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Tachycardia-induced myocardial ischemia and diastolic dysfunction potentiate secretion of ANP, not BNP, in hypertrophic cardiomyopathy

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Kido, Shinsuke, Naoyuki Hasebe, Yoshinao Ishii, and Kenjiro Kikuchi. Tachycardia-induced myocardial ischemia and diastolic dysfunction potentiate secretion of ANP, not BNP, in hypertrophic cardiomyopathy. *Am J Physiol Heart Circ Physiol* 290: H1064–H1070, 2006. First published September 19, 2005; doi:10.1152/ajpheart.00110.2005.—The aim of this study was to investigate what factor determines tachycardia-induced secretion of atrial and brain natriuretic peptides (ANP and BNP, respectively) in patients with hypertrophic cardiomyopathy (HCM). HCM patients with normal left ventricular (LV) systolic function and intact coronary artery ($n = 22$) underwent rapid atrial pacing test. The cardiac secretion of ANP and BNP and the lactate extraction ratio (LER) were evaluated by using blood samples from the coronary sinus and aorta. LV end-diastolic pressure (LVEDP) and the time constant of LV relaxation of tau were measured by a catheter-tip transducer. These parameters were compared with normal controls ($n = 8$). HCM patients were divided into obstructive (HOCM) and nonobstructive (HNOCM) groups. The cardiac secretion of ANP was significantly increased by rapid pacing in HOCM from 384 ± 101 to $1,268 \pm 334$ pg/ml ($P < 0.05$); however, it was not significant in control and HNOCM groups. In contrast, the cardiac secretion of BNP was fairly constant and rather significantly decreased in HCM ($P < 0.01$). The cardiac ANP secretion was significantly correlated with changes in LER ($r = -0.57$, $P < 0.01$) and tau ($r = 0.73$, $P < 0.001$) in HCM patients. Tachycardia potentiates the cardiac secretion of ANP, not BNP, in patients with HCM, particularly when it induces myocardial ischemia and LV diastolic dysfunction.

left ventricular outflow tract obstruction; lactate extraction ratio; left ventricular diastolic function; cardiac event; atrial and brain natriuretic peptides

THE CLINICAL SIGNIFICANCE of natriuretic peptides has been widely accepted in the management of heart failure. The plasma levels of brain natriuretic peptide (BNP) correlate well with the clinical severity of heart failure and hypertrophy (2, 8, 14). BNP is secreted mainly from the ventricle, whereas atrial natriuretic peptide (ANP) is produced and secreted not only from the atrium but from the ventricle in the hypertrophied heart (4, 23, 32). ANP synthesis is also enhanced in patients with heart failure (21, 36); however, the plasma ANP levels fluctuate more easily compared with BNP levels.

The plasma levels of natriuretic peptides have been reported to be increased despite the intact contractile function of the left ventricle (LV) in patients with hypertrophic cardiomyopathy (HCM). The hypertrophied heart is prone to complicate with diastolic dysfunction (35). Tachycardia induces heart failure in patients with hypertrophied LV because diastolic dysfunction

can be aggravated by shortening of diastolic phase (1, 12, 31). Tachycardia is also prone to induce myocardial ischemia even in HCM with angiographically normal coronary arteries. Although rapid pacing linearly increases coronary flow in control subjects, it decreases coronary flow at a high pacing rate in HCM patients (3). Tachycardia may reduce coronary perfusion, induce myocardial ischemia, and worsen diastolic relaxation in HCM. The vicious circle of myocardial ischemia and diastolic dysfunction potentially enhances the production and secretion of natriuretic peptides in HCM. However, the responses to tachycardia must be different in regulatory ANP secretion and in constitutive BNP secretion.

Few reports have demonstrated the mechanistic consequence of natriuretic peptide secretion and the tachycardia-induced hemodynamic derangement in HCM. The present investigation was designed to study the mechanism of tachycardia-induced secretion of natriuretic peptides in terms of myocardial ischemia and left ventricular (LV) diastolic dysfunction in HCM.

METHODS

Subjects. This study was conducted in accordance with the guideline of the ethical committee of Asahikawa Medical College. The purpose and potential risks of the study were fully explained to all subjects before they gave their voluntary written informed consent to participate.

Twenty-two patients with HCM were enrolled in the present study (13 men, 9 women; mean age 53 ± 11 yr). The diagnosis of HCM was made by the findings of an electrocardiogram, echocardiogram, cardiac catheterization, angiography, and myocardial biopsy. Exclusion criteria for patients were the following: 1) New York Heart Association functional class III or IV, 2) LV ejection fraction under 60% or LV segmental asynergy in left ventriculogram, 3) mitral regurgitation of Seller's II or over, 4) organic stenosis in coronary arteriogram, 5) chronic atrial fibrillation, 6) other organic heart disease including valvular heart disease and bundle branch block, and 7) hypertension or renal dysfunction. In the present study, 7 patients with intraventricular pressure gradient of 20 mmHg or over were defined as hypertrophic obstructive cardiomyopathy (HOCM), and the rest of 15 patients were defined as hypertrophic nonobstructive cardiomyopathy (HNOCM). Eight patients with chest pain syndrome, who were admitted because of chest pain but had been ruled out angina pectoris, were enrolled as controls (5 men, 3 women; mean age 56 ± 3 yr). All the patients studied have been periodically followed after the rapid pacing study. The major cardiac events, including admission for heart failure, serious arrhythmia attack, syncope, and worsening of chest pain as well as cardiac death were reported.

Rapid right atrial pacing test. All the drugs that potentially affect hemodynamics were discontinued at least 1 wk before the rapid

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pacing test. Right atrial pacing was initiated at a rate of 90 beats/min. The pacing rate was stepwise increased by 20 beats/min every 3 min up to the maximum rate of 150 beats/min. In case atrioventricular block appeared during the total of 12 min of pacing, the achievable maximum pacing rate was maintained.

Hemodynamic studies. A 6-Fr pigtail angiographic high-fidelity, micromanometer-tipped catheter (Millar Instruments) was retrogradely advanced into the LV through the femoral artery. The LV systolic pressure (LVSP) and LV end-diastolic pressure (LVEDP) were continuously monitored. To investigate the LV diastolic function, the peak negative rate of change of LV diastolic pressure (dp/dt) and the time constant of isovolemic relaxation of LV (τ) was used (22). τ was calculated using a modified method described by Raff and Glantz (28). We continuously recorded 12 leads of the electrocardiogram throughout the study. According to the electrocardiogram changes during pacing, we divided all patients with HCM into two groups: the ST-D(+) group consisted of patients who showed additional ST segment depression 0.1 mV or over on two or more leads of 12-lead electrocardiogram, and the ST-D(-) group consisted of patients who did not show additional significant ST segment depression by rapid pacing.

Cardiac secretion of natriuretic peptides and lactate extraction ratio. A 6-Fr Goodale-Lubin catheter was advanced into coronary sinus (CS) through the subclavian vein to obtain CS blood samples. Blood samples before and at the end of rapid pacing test for 12 min were obtained from CS and from the aorta (Ao) simultaneously via pigtail catheter. Plasma ANP concentration was measured with a specific immunoradiometric assay for α -human ANP (Shionoria ANP kit). Plasma BNP concentration was measured with a specific immunoradiometric assay for human BNP (Shionoria BNP kit). The cross reactivity of the ANP kit with human BNP and the BNP kit with α -human ANP were <0.001% on a molar basis, respectively (36). Cardiac secretion of ANP and BNP was determined as the difference of those levels in between CS and Ao. Lactate levels were measured using enzymatic method (Determiner LA, Kyowa Medics). The lactate extraction rate (LER) was calculated as:

$$\text{LER} = 100(\text{LAC}_{\text{Ao}} - \text{LAC}_{\text{CS}})/\text{LAC}_{\text{Ao}}$$

where LAC_{Ao} is the lactate level in Ao and LAC_{CS} is the lactate level in CS.

Echocardiographic data. Echocardiograms were performed using high-quality echocardiographic equipment (SSD 875, Aloka). Measurements were taken from the parasternal long- or short-axis M-mode or two-dimensional views obtained using 2.5- and 3.5-MHz transducers. Left atrial dimension (LAD), interventricular septal thickness (IVST), LV posterior wall thickness (PWT), LV end-diastolic dimension (LVDD), and end-systolic dimension (LVSD) were measured. The sum of IVST and PWT was defined as LV wall thickness. LV mass (LVM) was calculated by the method of Devereux and Reichek (5) as follows:

$$\text{LVM (in g)} = 1.04[(\text{LVDD} + \text{IVST} + \text{PWT})^3 - \text{LVDD}^3] - 14$$

which was divided by body surface area to determine LVM index [LVMi (g/m^2)].

Statistics. All values were expressed as means \pm SE. Values among three groups were compared by one-way analysis of variance (ANOVA), and the unpaired Student's *t*-test or χ^2 -test was used for comparison between two groups. The paired *t*-test was used to analyze difference between serial samples from the same group of patients. The two variable linear regression estimates were used for purposes of correlation. Statistical significance was defined as $P < 0.05$.

RESULTS

Patient characteristics and echocardiographic findings. There were no significant differences in age and gender between control and HCM patients. (Table 1).

Table 1. Patient characteristics

	Control	HCM		
		Total	HNCM	HOCM
No. of cases	8	22	15	7
Age, yr	56 \pm 3	54 \pm 2	54 \pm 3	55 \pm 5
Male/female	5/3	13/9	10/5	3/4
Echocardiogram				
LAD, mm	38 \pm 4	40 \pm 1	39 \pm 2	41 \pm 3
IVST, mm	9 \pm 1	18 \pm 1 \dagger	18 \pm 2 \dagger	18 \pm 2 \dagger
IVST + PWT, mm	18 \pm 2	28 \pm 1 \dagger	28 \pm 2 \dagger	29 \pm 2 \dagger
LVMi, g/m^2	102 \pm 7	199 \pm 13 \dagger	193 \pm 16 \dagger	211 \pm 23 \dagger
Left ventriculogram				
LVEF, %	70 \pm 3	77 \pm 1*	77 \pm 2*	77 \pm 2*

Values are numbers or means \pm SE. HOCM, hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic nonobstructive cardiomyopathy; LAD, left atrial dimension; IVST, intraventricular septal thickness; PWT, posterior wall thickness; LVMi, left ventricular (LV) mass index; LVEF, LV ejection fraction. * $P < 0.05$; $\dagger P < 0.01$ vs. Control.

LV wall thickness and LVMi were greater in HCM patients compared with control group; however, there were no significant differences in these indexes between HNCM and HOCM groups. The mean intra-LV pressure gradient of HOCM was 56.0 \pm 15.6 mmHg. There were no significant differences in LAD between control and HCM patients (Table 1).

Hemodynamics at the baseline and after pacing. The changes in hemodynamics at the baseline and 1 min after pacing were summarized in Table 2. There were no significant differences in heart rate (HR) between the control group and HCM patients. LVSP was significantly greater in the HOCM compared with control and HNCM patients before and after pacing. The maximum achievable pacing rate of total HCM patients was significantly higher compared with the control group ($P < 0.05$); however, there were no significant differences between HNCM and HOCM groups. HR was rapidly recovered to the baseline level in the control group at 1 min after pacing. In contrast, HR still remained at a significantly higher level in HCM groups at 1 min after pacing. LVEDP at the baseline and after pacing was significantly higher in HCM patients compared with the control group. LVEDP was not significantly affected by pacing in the control group; however, LVEDP significantly increased in total HCM patients ($P < 0.05$). Peak pressure change ($-\text{dp}/\text{dt}$) was significantly smaller in both HNCM and HOCM groups compared with the control group at the baseline as well as after pacing. τ in HCM patients was significantly greater at the baseline and after pacing compared with those in the control group. The induction of chest pain in HOCM was 100%, which was significantly higher compared with 12.5% in the control ($P < 0.01$) and 60% in HNCM ($P < 0.05$) groups (Table 2).

Changes in cardiac lactate production. In the control group, LER was not significantly affected by pacing. In contrast, LER was significantly decreased after pacing in total HCM patients. The changes in LER (ΔLER , LER after pacing - LER at the baseline) were significantly greater in HNCM and HOCM groups compared with control group (Table 2).

Changes in cardiac secretion of ANP and BNP. The cardiac secretion of ANP and BNP was well correlated with the levels in aortic as well as CS blood samples. In the control group, the cardiac secretion of ANP was slightly, but not significantly, increased by rapid pacing (baseline: 255 \pm 119 pg/ml, pacing:

Table 2. Changes in parameters by rapid atrial pacing

	Control		HCM					
	Baseline	Pacing	Total		HNCM		HOCM	
			Baseline	Pacing	Baseline	Pacing	Baseline	Pacing
HR, beats/min	61±4	62±4	66±2	75±3 ^{a,f}	67±3	75±4 ^{a,f}	65±3	76±6
LVSP, mmHg	128±5	128±5	150±9 ^a	153±7 ^b	129±5	136±6	194±19 ^{a,c}	190±8 ^{b,d}
LVEDP, mmHg	8±1	7±1	14±1 ^b	18±2 ^{b,e}	13±1 ^b	17±2 ^b	16±3 ^a	22±5 ^a
-dP/dt, mmHg/s	1,733±60	1,708±51	1,206±52 ^b	1,293±58 ^{b,e}	1,188±55 ^b	1,275±55 ^b	1,246±112 ^b	1,323±139 ^a
Tau, ms	43±2	39±3	51±1 ^b	51±3 ^a	49±1 ^a	47±2 ^a	54±2 ^b	60±9
maxPR, beats/min		133±5		144±3 ^a		144±4		145±4
Chest pain		1/8		16/22 ^b		9/15 ^a		7/7 ^{b,c}
ST-D (+)/(-)		0/8		10/12 ^a		4/11		6/1 ^{b,d}
ΔLER (%)		8±9		-17±4 ^a		-13±4 ^a		-23±8 ^a
ANP Ao	33±9	73±18 ^f	84±14 ^b	209±38 ^{b,f}	72±15 ^a	139±31 ^f	110±30 ^a	360±76 ^{b,f}
ANP CS	287±49	387±76	457±70	909±162 ^{a,f}	440±91	574±91	494±109	1,628±349 ^{a,c,f}
ΔANP, pg/ml		59±74		326±124		66±73		884±258 ^{a,d}
BNP Ao	15±5	17±7	69±19 ^a	92±25 ^{b,e}	64±21 ^a	68±23 ^a	81±41	144±60
BNP CS	31±11	31±11	172±47 ^b	157±45 ^a	130±40 ^a	111±32 ^a	263±120	257±124
ΔBNP, pg/ml		-2±2		-37±16 ^a		-24±9		-68±28

Values are numbers or means ± SE. HR, heart rate; LVSP, LV systolic pressure; LVEDP, LV end-diastolic pressure; maxPR, maximum pacing rate; -dP/dt, minimum rate of change of LV diastolic pressure; Tau, time constant; Chest pain, induction of chest pain; ST-D (+)/(-), patients with/without additional ST segment depression; ΔLER, changes in lactate extraction ratio; Ao, aorta; CS, coronary sinus; ΔANP and ΔBNP, the changes in cardiac secretion of ANP and BNP respectively. ^a*P* < 0.05 vs. control; ^b*P* < 0.01 vs. control; ^c*P* < 0.05 vs. HNCM; ^d*P* < 0.01 vs. HNCM; ^e*P* < 0.05 vs. baseline; ^f*P* < 0.01 vs. baseline.

314 ± 74 pg/ml) (Fig. 1, Table 2). In patients with HCM, the cardiac secretion of ANP was significantly increased by rapid pacing (baseline: 374 ± 65 pg/ml, pacing: 700 ± 139 pg/ml, *P* < 0.05) and was significantly greater compared with the

control group (*P* < 0.05). The increase in cardiac secretion of ANP was not significant in HNCM but was significant and marked in HOCM patients (baseline: 384 ± 101 pg/ml, pacing: 1,268 ± 334 pg/ml, *P* < 0.05) (Fig. 1, Table 2).

In contrast, the cardiac secretion of BNP was not increased in all groups, but it was rather significantly decreased in HCM patients by rapid pacing (baseline: 103 ± 43 pg/ml, pacing: 66 ± 31 pg/ml, *P* < 0.05) (Fig. 1, Table 2).

Comparison between ST-D (+) and ST-D (-) groups. HCM patients were divided into ST-D (+) and ST-D (-) groups. There were no significant differences in HR, LVSP, LVEDP, and peak negative dP/dt between ST-D (+) and ST-D (-) groups. The ST-D (+) group included significantly greater numbers of HOCM compared with the ST-D (-) (*P* < 0.01) (Table 3). The incidence of resting ECG abnormalities was not significantly different between the groups of ST-D (+) and ST-D (-) patients. Tau in the ST-D (+) group was significantly greater at the baseline and after pacing compared with those in the ST-D (-) group. The induction of chest pain in ST-D (+) was 100%, which was significantly higher compared with 50% in the ST-D (-) group (*P* < 0.01, Table 3).

Whereas LER was significantly decreased after pacing in both ST-D (+) and ST-D (-) groups, ΔLER was significantly greater in the ST-D (+) group compared with the ST-D (-) group (Table 3). The ΔLER of HCM patients were significantly correlated with the changes in ST level (ΔST: ST level after pacing - ST level at the baseline in the lead showing the maximal change) [*r* = 0.64, *P* < 0.01 (data not shown)]. Thus we considered that additional ST depression by rapid atrial pacing suggested myocardial ischemia in HCM patients.

The cardiac secretion of ANP in the ST-D (-) group was not significantly affected by rapid pacing. In contrast, the cardiac secretion of ANP in the ST-D (+) group was significantly increased and was significantly greater compared with the ST-D (-) group at the peak pacing (*P* < 0.05, Table 3).

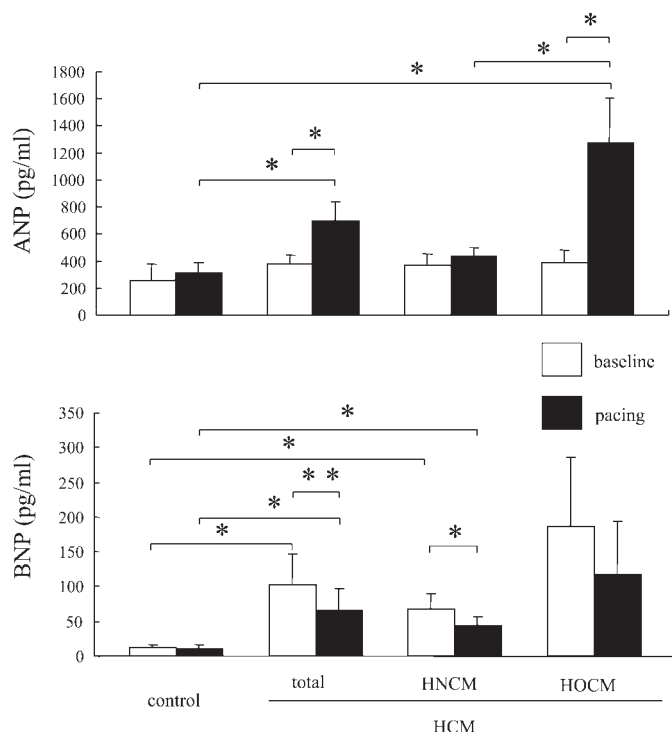


Fig. 1. Cardiac secretion of atrial natriuretic peptide (ANP) (top) after pacing (filled bar) was not significantly increased in control from the baseline (open bar) but was significantly increased by rapid pacing in hypertrophic cardiomyopathy (HCM), particularly in obstructive HCM (HOCM) patients. In contrast, the cardiac secretion of brain natriuretic peptide (BNP) (bottom) was not increased in all groups but rather significantly decreased in HCM patients by rapid pacing. **P* < 0.05; ***P* < 0.01.

Table 3. Comparison between ST-D (+) and ST-D (-) group

	HCM			
	ST-D (-) (n = 12)		ST-D (+) (n = 10)	
	Baseline	Pacing	Baseline	Pacing
HR, beats/min	68±3	77±4‡	64±2	74±4§
LVSP, mmHg	143±8	146±8	159±14	162±11
LVEDP, mmHg	13±2	17±2	16±2	20±3
-dP/dt, mmHg/s	1,281±55	1,305±59	1,117±77	1,277±104
Tau, ms	48±1	45±8	54±1†	58±6*
max PR, beats/min	145±5		148±5	
Chest pain	6/12		10/10	
HNCM/HOCM	11/1		4/6*	
ΔLER, %	-9±3		-25±5*	
ANP, pg/ml	356±100	404±97	419±77	1,058±225*‡
ΔANP, pg/ml	48±102		639±193*	
BNP, pg/ml	64±23	46±13	144.2±55.9	87.5±42.3§
ΔBNP, pg/ml	-18±14		-57±16	

Values are numbers or means ± SE. HR, heart rate; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; maxPR, maximum pacing rate; -dP/dt, minimum rate of change of left ventricular diastolic pressure; Tau, time constant; HOCM, hypertrophic obstructive cardiomyopathy; HNCM, hypertrophic nonobstructive cardiomyopathy; ANP and ΔANP, cardiac secretion and its changes of ANP; BNP and ΔBNP, cardiac secretion and its changes of BNP; ΔLER, changes in lactate extraction ratio, * $P < 0.05$ vs. ST-D (-); † $P < 0.01$ vs. ST-D (-); ‡ $P < 0.05$ vs. baseline; § $P < 0.01$ vs. baseline.

In contrast, the cardiac secretion of BNP was not increased but rather decreased in both groups, particularly in the ST-D (+) by rapid pacing ($P < 0.01$, Table 3).

Cardiac secretion of ANP and its related factors in HCM. The cardiac secretion of ANP was not significantly correlated with hemodynamic and echocardiographic variables at the baseline in HCM. In contrast, those at the peak pacing were significantly correlated with tau ($r = 0.77$, $P < 0.001$). The ΔANP was not significantly correlated with ΔLVEDP but significantly correlated with Δtau ($r = 0.73$, $P < 0.001$) and with ΔLER ($r = -0.57$, $P < 0.01$) (Fig. 2). The ΔLER was not significantly correlated with tau at the baseline; however, it was significantly correlated with tau after pacing ($r = -0.49$, $P < 0.05$) and Δtau ($r = -0.48$, $P < 0.05$) (Fig. 3).

Clinical consequence. All the patients studied have been followed up for 6.5 ± 0.2 yr after the rapid pacing study. Five major cardiovascular events occurred, including sudden death, cerebral infarction, renal infarction, syncopal attack due to arrhythmia, and admission for congestive heart failure. The incidence of major cardiovascular events was significantly greater in patients who showed greater cardiac secretion of ANP, i.e., 80% in HCM patients showing ANP ≥ 368 pg/dl (the median of cardiac secretion of ANP) and 7.1% in HCM patients showing ANP < 368 pg/ml. Inversely, the cardiac secretion of ANP in the patients suffered major cardiovascular events was significantly greater compared with that in the event-free patients (Fig. 4).

DISCUSSION

The present study demonstrated that the cardiac secretion of ANP, not BNP, was enhanced during tachycardia and was significantly correlated with tachycardia-induced hemodynamic derangement, particularly myocardial ischemia and LV diastolic dysfunction in patients with HCM.

Tachycardia is a crucial factor for deterioration of LV diastolic dysfunction in the patients with LV hypertrophy (1, 3). Tachycardia is also a stimulation to induce myocardial ischemia. It has been reported that myocardial ischemia per se enhances secretion of ANP in clinical as well as experimental studies (11, 13, 20, 33). Myocardial ischemia has been repeatedly related to a pathophysiological background of HCM (3, 6, 27, 30, 34). Several possible mechanisms for myocardial ischemia of HCM include the reduced coronary blood flow per unit of LV mass (27), the reduced coronary flow reserve by impaired LV relaxation, and coronary endothelial dysfunction (3, 30). Tachycardia-induced myocardial ischemia is a potential determinant of clinical severity in patients with HCM. It was noteworthy that the HR 1 min after the rapid atrial pacing was significantly higher in HCM patients compared with control despite the equivalent baseline HR, suggesting a prolonged recovery from the stress of tachycardia and prolonged effects of myocardial ischemia in chronic LV hypertrophy (9).

Tachycardia is a potent stimulation for ANP secretion, as reported in tachyarrhythmia (29) and in a rapid pacing study (24). In contrast, the cardiac secretion of BNP was fairly

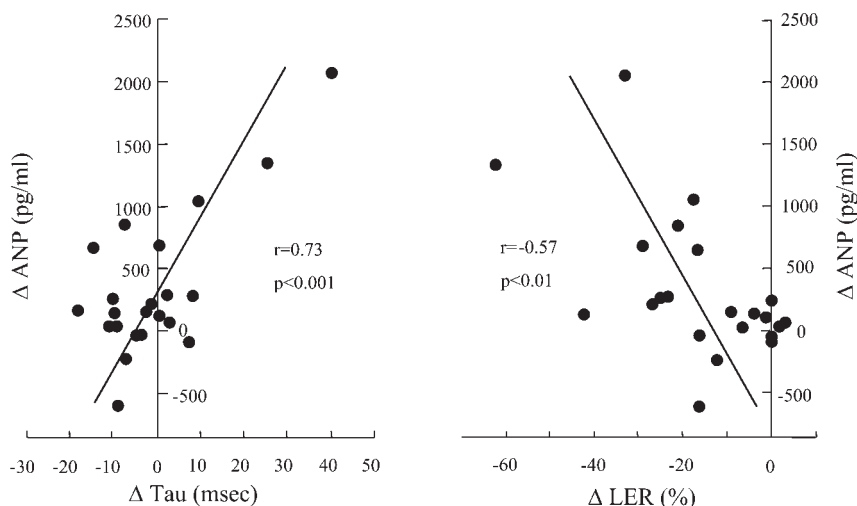
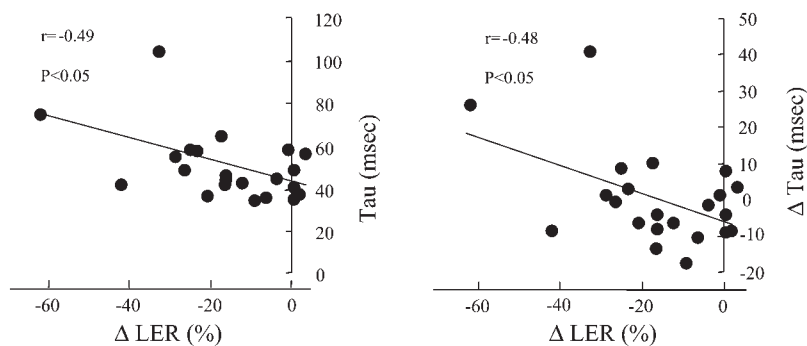


Fig. 2. Change in ANP (ΔANP) during rapid pacing was significantly and positively correlated with Δtau, an index of left ventricular (LV) diastolic dysfunction ($r = 0.73$, $P < 0.001$, left) and negatively correlated with change in lactate extraction ratio (ΔLER), a negative index of myocardial ischemia ($r = -0.57$, $P < 0.01$, right) in HCM.

Fig. 3. Δ LER was significantly and negatively correlated with tau after pacing ($r = -0.49$, $P < 0.05$, left) and Δ tau ($r = -0.48$, $P < 0.05$, right) in HCM.



constant during rapid pacing, rather decreasing in the present study. ANP is synthesized and stored in both the atria and ventricles, whereas BNP is synthesized and stored mainly in ventricles (36). ANP is stored in granules and released episodically in response to cardiac stress. In contrast, BNP is synthesized as preproBNP in bursts (14). Increase of coronary blood flow during rapid pacing may dilute plasma levels of natriuretic peptides. The balance between the enhanced cardiac secretion of natriuretic peptides and the diluting effects of increased coronary blood flow appeared to be positive for ANP and negative for BNP.

In the present study, the rapid atrial pacing itself did not enhance ANP secretion in control nor in HNCM of HCM, which mainly included patients lacking significant ST depression on electrocardiogram. The additional ST depression at tachycardia is believed to reflect myocardial ischemia in patients with HCM (25). The higher incidence of chest pain and greater production of lactate in the present study indicated more severe myocardial ischemia in HCM patients with additional significant ST depression. More importantly, the secretion of ANP was enhanced only in HCM patients with significant myocardial ischemia, suggesting a key role of myocardial ischemia in augmentation of ANP secretion in HCM. In patients with angina pectoris, ANP secretion has been reported to be increased with induction of myocardial ischemia by exercise (20), dipyridamole (13), and percutaneous transluminal coronary angioplasty (11). One plausible mechanism is that the

elevated left atrial pressure caused by myocardial ischemia stimulates secretion of ANP. On the contrary, Uusimaa et al. (33) have reported that myocardial ischemia directly stimulates secretion of ANP from the ventricle via energy metabolic mechanism. The secretion of ANP in HCM was closely correlated with tau, and the increase in ANP secretion was not significantly correlated with the increase in LVEDP but with the lactate production during rapid pacing. Moreover, there was no significant relationship between the left atrial dimension and the cardiac secretion of ANP during rapid atrial pacing (data not shown). These findings suggest that the enhanced secretion of ANP in HCM may be attributable to myocardial ischemia itself rather than hemodynamic overload to the left atrium. However, we could not definitely rule out an impact of increased left atrial stress and elevated LVEDP on enhanced secretion of ANP in HCM, particularly in HOCM patients and patients with ischemia during rapid atrial pacing. Masuyama et al. (19) reported that LV diastolic dysfunction could induce myocardial ischemia during tachycardia in patients without significant coronary stenosis, which was indicated by a significant correlation between the prolonged tau and impaired coronary flow reserve during tachycardia. Myocardial ischemia prolongs tau vice versa (7). In the present study, tau after pacing and changes in tau were significantly correlated with lactate production during tachycardia. These findings suggest that myocardial ischemia associated with LV diastolic dysfunction may directly stimulate secretion of ANP in patients with HCM during tachycardia.

Derchi et al. (4) reported that the plasma ANP level was significantly correlated with the morphological severity in HCM patients including severe heart failure. Takemura et al. (32) reported that the content of ANP in ventricular myocytes was dependent on the histological severity of hypertrophy but not dependent on the baseline hemodynamic variables in HCM patients. In the present study, we have recruited HCM patients with stable hemodynamic condition and found that the parameters of echocardiography were not significantly correlated with the secretion of ANP, suggesting that the morphological severity of hypertrophy does not seem to be the sole determinant of the baseline secretion of ANP. It was significantly correlated with tau after pacing, indicating that the more LV diastolic function was impaired, the more secretion of ANP was augmented at tachycardia. ANP is a potent compensatory factor for hemodynamic stress in hypertrophied heart, and the secretion of ANP is determined by the grade of stress and stiffness of LV in hypertrophied heart (10).

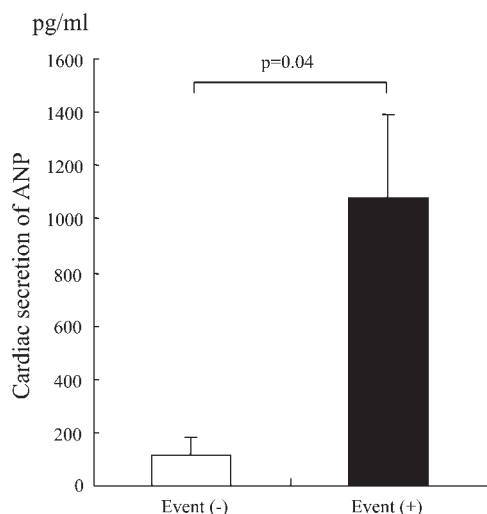


Fig. 4. Cardiac secretion of ANP was significantly greater in the subgroups of patients with major cardiovascular events.

The clinical outcome of HCM is known to be highly variable (16). In the present study, HOCM patients, particularly those who demonstrated significant myocardial ischemia during rapid pacing showed more serious outcome including one sudden death. Recent studies have demonstrated that outflow tract obstruction is independently associated with an increased risk of events in HCM (15, 17, 18). We believe that the tachycardia-induced vicious circle of myocardial ischemia and left ventricular diastolic dysfunction aggravate clinical outcome of patients with HCM. The augmented secretion of ANP during tachycardia, which is attributable to myocardial ischemia rather than hemodynamic overload, may predict serious outcome in patients with HCM.

Study limitations. In the present study, we did not measure the coronary blood flow. An inappropriate increase of coronary blood flow in HCM patients shown by Cannon et al. (3) would have been able to increase ANP concentration in the coronary sinus, despite similar ANP production. However, the amplitude of variation in coronary blood flow shown by Cannon et al. is not sufficient to affect the present findings. Furthermore, it could not explain the differences between ANP and BNP. The balance between the cardiac secretion of natriuretic peptides and the effects of coronary blood flow was positive to the ANP levels and negative to the BNP levels.

We monitored only the short-term changes in the cardiac secretion of natriuretic peptides. The longer term changes in the cardiac secretion of both peptides must be different. BNP is also synthesized in response to the stress of tachycardia, myocardial ischemia, and cardiac dysfunction; however, its cardiac secretion does not seem to be episodic as we demonstrated in the present study.

In conclusion, the cardiac secretion of ANP, not BNP, was enhanced during tachycardia in patients with HCM. The cardiac secretion of ANP was significantly correlated with the degree of myocardial ischemia and LV diastolic dysfunction. This positive relationship may facilitate a vicious circle of tachycardia and poor clinical outcome in patients with HCM.

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