Physiological hypertrophy of the heart and atrial natriuretic peptide during rest and exercise

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SUMMARY The influence of physiological cardiac hypertrophy on the concentration of plasma atrial natriuretic peptide was studied in six male athletes and six normally active, matched control men. They were examined by echocardiography during a graded exercise test on a bicycle ergometer. Plasma atrial natriuretic peptide was measured at rest, at each workload until exhaustion, and 15 and 30 minutes after the exercise test. Echocardiography showed that the athletes had a significantly larger left atrium, left ventricular end diastolic diameter, left ventricular posterior wall, interventricular septum, left ventricular ejection fraction, and left ventricular mass than the controls. The athletes performed significantly more work than the control group—325 W *v* 277 W. The plasma concentration of atrial natriuretic peptide rose by a mean factor of 2.76 (range 1.78–4.28) in all men from rest to maximum exercise. There were no differences between the athletes and the controls in the concentrations of plasma atrial natriuretic peptide at rest, at any workload, or at maximum workload. Neither was there any difference in the increase in plasma atrial natriuretic peptide between the groups. There was no correlation between the plasma concentrations of atrial natriuretic peptide and any of the variables measured by echocardiography.

In healthy young men plasma atrial natriuretic peptide rises by a factor of about 2.8 during maximum exercise and the size of the chambers on the left side of the heart or left ventricular hypertrophy does not seem to influence the concentration of plasma atrial natriuretic peptide at rest or during exercise.

Atrial natriuretic peptide is a circulating hormone secreted by the atrial myocytes of the heart. It is released in response to increased atrial pressure,¹ which is generally equal to increased stretch and dilatation of the atrial wall. Plasma atrial natriuretic peptide rose during exercise.²

The term "athlete's heart" was introduced by Henschen in 1899.³ In this condition all the chambers of the heart are dilated and there is hypertrophy of the myocardium due to physical training.^{4,5}

The purpose of this study was to determine whether the hypertrophy and dilatation of the heart seen in well trained persons influence the plasma concentration of atrial natriuretic peptide at rest or during exercise.

Patients and methods

We studied six male footballers who trained strenuously and six normally active healthy matched controls (aged 21–30 years). None was taking medical treatment. The controls did not participate in any form of athletics for more than four hours a week. They all gave informed consent and the study was approved by the local ethics committee.

All of the investigations were undertaken between 3 pm and 7 pm. Echocardiography, with cross sectional and M mode recordings, was performed with a Hewlett Packard 77020A ultrasonograph and a 3.5 MHz transducer on men in the supine position. All the M mode measurements originated from three or four consecutive cardiac cycles graded according to the system of the American Society of Echocardiography.⁶ Calculations of the left ventricular ejection fraction and the left ventricular mass were based on the assumption that the left ventricle is ellipsoid.⁷ We took Henry *et al*'s data as normal values,⁸ except

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for the calculation of the left ventricular mass, where we used the formula: left ventricular mass = $43.62 + 2.18 \times \text{weight(kg)}$. The upper normal limit was +2 standard deviations (that is the left ventricular mass plus 30%).⁹

The men had fasted for two hours before the exercise test and a cannula was inserted in an antecubital vein 30 minutes before the test. An electrocardiogram and auscultation of the heart were obtained before the test.

The subjects sat on the bicycle ergometer after a 30 minute rest in the supine position then blood pressure and pulse rate were measured. Graded exercise was performed by increasing the workload by 60 W every three minutes, starting at 120 W and continuing until exhaustion. Blood pressure and pulse rate were measured and a blood sample was drawn during the last 60 seconds of each work period and at 15 and 30 minutes after maximum exercise with the subject resting on the bicycle or a chair. Blood pressure was measured by the standard cuff technique.

Samples were collected in tubes coated in edetic acid and containing aprotinin (500 IU/ml blood) and kept in an ice bath. After centrifugation for 15 minutes at 7000 rpm at 4°C, the plasma was stored at minus 20°C. Concentrations of plasma atrial

natriuretic peptide were measured by a kit from INC Holland by radioimmunoassay after extraction on Sep-Pak C-18 cartridges.¹⁰ We have tested the kit in our laboratory: intra-assay and interassay variation did not exceed 5% and 10%, respectively, within the useful range ($B = 15-85\%$ of B_0 where B is the count for the standard (or sample) and B_0 is the count for the standard without atrial natriuretic peptide). Recovery of added atrial natriuretic peptide was 99%. Sensitivity was 0.8 pg/tube (4 pg/ml (1.3 pmol/l) plasma).

Statistical analysis was performed by Student's *t* test for paired and unpaired data. The dependence of the plasma concentration of atrial natriuretic peptide on the amount of work was examined by analysis of variance on the logarithm of the plasma concentration of atrial natriuretic peptide (figure). A *p* value < 0.05 was considered to be significant.

Results

Age, weight, and body surface area were similar in the trained and the untrained groups.

Table 1 shows echocardiographic results. The left ventricular mass was bigger in the athletes ($p < 0.0001$). Each athlete had a calculated left

Figure Response of plasma concentration of atrial natriuretic peptide (on a logarithmic scale) to graded exercise on a bicycle ergometer. Closed circles, athletes; open circles, untrained controls; double circles, maximum exercise. 1 pg/ml of atrial natriuretic peptide = 0.325 pmol/l.

Table 1 Measurements in athletes and controls (mean (SD))

	Athletes (n = 6)	Controls (n = 6)	p
Age (yr)	25.8 (2.3)	24.2 (4.2)	0.4
Height (cm)	182 (7.4)	182 (3.8)	0.9
Weight (kg)	75.7 (8.7)	73.5 (7.3)	0.7
Body surface area (m ²)	1.97 (0.15)	1.94 (0.11)	0.7
Pulse rate:			
At rest	60.3 (0.8)	95.0 (18.7)	0.001
At maximal work	187 (13.7)	192 (7.5)	0.5
BP(s):			
At rest (mm Hg)	121 (11)	118 (10)	0.7
At max work (mm Hg)	195 (14)	185 (15)	0.26
Maximal work (W)	325 (30)	277 (27)	0.01
Left atrium (mm)	35.2 (1.7)	30.7 (4.1)	0.03
LV ESD (mm)	34.8 (3.3)	33.8 (2.0)	0.5
LV EDD (mm)	55.8 (4.9)	47.7 (2.9)	0.005
Interventricular septum (mm)	10.3 (1.2)	8.33 (1.0)	0.01
LV posterior wall (mm)	11.0 (0.9)	8.67 (0.8)	0.001
LV fractional shortening (%)	37.7 (3.7)	29.0 (2.5)	0.001
LV ejection fraction (%)	76.8 (3.8)	67.1 (3.2)	0.001
LV mass (g)	299 (28)	170 (15)	<0.0001

BP(s), systolic blood pressure; LV, left ventricular; ESD, end systolic diameter; EDD, end diastolic diameter.

ventricular mass that was above normal (2.11–4.08 SD above normal mean), whereas all the controls had a left ventricular mass within the normal range (± 2 SD of normal mean). The diameters of the left atria did not exceed the normal range. The calculated left ventricular fractional shortening and ejection fraction were below the upper normal limits.

The athletes had a larger left atrium, a larger left ventricular end diastolic dimension, thicker interventricular septum and left ventricular posterior wall, and a greater left ventricular fractional shortening than the control group. The left ventricular end systolic dimension was similar in both groups.

The pulse rate at rest was higher in the non-athletes than in the athletes, probably because the non-athletes were more nervous before the exercise test. The blood pressure both before and during the exercise test was similar in the two groups. As expected the athletes reached a higher maximum workload.

Table 2 Plasma concentration of atrial natriuretic peptide at rest and at maximum work in athletes and non-athletes (mean (SD))

P-ANP	Athletes (n = 6)	Controls (n = 6)	p
At rest (pg/ml)	41.4 (32.1)	28.0 (12.1)	0.6
At max work (pg/ml)	90.6 (52.1)	74.5 (10.1)	0.5
Increase (pg/ml)*	49.2 (22.4)	46.5 (9.13)	0.8
Factor†	2.57 (0.94)	2.95 (0.92)	0.5

P-ANP, plasma atrial natriuretic peptide.

*P-ANP at maximal work – P-ANP at rest.

†P-ANP at maximal work/P-ANP at rest.

1 pg/ml = 0.325 pmol/l.

The figure shows the values of the plasma atrial natriuretic peptide on a logarithmic scale for the athletes and the controls before, during, and after exercise. Both the untrained and trained men had a significant rise in the concentration of atrial natriuretic peptide during exercise. There were no differences between the two groups in plasma concentrations of atrial natriuretic peptide at rest, at any workload, at maximal workload, or after the exercise. The factor by which the plasma atrial natriuretic peptide concentration rose during the exercise test was similar in both groups (table 2). Therefore the data were pooled in order to obtain plasma concentrations of atrial natriuretic peptide for all the healthy young men both at rest and at maximum workload (table 3).

There was no correlation between the plasma concentration of atrial natriuretic peptide at rest and any of the variables measured during echocardiography ($r \leq 0.36$, $p \geq 0.25$). Despite the fact that atrial natriuretic peptide is produced in the atrial wall the correlation between plasma atrial natriuretic peptide and the diameter of the left atrium was only 0.21 ($p = 0.5$). Further, both the blood pressure and the pulse rate were correlated poorly with the plasma concentration of atrial natriuretic peptide.

Discussion

It is known that the heart is hypertrophic and dilated in well-trained athletes.^{4,5} In our male athletes we found a significantly increased diastolic cavity dimension, left ventricular posterior wall, interventricular septal thickness, left ventricular ejection fraction, and left ventricular mass compared with our untrained controls. These observations have been described earlier.^{11 12}

We were unable to show any difference in the plasma concentration of atrial natriuretic peptide between the trained and the untrained group, even though the heart was significantly larger in the athletes than in the control subjects.

Physiological hypertrophy of the heart, as seen in athletes after a period of intensive training, does not seem to influence the plasma concentration of atrial

Table 3 Plasma concentrations of atrial natriuretic peptide (P-ANP) at rest and maximal work in 12 healthy young men

P-ANP	Mean	SEM	Range
At rest (pg/ml)	34.7	6.97	14.5–96.5
At max work (pg/ml)	82.5	10.6	51.5–172
Increase (pg/ml)	47.8	4.73	27.5–78.5
Factor	2.76	0.26	1.78–4.28

See footnote to table 2.

natriuretic peptide or the release of atrial natriuretic peptide during exercise.

It is known that excretion of plasma atrial natriuretic peptide increases during exercise.^{2,13} Plasma atrial natriuretic peptide is controlled by stretch receptors in the left and right atria of the heart. The plasma concentrations of atrial natriuretic peptide during chronic or acute cardiac failure correlated with pulmonary capillary wedge pressure.^{14,15} Because pulmonary capillary wedge pressure increases during exercise,¹⁶ the rising concentrations of plasma atrial natriuretic peptide during exercise may be a response to the stretch that results from the increased pressure in the left atrium. The plasma concentrations of atrial natriuretic peptide did not differ in the athletic and non-athletic groups in our study. This suggests that there was no difference in the left atrial pressure between the two groups either at rest or during exercise. As far as we know this has not been reported before.

Although the left atrium was larger in the athletes than in the controls, the correlation between this enlargement and plasma concentrations of atrial natriuretic peptide at rest was only minor and not statistically significant. A similarly poor correlation between the left atrium measured by echocardiography and the plasma concentration of atrial natriuretic peptide ($r = 0.28$, $p > 0.2$) was described in 30 patients with various heart diseases or no heart disease at all, who were referred for routine echocardiography,¹⁷ whereas a good correlation ($r = 0.61$, $p < 0.01$) between the size of the left atrium and the plasma concentration of atrial natriuretic peptide was reported in 14 patients with various organic heart diseases.¹⁸ The plasma concentration of atrial natriuretic peptide may therefore reflect the size of the left atrium in the sick and failing heart, while the size of the left atrium is of little, if any, importance to the plasma concentration of atrial natriuretic peptide released by the healthy heart.

In patients with chronic heart failure, the heart works harder, and this will result in a hypertrophy of the heart. A production of atrial natriuretic peptide in this condition might be detected not only in the myocytes of the atria, but also in the ventricular myocytes.^{19,20} The mechanisms responsible for the ventricular production are unknown. As in the atria, stretching of the muscle wall may trigger the production of the peptide by the ventricle.²¹ It has been suggested that the higher concentrations of the peptide in the failing ventricles may be the result of hypertrophy. Our results indicate that hypertrophy does not initiate a production of natriuretic peptide in the ventricles sufficiently to increase significantly the concentration of plasma atrial natriuretic peptide above that in normal people with non-hypertrophic

hearts.

We conclude that plasma atrial natriuretic peptide increases by a factor of about 2.8 during maximum exercise in healthy young men. Neither the size of the chambers of the left side of the heart nor left ventricular hypertrophy seem to be important to the concentration of plasma atrial natriuretic peptide during rest and exercise.

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