Figure 1 At admission, perfusion defects on ^{99m}Tc myocardial scintigraphy were revealed around the septum. (**Left**) Vertical long-axis images. (**Right**) Short-axis images.

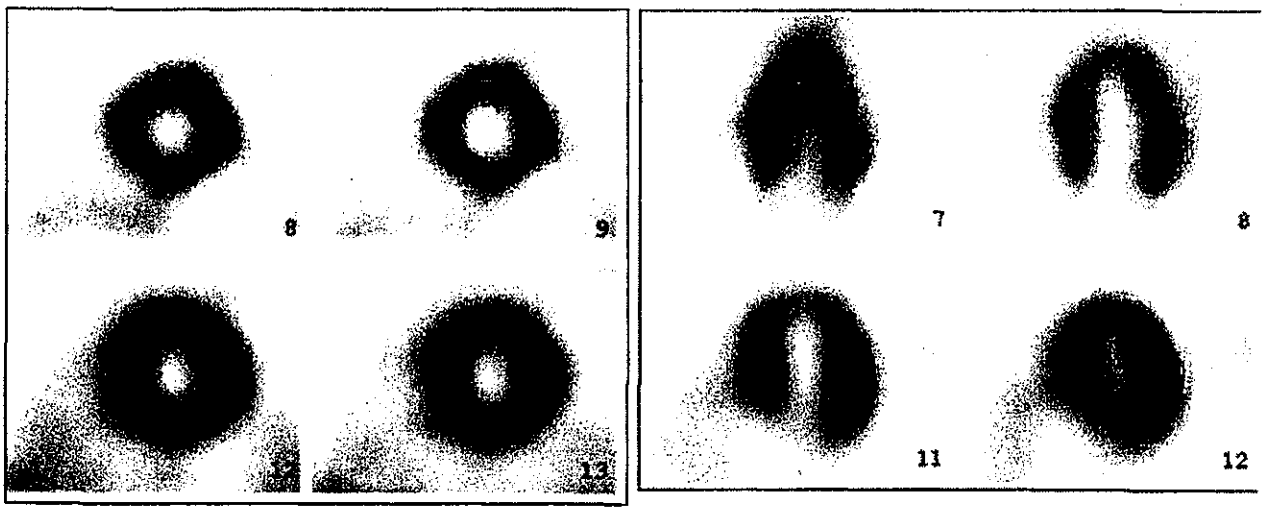

Figure 2 One month after operation, perfusion defects on ^{99m}Tc myocardial scintigraphy disappeared, (**Left**) Vertical long-axis images. (**Right**) Short-axis images.

Discussion

The prognosis for children diagnosed with CCAVB *in utero* or CCAVB associated with structural cardiac disease is generally poor. In contrast, the prognosis for children with isolated CCAVB has been considered relatively benign, with a normal life expectancy, although most patients require pacemaker implantation at some stage [4, 6, 8]. Recently, evidence has emerged that a subset of patients with isolated CCAVB develop chronic heart failure resembling DCM during follow-up, despite early pacemaker implantation [3, 11, 14]. Consequently, the long-term prognosis for isolated CCAVB is now more uncertain. One of the mechanisms of CCAVB was thought to be due to, autoimmune injury of the fetal conduction system by maternally derived IgG antibodies(anti-SSA/Ro and anti-SSB/La). Furthermore, maternal anti-SSA/Ro and anti-SSB/La antibodies react not only with the fetal conducting system but also with all fetal myocardial tissue [4]. Nevertheless, the etiology of isolated CCAVB with DCM is not fully explained [5, 8]. In our patient, maternal anti-SSA/Ro and anti-SSB/La antibodies were negative; it is difficult to believe that maternal antibody reacted with the entire fetal myocardial tissue and that isolated CCAVB with DCM developed despite pacing from the neonatal period.

Recently, it has been proposed that interventricular conduction abnormalities may impair cardiac function through ventricular asynchrony leading to cardiac failure. Therefore, biventricular or left ventricular pacing is emerging as a treatment for patients with severe heart failure or DCM with ventricular asynchrony [1, 2, 7, 12]. In patients with interventricular conduction abnormality such as LBBB, isolated LBBB caused global ventricular abnormalities manifested by shorting of diastolic filling times, changes in heart sounds, abnormal interventricular septal motion, and reduced left ventricular ejection fraction [5]. Myocardial scintigraphical studies of isolated LBBB

patients demonstrated perfusion defects in the septum without coronary artery disease. LBBB may reduce myocardial perfusion and glucose uptake in the septum because interventricular asynchrony associated with LBBB causes excess systolic thickening and augmented intramyocardial pressure in the septum [9]. In addition, in patients with right ventricular pacing, a high incidence of myocardial perfusion defects in the septum associated with pacing-induced artificial LBBB has been reported [10, 12].

In our patient, right ventricular epicardial VVI pacing from the neonatal period was associated with a gradual reduction in left ventricular function and a perfusion defect on myocardial scintigraphy in the septum to inferior segment. We thought that artificial LBBB-induced interventricular asynchrony contributed to left ventricular dysfunction, and that DDD pacing mode would be more physiological than VVI. We changed the pacing site from the right ventricular epicardium to the left ventricular epicardium and the pacing mode from VVI to DDD. The rate of 120 bpm on VVI mode is quite fast for a 5-year-old, and we cannot exclude the possibility that a tachycardia-induced cardiomyopathy may have resolved when changing to the DDD mode. However, changing the pacing site may have induced the disappearance of left ventricular asynchrony and the perfusion defects on ^{99m}Tc myocardial scintigraphy, resulting in an improved ejection fraction on QGS and echocardiography. We speculate that some patients with isolated CCAVB will develop left ventricular dysfunction caused by artificial LBBB-induced interventricular asynchrony. In patients with CCAVB and right ventricular pacing, if decreasing cardiac function or perfusion defects on myocardial scintigraphy are found, it is worthwhile to change the pacing site.

Acknowledgments We thank Professor Peter Olley and Dr. Setsuko Olley for their kind English language consultation.

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Abnormalities of Neurohormonal and Cardiac Autonomic Nervous Activities Relate Poorly to Functional Status in Fontan Patients

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Background—Impaired cardiac autonomic nervous activities and increased neurohumoral activities (CANA, NHA) characterize Fontan patients. However, the clinical significance of these changes is not clearly understood. Our purpose was to clarify the clinical significance of the CANA and NHA in stable Fontan patients.

Methods and Results—We divided 22 atriopulmonary connection (APC) and 75 total cavopulmonary connection (TCPC) patients into 4 subgroups according to New York Heart Association (NYHA) class (1.8±0.6) and measured various CANA and NHA indices. All NHA indices were elevated in the symptomatic patients ($P<0.001$). Natriuretic peptides were higher in the APC than in the TCPC patients, and the hemodynamics showed no correlation with brain natriuretic peptide in the APC patients. Low arterial oxygen saturation and impaired hemodynamics greatly influenced all elevated NHA indices ($P<0.01$), except for plasma renin activity, in the TCPC patients. Impaired CANA indices did not relate to NYHA class, although surgeries were associated with lower heart rate variability. In addition to poor correlation between NHA and CANA, age and ventricular morphology had no impact on all CANA and NHA indices, except for high norepinephrine in right ventricular Fontan patients.

Conclusions—Although symptomatic Fontan patients exhibit higher NHA, CANA is not related to either NYHA class or NHA. APC itself is responsible for higher natriuretic peptides, and arterial oxygen desaturation has a great impact on elevated NHA in the TCPC patients. These characteristics of the NHA and CANA differ from those of heart failure patients with biventricular physiology. **(*Circulation*. 2004;110:2601-2608.)**

Key Words: Fontan procedure ■ heart defects ■ nervous system, autonomic ■ hormones ■ heart failure

Activated neurohumoral activity (NHA), impaired cardiac autonomic nervous activity (CANA), and low cardiac output and reduced exercise capacity characterize Fontan patients.[1–4] These changes resemble those in adult patients with chronic heart failure (CHF) and NHA and CANA have been useful in stratifying these adult CHF patients and predicting their prognosis.[5–10] These 2 indices are also, to some extent, applicable to postoperative patients with congenital heart disease after biventricular repair, especially in adult patients.[11] However, comprehensive evaluation of Fontan patients using NHA and CANA has not been undertaken. Our hypothesis was that relationships between these 2 indices and clinical status in Fontan patients with unique single-ventricular physiology might differ from those in biventricular physiology. In addition, we thought that the type of repair and ventricular morphology and surgery-related damage might influence these 2 indices. Therefore, the purpose of the present study was to measure various NHA and CANA indices and compare the results with clinical status, including hemodynamic and cardiopulmonary capacity.

Methods

Subjects

We studied prospectively 97 clinically stable Fontan patients (2 to 34 years old) and 48 control subjects. Clinical stability meant that patients were free from intravenous medications with no major change of oral medications, and the postoperative follow-up period was at least 4 months. Of the Fontan patients, a total cavopulmonary connection (TCPC) was created in 75 and an atriopulmonary connection (APC) in 22 (Table 1). All patients had undergone cardiac catheterization within the previous 1 year. Recently, our follow-up policy has included cardiac catheterization every 5 years after the operation to evaluate hemodynamics and exercise performance unless the patient had significant neurological or orthopedic complications. Of the present Fontan patients, there were no patients with sick sinus syndrome or possible renal dysfunction (creatinine >1.0). A patient with tricuspid atresia (20 years old) who had a ventricular tachycardia easily induced during exercise was excluded from the study. We divided our patients into 2 groups according to age <16 years (low-age group, 11±3 years old, n=63) and age ≥16 years (high-age group, 19±5 years old, n=34). Medications included digoxin (n=11), diuretics (n=49), anticoagulant agents (n=56), ACE inhibitors (n=8), antiarrhythmics (n=2), and

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TABLE 1. Subject Characteristics

	Fontan			
NYHA Class	I	II	III+IV	Control
No.	29	58	10	48
Age, y	14±4	14±6	14±4	15±4
Height, cm	152±18	145±16‡	144±25*	159±16
Weight, kg	42±15*	39±14‡	34±12†	50±14
Age at Fontan, y	6±4	7±5	8±5	...
Follow-up, y	8±4	8±4	6±4	...
Diagnosis				
Isomerism	9	14	7	...
TA	8	18	1	...
UVH	8	15	3	...
DORV	6	10	3	...
MA	3	7	2	...
PA	4	1	0	...
Others	0	7	1	...
Ventricular morphology				
LV/BV/RV	16/5/8	28/11/19	0/3/7	48/0/0
Type of repair				
APC	6	14	2	...
IAR	5	16	0	...
IAG	14	19	5	...
ECR	4	9	3	...
Previous or additional procedures at Fontan				
APS	16	36	7	...
PAB	8	12	3	...
Glenn	4	13	5	...
AVVP	3	6	4	...
AAPA	2	2	1	...
Fenestration	1	2	2	...
Medications				
Digoxin	0	5	6	...
Diuretics	11	29	9	...
Anticoagulant	14	33	9	...
Antiarrhythmics	0	1	1	...
Enalapril	0	3	5	...
β-Blockers	0	1	3	...

AAPA indicates additional aortopulmonary anastomosis; APC, atriopulmonary connection; APS, aortopulmonary shunt; AVVP, atrioventricular valve plasty; BV, biventricle; DORV, double-outlet right ventricle; ECR, extracardiac rerouting; IAG, intracardiac grafting; IAR, intraatrial rerouting; LV, left ventricle; MA, mitral valve atresia; PA, pulmonary valve atresia; PAB, pulmonary artery banding; RV, right ventricle; TA, tricuspid valve atresia; and UVH; univentricular heart. Values are mean±SD.

*$P<0.05$, †$P<0.01$, ‡$P<0.001$ vs control.

β-blockers (n=4). The total number of surgical procedures including the Fontan operation ranged from 1 to 6 (mean, 2.6 operations per patient). Operations before the Fontan included systemic-to-pulmonary shunt(s) (n=59), pulmonary arterial banding (n=23), Glenn anastomosis (n=22), and atrioventricular valvuloplasty or valve replacement (n=13). Fenestration was created in 5 patients at the time of the Fontan operation and spontaneously closed in 2 patients 1 year after the operation. The age-matched control subjects were being followed up at our institute because of a history of coronary artery dilatation, aneurysm, or both because of Kawasaki disease, and all underwent follow-up selective coronary angiography to evaluate possible stenosis of the coronary arteries. Our control subjects showed no significant stenotic lesions of the coronary arteries.[1,5]

Postoperative Status Based on New York Heart Association Classification

Because the New York Heart Association (NYHA) classification of cardiac status applies to adult cardiac patients, a modification of the classification was used for child patients.[12]

Hemodynamics, Ventricular Morphology, and Calculation of Volume

Cardiac catheterization was performed in 95 patients and 46 control subjects within 1 week of exercise testing. We measured pressures in the cardiac chambers and great vessels. We estimated oxygen consumption from the age, sex, and heart rate (HR) and measured cardiac index ($L \cdot min^{-1} \cdot m^{-2}$) using the Fick principle with the assumption that right and left pulmonary arterial saturations were equal in patients with either a Glenn anastomosis or a TCPC, because it is clinically difficult to measure accurate flow distribution of the bilateral pulmonary arteries. Ventricular morphology was determined angiographically, and patients were divided into 3 groups,[1] ie, those with (1) a dominant left ventricle with or without a rudimentary right ventricle, (2) presence of both right and left ventricles, and (3) a dominant right ventricle with or without a rudimentary left ventricle. In this study, the groups consisted of 43, 19, and 35 patients, respectively. Patients with 2 ventricles in whom the volume of the smaller ventricle was either >30% of the main ventricle or was >50% of the predicted normal value were included in the biventricular group.[1] We used Simpson's rule to estimate morphological right and left ventricular volumes. End-diastolic ventricular volume was divided by body surface area to obtain end-diastolic volume index (EDVI), and systemic ventricular ejection fraction (EF) was calculated.[1,5]

Neurohumoral Activities

After at least 15 minutes of supine rest, the plasma norepinephrine (NE) level,[13] atrial and brain natriuretic peptides (ANP, BNP), and renin activity (PRA) were determined in 95, 96, and 94 Fontan patients, respectively, and in all control subjects.[14–16] Plasma endothelin-1 (ET-1) was determined by radioimmunoassay in 62 Fontan patients and 22 control subjects.[17]

Heart Rate Variability and Arterial Baroreflex Sensitivity

Heart rate variability (HRV) and arterial baroreflex sensitivity (BRS) were measured in 138 and 132 patients, respectively. The methods have been reported previously.[5] Briefly, after a 15-minute supine rest, ECG signals were recorded for 5 minutes, and beat-to-beat fluctuations were transformed into frequency domains by use of a fast Fourier transformation. The spectral HRV was expressed as a low-frequency (LF) component (0.04 to 0.15 Hz) and a high-frequency (HF) component (0.15 to 0.40 Hz), and the logarithmic values log LF and log HF were used. We used a bolus phenylephrine method to measure BRS (ms/mm Hg).[18]

[^{123}I]Metaiodobenzylguanidine Scintigraphy

The methodology for this index was identical to that previously reported.[5] Metaiodobenzylguanidine (MIBG) scintigraphy was performed in 70 patients to evaluate myocardial adrenergic nervous activity. Myocardial images were acquired 4 hours after tracer injection, and the heart-to-mediastinal activity ratio (H/M) was calculated.

Pulmonary Function Tests

We measured vital capacity (VC, in liters) and percent forced expiratory volume in 1 second in 134 patients (Spirosift, SP-600, Fukuda Denshi), and VC was calculated as the percentage of the body height–predicted normal value for our institute.

Exercise Protocol

One hundred forty-two patients underwent symptom-limited treadmill exercise,[19] and peak oxygen uptake ($pV\dot{O}_2$) ($mL \cdot kg^{-1} \cdot min^{-1}$) and systolic blood pressure were measured and calculated as the percentage of body weight–predicted normal value for our institute. We used a 12-lead ECG to determine HR. Ventilation and gas exchange were measured by use of a breath-by-breath method using a hot-wire anemometer (Riko AS500, Minato Medical Science) with a mass spectrometer (MG-300, Perkin Elmer). Minute ventilation versus carbon dioxide production slope ($\dot{V}_E$-$\dot{V}CO_2$ slope) was determined and expressed as the percentage of our age- and sex-matched predicted normal values.

Informed Consent

Informed consent was obtained from all patients and/or their parents. We asked control subjects and/or their parents to participate as volunteers. The Ethics Committee of the National Cardiovascular Center approved the study protocol.

Statistical Analysis

Differences in hemodynamics, NHA, CANA, and exercise variables were evaluated using 1-way ANOVA with Bonferroni post hoc test. Univariate and stepwise multivariate linear regression analysis was used to detect independent determinants of CANA, NHA, and cardiopulmonary variables. Data are expressed as the mean±SD. A probability value of $P<0.05$ was considered statistically significant.

Results

NYHA Classification

The numbers of patients in the control and NYHA I, II, and III+IV categories were 48, 29, 58, and 10, respectively. Hemodynamics, NHA, CANA, and exercise variables for each category are shown in Table 2. Representative data according to NYHA classification are shown in the Figure.

Hemodynamics

Low cardiac output was observed in proportion to functional severity, whereas a low EF with increased EDVI and elevated central venous and pulmonary artery pressures was present in NYHA III+IV. When symptomatic patients (NYHA II–IV) were compared with asymptomatic patients (NYHA I), there was no difference in any index between low- and high-age groups, except for a lower cardiac index in the high-age group ($P<0.05$) (Figure). Cardiac index was higher and arterial oxygen saturation (Sao_2) was lower in the TCPC than in the APC patients ($P<0.01$).

Neurohumoral Activity

All NHA indices were elevated in proportion to functional capacity ($P<0.001$). BNP and NE in particular differentiated NYHA II from NYHA III+IV ($P<0.01$ to 0.001). Although all NHA indices were higher in the symptomatic patients than in the asymptomatic patients, no differences in these indices were observed between the asymptomatic patients and control subjects, except for ANP. Natriuretic peptides were higher in the APC than in the TCPC patients ($P<0.001$). There were no differences in NHA indices between low- and high-age groups.

Cardiac Autonomic Nervous Activity

All CANA indices were markedly abnormal; however, they could not differentiate these patients on the basis of their functional classification, except for H/M in NYHA class III+IV. Moreover, there was no difference in CANA indices between symptomatic and asymptomatic patients, between low- and high-age groups, or between the APC and the TCPC patients.

TABLE 2. Hemodynamics, Neurohormonal and Cardiac Autonomic Nervous Activities, and Cardiopulmonary Variables According to NYHA Functional Status in Fontan Patients

		NYHA Class		
Group	Control (n=48)	I (n=29)	II (n=58)	III+IV (n=10)
Hemodynamics	(n=46)	(n=29)	(n=57)	(n=10)
Central venous pressure, mm Hg	3±1	11±3‡	12±3‡	14±4‡‖#,
Pulmonary artery pressure, mm Hg	13±2	10±2‡	11±3†	13±4‖#
EDP, mm Hg	11±2	7±3‡	8±3‡	9±4
EF, %	65±8	55±11‡	52±11‡	38±16‡¶‡‡
EDVI, mL/m^2	80±15	77±20	79±27	115±47‡¶‡‡
Cardiac index, L·min^{-1}·m^{-2}	3.6±0.6	2.7±0.7‡	2.4±0.6‡§	2.1±0.5‡§
Arterial oxygen saturation, %	98±1	95±2‡	95±3‡	90±8‡¶‡‡
Neurohormonal activity				
Norepinephrine, pg/mL	158±71	205±76	256±130‡§	365±195‡¶††
ANP, pg/mL	20±10	45±45*	68±53‡§	95±83‡‖
BNP, pg/mL	5±4	24±27	43±62‡	127±148‡¶‡‡
PRA, ng·mL^{-1}·h^{-1}	3.0±2.2	5.3±3.2*	8.3±11.1‡	12.1±8.2‡!
ET-1, pg/mL	3.2±1.4	3.7±1.1	5.4±2.8†§	7.2±5.6‡‖
Cardiac autonomic nervous activity				
log LF	2.6±0.4	1.7±0.5‡	1.5±0.6‡	1.5±0.4‡
log HF	2.5±0.5	1.4±0.6‡	1.2±0.5‡	1.3±0.6‡
BRS	17.5±5.9	3.8±3.5‡	3.0±3.0‡	1.9±2.2‡
H/M	2.9±0.5	1.8±0.3‡	1.7±0.4‡	1.4±0.5‡§
Exercise variables	(n=48)	(n=29)	(n=56)	(n=9)
Peak $\dot{V}o_2$, % predicted	96±13	60±8‡	50±7‡¶	36±6‡¶‡‡
$\dot{V}E$-$\dot{V}co_2$ slope, % predicted	99±13	125±21‡	135±24‡§	168±54‡¶‡‡
Pulmonary function	(n=43)	(n=28)	(n=54)	(n=9)
Vital capacity, % predicted	99±14	76±16‡	70±17‡	57±10‡‖#
Forced expired volume in 1 second, %	91±8	89±6	88±7	86±9

ANP indicates atrial natriuretic peptide; BNP, brain natriuretic peptide; BRS, arterial baroreflex sensitivity; EDP, end-diastolic pressure; EF, ventricular ejection fraction; EDVI, end-diastolic volume index; H/M, heart-to-mediastinal metalodobenzylguanidine activity ratio; PV, pulmonary ventricle; SV, systemic ventricle; LF and HF, low- and high-frequency components of heart rate variability; and $\dot{V}E$-$\dot{V}co_2$ slope, ventilation versus bicarbon dioxide production slope.

*P<0.05, †P<0.01, ‡P<0.001 vs control; §P<0.05, ‖P<0.01, ¶P<0.001 vs I; #P<0.05, ††P<0.01, ‡‡P<0.001 vs II. Values are mean±SD.

Vital Capacity

VC was small in all Fontan groups, especially in the III+IV patients, whereas their percent forced expiratory volume in 1 second was maintained. However, no significant difference in pulmonary function was observed between low- and high-age groups or between the APC and TCPC patients.

Exercise Variables

Although there was no difference between the low- and high-age groups or the APC and the TCPC patients, $p\dot{V}o_2$ decreased and $\dot{V}E$-$\dot{V}co_2$ slope increased in proportion to NYHA classification (P<0.001).

Correlation Between NHA and CANA

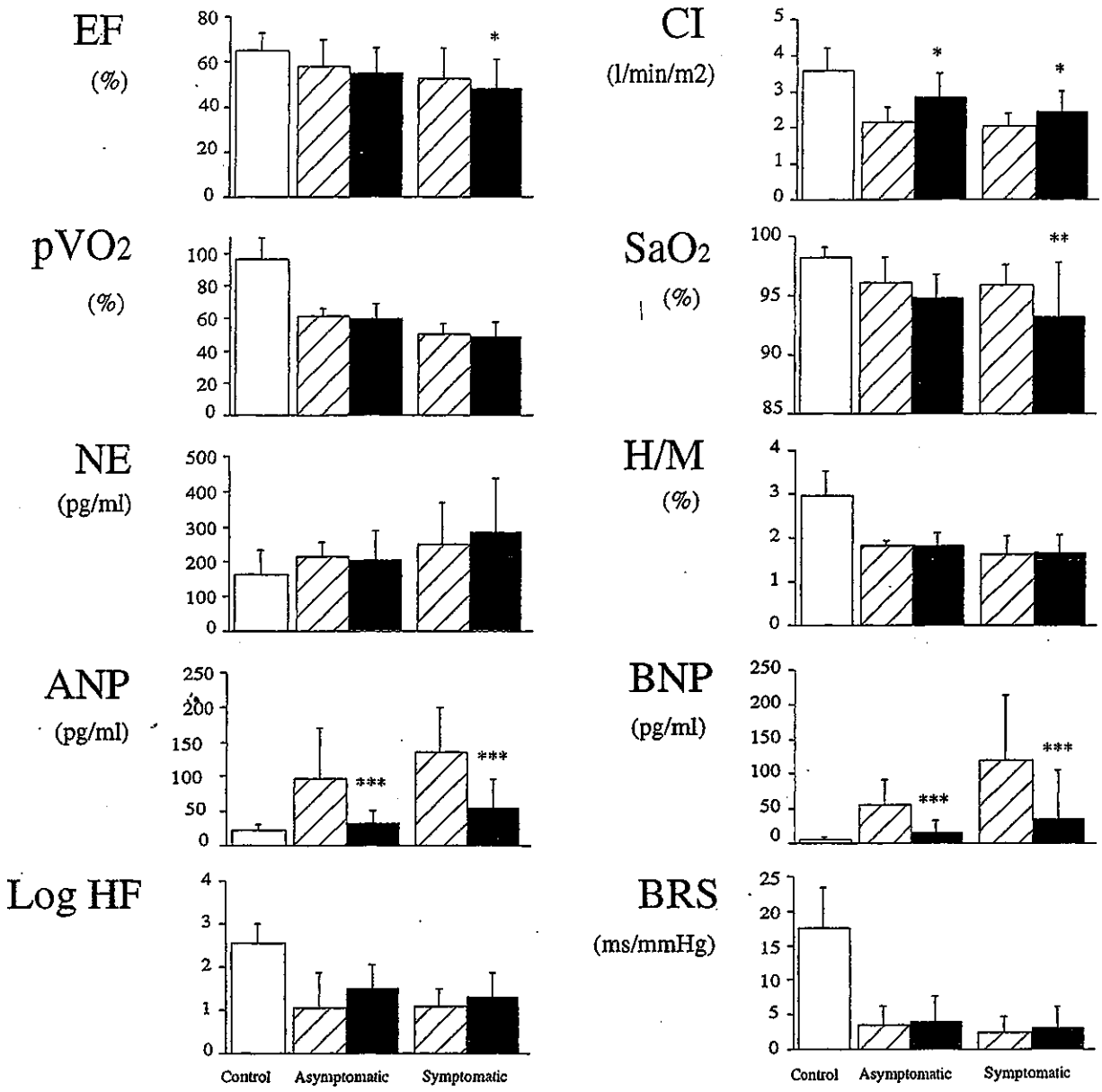
Relationships between NHA and CANA indices are shown in Table 3. NE correlated weakly with PRA and H/M. Natriuretic peptides and ET-1 correlated well with each other; however, relationships between NHA and CANA indices were either weak or nonexistent. BRS correlated closely with HRV, whereas no correlation between H/M and HRV or BRS was observed, except for log LF. Although NE, BNP, and ET-1 correlated inversely with $p\dot{V}o_2$, only H/M showed a weak positive correlation with $p\dot{V}o_2$.

Multivariate Analysis

To determine the independent factors, the following parameters were used: age at tests and definitive repair, sex, follow-up period, number of surgeries, hemodynamics, VC, medications (diuretics), and exercise capacity (Table 4).

New York Heart Association

High BNP and low EF were major determinants of low NYHA class in all Fontan patients (P<0.0001). When the TCPC patients were analyzed separately, ANP and EF were the major determinants of NYHA classification.



Relationship between categorized groups according to symptom-based classification and clinical variables. Abbreviations as in Table 2. CI indicates cardiac index. White, shaded, and black bars represent control subjects, APC, and TCPC patients, respectively. *$P<0.05$, **$P<0.01$, and ***$P<0.001$ versus APC patients.

Neurohumoral Activity

A high NE was determined by high age at operation and large EDVI ($P<0.01$). Both high natriuretic peptides were determined by the repair of APC, large EDVI, low Sao_2, and low cardiac output ($P<0.0001$). Male sex also determined high ANP. High PRA depended on the use of diuretics and low aortic blood pressure ($P<0.0001$) and high ET-1 on low cardiac output and low VC ($P<0.01$).

When the APC patients were analyzed, although low cardiac output and high ventricular end-diastolic pressure correlated with high ANP ($P<0.01$), no other indices were associated with high natriuretic peptides, except for use of diuretics for high PRA and ET-1 ($P<0.05$). When the TCPC patients were analyzed, high age at exercise and low Sao_2 correlated with high NE ($P<0.005$). Low Sao_2 also correlated with high natriuretic peptides and ET-1. In addition, low cardiac output and large EDVI were associated with high ANP and BNP, respectively. High PRA was determined by low arterial pressure and the use of diuretics ($P<0.0001$). Higher age at repair, short follow-up duration, and the use of diuretics were associated with high ET-1.

Autonomic Nervous Activity

A large number of surgical procedures, APC type repair, and low cardiac output correlated with low log LF and HF ($P<0.005$ for both). BRS was determined by low cardiac output and VC ($P<0.005$). Only the use of diuretics correlated with low H/M ($P<0.01$).

In APC patients, a high EDP correlated with a low BRS ($P<0.05$), and a low H/M was determined by a large number

TABLE 3. Correlation Coefficients Between Neurohumoral and Cardiac Autonomic Nervous Activities in Fontan Patients

	Neurohormonal Activity					Cardiac Autonomic Nervous Activity			Exercise
	ANP	BNP	PRA	ET-1	log LF	log HF	BRS	H/M	Peak Vo_2, %
Neurohormonal activity									
Norepinephrine	NS	NS	0.23*	NS	NS	NS	NS	−0.33†	−0.37‡
ANP	...	0.83‡	NS	0.50‡	−0.21*	0.25*	NS	NS	NS
BNP	...	...	NS	0.58‡	NS	NS	−0.21*	NS	−0.21*
PRA	...	...	...	NS	NS	NS	NS	NS	NS
ET-1	...	...	...	...	−0.34†	−0.35†	−0.40‡	−0.40†	−0.42‡
Cardiac autonomic nervous activity									
log LF	...	...	...	...	...	0.81‡	0.68‡	0.34†	NS
log HF	...	...	...	...	...	...	0.59‡	NS	NS
BRS	...	...	...	...	...	...	...	NS	NS
H/M	...	...	...	...	...	...	...	...	0.27*

Abbreviations as in Table 2.
†$P<0.001$; ‡$P<0.0001$.

of surgical procedures and high central venous pressure ($P<0.001$). For the TCPC patients, only a large number of surgical procedures correlated with low HRV and BRS ($P<0.001$), whereas a longer follow-up period was associated with high H/M ($P<0.05$).

Vital Capacity

In addition to low Sao_2 and higher age at Fontan repair, a large number of surgical procedures correlated with a low VC ($P<0.0001$).

$\dot{V}E$-$\dot{V}co_2$ Slope

High NE and low EF and Sao_2 correlated with a high $\dot{V}E$-$\dot{V}co_2$ slope ($P<0.0001$).

Subgroup Analysis

Normal Versus Abnormal Natriuretic Peptides in NYHA I

Of 29 Fontan patients in NYHA I, 9 and 14 patients showed high ANP (>40 pg/mL) and BNP (>13 pg/mL), respectively. However, no differences in cardiovascular reserve (peak HR, systolic blood pressure, $p\dot{V}o_2$, including VC) were observed between the high natriuretic peptide and the normal-range patients. The percentage of patients receiving diuretics was not different between the 2 groups.

Influence of Ventricular Morphology on CANA and NHA

NYHA class, EF, Sao_2, and $p\dot{V}o_2$ were lower and $\dot{V}E$-$\dot{V}co_2$ slope was higher in the right ventricular type than the left ventricular type Fontan patients (Table 5, $P<0.05$ to 0.0001). However, ventricular morphology had no influence on the CANA or NHA indices, except for higher NE in the right ventricular type group ($P<0.05$).

Discussion

We found that, in Fontan patients, (1) natriuretic peptides and EF were major determinants of NYHA status; (2) all NHA indices were elevated, although there was no difference between asymptomatic patients and control subjects; (3) APC

TABLE 4. Major Determinants and Their Standard β-Coefficients for Neurohumoral and Cardiac Autonomic Nervous Activities

		Surgery			Hemodynamics				Medications	Lung	
Variables	Sex	Number	Age at Fontan	APC/TCPC	EDVI	MAO	Sao_2	CI	Diuretics	VC	*P*
NE			0.23		0.22						<0.01
ANP	−0.21			−0.60	0.16		−0.27	−0.26			<0.0001
BNP				−0.52	0.24		−0.34	−0.19			<0.0001
PRA						−0.33			0.36		<0.0001
ET-1								−0.37		−0.28	<0.01
log LF		−0.35		0.24				0.24			<0.001
log HF		−0.33		0.26				0.22			<0.005
BRS								0.29		0.31	<0.005
H/M									−0.39		<0.005
VC		−0.68	0.17				0.17			...	<0.0001
$\dot{V}E/\dot{V}co_2$							−0.53				<0.0001

MAO indicates mean aortic pressure. Other abbreviations as in Table 2.

TABLE 5. Hemodynamics, Neurohormonal and Cardiac Autonomic Nervous Activities, and Cardiopulmonary Variables According to Systemic Ventricular Morphology

Group	LV (n=43)	BV (n=19)	RV (n=35)
Age, y	14±5	14±6	14±5
NYHA class	1.6±0.5	1.9±0.7	2.0±0.7†
APC/TCPC	14/29	3/16	5/30
Hemodynamics			
Central venous pressure, mm Hg	11±3	12±3	12±3
EF, %	55±12	49±12	48±13*
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.6±0.7	2.5±0.5	2.3±0.6
Arterial oxygen saturation, %	95±2	95±2	93±5*
Neurohormonal activity			
Norepinephrine, pg/mL	228±121	234±112	291±148*
ANP, pg/mL	72±62	51±48	61±52
BNP, pg/mL	52±70	38±60	44±85
Cardiac autonomic nervous activity			
log HF	1.2±0.6	1.3±0.7	1.3±0.5
BRS	2.9±3.3	3.7±3.2	3.0±3.0
H/M	1.7±0.3	1.7±0.5	1.7±0.4
Exercise variables			
Peak $\dot{V}o_2$, % predicted	56±8	50±12*	48±10‡

LV, BV, and RV indicate left, biventricular, and right ventricular type ventricle as a systemic ventricle, respectively. Other abbreviations as in previous tables. Values are mean±SD.

*$P<0.05$, †$P<0.01$, ‡$P<0.001$ vs LV.

itself was responsible for high natriuretic peptides, and decreased Sao_2 had a great impact on the elevated NHA in the TCPC patients; and (4) although cardiac surgeries were related to CANA, impaired CANA had no influence on NHA or NYHA status.

Neurohormonal Activities

Bolger et al[20] described the clinical use of NHA to stratify adult patients with congenital heart disease. However, it is not clear whether the relationship between NHA abnormalities and functional status applies to Fontan patients because of the wide variety of their diseases. Our study demonstrates that stratification based on the abnormal NHA is less significant in Fontan patients than has been reported in biventricular physiology patients, although symptomatic patients exhibit a high NHA. In fact, we could not find any difference in hemodynamics and cardiovascular reserve between asymptomatic patients with elevated NHA and those without. APC itself, rather than the hemodynamics, has a great impact on higher natriuretic peptides and ET-1. An increased secretion of BNP and ANP from the hypertrophied atrial myocardium in the APC patients may be responsible for the high natriuretic peptides.[21] Interestingly, Sao_2 has a significant impact on the elevated NHA in the TCPC patients. Resting (and maybe exercise-induced) decreased Sao_2 also causes sympathetic nervous activation[22] and excess ventilation,[23] and these are related to poor prognosis in adult heart failure patients.[10] Moreover, in addition to sympathetic dominant CANA,[24] high natriuretic peptides may worsen the Fontan patients' hypercoagulable state because of their diuretic effect.[25] The mechanism responsible for high ET-1 is unidentified in the present study, but the low pulmonary arterial oxygen saturation because of low cardiac output in addition to nonpulsatile flow may be an explanation.[26] The presence of a low systemic blood pressure and the use of diuretics imply that the renin-angiotensin system is important to maintaining perfusion pressure in these patients.

Cardiac Autonomic Nervous Activity

CANA indices are prognostic guides in patients after myocardial infarction[8] and with heart failure.[9,27] However, the benefit of HRV in severe patients may be slight,[28] and this is especially true in Fontan patients because of their severely impaired CANA.[11] In addition, the lack of a relationship between CANA and exercise capacity also makes clinical classification difficult. In contrast to biventricular patients,[11] the prolonged lack of reinnervation after the Fontan procedure may explain the absence of a difference in CANA indices between child and adult patients.[5] In addition to the influence of surgical technique, low cardiac output is associated with a lower HRV and BRS and high NHA; consequently, maintaining a good cardiac output is important in patients with Fontan physiology. Alternatively, the Fontan circulation per se may cause a low H/M, because even the NYHA I patients without significant elevation in NE showed a low value, and no correlation between surgical procedures and H/M was observed. The reason why the use of diuretics had a significant impact on the low H/M, as observed in the biventricular patients, is unclear in the present study.[11]

Exercise Variables and VC

Exercise capacity by definition determines the NYHA classification. VC distinguished the asymptomatic from the symptomatic patients, and the $\dot{V}E/\dot{V}Co_2$ slope identified relatively severe patients.[29] Mismatched ventilation-perfusion in the lung and elevated dead space ventilation have been considered to be major determinants of the excess ventilation in Fontan patients. However, the significant arterial desaturation also has a great impact on the excess ventilation in these patients, as demonstrated in the present study.

Clinical Implications

Although natriuretic peptides and ventricular function stratify patients in line with their NYHA classification, we should be aware of the discrepancy between NHA and functional status, especially the lack of relationship between BNP and EF in the APC patients and the decreased sensitivity of NHA and CANA for detecting a reduced cardiovascular capacity. These present results imply that the diagnostic information from NHA and CANA indices cannot be applied to Fontan patients in the same manner as for patients with biventricular physiology.[11]

Nevertheless, considering the many clinical findings in adult cardiac patients, the abnormal physiological and biochemical findings in Fontan patients, even when they are asymptomatic, imply that they have a poor prognosis and suggest the need for treatment for these patients. In addition to congenitally determined factors (ventricular morphology,

function of the atrioventricular valve) and surgery-associated issues such as age at operation, functional status (NYHA class) is a possible determinant of their poor long-term prognosis.[30] In this respect, nonsurgical interventions that focus on maintaining physical fitness through exercise training and medication to prevent deterioration in EF and NHA are rational. Furthermore, we need to follow the unique contributions of NHA and CANA to the long-term prognosis in these patients.

Study Limitations

Although we focused on Fontan patients, their surgical procedures varied from patient to patient. In addition, the structural anatomic variability in our study population is marked. However, a prospective randomized trial in these patients is clinically difficult and would require a very large number of patients. Another limitation is that our control subjects are not entirely normal; microangiitis may exist even when there is no apparent radiographic abnormality, and this may influence CANA or NHA or both.

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Successful Treatment of Refractory Vasospastic Angina With Corticosteroids

—— Coronary Arterial Hyperreactivity Caused by Local Inflammation? ——

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Background Although vasospastic angina usually responds well to treatment with calcium antagonists and/or nitrates, there have been anecdotal case reports of refractory vasospastic angina resistant to intensive treatment with high doses of calcium antagonists and nitrates.

Methods and Results Four patients with vasospastic angina, which was refractory to intensive treatment with high doses of calcium antagonists and nitrates, were completely controlled after administration of corticosteroids. Although none of the 4 patients showed eosinophilia, all had bronchial asthma or chronic thyroiditis, and in 2 cases, the activity of vasospastic angina corresponded with that of bronchial asthma.

Conclusions These findings suggest that in these patients, coronary spasm may have been induced by arterial hyperreactivity because of local inflammation in the coronary arterial wall and that the corticosteroids suppressed the arterial hyperreactivity by alleviating the inflammation. Corticosteroids may be considered as a treatment choice for patients with refractory vasospastic angina, particularly when the patient has an allergic tendency, such as bronchial asthma. (*Circ J* 2004; **68:** 17–22)

Key Words: Coronary artery spasm; Corticosteroids; Inflammation; Vasospastic angina

Vasospastic angina (VSA) usually well responds to treatment with calcium antagonists and nitrates. We present 4 cases of VSA that was refractory to intensive anti-anginal treatment with high doses of calcium antagonists, nitrates and nicorandil.

Clinical Reports

Case 1

A 39-year-old woman was admitted to hospital because of frequent chest pain at rest (Table 1). She had chronic thyroiditis, which had been controlled with medications 11 years ago. Ten years ago, she suffered from anteroseptal myocardial infarction, and thereafter, had chest pain of short duration at rest 3–4 times per year for several years. Four years ago, she was admitted to hospital for work-up for worsening chest pain. A diagnosis of VSA was made because the 12-lead electrocardiogram (ECG) showed transient ST segment elevation in leads II, III and aVF during her chest pain attacks and coronary arteriography (CAG) showed normal coronary arteries without any atherosclerotic stenosis. Treatment with nifedipine 80 mg/day was begun, which effectively controlled her angina.

One month before the current admission, chest pain attacks at rest occurred 5–10 times per day despite intensive treatment with nifedipine (80 mg/day), isosorbide dinitrate (ISDN) (160 mg/day) and nicorandil (80 mg/day), and she was admitted with the diagnosis of unstable angina. The angina attacks were not related to her menstrual cycle. Analysis of her blood sample did not show any eosinophilia or elevation of serum inflammatory markers. Despite continuous intravenous infusion of both nitroglycerin ($2\mu g \cdot kg^{-1} \cdot min^{-1}$) and nicorandil (2 mg/h), the frequent chest pain attacks with ST segment elevation were not suppressed (Fig 1). CAG showed normal coronary arteries without any atherosclerotic stenosis and ultrasound cardiography (UCG) showed the anteroseptal old myocardial infarction without any new contraction abnormality. Oral administration of prednisolone 40 mg/day was begun, resulting in a complete relief of the chest pain attacks within 1 week, and the intravenous nitroglycerin and nicorandil were discontinued uneventfully. Because her angina recurred after a quick tapering of prednisolone to 5 mg/day, the dose was increased to 20 mg/day, resulting in amelioration of the angina again.

After her angina was satisfactorily controlled with prednisolone, we administered a placebo of prednisolone, while keeping other anti-anginal drugs unchanged, and her angina worsened again. Thereafter, prednisolone was slowly tapered off without a relapse of the angina. She remained well controlled with nifedipine, ISDN and nicorandil until 6 months after discontinuation of prednisolone, when she was re-admitted to hospital with a severe attack of VSA complicated with ventricular fibrillation. Despite intensive therapy, she died of multiple organ failure on the

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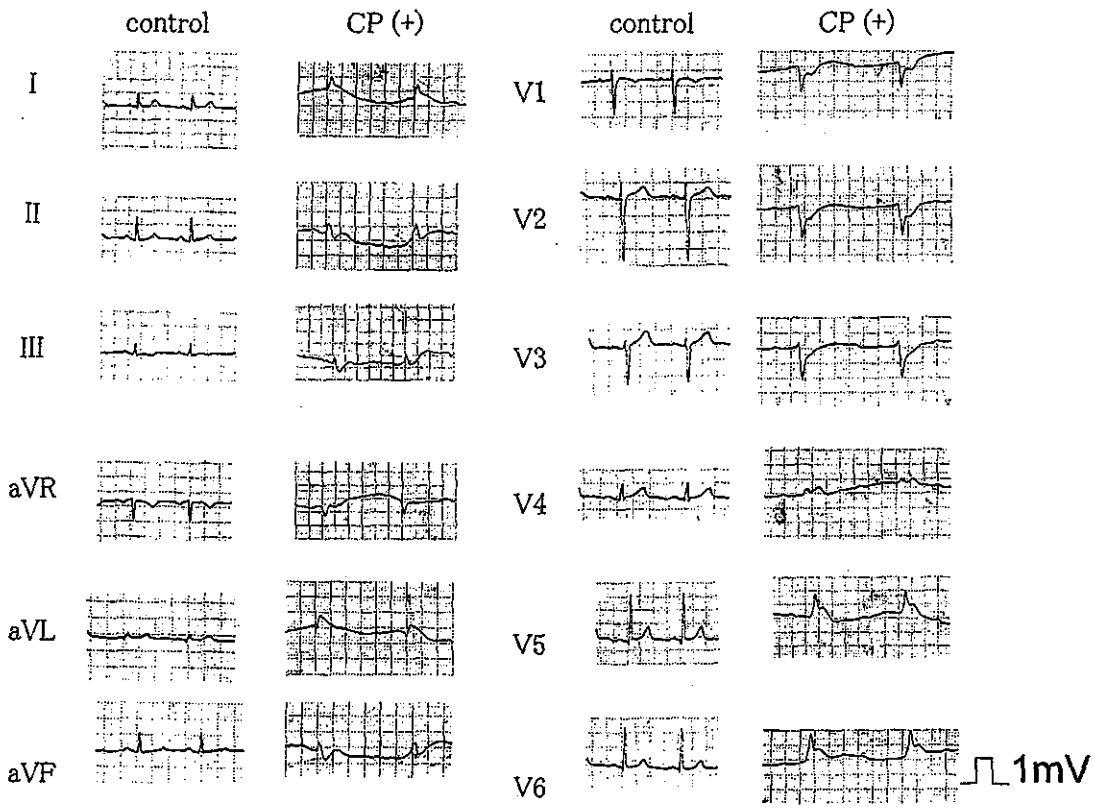

Fig 1. ECG of Case 1 showing bradycardia (heart rate: 50 beats/min), ST elevation in leads I, aV_L and V_{4-6} and ST depression in leads V_{1-3} during chest pain (CP (+)) compared with control ECG.

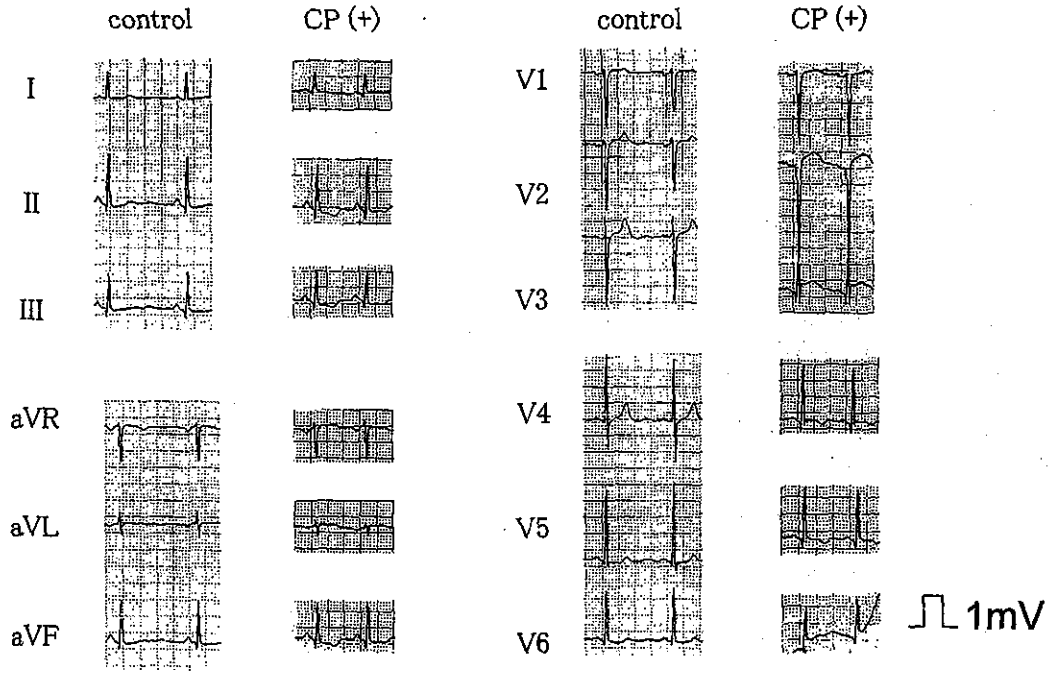

Fig 2. ECG of Case 2 showing ST elevation in leads V_{2-4} during chest pain (CP (+)) compared with control ECG.

82nd hospital day.

Case 2

A 43-year-old woman was admitted to hospital as an emergency because of frequent chest pain attacks at rest. She had bronchial asthma, which was controlled with medications 2 years ago. In the same year, she was admitted to hospital for work-up for episodes of chest pain at rest. CAG

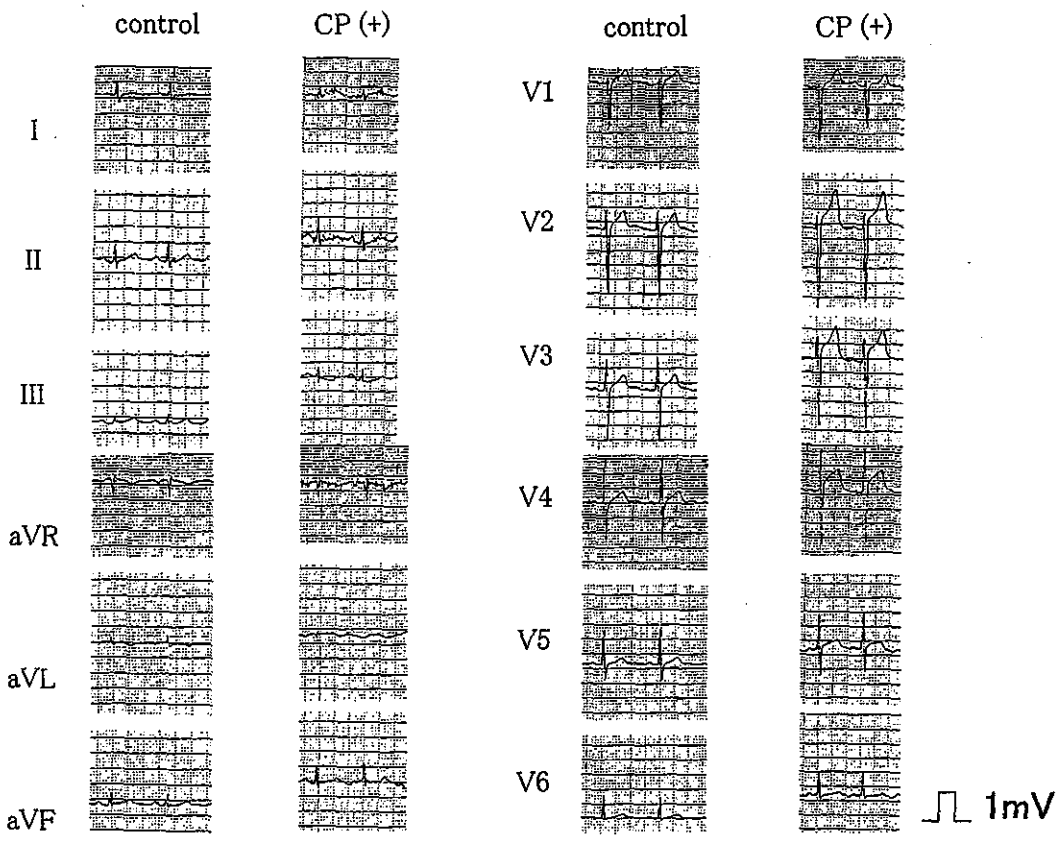

Fig 3. ECG of Case 3 showing ST elevation in leads I, aV_L and V_{2-5} during chest pain (CP (+)) compared with control ECG.

Table 1 Characteristics of the 4 Cases

	Case no.			
	1	*2*	*3*	*4*
Gender	*Female*	*Female*	*Male*	*Female*
Onset age (year)	*29*	*41*	*45*	*43*
Smoking habit	*(–)*	*Past**	*(–)*	*(–)*
Diabetes mellitus	*(–)*	*(–)*	*(–)*	*(–)*
Hyperlipidemia	*(–)*	*(–)*	*(+)*	*(–)*
Hypertension	*(–)*	*(–)*	*(+)*	*(+)*
Complicating disease	*Chronic thyroiditis*	*Bronchial asthma*	*Bronchial asthma*	*Bronchial asthma*

Onset age, age at the onset of vasospastic angina; Past, history of smoking when 20–38 years old.*

showed no atherosclerotic stenosis in the coronary arteries and intracoronary administration of ergometrine maleate (40 μg) induced a transient occlusion of the left anterior descending coronary artery accompanied by ST segment elevation in leads V_{2-4} and chest pain, which were promptly relieved by intracoronary administration of 0.5 μg nitroglycerin (Fig 2). A diagnosis of VSA was made and treatment with nifedipine (40 mg/day), diltiazem (120 mg/day), nicorandil (20 mg/day) and ISDN (160 mg/day) effectively controlled her angina.

Ten days before the current admission, her bronchial asthma and chest pain attacks at rest recurred and worsened progressively. She was admitted as an emergency. There was no sign of heart failure and the chest pain attacks were not related to her menstrual cycle. Analysis of her blood sample showed a slight elevation of C-reactive protein (CRP: 0.5 mg/dl; normal <0.3 mg/dl), but did not show eosinophilia or an elevation of the erythrocyte sedimentation rate. Apart from the bronchial asthma, her chest pain at rest was diagnosed as VSA because it was accompanied by ST segment elevation in the anterior chest leads on ECG. Intravenous administration of corticosteroids (hydrocortisone sodium succinate 600 mg/day) and aminophylline (500 mg/day) was added to her regimen of oral anti-anginal drugs (nifedipine 40 mg/day, diltiazem 120 mg/day, nicorandil 20 mg/day and ISDN 160 mg/day) and a broncho-dilator (procaterol hydrochloride 100 μg/day), which successfully relieved both the bronchial asthma and angina attacks with ST segment elevation. Oral prednisolone (5 mg/day) was administered thereafter without any relapse of angina attacks. An uneventful course was confirmed at 5-year follow-up.

Case 3

A 55-year-old man was admitted to hospital as an emergency because of frequent chest pain attacks at rest. He had

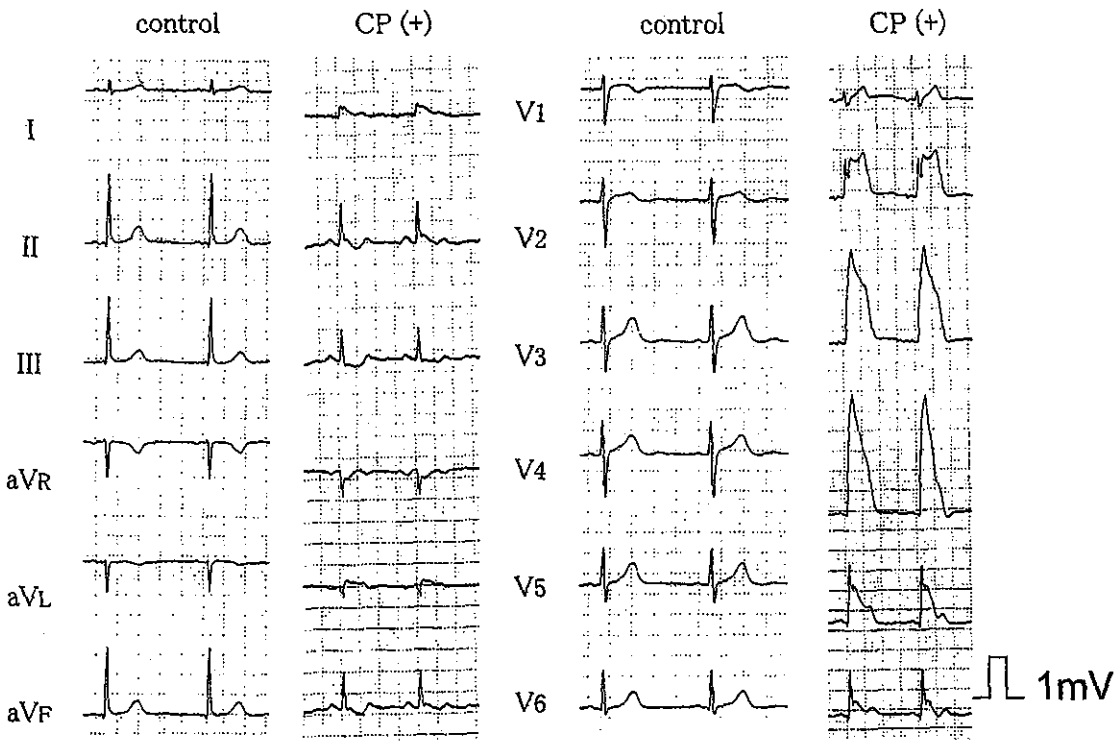

Fig4. ECG of Case 4 showing ST elevation in leads I, aVL and V2-6 and ST depression in leads III and aVF during chest pain (CP (+)) compared with control ECG.

bronchial asthma, which was controlled with medications 27 years ago. Ten years ago, he was admitted to hospital because of episodes of chest pain at rest. CAG showed no atherosclerotic stenosis in the coronary arteries and intracoronary administration of ergometrine maleate (40μg) induced a transient occlusion of the left anterior descending coronary artery with ST segment elevation in leads V1-6, which was relieved by intracoronary administration of nitroglycerin. A diagnosis of VSA was made and medications with diltiazem (200 mg/day) and ISDN (40 mg/day) effectively controlled his angina.

One month before the current admission, his bronchial asthma and chest pain attacks at rest recurred despite the unchanged medications. At 06.00 h on the day of admission, severe chest pain occurred and did not respond to sublingual nitroglycerin. He was admitted as an emergency. Analysis of his blood sample did not show any elevation of serum inflammation markers or eosinophilia. CAG showed no atherosclerotic stenosis in the coronary arteries and the UCG findings were within normal limits. Because transient ST segment elevation in leads V1-6 was documented during his chest pain attack at rest (Fig 3), the chest pain attack was diagnosed as VSA and nifedipine (80 mg/day) was added to the treatment regimen. Because the attacks of both bronchial asthma and VSA did not improve, oral corticosteroid therapy (prednisolone 30 mg/day) was started, which successfully relieved both conditions. At 5-year follow-up, he has been taking oral prednisolone 5 mg/day with occasional asthma attacks, but without any angina.

Case 4

A 46-year-old woman was admitted to hospital because of chest pain at rest. Although she was diagnosed as having bronchial asthma in childhood, she has not had symptoms in the past 5 years and was not taking any anti-asthmatic medication. Ten years ago, she started to have episodes of chest pain at rest 2–3 times a day, and 3 years ago, she was admitted to another hospital because she had severe chest pain accompanied by syncope. CAG showed no atherosclerotic stenosis in the coronary arteries and intracoronary administration of ergometrine maleate induced transient stenoses (vasospasm) in the left anterior descending and circumflex coronary arteries with ST segment elevation in leads V3-6. A diagnosis of VSA was made and medication with nifedipine 20 mg/day, diltiazem 120 mg/day, amlodipine 10 mg/day, nicorandil 20 mg/day, ISDN 80 mg/day, and isosorbide mononitrate 80 mg/day significantly, but not completely, decreased her angina attacks.

At 04.30 h on the day of the current admission, she had severe chest pain at rest accompanied by syncope and urinary incontinence, and was admitted as an emergency. The angina attacks were not related to her menstrual cycle. Neurological examinations revealed no abnormality and the chemical analysis of her blood samples and the UCG findings were within normal limits. Although her angina attacks with ST segment elevation in leads V3-6 were effectively controlled with intravenous infusion of nitroglycerin, they relapsed when the infusion was tapered (Fig 4). Increasing doses of the oral anti-anginal medications (nifedipine 80 mg/day, diltiazem 240 mg/day, nicorandil 40 mg/day, ISDN 120 mg/day) controlled the spontaneous angina attacks, but did not suppress the attacks with ST depression in leads V3-6 provoked by a hyperventilation test performed 10 days after increasing the dosages of the anti-anginal medications. Oral corticosteroid (prednisolone 30 mg/day) was started, which completely suppressed the spontaneous angina attacks, and neither chest pain nor ST segment change was provoked in a hyperventilation test

performed 10 days after starting the corticosteroid.

One year after hospital discharge when the dose of prednisolone was gradually decreased and reached 10 mg/day, her angina attacks at rest relapsed and the dosage had to be increased again to 15 mg/day, resulting in symptomatic improvement.

Discussion

This is the first report demonstrating that there is a group of patients with severe VSA refractory to intensive antianginal treatment who benefit from corticosteroid therapy. The allergic component and the effectiveness of corticosteroids suggest that coronary vascular hyperreactivity because of local inflammation of the vessel wall may be responsible for coronary artery spasm in these patients.

Refractory VSA

Vasospastic angina usually responds well to treatment with calcium antagonists and/or nitrates, but there have been case reports of refractory VSA resistant to intensive treatment with high doses of these drugs[1,2] and all of the 4 cases presented here were highly resistant to intensive treatment with high doses of calcium antagonists, nitrates and nicorandil. Although percutaneous coronary intervention with stenting has been reported to be effective in such cases,[1,2] it may not work in cases of multivessel coronary spasm or diffuse spasm in the entire coronary artery tree, and the problem of restenosis affecting the long-term prognosis has not been solved.[3]

Mechanism of Efficacy of Corticosteroids

Several reports have suggested a possible link between allergic diseases and coronary spasm.[4–8] Okada et al reported a case of VSA accompanied by chronic thyroiditis and eosinophilia in which corticosteroid therapy effectively alleviated the VSA, suggesting that the corticosteroids suppressed some allergic response of the coronary artery associated with eosinophilia.[4] Although none of the present cases showed eosinophilia, all 4 had either bronchial asthma or chronic thyroiditis, and in 2 cases, the occurrence of the VSA coincided with that of bronchial asthma.

The pathogenesis of bronchial asthma has been recently attributed to hyperreactivity of the airway caused by inflammation and corticosteroids are considered to work by alleviating that inflammation.[9,10] There is an analogy with the pathophysiology of VSA; that is, coronary spasm may be induced by arterial hyperreactivity caused by local inflammation in the coronary arterial wall and corticosteroids suppress the hyperreactivity by alleviating the inflammation in the vessel wall. In fact, Forman et al reported a patient with VSA complicated by sudden death in whom mast cell infiltration was found at the site of angiographic documentation of coronary spasm.[11] Also, Kohchi et al reported that focal infiltration of inflammatory cells was seen in the adventitia of the coronary artery in patients with VSA.[12,13] Thus, local inflammation of the coronary arterial wall is likely to play an important role in the pathogenesis of coronary spasm.

Another potential mechanism of the efficacy of corticosteroids in VSA is a direct action on coronary arterial vascular smooth muscle cells. Miyagawa et al suggested that vascular hyperreactivity in postmenopausal women can be normalized by ovarian steroid hormone through its direct action on the intracellular Ca^{2+} signals and protein kinase C of coronary arterial vascular smooth muscle cells.[14–16]

Clinical Implications

The result of the present study indicates that corticosteroids should be considered in the choice of treatment for patients with refractory VSA. Because the exact underlying mechanisms of vasospastic angina remain unknown, corticosteroid therapy deserves further investigation in a larger number of patients with VSA.

Whether this treatment strategy can be applied to patients with the usual (non-vasospastic) type of unstable angina is unknown. Intriguingly, there is an emerging view that inflammation in the coronary arterial wall may play a significant role in the pathogenesis of unstable angina.[17,18] However, Azar et al reported that anti-inflammatory therapy with methylprednisolone was not effective in the treatment of patients with unstable angina[19] and therefore, the present result can not be generalized.

On the basis of the present findings, the therapeutic options for refractory VSA not responding to intensive treatment with high doses of 2 kinds of calcium antagonists and a sufficient dose of nitrate can be discussed. When localized coronary spasm at the site of a segmental arteriosclerotic stenosis is responsible for the symptoms, percutaneous coronary intervention may be the choice. When a patient with refractory VSA has an allergic tendency, such as bronchial asthma, corticosteroids may be the choice. Alternatively, there are case reports showing that β-stimulants were effective.[20,21] Of course, further studies are necessary to determine the long term efficacy of each treatment option and thereby establish the definitive treatment strategy for refractory VSA.

Conclusion

We report 4 cases of VSA that were refractory to the usual intensive treatment, but were successfully treated with corticosteroids. Therefore, corticosteroids should be considered in the treatment of patients with refractory VSA.

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Predictors of Left Ventricular Remodeling in Patients With Acute Myocardial Infarction Participating in Cardiac Rehabilitation

— Brain Natriuretic Peptide and Anterior Infarction —

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Background This study was designed to determine the factors influencing the development of left ventricular (LV) remodeling in patients participating in a comprehensive cardiac rehabilitation (CR) program after acute myocardial infarction (AMI), with special reference to exercise intensity and frequency.

Methods and Results A total of 72 patients with AMI participated in CR consisting of exercise training of moderate intensity (heart rate reserve 40–60%) and education for 12 weeks. Plasma concentration of brain natriuretic peptide (BNP) was measured at the beginning and the end of CR. Echocardiography was performed before and 1 year after CR. An increase in LV end-diastolic dimension (delta-LVDd) from baseline was used as an index of remodeling. Delta-LVDd was significantly greater in patients with an anterior AMI than with other infarct locations ($p<0.05$) and correlated significantly with baseline BNP concentration ($p<0.05$). Delta-LVDd >5 mm occurred exclusively in patients with baseline BNP >150 pg/ml. Variables representing the intensity and frequency of exercise training did not correlate with delta-LVDd.

Conclusion In patients with AMI participating in CR, those having both anterior infarction and baseline BNP concentration >150 pg/ml are at high risk for subsequent LV remodeling, whereas neither exercise intensity nor participation frequency in CR appears to be associated with LV remodeling. (*Circ J* 2004; **68:** 214–219)

Key Words: Acute myocardial infarction; Brain natriuretic peptide; Cardiopulmonary exercise test; Exercise training; Ventricular remodeling

Comprehensive cardiac rehabilitation (CR) has been shown to improve exercise capacity in patients with acute myocardial infarction (AMI), even in patients with moderate or severe left ventricular (LV) dysfunction[1–7] However, Jugdutt et al reported possible detrimental effects of exercise training on LV function and remodeling among patients with anterior Q-wave infarction[8] In contrast, the EAMI trial reported that patients with a baseline left ventricular ejection fraction (LVEF) <40% were prone to LV dilatation, and that physical training did not appear to worsen this anticipated effect[9] Moreover, the ELVD study reported attenuation of unfavorable remodeling by exercise training in postinfarction patients with LV dysfunction[10] In all those studies, however, exercise training was started late (3–8 weeks) after the onset of AMI, which may differ from the current clinical practice of early (2 weeks after onset) start of exercise training. In addition, those studies did not comprehensively analyze the predictive factors of LV remodeling in their study patients.

LV remodeling is a complex pathologic process of progressive dilatation, leading to dysfunction and heart failure in patients after myocardial infarction[11–16] Many factors have been reported to be related to LV remodeling in patients with AMI[17] and we have previously reported that the plasma brain natriuretic peptide (BNP) concentration is a predictor of progressive ventricular remodeling after AMI[13] However, the predictive factors of LV remodeling in patients participating in exercise CR have not been fully studied and this issue is important because exercise prescription with an appropriate exercise intensity should be given to all patients after AMI. Accordingly, the purpose of the present study was to clarify the predictive factors of LV remodeling in patients after AMI participating in CR with exercise training starting early (10–20 days) after onset. Our hypotheses were that the baseline plasma BNP concentration would be a predictive factor of LV remodeling in postinfarction patients participating in exercise CR and that variables representing exercise intensity or frequency may not unfavorably affect LV remodeling in these patients.

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Methods

Patients

The study group included 72 patients with an AMI who completed the recovery phase CR program with exercise training. The diagnosis of AMI was confirmed by typical chest pain, electrocardiographic (ECG) findings and subsequent elevation of cardiac enzymes. Patients with the usual contraindications for exercise training were excluded. Written informed consent was obtained from all enrolled

patients. Baseline clinical characteristics and medications are shown in Table 1. All patients underwent coronary arteriography and left ventriculography 3–4 weeks after the onset of infarction. The LVEF averaged 44±10% (range, 19–67%).

Exercise Training

The CR program consisted of exercise training of moderate intensity and education for 12 weeks[18,19] Patients who did not have angina or ischemic changes on the ECG at a low level of exercise intensity (500 m walking) were enrolled in the exercise training approximately 10–20 days (median 15 days) after AMI[20] The exercise program consisted of walking, bicycling on ergometer, and aerobic dance with a duration of 50–90 min per session and a frequency of 3–5 sessions per week for 3 months. Exercise intensity was determined individually at 50–60% of heart rate reserve (Karvonen's equation, k=0.5–0.6)[21] obtained in maximal symptom-limited cardiopulmonary exercise testing (CPX) or at level 13 ('a little hard') of the 6–20 scale perceived rating of exercise (original Borg's score)[22] Care was taken to prescribe a slightly lower level of exercise intensity (40–50% of heart rate reserve) to patients with low LVEF (<40%). The exercise program was started with supervised sessions for 2 weeks, followed by home exercise combined with once or twice-a-week supervised sessions for the remaining 10 weeks. Home exercise consisted mainly of brisk walking at a prescribed heart rate for 30–60 min 3–5 times a week. At the end of the 3-month program, patients were encouraged to continue exercise training at home by giving them an individual exercise prescription[19] Although exercise intensity during home exercise was not investigated in the present study, the average adherence rate to home exercise was 84% at 6 months and 64% at 1 year after the completion of the 3-month CR in our program.

Cardiopulmonary Exercise Testing (CPX)

A maximal symptom-limited cardiopulmonary exercise test (CPX) was performed at the beginning and the end of the 12-week CR program. In the CPX, after a 2-min rest on the bicycle ergometer (Examiner, Lode B.V. Groningen-Holland), patients started pedaling at an intensity of 0 W for 1 min (warm-up), then performed an incremental (15 W/min) exercise test until exhaustion. During exercise testing, breathed gas was continuously collected, and the respiration rate, tidal volume, oxygen consumption ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$) and minute ventilation (VE) were measured breath by breath. A face mask was used to collect gas samples, which were analyzed using a gas analyzer AE280 (Minato Medical Electronics, Osaka, Japan) connected to a personal computer equipped with analyzing software. Blood pressure was measured every minute by a manual method. A 12-lead ECG was also continuously monitored during exercise. Only 2 patients showed definite ischemic ECG changes in the initial exercise test; one underwent percutaneous coronary intervention therapy 2 days after the CPX, and the other patient refused coronary intervention therapy, although no ischemic change on the ECG was noted during subsequent exercise training.

Plasma BNP Concentration

Plasma BNP concentration was measured at the beginning and the end of the 12-week CR program, using a specific immunoradiometric assay kit from Shionoria BNP (Shionogi Co, Ltd, Japan) for human BNP in the SRL Inc (Tokyo, Japan).

Table 1 Patient Characteristics and Medications (n=72)

Age (years)	*62±10*
M/F	*58/14*
Hypertension	*36 (50)*
Diabates mellitus	*25 (35)*
Hyperlipidemia	*37 (51)*
Smoking	*44 (61)*
Family history	*16 (22)*
Prior MI	*9 (13)*
≥killip II	*9 (13)*
Anteroseptal AMI	*36 (50)*
Successful reperfusion therapy	*47 (65)*
Restenosis of culprit lesion#	*0 (0)*
Peak CK (U/L)	*3,529±2,453*
Ejection fraction (%)	*44±10*
No. of diseased arteries	*0.8±0.8*
Medication	
ACEI	*46 (64)*
β-blocker	*15 (21)*
Ca antagonist	*32 (44)*
Digitalis	*5 (7)*
Nitrates	*32 (44)*
Diuretics	*5 (7)*

Data are presented as the mean value±SD or number (%) of patients. AMI, acute myocardial infarction; CK, serum creatine kinase; ACEI, angiotensin-converting enzyme inhibitor; #no. of restenoses of culprit lesion during the cardiac rehabilitation program.

Echocardiography

All patients underwent a complete Doppler echocardiographic study at the beginning and 1 year after the end of the CR program. Standard views, including the parasternal long-axis, short-axis at the papillary muscle level, and apical 4- and 2-chamber views were recorded. An increase in LV end-diastolic dimension (delta-LVDd) from the baseline to follow-up was used as an index of LV remodeling.

Statistical Analysis

Values are expressed as mean±SD. Univariate analysis was performed using paired or unpaired Student's t-tests. Categorical data were compared against a chi-square distribution. Linear regression analysis was used to determine the correlation between continuous variables. Multivariate analyses were performed using the StatView statistical software packages (SAS Institute Inc, Cary, NC, USA). A p-value less than 0.05 was considered statistically significant.

Results

Changes in Clinical Variables After Cardiac Rehabilitation

All patients safely completed the 12-week CR program. Peak $\dot{V}O_2$ increased significantly from 1,283±409 ml/min to 1,457±470 ml/min ($p<0.05$) at the end of the 12-week program. Plasma BNP concentrations decreased significantly from 232±211 pg/ml to 146±239 pg/ml ($p<0.05$). However, LVDd did not significantly change from baseline to follow-up (52.0±5.7 mm to 51.5±6.5 mm, NS).

Relation Between Clinical Characteristics and Delta-LVDd

To assess determinants of LV remodeling, delta-LVDd was compared between subgroups of patients according to clinical characteristics and medications. There were no significant differences in delta-LVDd between subgroups

Table 2 Comparison of Delta-LVDd According to the Clinical Characteristics

	Delta-LVDd (mm)	p value
M/F	−0.8±4.2 / 1.1±4.6	NS
Age (≥70/<70 years)	−0.7±4.6 / −0.3±4.6	NS
Hypertension (with/none)	−0.1±5.0 / −0.8±4.3	NS
Diabates mellitus (with/none)	−0.4±4.3 / −0.5±4.8	NS
Hyperlipidemia (with/none)	−0.7±5.0 / −0.1±5.0	NS
Smoking (with/none)	−0.6±4.6 / 0.9±4.2	NS
Family history (with/none)	−0.1±4.0 / −0.7±4.9	NS
Prior MI (with/none)	1.2±4.1 / −0.9±4.5	NS
≥Killip II (with/none)	1.4±4.7 / −0.8±4.6	NS
Anteroseptal MI (with/none)	0.7±4.6 / −1.6±4.2	<0.05
Successful coronary artery reperfusion (with/none)	−0.6±4.3 / −0.2±5.1	NS
ACEI (with/none)	−0.3±4.2 / −1.0±5.1	NS
β-blocker (with/none)	−0.9±4.3 / −0.4±4.7	NS
Ca antagonist (with/none)	−1.1±4.6 / 0.01±4.5	NS
Digitalis (with/none)	2.1±4.9 / −0.7±4.5	NS
Nitrates (with/none)	−0.2±4.7 / −0.2±4.4	NS
Diuretics (with/none)	2.3±3.0 / −0.7±4.6	NS

Data are presented as mean value±SD. MI, myocardial infarction; ACEI, angiotensin-converting enzyme inhibitor; Successful reperfusion, successful reperfusion of an infarct-related artery within 24 h of onset.

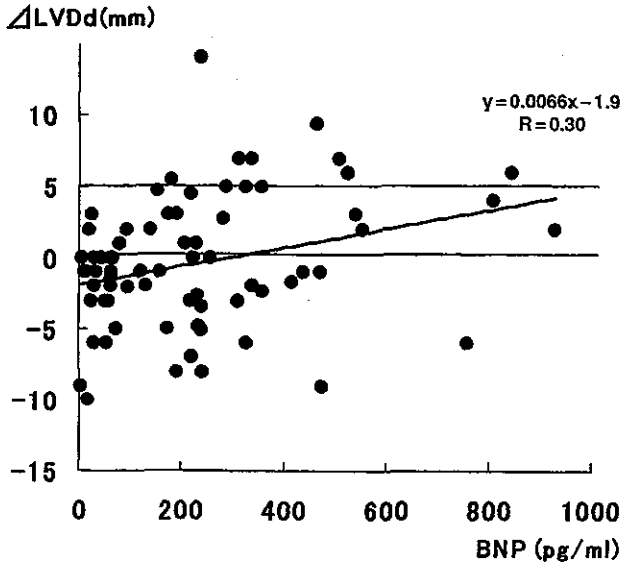

Fig 1. Correlation between plasma BNP concentrations and delta-LVDd (ΔLVDd). Increases in the left ventricular end-diastolic dimension (delta-LVDd) from baseline to follow-up were plotted against plasma BNP concentrations measured at the beginning of the cardiac rehabilitation program. Plasma BNP concentration significantly correlated with delta-LVDd (Y=0.0066X−1.9, r=0.30, p<0.05).

of patients divided by sex, age (≥70/<70 years), presence or absence of coronary risk factors, prior myocardial infarction (MI), Killip's classification≥II, successful/unsuccessful coronary reperfusion, or medications (Table 2).

Of note, delta-LVDd was significantly greater in patients with an anterior MI than in patients with other infarct locations (0.7±5.1 vs −1.60±3.7 mm, p<0.05, unpaired t-test). There was a weak trend that delta-LVDd in the subgroups with prior MI, Killip's classification≥II, with nitrates, and with diuretics was greater than the delta-LVDd in the subgroups without these factors, although none of these differences reached statistical significance (0.1<p<0.2).

Table 3 Effect of the Factors of Cardiac Function on Delta-LVDd

	r	p value
LVDd	−0.21	NS
LVDs	0.08	NS
FS	−0.19	NS
EF (left ventriculography)	−0.17	NS
No. of diseased arteries	−0.07	NS
LVEDVI	0.11	NS
LVESVI	0.18	NS
BNP (pre)	0.30	<0.05
BNP (post)	0.25	NS
Delta-BNP	−0.06	NS
Peak $\dot{V}O_2$	0.11	NS
VE/VCO_2 slope (pre)	−0.07	NS
VE/VCO_2 slope (post)	−0.04	NS
VE/VCO_2 slope (delta)	0.003	NS

LVDd, end-diastolic left ventricular dimension; LVDs, end-systolic left ventricular dimension; FS, fractional shortening; EF, ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; BNP (pre), BNP measured at the beginning of cardiac rehabilitation; BNP (post), BNP measured at the end of 12-week cardiac rehabilitation; Delta-BNP, decrease in BNP from the beginning to the end of cardiac rehabilitation; Peak $\dot{V}O_2$, peak oxygen uptake at the beginning of cardiac rehabilitation; VE/VCO_2 slope, the slope of the relation between minute ventilation and carbon dioxide production during initial exercise testing.

Relation Between Angiographic, Neurohumoral, and Exercise Variables and Delta-LVDd

Correlations between angiographic, neurohumoral, and exercise variables and delta-LVDd are summarized in Table 3. There was no significant correlation, except for baseline plasma BNP concentrations (r=0.30, p<0.05, Fig 1). In addition, none of the 29 patients with baseline plasma BNP concentration≤150 pg/ml had an increase in delta-LVDd >5 mm, whereas 8 of 43 patients (18.6%) with plasma BNP concentration >150 pg/ml had increases in delta-LVDd >5 mm (p<0.05) (Fig 2).

With regard to infarct location, there was a tendency that patients with an anterior infarction had a higher incidence of delta-LVDd >5 mm than patients with other infarct locations (16.7% vs 5.6%, p=0.14), although the difference did not reach statistical significance. Of note, 3 of 8 patients (37.5%) with both an anterior MI and a baseline BNP con-