of myocardial perfusion to the ischemic region. We recently reported (24) that the infusion of atrial natriuretic peptide prevented coronary spasm induced by hyperventilation in patients with variant angina. Thus, atrial natriuretic peptide seems to be beneficial for treatment of myocardial ischemia. However, the role of brain natriuretic peptide in the treatment of myocardial ischemia has been unclear. We recently showed (33) that intravenous infusion of brain natriuretic peptide at 0.05 µg/kg per min for 20 min effectively prevented coronary spasm induced by hyperventilation in patients with variant angina. This can be explained by the primary vasodilator effect of brain natriuretic peptide on the epicardial coronary artery.

**Effect of brain natriuretic peptide on the coronary resistance vessels.** When brain natriuretic peptide was infused into the left coronary artery, it increased coronary sinus blood flow and decreased coronary vascular resistance as well as systemic vascular resistance. This indicates that brain natriuretic peptide shows a vasodilator effect on both coronary and systemic resistance vessels. In contrast, when brain natriuretic peptide was administered in the pulmonary artery, it decreased coronary sinus blood flow and did not affect coronary vascular resistance while decreasing systemic vascular resistance. The analysis of the plasma levels of brain natriuretic peptide revealed that when the peptide was infused into the coronary artery (Group A), its plasma level in the coronary sinus was 10 to 20 times higher than that in the femoral vein, whereas when the peptide was infused into the pulmonary artery (Group B), its plasma level in the coronary sinus was almost equal to that in the femoral vein. Because the change in mean arterial pressure (i.e., coronary perfusion pressure) after the infusion of brain natriuretic peptide was not different between the two groups, brain natriuretic peptide is likely to show its vasodilator effect on the coronary resistance vessels only when the plasma level in coronary circulation is extremely increased. Thus, the sensitivity of the coronary resistance vessels to the vasodilator effect of brain natriuretic peptide is low compared

with that of the peripheral resistance vessels of systemic circulation and also that of the epicardial coronary artery.

The mechanism for the disparity of the sensitivity to the vasodilator effect of brain natriuretic peptide between the coronary conduit artery and resistance vessels and between coronary and systemic resistance vessels was not clarified in this study. The distribution of the atrial natriuretic peptide-A receptors in the coronary resistance vessels may be different from that in the other vascular systems. It has been reported (22) that atrial natriuretic peptide also shows its effect preferentially on the proximal coronary artery rather than the distal, resistance vessels in humans. The role of particulate guanylate cyclase-mediated vasodilation is thus suggested to be of less importance in the coronary resistance vessels than in the epicardial conduit artery and systemic peripheral vessels. It should be recalled that nitroglycerin, a soluble guanylate cyclase activator (34), also exhibits a smaller vasodilator effect on the coronary resistance vessels while markedly dilating the epicardial conduit coronary artery (35). Brain natriuretic peptide, when infused into the systemic circulation, seems to show a vasodilator effect similar to nitroglycerin.

Finally, it should be emphasized that the plasma level of brain natriuretic peptide was markedly increased after the infusion of brain natriuretic peptide in both groups (~500-fold increase in the femoral vein just after the infusion). Thus, the effects of brain natriuretic peptide shown in the present study were not those at its physiologic level but those of the pharmacologic dose. Plasma levels of brain natriuretic peptide are markedly increased in patients with congestive heart failure (5,7,8). In patients with severe left ventricular dysfunction, it is not unusual to see a plasma level of brain natriuretic peptide >1,000 pg/ml in the peripheral vein (8). Further studies are necessary to clarify whether highly increased brain natriuretic peptide levels in patients with congestive heart failure act as a physiologic vasodilator in the coronary vasculature.

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