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Disturbed Secretion of Atrial Natriuretic Peptide in Patients With Persistent Atrial Standstill: Endocrinologic Silence

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Persistent atrial standstill is a very rare pathophysiologic condition whose diagnosis is established when both electrical and mechanical silence of the atria are confirmed. To test the hypothesis that secretion of atrial natriuretic peptide is disturbed in patients with persistent atrial standstill, the response of atrial natriuretic peptide secretion and other neurohormonal factors during exercise was investigated in three patients with a rate-responsive ventricular demand (VVI) pacemaker implanted for confirmed persistent atrial standstill. The results were compared with those observed in eight normal subjects and patients with a rate-responsive VVI (Group A) or atrial demand (AAI) (Group B) pacemaker implanted for confirmed sick sinus syndrome.

Patients in Group A displayed significant elevation of alpha-human atrial natriuretic peptide secretion both before and during exercise (122.5 ± 14.8 and 207.5 ± 8.3 pg/ml, respectively) compared with those in Group B (55 ± 14.1 and 116.4 ± 51.5 pg/ml, respectively) and the normal subjects (18.9 ± 9.8 and 30.8 ± 19.2 pg/ml, respectively). This indicated development of a nonphysiologic increase in atrial volume or pressure overload, or both, in rate-responsive VVI pacing because of lack of atrioventricular synchrony. However, patients with persistent atrial standstill had undetectable (<10 pg/ml) or almost undetectable secretion of atrial natriuretic peptide as well as lower levels of cyclic guanosine monophosphate in the circulation both before and during exercise. Changes in plasma catecholamines during exercise were similar in patients with persistent atrial standstill compared with the other groups.

This study indicates that "endocrinologic silence" accompanies electrical and mechanical silence of the atria, which may constitute a third diagnostic clue to persistent atrial standstill.

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Persistent atrial standstill is a rare pathophysiologic condition that is clinically diagnosed on the basis of characteristic findings on electrophysiologic and cardiodynamic examinations. Electrophysiologic study demonstrates absence of atrial excitation either spontaneously or after atrial electrical stimulation (electrical silence) and the right atrial pressure curve or echocardiographic investigation reveals absence of atrial contraction (mechanical silence) (1–4).

Recent endocrinologic studies (5–7) have revealed that atrial peptides contained in specific granules of the mammalian atrial myocyte are released into the circulation during atrial distension and play an important role as a volume-regulating hormone by virtue of potent vasodilating and diuretic actions. Because secretion of atrial natriuretic peptide is associated with electrophysiologic or mechanical excitation of the atria, we reasoned that this secretion might be disturbed in patients with persistent atrial standstill. If so, this "endocrinologic silence" might constitute a third diagnostic clue to persistent atrial standstill. To test this hypothesis, we investigated the responses of atrial natriuretic peptide secretion and other neurohormonal factors during exercise in patients with persistent atrial standstill and compared the results with those observed in normal subjects and patients with sick sinus syndrome.

Methods

Study patients. Persistent atrial standstill was diagnosed in eight patients, and five of these were followed up at the Nippon Medical School Hospital in Tokyo; our first three cases were reported in 1975 (8). Table 1 shows the profiles of the eight patients with confirmed persistent atrial standstill. All eight patients had Stokes-Adams attacks as well as characteristic features of persistent atrial standstill, such as absence of the P wave on the standard 12-lead electrocardiogram (ECG) and Holter monitor and absence of atrial excitation on the His bundle electrogram (Fig. 1). A markedly reduced A wave was recorded only at the isolated low right atrial area in two patients (Patients 4 and 6). Electrophysiologic studies revealed lack of response to electrical stimulation of the atria (Fig. 1) and right atrial pressure curves and echocardiographic investigation revealed absence of atrial contraction. The diagnosis of persistent atrial standstill was considered definite when both electrical and

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Table 1. Clinical Characteristics of Eight Patients With Persistent Atrial Standstill

Pt No. (yr)	Age (yr)/ Gender	RA A Wave	Esophageal A Wave	His	RA Pacing	QRS	CTR	Underlying Disease	LV Wall Motion*	Treatment or Prognosis
1 (1971)	23/M	–	–	–	–	Narrow	59	Familial cardiomyopathy	–	
2 (1972)	38/F	–	–	HV 35 ms	–	Narrow	490	Unknown	–	Isoproterenol
3 (1975)	59/F	–	–	–	–	RBBB	70	Familial cardiomyopathy	–	Died (CHF)
4 (1976)	58/M	Partial low RA	+	HV 60 ms	–	Narrow	63	Unknown	3,6 hypokinesia	VVI→RR-VVI
5 (1981)	49/F	–	+	–	–	RBBB	68	Unknown	2,4,6,7 hypokinesia 3 akinesia	VVI
6 (1984)	72/F	Partial low RA	–	HV 35 ms	–	Narrow	65	Cardiomyopathy	3,6 hypokinesia	VVI
7 (1987)	39/M	–	–	HV 40 ms	–	Narrow	63	Muscular dystrophy	Normokinesia	RR-VVI
8 (1988)	50/M	–	–	HV 35 ms	–	Narrow	63	Unknown	Normokinesia	RR-VVI

*Left ventricular (LV) wall motion is described at the segment according to Austen et al. [Austen WG, Edwards JE, Frye RL, et al. AHA committee report. a reporting system on patients evaluated for coronary artery disease. Circulation 1975;51:5–40]. CHF = congestive heart failure; CTR = cardiothoracic ratio; F = female; His = His bundle electrogram; HV = His-ventricle interval; M = male; Pt = patient; RA = right atrial; RBBB = right bundle branch block pattern; RR = rate-responsive; VVI = ventricular demand pacemaker; + = present; – = absent.

mechanical silence were confirmed. These patients required pacemaker implantation to prevent Stokes-Adams attacks. A recently developed rate-responsive ventricular demand (VVI) pacemaker was implanted or reimplanted in three patients to provide adequate physiologic activity.

These 3 patients (Patients 4, 7 and 8) with a rate-responsive VVI pacemaker implanted for confirmed persistent atrial standstill were included in the present study together with 8 normal subjects and 11 patients with confirmed sick sinus syndrome (5 patients with a rate-responsive VVI pacemaker and 6 with a rate-responsive atrial demand [AAI] pacemaker). Patients with atrial tachyarrhythmias were excluded from this study. The study protocol was approved by the Nippon Medical School Institutional Review Board. Signed informed consent was obtained from each patient.

Study protocol. The patients performed ECG-monitored treadmill exercise according to Naughton's protocol. Blood was drawn from the antecubital vein for measurement of plasma concentrations of norepinephrine, epinephrine, alpha-human atrial natriuretic peptide, cyclic adenosine monophosphate (AMP) and cyclic guanosine monophosphate (GMP) before the start of exercise and when the heart rate reached 120 beats/min during exercise. It was confirmed that the patients were undergoing rate-responsive VVI or AAI pacing throughout this study. Plasma concentrations of norepinephrine and epinephrine were measured by high pressure liquid chromatography; alpha-human atrial natriuretic peptide and cyclic nucleotides were quantified by radioimmunoassay methods.

Statistics. All data were expressed as mean values ± SD. Statistical analyses were performed with use of Student's

Figure 1. Patient 8. Absence of P and A waves (upper panel) and lack of atrial excitation during right atrial pacing (lower panel) in this patient with persistent atrial standstill. CSd = coronary sinus (distal); CSp = coronary sinus (proximal); His.d = His bundle (distal); His.p = His bundle (proximal); HRA = high right atrium.

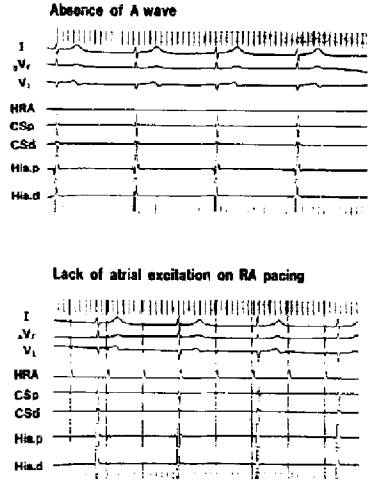

Table 2. Changes in Neurohormonal Factors During Exercise in 11 Patients With Sick Sinus Syndrome and 8 Normal Subjects

	SSS (RR-VVI)		SSS (RR-AAI)		Normal Subjects	
	Before Ex	Ex (HR 120 beats/min)	Before Ex	Ex (HR 120 beats/min)	Before Ex	Ex (HR 120 beats/min)
		$p < 0.05$		$p < 0.001$		$p < 0.001$
ANP (pg/ml)	122.5 ± 14.8	207.5 ± 8.3†	55.0 ± 14.1	116.4 ± 51.5*	18.9 ± 9.8	30.8 ± 19.2*
	$p < 0.005$		$p < 0.001$		$p < 0.001$	
Norepinephrine (ng/ml)	0.33 ± 0.20	1.15 ± 0.63*	0.22 ± 0.07	0.75 ± 0.29*	0.30 ± 0.07	0.65 ± 0.29*
Epinephrine (ng/ml)	0.05 ± 0.03	0.10 ± 0.03*	0.02 ± 0.01	0.05 ± 0.05	0.07 ± 0.04	0.08 ± 0.04
Cyclic AMP (pmol/liter)	19.0 ± 1.7	23.8 ± 3.6*	13.6 ± 1.0	18.6 ± 4.6*	15.6 ± 2.1	18.1 ± 1.6‡
	$p < 0.005$					
		$p < 0.01$		$p < 0.05$		
Cyclic GMP (pmol/liter)	7.8 ± 2.1	11.3 ± 3.8*	3.4 ± 1.2	8.1 ± 2.9*	3.3 ± 1.3	4.5 ± 1.6†
	< 0.005		$p < 0.05$			

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.005$. ANP = alpha-human atrial natriuretic peptide; AMP = adenosine monophosphate; Ex = exercise; GMP = guanosine monophosphate; HR = heart rate; SSS (RR-AAI) = Group B patients with a rate-responsive atrial demand (AAI) pacemaker implanted for sick sinus syndrome; SSS (RR-VVI) = Group A patients with a rate-responsive ventricular demand (VVI) pacemaker implanted for sick sinus syndrome.

t test for comparison of paired data before and during exercise and for unpaired data comparison between groups.

Results

Changes in neurohormonal factors during exercise in patients with sick sinus syndrome and normal subjects. Table 2 summarizes the data in the five patients with a rate-responsive VVI pacemaker (Group A) or the six patients with a rate-responsive AAI pacemaker (Group B) implanted for sick sinus syndrome, as well as the eight normal subjects. The mean concentrations of alpha-human atrial natriuretic peptide and cyclic GMP were already significantly higher before exercise in Group A compared with values in Group B and the normal group, which suggested development of nonphysiologic atrial volume or pressure overload during rate-responsive VVI pacing. During exercise (heart rate 120 beats/min), plasma concentrations of alpha-human atrial natriuretic peptide, norepinephrine, cyclic AMP and cyclic GMP were significantly elevated in all three groups; however, the mean plasma concentration of alpha-human atrial natriuretic peptide was significantly higher in Group A than in Group B and the normal group, which suggested a further increase in nonphysiologic atrial overload developed during rate-responsive VVI pacing because of lack of atrioventricular (AV) synchrony.

Disturbed secretion of atrial natriuretic peptide in patients with persistent atrial standstill. Table 3 shows the data on neurohormonal changes during treadmill exercise in the three patients with a rate-responsive VVI pacemaker im-

Table 3. Changes in Neurohormonal Factors During Exercise in Three Patients With Persistent Atrial Standstill

Patient	Pt 4 (69 yr/M)		Pt 7 (40 yr/M)		Pt 8 (50 yr/M)	
Period from Pacemaker Implantation	VVI (10 yr) RR-VVI (2 yr)		RR-VVI (13 mo)		RR-VVI (11 mo)	
	Before Ex	Ex (HR 120 beats/min)	Before Ex	Ex (HR 120 beats/min)	Before Ex	Ex (HR 120 beats/min)
ANP (pg/ml)	<10	14	<10	<10	<10	<10
Norepinephrine (ng/ml)	0.70	1.74	0.46	0.69	0.35	1.30
Epinephrine (ng/ml)	0.04	0.07	0.02	0.09	0.03	0.07
Cyclic AMP (pmol/liter)	16.9	19.9	12.0	12.0	8.5	10.0
Cyclic GMP (pmol/liter)	4.8	6.2	2.2	2.3	2.0	2.1

Abbreviations as in Tables 1 and 2.

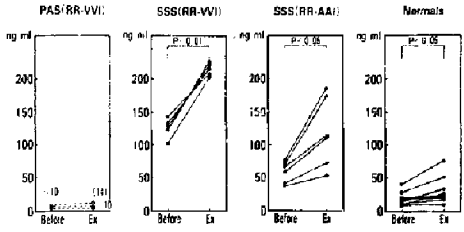

Figure 2. Changes in plasma alpha-human atrial natriuretic peptide levels during exercise at a heart rate of 120 beats/min. Normals = eight normal subjects; PAS(RR-VVI) = three patients with a rate-responsive ventricular demand (VVI) pacemaker implanted for persistent atrial standstill; SSS(RR-AAI) (Group B) = six patients with a rate-responsive atrial demand (AAI) pacemaker implanted for sick sinus syndrome; SSS(RR-VVI) (Group A) = five patients with a rate-responsive VVI pacemaker implanted for sick sinus syndrome.

planted for confirmed persistent atrial standstill. Plasma alpha-human atrial natriuretic peptide concentration before exercise was undetectable (<10 pg/ml) by radioimmunoassay in all three patients and was still undetectable during exercise (heart rate 120 beats/min) except in Patient 1, whose level was very low (14 pg/ml) compared with that in normal subjects and patients with a pacemaker implanted for sick sinus syndrome (Fig. 2).

Discussion

Atrial natriuretic peptide secretion in rate-responsive VVI pacing. The patients with a rate-responsive VVI pacemaker implanted for sick sinus syndrome displayed marked elevation of alpha-human atrial natriuretic peptide secretion both before and during exercise. None of these five patients had atrial fibrillation or atrial tachyarrhythmia that might have caused an increase in alpha-human atrial natriuretic peptide secretion during the study. The mean concentrations of this peptide before and during exercise in these patients reached levels seven times those of normal subjects and three times those of patients with a rate-responsive AAI pacemaker implanted for sick sinus syndrome. This indicated the development of a nonphysiologic increase in atrial volume or pressure overload, or both, in rate-responsive VVI pacing because of lack of AV synchrony.

In the condition of AV asynchrony, atrial contraction during more or less complete closure of the AV valves causes an increase in atrial volume and pressure overload and atrial stretching, which are known predominant mechanical stimulating factors in atrial natriuretic peptide secretion (9). Elevation of atrial pressure due to intact ventriculoatrial retrograde conduction during VVI pacing also increases atrial pressure by the near simultaneous activation of the atria and ventricles, which has been reported (10) to be associated with pacemaker syndrome.

Endocrinologic silence of the atria in patients with persistent atrial standstill. If atrial function was maintained endocrinologically, one would expect that rate-responsive VVI pacing in patients with persistent atrial standstill would also elicit increased alpha-human atrial natriuretic peptide secretion before and during exercise, as observed in patients with a rate-responsive VVI pacemaker implanted for sick sinus syndrome. However, the three patients in the present study displayed undetectable (<10 pg/ml) or almost undetectable secretion of this peptide in the circulation, which clearly indicated endocrinologic silence accompanying electrical and mechanical silence in persistent atrial standstill. This overall electrical, mechanical and endocrinologic silence of the atria suggests that persistent atrial standstill is not a disorder of the conduction system but an abnormality of the atrial myocardium itself and is basically different from sick sinus syndrome. The atrial myocardial biopsy specimen obtained from three patients (Patients 3, 4 and 8) revealed marked atrophy and degeneration of atrial myocytes with interstitial fibrosis and monocyte infiltration. Atrial-specific granules were relatively preserved although the electron microscopic views of the atrial myocytes in Patient 4 revealed an increase in Z band-like substance and sparsity and disarray of myofibrils that were consistent with primary degeneration of the atrial myocytes themselves. Further studies are needed to clarify the mechanism of disturbed atrial natriuretic peptide secretion in patients with persistent atrial standstill.

The lower levels of cyclic GMP before exercise and lack of elevation during exercise observed in patients with persistent atrial standstill were fully consistent with the findings on alpha-human atrial natriuretic peptide secretion, because cyclic GMP is regarded as the second messenger of this peptide.

Role of pacing mode. Before and during exercise, patients with persistent atrial standstill had changes in plasma norepinephrine, epinephrine and cyclic AMP (the second messenger of beta-agonists) very similar to those observed in patients with a rate-responsive VVI pacemaker implanted for sick sinus syndrome. We (11) recently reported data relating to the cardiodynamic and neurohormonal importance of physiologic pacing. In patients undergoing cardiac pacing, AV synchrony in addition to the rate responsiveness and augmentation of myocardial contractility by increasing circulating catecholamines also contributed to the increase in cardiac output during exercise by 10% (heart rate 90 beats/min) to 15% (heart rate 110 beats/min). In contrast to the rate-responsive VVI pacemakers that did not provide

AV synchrony, DDD (dual-chamber) and rate-responsive AAI pacemakers provided all three contributing factors (namely, rate responsiveness, AV synchrony and augmented contractility). The reason a DDD or rate-responsive AAI pacemaker could not be implanted in patients with persistent atrial standstill was absence of atrial excitation that could be detected by the sensor and no response to atrial pacing stimuli (electrical and mechanical silence).

Role of ventricular release of atrial natriuretic peptide. Recently, using immunohistochemical and immunofluorescence methods, Tsuchimochi et al. (12,13) verified that atrial natriuretic peptide was released not only from atrial but also from ventricular myocardium in patients with severe congestive heart failure due to dilated cardiomyopathy. They explained the release of atrial natriuretic peptide from ventricular muscle as a compensatory mechanism for the regulation of sodium and water balance in patients with cardiac decompensation. Although the quantity of circulating alpha-human atrial natriuretic peptide released from ventricular myocardium was not clearly indicated in their reports, the results of the present study do not necessarily support their hypothesis because plasma concentrations of the peptide were undetectable in our patients with persistent atrial standstill and no evidence of ectopic secretion of the peptide was found.

Several reports on animal models (14,15) and humans (16) have suggested that ventricular atrial natriuretic peptide or its gene expression is closely associated with myocardial hypertrophy rather than a compensatory mechanism for cardiac decompensation. Right ventricular myocardial biopsy specimens obtained from two patients (Patients 3 and 8) with persistent atrial standstill revealed no evidence of myocardial hypertrophy or myocardial fiber disarray and echocardiographic studies showed no finding suggestive of ventricular hypertrophy in all three patients.

Effects on serum electrolytes and volume loading. In the present study, serum electrolytes (sodium, potassium and chlorine), blood urea nitrogen and creatinine levels in patients with persistent atrial standstill were all in the normal range. Although we did not investigate the condition of the renin-angiotensin-aldosterone system or the recently discovered brain natriuretic peptide (17), which also possessed similar physiologic action and was synthesized in ventricular myocardium and brain, further studies are required to clarify how these patients handle volume and sodium load in the specific circumstance of lack of atrial natriuretic peptide.

Conclusions. This study demonstrated that disturbed alpha-human atrial natriuretic peptide secretion (endocrinologic silence) is associated with electrical and mechanical silence in patients with persistent atrial standstill. Because persistent atrial standstill is an extremely rare disorder, we have studied only three such patients with a previously implanted rate-responsive VVI pacemaker, and have not yet studied such patients at the stage of initial electrophysiologic studies before pacemaker implantation. Further study is required to evaluate the significance of endocrinologic silence as a third diagnostic clue to persistent atrial standstill.

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