Differential Increase in Natriuretic Peptides in Elite Dynamic and Static Athletes

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The echocardiographic measures and plasma concentrations of either atrial natriuretic peptide (ANP) or brain natriuretic peptide (BNP) were compared in elite judo practitioners (static athletes), elite marathon runners (dynamic athletes) and healthy controls to investigate the relationship between the different types of left ventricular (LV) hypertrophy and plasma concentrations of natriuretic peptides in athletes. The LV mass and LV wall thickness of marathon runners and judo practitioners were significantly greater than those of controls. The LV end-diastolic dimension index was significantly larger in the marathon group, but smaller in the judo group. The left atrial dimension (LAD) index was significantly larger only in marathon runners. Plasma BNP concentrations were higher in both the judo and marathon groups than in controls, and positively correlated with LV mass as well as with deceleration time. Plasma ANP concentrations were significantly higher in marathon runners than in the controls and judo groups, and positively correlated with the LAD index, but negatively correlated with ejection fraction. Multivariate analyses showed that the type of athlete and LAD index were independent predictors of plasma BNP and ANP concentrations, respectively. Thus, there is an intimate link between plasma concentrations of natriuretic peptides and cardiac morphology in different types of athletes. (*Circ J* 2003; **67**: 691–696)

Key Words: Athlete's heart; Atrial natriuretic peptide; Brain natriuretic peptide

An increase in left ventricular (LV) chamber size, wall thickness and mass as a result of athletic training are generally described as 'athlete's heart'.¹ Mitchell et al classified individual sports as dynamic or static depending on the level of intensity of the exercise and according to these criteria, judo is classified as high static–low dynamic, whereas marathon running is considered low static–high dynamic.² The athletes in these classifications have distinct types of LV hypertrophy: dynamic athletes have eccentric hypertrophy whereas static athletes develop concentric hypertrophy.

Atrial natriuretic peptide (ANP) is a cardiac hormone that is secreted from the atria and has diuretic, natriuretic, and vasodilator actions.^{3,4} Brain natriuretic peptide (BNP) is secreted mainly from the ventricles and although it has striking similarity to ANP with respect to amino acid sequence and pharmacological spectrum, they are derived from distinct genes.⁵ A growing body of evidence has demonstrated that in various heart diseases, the plasma concentrations of ANP and BNP are increased^{6–9} and the latter is a useful marker of diagnosis and prognosis.^{10–12} The LV geometry affects the plasma concentrations of ANP and BNP in patients with essential hypertension,⁷ but the relationship between cardiac hypertrophy and plasma natriuretic peptides in athletes remains unknown. We investigated the plasma concentrations of ANP and BNP in dynamic and static athletes. We used echocardiography to also evaluate

the effects of different types of sports on cardiac morphology and function. The aim of this study was to elucidate the relationship between plasma natriuretic peptides and either cardiac morphology or function in the different types of athletes.

Methods

Subjects

Written informed consent to participate in the study was obtained from 20 elite marathon runners (26.8±8.5 years), 15 elite judo practitioners (24.7±2.6 years) and 16 controls (26.2±1.7 years). All participants were male and none were taking any form of medication or special nutritional supplements such as protein powder. The dietary patterns of the judo practitioners and marathon runners were essentially the same. The duration of their athletic commitment was 20.1±10.0 years for the marathon runners and 16.5±3.9 years for the judo practitioners. The former run more than 20 km and latter practice for 2 h, every day of the week. Controls were age-matched, healthy physicians who had not recently trained or been involved in high performance sport.

Echocardiographic Recording

Echocardiographic examination was performed using a phased array, ultrasound system (Sonos 5500, Philips Medical System, USA) with a 2.5-MHz transducer. Echocardiograms were evaluated according to the recommendations of the American Society of Echocardiography.¹³ Left atrial dimension (LAD) at end-systole was measured at the maximal dimension from the leading edge of the posterior wall of the aorta to the dominant line representing the posterior wall of the LA. Interventricular septal (IVS) diastolic thickness, LV posterior wall diastolic thickness, and

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Table 1 Baseline Characteristics of the 2 Types of Athletes and the Controls

	Dynamic athletes (n=20)	Static athletes (n=15)	Controls (n=16)
Age (years)	26.8±8.5	24.7±2.6	26.2±1.7
BW (kg)	53.4±12.2 [‡]	107.7±21.1 [‡]	62.1±5.7
BMI (kg/m ²)	18.2±8.5 [‡]	34.1±6.0 [‡]	21.4±1.66
MBP (mmHg)	89.3±1.7 [‡]	100.5±2.4	97.5±1.7
HR (beats/min)	56.0±8.56 [‡]	65.9±7.54	70.1±7.74

**p*<0.05 vs controls; †*p*<0.01 vs controls; ‡*p*<0.001 vs controls; §*p*<0.01 vs static athletes; ||*p*<0.001 vs static athletes. Values are means±SD.

BMI, body mass index; BW, body weight; HR, heart rate; MBP, mean blood pressure.

Table 2 Echocardiographic Measures and Resting Natriuretic Peptide Concentrations in the 2 Types of Athletes and the Controls

	Dynamic athletes (n=20)	Static athletes (n=15)	Controls (n=16)
LAD index (mm/m ²)	22.4±2.03 [‡]	17.3±2.19	18.5±1.77
LVD index (mm/m ²)	31.2±2.11 [‡]	22.7±2.95*	26.9±2.26
LVWT (mm)	21.9±1.9 [‡]	25.5±3.5*	16.2±2.72
LV mass (g)	318.3±48.0 [‡]	496.2±114.8 [‡]	189.7±36.0
EF (%)	62.3±8.05	64.9±8.12	65.9±0.3
E/A ratio	2.13±0.556	1.93±0.55	1.91±0.45
DT (ms)	176±33.0	199±33.9	182±30.5
MSWS (kdynes/cm ²)	164.1±34.3	158.8±31.5	169.1±39.1
ANP (pg/ml)	11.48±5.80 [‡]	5.44±5.38	5.33±1.86
BNP (pg/ml)	6.91±6.85	8.16±3.66 [‡]	2.59±3.04

||*p*<0.05 vs controls; **p*<0.001 vs controls; ‡*p*<0.0005 vs controls; §*p*<0.0001 vs controls; §*p*<0.005 vs static athletes; †*p*<0.001 vs static athletes; #*p*<0.0001 vs static athletes.

Values are means±SD.

DT, deceleration time; E/A ratio, ratio of E wave to A wave; EF, ejection fraction; LAD index, left atrial dimension index (LAD/m²); LVD index, left ventricular end-diastolic dimension index (LVD/m²); LV mass, left ventricular mass; LVWT, left ventricular wall thickness, (=interventricular septal diastolic thickness + left ventricular posterior wall diastolic thickness); MSWS, meridional systolic wall stress.

LV diastolic dimension (LVD) were measured from the LV short-axis view at the papillary muscle tip level using 2-dimensionally guided M-mode echocardiography. Three consecutive cardiac cycles were measured and averaged. Images were recorded on a 0.5-inch S-VHS video tape recorder. The LV mass was calculated using the Penn-cube formula described by Devereux and Reichek¹⁴ as follows:

LV mass = 1.04 ((IVS diastolic thickness + LVD + LV posterior wall thickness)³ - LVD³) - 13.6 g.

The values of LAD and LVD were then adjusted for body surface area to generate the index values. The LV wall thickness was defined as IVS diastolic thickness + LV posterior wall diastolic thickness. LV ejection fraction (LVEF) was obtained using a modified Simpson method based on the American Society of Echocardiography recommendation.¹⁵ Pulse Doppler echocardiography measured mitral inflow velocity in the apical 4-chamber view with the sampling volume placed at the tip of the mitral valve. The diastolic parameters of peak mitral flow velocity of the early rapid filling wave (E), peak velocity of the late filling wave due to atrial contraction (A), the E/A ratio and deceleration time of the E wave were then measured. The value for meridional systolic wall stress was calculated using Grossman's equation¹⁶ and is defined as follows:

$$m = \text{PRI} / 2H(1 + H/2R_i),$$

where *m* is meridional systolic wall stress, *P* is systolic LV pressure, *R_i* is the inner radius and *H* is the systolic wall thickness of the LV. Because this was a non-invasive study, we substituted systolic blood pressure for systolic LV pressure.

Assays of ANP and BNP

Venous blood samples were obtained from the athletes in the late morning before lunch and at least 12 h after the last training session. Plasma concentrations of ANP were measured using a specific immunoradiometric assay (Shiono RIA ANP assay kit, Shionogi Co, Ltd) as reported.¹⁷ This assay sandwiches -human ANP between 2 monoclonal antibodies, one against its carboxy-terminal sequence and the other against its ring structure, and plasma extraction is not required. Plasma concentrations of BNP were measured using a highly sensitive immunoradiometric assay (Shiono RIA BNP assay kit, Shionogi Co) as reported.¹⁸ This assay sandwiches human BNP between one monoclonal antibody that recognizes its carboxy-terminal and another that recognizes its ring structure. Plasma extraction is not necessary. Cross-reactivity of ANP with BNP was less than 0.001% on a molar basis.

Statistics

All statistical comparisons were performed using the Statistical Package Stat View-J 4.5 (Abacus Concepts Inc, Calabasus, CA, USA). Data are expressed as means±SD. Unpaired two-tailed *t*-tests examined differences among the marathon runners, judo practitioners and controls. The relationship between plasma natriuretic peptides and predictor variables was explored by univariate analysis followed by stepwise multivariate regression analyses. Plasma concentrations of ANP or BNP constituted dependent variables in our model. Age, body weight, body mass, mean blood pressure, heart rate, LAD index, LVD index, LV wall thickness, LV mass, LVEF, E/A ratio, deceleration time, meridional systolic wall stress and type of athlete

Table 3 Univariate and Multivariate Analysis for Predicting Plasma Concentration of ANP

Variable	Univariate analysis		Multivariate analysis	
	Coefficient	p value	Coefficient	p value
LAD index (mm/m ²)	0.442	0.0015	0.54	0.0199
Age (years)	0.437	0.0017	0.379	0.0013
EF (%)	-0.403	0.0041	-0.227	0.0112
LVD index (mm/m ²)	0.386	0.0062		
BMI (kg/m ²)	-0.386	0.0062		
BW (kg)	-0.378	0.0074		
HR (beats/min)	-0.279	0.0522		
MBP (mmHg)	-0.246	0.0887		
LVWT (mm)	0.106	0.4684		
LV mass (g)	-0.049	0.7382		
MSWS (kdynes/cm ²)	0.021	0.8842		
Type of athlete	0.019	0.8994		
E/A ratio	-0.004	0.9758		
DT (ms)	0.0005	0.9974		

BMI, body mass index; BW, body weight; DT, deceleration time; E/A ratio, ratio of E wave to A wave; EF, ejection fraction; HR, heart rate; LAD, left atrial dimension; LVD index, left ventricular end-diastolic dimension index; LV mass, left ventricular mass; LVWT, left ventricular wall thickness; MBP, mean blood pressure; MSWS, meridional systolic wall stress.

Table 4 Univariate and Multivariate Analysis for Predicting Plasma Concentration of BNP

Variable	Univariate analysis		Multivariate analysis	
	Coefficient	p value	Coefficient	p value
Age (years)	0.636	<0.0001	0.685	<0.0001
Type of athlete	0.418	0.0028	0.487	<0.0001
LV mass (g)	0.401	0.0043		
LVWT (mm)	0.38	0.0071		
DT (ms)	0.285	0.047		
E/A ratio	-0.265	0.0662		
BW (kg)	0.238	0.0991		
BMI (kg/m ²)	0.219	0.1306		
EF (%)	-0.201	0.1654		
MBP (mmHg)	0.16	0.2707		
LAD index (mm/m ²)	0.127	0.385		
LVD index (mm/m ²)	-0.104	0.4764		
MSWS (kdynes/cm ²)	-0.076	0.6035		
HR (beats/min)	-0.056	0.7036		

BMI, body mass index; BW, body weight; DT, deceleration time; E/A ratio, ratio of E wave to A wave; EF, ejection fraction; HR, heart rate; LAD, left atrial dimension; LVD index, left ventricular end-diastolic dimension index; LV mass, left ventricular mass; LVWT, left ventricular wall thickness; MBP, mean blood pressure; MSWS, meridional systolic wall stress.

(dynamic or static) represented independent variables. Relationships between continuous variables were determined by linear regression analysis. Differences were considered significant at p-values below 0.05.

Results

Characteristics of the 3 Exercise Groups

The baseline characteristics of the athletes and controls are summarized in Table 1. Age did not significantly differ among the 3 groups. The values for body weight and body mass index were smaller in the marathon runners than in the judo practitioners and controls. Mean blood pressure was also lower in the marathon group than in the judo and control groups. The marathon group had lower heart rates than the judo and control groups.

Echocardiographic Findings

Echocardiographic findings are summarized in Table 2. The value of the LAD index was significantly larger in the marathon group than in either the judo or the control group. The LVD index was significantly larger in the marathon group and smaller in the judo group compared with the

control group. LV wall thickness and LV mass were significantly larger in both athlete groups than in the controls. Systolic function (LVEF), diastolic function (E/A ratio and deceleration time) and meridional systolic wall stress did not differ among the 3 groups.

Plasma Concentrations of ANP and BNP

Plasma ANP concentrations were significantly higher in marathon runners (11.48 ± 5.80 pg/ml) than in the control (5.33 ± 1.86 pg/ml) or judo group (5.44 ± 5.38 pg/ml) (marathon vs control, $p < 0.0005$; marathon vs judo, $p < 0.005$), whereas plasma BNP concentrations were higher in both the judo (8.16 ± 3.66 pg/ml) and marathon groups (6.91 ± 6.85 pg/ml) compared with controls (2.59 ± 3.04 pg/ml) (judo vs control, $p < 0.0001$; marathon vs control, $p < 0.05$) (Table 2). Tables 3 and 4 show the results of univariate and multivariate analyses that evaluated the factors contributing to plasma ANP and BNP concentrations, respectively. Univariate analysis showed that LAD index, age, LVEF, LVD index, body mass index and body weight correlated with plasma ANP concentrations. Among these variables, LAD index, age and LVEF were independent predictors of the plasma concentration of ANP (Table 3), as revealed by

Fig 1. Correlation between atrial natriuretic peptide (ANP) and left atrial dimension (LAD) index (A) and between brain natriuretic peptide (BNP) and left ventricular (LV) mass (B) in all study participants. Plasma ANP concentrations positively correlate with LAD index ($r=0.442$, $p=0.0015$) (A) and plasma BNP concentrations positively correlate with LV mass ($r=0.401$, $p=0.0043$) (B).

stepwise multivariate analysis. Univariate analysis correlated age, type of athlete, LV mass, LV wall thickness and deceleration time with plasma BNP concentrations. Age and type of athlete were significant determinants of plasma BNP concentrations (Table 4). Linear regression analysis revealed a significant relationship between plasma ANP concentrations and LAD index ($r=0.442$, $p=0.0015$) and between plasma BNP concentrations and LV mass ($r=0.401$, $p=0.0043$) (Fig 1). In addition, ANP concentrations negatively correlated with LVEF ($r=-0.403$, $p=0.0041$), whereas BNP concentrations positively correlated with deceleration time ($r=0.285$, $p=0.047$) (Fig 2) and also tended to correlate with the E/A ratio ($r=-0.265$, $p=0.0662$).

Discussion

The principal finding of the present study is that plasma BNP concentrations were high in both static and dynamic athletes, whereas plasma ANP concentrations were high only in dynamic athletes. Plasma BNP positively correlated with LV mass and LV wall thickness, but not with LVD index or LAD index. In contrast, plasma ANP positively correlated with LAD index and LVD index, but not with LV mass or LV wall thickness. The type of athlete was a significant determinant of BNP, but not of ANP concentrations, whereas the LAD index was a significant determinant of ANP concentrations. Plasma ANP concentrations negatively correlated with LV systolic function, whereas plasma BNP concentrations positively correlated with LV diastolic function in these study groups.

Multivariate analysis suggested that the type of athlete might affect the plasma BNP concentrations via a mechanism(s) other than that of cardiac morphology. Regardless,

Fig 2. Correlation between atrial natriuretic peptide (ANP) and left ventricular ejection fraction (LVEF) (A) and between brain natriuretic peptide (BNP) and deceleration time of E wave (DT) (B) in all study participants. Plasma ANP concentrations negatively correlate with LVEF ($r=-0.403$, $p=0.0041$) (A) and plasma BNP concentrations positively correlate with DT ($r=0.285$, $p=0.047$) (B).

linear regression analysis revealed that plasma BNP concentrations closely correlated with LV mass. The left ventricle is the predominant site of BNP synthesis in healthy men^{19,20} and the plasma concentration of BNP increases in response to various degrees of ventricular overload⁶⁻⁸ BNP is also secreted from the atria, but to a far lesser extent than from the ventricles, in patients with congestive heart failure^{6,19} We also measured systolic wall stress at rest in the present study. However, because it was not elevated in either the judo or the marathon group compared with the control group, it was not a dependent variable that stimulated the release of natriuretic peptide. This is because systolic wall stress is most simply described by the following LaPlace relationship: $(P \times R)/2H$, where P is systolic pressure, R is the radius of the LV and H is the thickness of the LV wall²¹ and it was normalized by the correspondingly augmented LV wall thickness in both types of athlete.

Unlike BNP, plasma ANP concentrations were high only in the marathon group and correlated with both LAD index and LVD index, suggesting that ANP is secreted from the dilated LA and/or LV. Although ANP is predominantly produced in and secreted from the atria^{3,4} the ventricular ANP gene is expressed during LV hypertrophy²² and heart failure²³ suggesting that the ventricular myocardium produces and secretes ANP into the blood circulation. ANP is stored and released by a regulated pathway in the atrium whereas it is released from the ventricle by constitutive secretory pathways in a similar manner to BNP²⁴ Indeed, Yasue et al have reported that ANP is secreted from the LV as well as from the LA in patients with dilated cardiomyopathy^{9,25} However, plasma ANP in patients with essential hypertension accompanied by LV hypertrophy could be

released from the LA in association with increased atrial work or atrial pressure rather than the hypertrophied LV per se⁷ because LV compliance decreases in such patients.²⁶ Furthermore, Roman et al suggested that the major source of ANP secretion is not the volume-overloaded or hypertrophied LV, but the enlarged LA in valvular heart disease.²⁷ The right atrium may also contribute to the increased plasma ANP concentrations in the volume-overloaded heart. The present study also revealed that the LAD index was a significant determinant, suggesting that the LA is the predominant site of ANP secretion in the heart of dynamic athletes. We speculate that LA distension could be a more potent stimulus to ANP release than LV enlargement or hypertrophy in the presence of LV volume overload. Age significantly and independently contributed to the stepwise multivariate regression analyses for plasma concentrations of both ANP and BNP, which was consistent with previous reports showing a positive correlation between age and either ANP or BNP in healthy individuals²⁸ and in patients with heart disease.²⁹

LV systolic and diastolic functions were within the normal ranges in both static and dynamic athletes in the present study. Additionally, correlations between the increase in ANP and the decrease in LV systolic function, and between the increase in BNP and the decrease in LV diastolic function were significant. The findings in patients with hematological malignancies treated with cardiotoxic chemotherapeutic agents are similar insofar as increased ANP concentrations reflect systolic dysfunction,³⁰ whereas increased BNP concentrations reflect diastolic dysfunction.³¹ Hence, natriuretic peptides in athletes may also, at least in part, affect ventricular function. However, because the magnitude of the increase in natriuretic peptides in these athletes remained within much lower concentrations than those associated with pathological states, the physiological role(s) of elevated plasma concentrations of ANP and BNP in athletes remains unclear.

LV hypertrophy results from an adaptation to cardiac overload.¹³ The athlete's heart is also a result of functional and morphological adaptations to repeated exercise.³² The present study found that plasma concentrations of natriuretic peptide in 2 types of athletes differed according to the type of cardiac hypertrophy.

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