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Elevated Levels of Brain Natriuretic Peptide as a Predictor of Impaired Coronary Endothelial Function in Patients With Left Ventricular Remodeling

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Abstract

Background. Plasma levels of brain natriuretic peptide (BNP) correlate with left ventricular remodeling, but the relationship between BNP induction and coronary function remains unclear.

Objectives. The present study assessed BNP production in response to left ventricular enlargement and investigated the relationship between BNP production and coronary vasodilating function in patients with left ventricular remodeling.

Methods. Patients ($n = 63$) with normal or mildly diseased coronary arteries underwent Doppler flow study of the left anterior descending coronary artery. Vascular reactivity was examined using intracoronary acetylcholine, papaverine and nitroglycerin using a Doppler guidewire.

Results. Left ventricular end-diastolic dimension was positively correlated with BNP ($r = 0.45$, $p < 0.001$) in all patients. BNP was significantly and inversely correlated with percentage change in coronary artery diameter induced by acetylcholine ($r = -0.56$, $p < 0.001$) but not by nitroglycerin ($r = -0.20$, $p = 0.28$) in patients with left ventricular end-diastolic dimension ≥ 55 mm ($n = 32$). By contrast, BNP was not significantly correlated with percentage change in coronary artery diameter induced by either acetylcholine or nitroglycerin in patients with left ventricular end-diastolic dimension < 55 mm ($n = 31$). Further, BNP was not correlated with the percentage change in coronary blood flow induced by acetylcholine or by papaverine in patients with or without left ventricular remodeling.

Conclusions. The elevation in plasma BNP levels that occurs in association with left ventricular enlargement is a predictor of impaired endothelium-dependent vasodilation in conductance coronary arteries.

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Key Words
■Acetylcholine ■Coronary circulation ■Natriuretic peptides, brain
■Doppler ultrasound (guidewire) ■Ventricular remodeling

INTRODUCTION

The cardiovascular system is regulated by hemodynamic and neurohumoral mechanisms. These regulatory systems play a key role in modulating cardiac function, vascular tone, and structure. Although neurohumoral systems are essential in vascular homeostasis, they became maladaptive in disease states such as hypertension, coronary disease, and heart failure. Plasma levels of brain natriuretic peptide (BNP) are increased in patients with congestive heart failure,[1] possibly due to an increase in the intraventricular pressure or ventricular wall stretch.[2] However, the relationship between BNP induction and coronary artery vasodilatory function remains unclear. Therefore, the present study assessed BNP production in response to left ventricular enlargement and investigated the relationship between BNP production and coronary vasodilating function in patients with left ventricular remodeling.

SUBJECTS AND METHODS

Study population

Sixty-three patients (16 women) with normal or mildly diseased coronary arteries (% diameter stenosis $< 30\%$) underwent Doppler flow study of the left anterior descending coronary artery. Patients were divided into two groups according to left ventricular end-diastolic dimension (LVDd), as assessed by echocardiography. Group 1 consisted of 32 patients with LVDd ≥ 55 mm, and Group 2 consisted of 31 patients with LVDd < 55 mm.

Patients were included in this study if their coronary vessels met the following criteria: angiographically smooth arteries, mild irregularities with no coronary artery lesion, $> 30\%$ lumen diameter stenosis by visual assessment in major epicardial vessels, and proximal coronary arteries > 2.0 mm. Patients with previous myocardial infarction, previous coronary revascularization, or vasospastic angina were excluded. Written informed consent was obtained from all patients before catheterization in accordance with guidelines established by the Committee for the Protection of Human Subjects at our institution.

Study protocol

Diagnostic coronary angiography was performed by the standard femoral percutaneous approach using a 6F Judkins catheter. Five thousand units of heparin were administered at the beginning of the procedure. Non-ionic contrast material was used for all patients. No nitroglycerin was given prior to the diagnostic procedure.

Coronary blood flow response to papaverine, acetylcholine and nitroglycerin was studied as previously described.[3–5] Briefly, after completion of the diagnostic catheterization, the following interventions were performed: Introduction of a 0.014-inch Doppler guidewire (Cardiometrics) into the left anterior descending coronary artery; after obtaining a stable Doppler signal, a bolus of papaverine [an endothelium-independent vasodilator in resistance coronary arteries] (12.5 mg/5 m*l*) was injected through a catheter; infusion of acetylcholine [an endothelium-dependent vasodilator in resistance and epicardial coronary arteries] (0.5 m*l*/min) at dosages of 3 μg/min for 2 min via the catheter; and a bolus of nitroglycerin [an endothelium-independent vasodilator in epicardial coronary artery] (200 μg/5 m*l*).[6,7] Drugs were infused at least 5 min apart. Coronary arteriography was performed before and after each administration of papaverine, acetylcholine, and nitroglycerin. Phasic coronary blood flow velocities, arterial blood pressure, and heart rate were monitored and recorded continuously. Measurements obtained during steady state conditions were used as control values for later analysis.

Assessment of coronary blood flow

Doppler flow velocity spectra were analyzed online to determine the time-averaged peak velocity. Volumetric coronary blood flow (CBF) was determined from the formula: CBF = cross-sectional area × average peak velocity × 0.5.[8] Coronary flow reserve to papaverine was calculated as the ratio of maximal CBF induced by papaverine to basal CBF and was used as a measure of the endothelium-independent function of the resistance coronary artery. By contrast, endothelium-dependent function of the resistance coronary artery was

calculated as the percentage increase of CBF in response to acetylcholine.[3–5]

Quantitative coronary angiographic images

Technically suitable single-plane angiograms were selected for computer analysis. Quantitative coronary angiographic images (DBAC-1000; MID Corporation) were recorded using validated densitometric analysis, as previously reported.[9] An end-diastolic still frame at each infusion (baseline, acetylcholine, nitroglycerin) was selected from the angiographic sequence. Endothelium-dependent and -independent vasodilation of the conduit coronary artery was estimated by measuring the luminal diameter at the tip of the Doppler guidewire positioning at the proximal site of left anterior descending coronary artery. These measurements were made by experienced observers unaware of the coronary vascular reactivity tests or BNP levels.

Assessment of coronary vasoreactivity

Doppler flow velocity spectra were analyzed online to determine time-averaged peak velocity. Volumetric CBF was determined using the formula: CBF = cross-sectional area × average peak velocity × 0.5.[8] Coronary flow reserve to papaverine was calculated as the ratio of maximal CBF induced by papaverine to basal CBF, which reflects the endothelium-independent function of the resistance coronary artery. Endothelium-dependent function was calculated as the percentage increase of CBF or coronary artery diameter in response to acetylcholine. Endothelium-independent vasodilation of the conduit coronary artery was assessed by the percentage increase of coronary artery diameter in response to nitroglycerin.[3–5] This analysis was performed by experienced observers unaware of the BNP levels.

Echocardiography

M-mode echocardiographic images were obtained in left parasternal long-axis views to measure the chamber dimension and wall thickness. Left ventricular ejection fraction was derived from two-dimensional apical four-chamber views with a modified Simpson's rule algorithm. The left ventricular end-systolic and end-diastolic volumes were also measured using the modified biplane Simpson method using the apical four-chamber and two-chamber views.[10] The left ventricular mass (LVM) was also calculated using the following formula:

$$LVM = 1.04\,[\,(IVSth + LVDd + PWth)^3 - LVDd^3\,] - 13.6$$

where IVSth is wall thickness of the intraventricular septum, and PWth is the left ventricular posterior wall thickness.[11]

BNP measurements

Blood samples were drawn via an antecubital vein after 30 min of rest on the morning of the day of the diagnostic coronary angiography. Serum BNP levels were determined by immunoradiometric assay (Shionoria kit, Shionogi and Co., Ltd).

Statistical analysis

Values are expressed as the mean ± SD. Statistical significance was designated as a p value < 0.05. Relationships between two parameters were evaluated with linear regression analysis. Comparison of the baseline cardiovascular risk variables between the two groups was performed using the Pearson chi-square test. Comparisons of hemodynamic and echocardiographic data between the study groups were performed using one-way analysis of variance.

RESULTS

A total of 63 patients were evaluated. Patient characteristics of both groups are summarized in **Tables 1** and **2**. Sex distribution, age, body mass index, coronary risk factors and medications were similar except in the two groups for a higher frequency of patients with hyperlipidemia and statin therapy in patients with LVDd $<$ 55 mm. BNP levels were significantly higher in patients with LVDd $\geq$ 55 mm than in patients with LVDd $<$ 55 mm. LVDd and left ventricular mass was significantly higher in patients with LVDd $\geq$ 55 mm than in patients with LVDd $<$ 55 mm. By contrast, left ventricular ejection fraction was significantly lower in patients with LVDd $\geq$ 55 mm than in patients with LVDd $<$ 55 mm. The ratio of patients designated as New York Heart Association (NYHA) class I was significantly lower in patients with LVDd $\geq$ 55 mm than in patients with LVDd $<$ 55 mm, whereas the ratio of patients designated as NYHA class was significantly higher in patients with LVDd $\geq$ 55 mm than in patients with LVDd $<$ 55 mm. Finally, cardiac index was significantly lower in patients with LVDd $\geq$ 55 mm than in patients with LVDd $<$ 55 mm (**Table 2**). LVDd was

Table 1 Patient characteristics

	Group 1 (n=32)	Group 2 (n=31)	p value
Men/women	25/7	22/9	NS
Age (yr, mean±SD)	60±16	61±13	NS
BMI (kg/m², mean±SD)	24±4	25±4	NS
Coronary risk factors			
Hyperlipidemia	8(25)	15(48)	<0.05
Diabetes mellitus	5(16)	4(13)	NS
Hypertension	20(63)	15(48)	NS
Smoking	8(25)	7(23)	NS
Medication			
ACE inhibitor	14(44)	7(23)	NS
AT-II antagonist	16(50)	10(32)	NS
Calcium blocker	14(44)	15(48)	NS
Statin	2(6)	8(26)	<0.05
Nitrate	11(34)	12(39)	NS

( ) : %.
Group 1 : LVDd≥55 mm, Group 2 : LVDd<55 mm.
LVDd=left ventricular end-diastolic dimension ; BMI=body mass index ; ACE=angiotensin converting enzyme ; AT=angiotensin.

Table 2 Patient characteristics

	Group 1 (n=32)	Group 2 (n=31)	p value
BNP(pg/m*l*)	228±278	52±45	<0.01
Echocardiogram			
LVDd(mm)	62±5	47±4	<0.01
LVEF(%)	55±16	73±12	<0.01
LV mass (g)	331±73	234±83	<0.01
NYHA classification			
Class I	9(28)	16(52)	<0.05
Class II	15(47)	4(13)	<0.01
ClassIII	2(6)	1(3)	NS
ClassIV	0	0	NS
Hemodynamics			
Mean AoP(mmHg)	87±18	92±18	NS
Mean PAP(mmHg)	15±5	15±4	NS
Heart rate (beats/min)	68±10	69±12	NS
PCWP(mmHg)	9±5	9±4	NS
CI (*l*/min/m²)	2.7±0.6	3.1±0.7	<0.05
SVI (ml/beat/m²)	41±9	45±9	NS

Continuous values are mean±SD. ( ) : %.
BNP=brain natriuretic peptide ; LVEF=left ventricular ejection fraction ; NYHA=New York Heart Association ; AoP=aortic pressure ; PAP=pulmonary artery pressure ; PCWP=pulmonary capillary wedge pressure ; CI=cardiac index ; SVI=stroke volume index. Explanation of the groups and other abbreviations as in Table 1.

positively correlated with BNP ($r=0.45$, $p<0.001$) in all patients (**Fig. 1**).

BNP and epicardial coronary artery

The percentage change in coronary artery diameter induced by acetylcholine is shown in **Fig. 2**. The percentage change in coronary artery diameter induced by acetylcholine in patients with LVDd ≥ 55 mm was inversely correlated with BNP level ($r=-0.56$, $p<0.001$), whereas the percentage change in coronary artery diameter induced by acetylcholine in patients with LVDd < 55 mm had no significant correlation with BNP level ($r=-0.25$, $p=0.17$). The percentage change in coronary artery diameter induced by nitroglycerin was not correlated with BNP in patients with LVDd ≥ 55 mm or in patients with LVDd < 55 mm ($r=-0.20$, $p=0.28$; $r=-0.11$, $p=0.54$, respectively). Coronary artery diameter at baseline was similar in the two groups (3.1±0.8 vs 2.8±0.8 mm, p=NS). Moreover, basal coronary artery diameter was not correlated with BNP in either of the two groups. These findings suggest that impairment in endothelium-dependent vasodilation of the epicardial coronary artery is associated with elevated plasma level of BNP in patients with left ventricular remodeling. Moreover, this impairment is not caused by increased basal coronary artery diameter in patients with left ventricular enlargement.

BNP and resistance coronary artery

CBF at baseline was similar in the two groups (100±48 vs 80±56 m*l*/min). The percentage change in CBF induced by acetylcholine in patients with LVDd ≥ 55 mm was not significantly correlated with BNP ($r=-0.31$, $p=0.17$). The percentage change in CBF induced by papaverine was not significantly correlated with BNP in patients with LVDd ≥ 55 mm ($r=-0.25$, $p=0.17$). Neither the percentage change in CBF induced by acetylcholine nor the percentage change in CBF induced by papaverine were correlated with BNP level in patients with LVDd < 55 mm ($r=-0.17$, $p=0.50$; $r=-0.28$, $p=0.18$, respectively). These results suggest that endothelium-dependent and -independent vasodilation of the resistance coronary artery is not associated with BNP regardless of the presence of left ventricular enlargement.

DISCUSSION

The present study demonstrated that elevated levels of BNP were associated with impairment in endothelium-dependent vasodilation of the epicardial coronary artery in patients with left ventricular remodeling.

Mechanisms of impaired coronary vasodilating function in the enlarged left ventricle

In the context of normally functioning endothelium, vasodilatory factors dominate and allow an appropriate increase in blood flow, primarily secondary to continuous synthesis and release of nitric oxide (NO).[12] However, abnormal endothelium and subsequent impairment in vasodilatory function is a hallmark of several vascular diseases, including heart failure.[13,14] A loss of bioactive endothelial NO has been demonstrated in the context of heart failure as a result of reduced NO synthesis, increased oxidative NO inactivation by reactive oxygen intermediate, or both.[15,16] In fact, previous studies have shown improvement in NO-mediated vasodilation after treatment with antioxidants.[17]

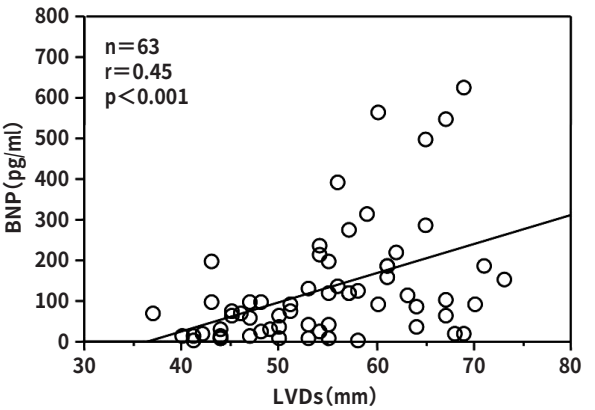

Fig. 1 Scattergram illustrating the correlation between brain natriuretic peptide and left ventricular end-diastolic dimension
Abbreviations as in Tables 1, 2.

Association of coronary endothelial function with left ventricular remodeling

Endothelium-dependent vasodilation of the coronary microvasculature was impaired in patients with dilated cardiomyopathy.[13] Other studies of hereditary cardiomyopathy in the Syrian hamster suggest that microvascular spasm related to impairments in endothelium-dependent vasodilation could result in myocardial necrosis.[18,19] By contrast, normal endothelium provides trophic support to the surrounding tissues by producing a variety of growth factors, including platelet-derived growth factor.[20,21] Therefore, deranged regulation of the production or release of these growth factors or other trophic substances could be a pathogenic feature of various cardiomyopathies. These ideas are consistent with findings from the present study that left ventricular enlargement was associated with impaired coronary endothelial function.

Association of coronary endothelial dysfunction with changes in BNP levels

The present study demonstrated that BNP levels

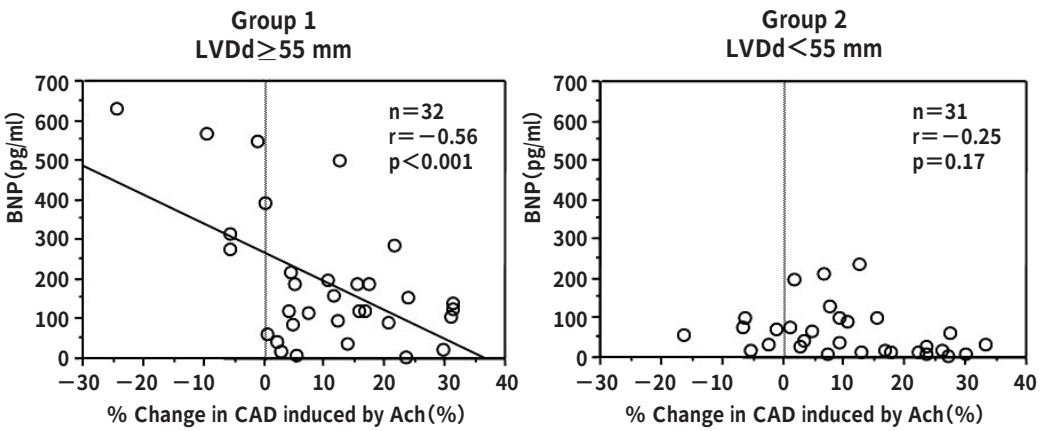

Fig. 2 Scattergrams illustrating the correlation between brain natriuretic peptide and percentage change in coronary artery diameter induced by acetylcholine in the study groups
CAD = coronary artery diameter; Ach = acetylcholine. Other abbreviations as in Tables 1, 2.

were inversely correlated with the percentage change in coronary artery diameter induced by acetylcholine in patients with left ventricular remodeling. This suggests that the increase in BNP levels in the context of left ventricular enlargement is also associated with coronary endothelial dysfunction.

Several human studies have reported a reduction in resistance vessel responsiveness to natriuretic peptides in patients with heart failure.[22–24] Although earlier data suggested that natriuretic peptides exert their effects solely via an endothelium-independent particulate guanylate cyclase pathway,[25] recent evidence suggests that the vasodilating effects may be at least partially mediated via an endothelium-dependent pathway involving NO and soluble guanylate cyclase.[26,27] Thus, endothelial dysfunction may contribute to the phenomenon of hyporesponsiveness to natriuretic peptides.

Recent studies have reported that natriuretic peptides and NO participate in reciprocal regulation of vascular tone by activating the particulate and soluble isoforms of guanylate cyclase, respectively.[26,28] These two parallel, cGMP-generating systems appear to work in tandem to regulate vascular homeostasis, and dysfunction of one system may be compensated by the intact function of the other system. Moreover, the biological activity of endothelium-derived NO is also influenced by the ambient concentration of NO and natriuretic peptides, providing further evidence that this heterologous feedback loop regulates the guanylate cyclase family of proteins and is important in determining vascular tone and local blood flow.[29,30] Such an auto-regulatory pathway may represent an important physiological homeostatic mechanism and link the paracrine activity of NO and natriuretic peptides to the regulation of vascular tone and blood pressure.

In our study, there was a significant correlation between BNP levels and endothelium-dependent vasodilation in the conductance level but not in the resistance level of the coronary artery. BNP exerts coronary vasodilator effects, predominantly in the conductance coronary artery.[31] Moreover, reciprocal regulation of vascular tone by natriuretic peptides and NO may represent an important physiological homeostatic mechanism in the regulation of blood flow, and dysfunction of one system may be compensated by the intact function of the other system.[27,28] These results may be associated with our finding of a relationship between BNP levels and endothelium-dependent vasodilation in the conductance coronary artery.

Clinical implications

Although the relationship between attenuated endothelium-dependent vasodilation and heart failure has been clearly established, further information is required to determine the role of this phenomenon in the progression of disease caused by vascular and ventricular remodeling. The improvement of cardiac function in congestive heart failure as described for statins could result in enhanced shear-stress leading to higher expression of vascular endthelial NO synthase, and so improve vascular function.[32] Therefore, the relationship between BNP levels and coronary endothelial function may be useful for monitoring the efficacy of various therapeutic interventions.

CONCLUSIONS

The elevation in plasma BNP levels that occurs in association with left ventricular enlargement is a predictor of impaired endothelium-dependent vasodilation in conductance coronary arteries.

要　約

脳性ナトリウム利尿ペプチドは左室リモデリング症例における冠動脈内皮機能の予測因子となりうる

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奥井　英樹　折原　弘治　福留　剛　新里　拓郎　市来　智子
溝口　悦子　尾辻　豊　鄭　忠和

背　景: 脳性ナトリウム利尿ペプチド（BNP）と左室リモデリングとの関連性については多くの報告があるが，冠血管機能とBNPとの関連性については不明な点が多い．

目　的: 左室の拡大に伴って増加するBNP産生と冠血管拡張機能との関連について左室リモデリングの有無に分けて検討を行った.

方　法: 冠動脈造影上，正常あるいは軽度病変の冠動脈を有する63例においてドップラーガイドワイヤーを左前下行枝に留置し，パパベリン，アセチルコリン，ニトログリセリンを投与したときの冠血流量の変化率と冠血管径の変化率を算出して冠血管機能を評価した．そして，左室拡張末期径≥55 mm群（32例）と左室拡張末期径＜55 mm群（31例）に分けてBNPと冠血管拡張能との関連について検討した.

結　果: 全症例における検討で，左室拡張末期径とBNPは有意な負の相関関係を示した（$r=0.45$，$p<0.001$）．左室拡張末期径≥55 mm群においては，BNPはニトログリセリンによる冠血管径変化率とは有意の相関は認められなかった（$r=-2.0$，$p=0.28$）ものの，アセチルコリンによる冠血管径変化率とは有意の負の相関関係を認めた（$r=-0.56$，$p<0.001$）．一方，左室拡張末期径＜55 mm群ではBNPと冠血管変化率に有意の相関関係は認められなかった．さらに，BNPと冠血流変化率の関連については，パパベリン，ニトログリセリンいずれの場合も，左室拡張末期径≥55 mm群，左室拡張末期径＜55 mm群の両群ともに有意差は認められなかった.

結　論: 左室リモデリングをきたした症例において，BNPは導管レベルの冠動脈の内皮機能の予測因子となりうる.

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