CLINICAL STUDY

Increases in plasma levels of atrial and brain natriuretic peptides after running a marathon: are their effects partly counterbalanced by adrenocortical steroids?

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Abstract

Objective: Long-distance running results in considerable stress. Little evidence exists about the role of the atrial and brain natriuretic peptides, ANP and BNP, deriving from the myocardium. The aim of our study was to investigate the influence of running 42.195 km on changes in circulating natriuretic propeptides and adrenocortical steroids.

Design and methods: We studied 17 male and 2 female runners (age: 28–62 years) participating in a marathon. Blood samples were obtained before and immediately after the competition. proANP(1–98) and proANP(1–30) as well as Nt-proBNP(8–29) were determined by enzyme immunoassays.

Results: Runners finished the competition between 2 h 58 min and 4 h 25 min. We observed a more pronounced increase in proANP(1–98) (+58%) and proANP(1–30) (+99%, both $P < 0.001$) compared with Nt-proBNP(8–29) (+6%; $P = 0.005$). Increases in proANP(1–30) positively correlated with runners' age ($r = 0.53$; $P = 0.02$). We also observed a marked increase in cortisol (+73%) and especially in aldosterone (+431%, both $P < 0.001$).

Conclusions: Cardiac strain during long-distance running may explain the pronounced increase in proANP. Other explanations for the observed rise in plasma levels might be a change in the permeability of myocardial cells and an impaired clearance. A rise in adrenocortical steroids may compensate for the negative influence of ANP on natriuresis and blood pressure. Positive effects of ANP during a marathon could be the regulation of body temperature by influencing sweat glands as well as the stimulation of lipolysis compensating for the enormous energy demand.

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Introduction

Running the marathon distance of 42.195 km results in considerable physical and mental stress. Selye (1950) described the important influence of endocrine regulations in response to such a condition (1). The activation by endurance running up-regulates circulating catecholamines (2–4) and stimulates the 'classic hormones of adaptation' corticotropin releasing hormone–adrenocorticotropin–cortisol (2, 5–7). Somatotropic hormone (8) as well as leptin (9, 10) are responsible for the provision of energy, which is critical for running such a long distance. There are still few data about a response of atrial natriuretic peptide (ANP) (11) and brain natriuretic peptide (BNP) (12, 13) during a marathon. Deriving predominantly from myocardial cells due to elevated strain they increase natriuresis (14, 15). In addition, ANP seems to reduce systemic blood pressure (16–18). The aim

of our study was to investigate the change in natriuretic peptides in response to running a marathon by determining their circulating precursors. Moreover, we investigated their interaction with adrenocortical steroids in the regulation of circulation and body fluids.

Subjects and methods

We studied 17 male and two female runners competing in a marathon in Maranello (Italy). Their ages ranged from 28 to 62 years. Demographic data are presented in Table 1. The runners finished the race between 2 h 58 min and 4 h 25 min indicating their state of fitness. Temperatures were fairly warm being 24 °C in the morning. During the race athletes were encouraged to drink sufficient amounts of an isotonic dextrose/electrolyte solution, which was offered every 5 km.

Table 1 Demographic data. Results are expressed as means $\pm$ S.D.

Age (years)	44.7 $\pm$ 9.2
Gender (F/M)	2/17
Marathon (h:min)	03:42 $\pm$ 00:41

No one needed medical assistance during the marathon or afterwards.

Venous blood samples were obtained before the start and immediately after finishing the marathon. The native venous blood was stored without anticoagulant and transported to the laboratory in Vienna by plane at room temperature. Only then were the sera centrifuged and stored at -40°C until analyses. This lack of cooling during transportation did not allow all desirable determinations because of the known instability of certain parameters.

Fractions 1–30 and 1–98 of proANP as well as the N-terminal fraction 8–29 of proBNP were determined by commercially available enzyme immunoassays (Biomedica, Vienna, Austria). As indicated by the manufacturer, respective reference ranges (5th–95th percentiles) were 0.11–0.47 nmol/l for proANP(1–30), <1.95 nmol/l for proANP(1–98) and <0.25 nmol/l for Nt-proBNP(8–29). We used commercial kits for the determination of cortisol and aldosterone (Immunotech, Marseille, France). Troponin-I and creatine kinase-MB (CK-MB)-mass were determined using standardized methods as previously described (19).

Data are given as median (interquartile range) if not stated otherwise. The Wilcoxon signed rank test was used to test for differences in serum levels of hormones before and after the competition. Spearman's correlation coefficient was calculated for changes in serum levels of the determined hormones, troponin-I and CK-MB-mass as well as for individual age and running time. A value of $P < 0.05$ (2-tailed) was considered statistically significant. The SAS statistical program was used for data analysis (SAS Institute Inc., Cary, NC, USA).

Results

All fractions of natriuretic propeptides were significantly increased after running the marathon compared

with basal levels (Table 2). We observed a pronounced rise in proANP(1–98) (+58%) and proANP(1–30) (+99%) (Table 2 and Fig. 1, $P < 0.0001$). Increases in proANP(1–30) but not in proANP(1–98) positively correlated with the age of the runners ($r = 0.53$, $P = 0.02$). Furthermore, there was a trend towards a positive correlation for changes in proANP(1–30) with troponin-I ($r = 0.44$, $P = 0.06$) and CK-MB-mass ($r = 0.44$, $P = 0.08$).

Nt-proBNP(8–29) also increased significantly during the marathon but more moderately (+6%) compared with fractions of proANP (Table 2 and Fig. 1, $P = 0.005$). Changes in Nt-proBNP(8–29) showed a positive and almost significant correlation with runners' age ($r = 0.44$, $P = 0.06$). There was no association with CK-MB-mass or troponin-I. Increases in natriuretic propeptides did not correlate with the individual running time.

Plasma levels of adrenocortical steroids also increased significantly. Aldosterone showed a 4.3-fold increase from 0.17 (0.14–0.23) nmol/l to 0.69 (0.52–1.39) nmol/l (Table 2 and Fig. 1, $P < 0.0001$). Plasma levels of cortisol rose by 73% ($P < 0.0001$). Increases in aldosterone and cortisol were positively correlated ($r = 0.71$, $P = 0.001$). They were not associated with individual age and running time or with CK-MB-mass and troponin-I.

Discussion

Our results demonstrate a significant increase in fractions of the myocardial prohormones proANP and proBNP in blood samples of well-trained healthy runners after a marathon. The Nt-proBNP(8–29) fraction rose considerably less than the fractions of proANP. These results correspond to data obtained after acute exercise showing a low BNP/ANP ratio in healthy subjects (20). The higher BNP/ANP ratio after an ultramarathon of 100 km in healthy individuals observed by Ohba *et al.* (21) indicates a distance-dependent influence.

Myocardial stretch due to an increase in atrial dimensions is the main stimulus for an increased ANP release at rest (22, 23). During acute exercise an increase in atrial distension (24, 25) probably due to increased central blood volume (26) and a corresponding rise in

Table 2 Serum levels of natriuretic propeptides and corticosteroids before and after running a marathon. Results are expressed as median (interquartile range).

	Before marathon	After marathon	<i>P</i> *
proANP(1–98)(nmol/l)	2.19 (1.47–2.90)	3.88 (2.63–4.80)	<0.0001
proANP(1–30)(nmol/l)	0.78 (0.60–0.97)	1.58 (1.10–2.46)	<0.0001
Nt-proBNP(8–29)(nmol/l)	0.18 (0.15–0.21)	0.19 (0.18–0.25)	0.0052
Cortisol (nmol/l)	622.0 (543.0–683.0)	897.0 (730.0–1249.0)	<0.0001
Aldosterone (nmol/l)	0.166 (0.136–0.227)	0.693 (0.515–1.385)	<0.0001

* Wilcoxon signed rank test.

Figure 1 Changes in natriuretic propeptides and adrenocortical steroids after running a marathon. proANP(1–98) and proANP(1–30) = fractions 1–98 and 1–30 of proANP. Nt-proBNP(8–29) = N-terminal fraction 8–29 of proBNP. Boxplots show median (line), interquartile range (box) and values within 3 interquartile ranges (whiskers) excluding the following outliers: Nt-proBNP(8–29) +108%, aldosterone +1955% and cortisol +239%.

atrial pressure (27, 28) have been associated with an increase in ANP in healthy individuals. However, during prolonged strenuous exercise, atrial size (29) and pressure (30, 31) decrease. The influence of other hormones (4, 32, 33) or a rise in the heart rate (32, 34) could increase secretion of ANP under these circumstances.

On the other hand, less elevated plasma levels of ANP after prolonged exercise compared with acute exercise (34, 35) might reflect impaired clearance of initially secreted ANP because of a decreased blood flow in internal organs such as the kidneys (36). But we think that a significantly decreased clearance of natriuretic peptides during the marathon would have altered plasma levels of BNP to a greater extent because of its delayed clearance (23).

Additionally, a partial correlation of ANP and troponin release (19, 21) could indicate a transient pathological process of simultaneous release from myocardial cells due to exercise. A change in cellular permeability by means of oxidative stress (37) and subsequent leakage of proteins might explain this phenomenon, although ANP and troponin derive from different compartments of the myocardial cell. We conclude that the origin of prominently elevated plasma levels of ANP after prolonged exercise includes various stimuli for secretion and probably to a minor extent impaired clearance as well as pathological leakage.

Different factors may influence the individual rise in ANP after prolonged exercise. The observed correlation of increases in proANP(1–30) with the individual age of the runners confirms data about an exaggerated

release of ANP in older individuals (34, 38, 39). A polymorphism of the angiotensin-converting enzyme may also influence the release of ANP (40). Furthermore, hot environmental temperatures result in decreased secretion of ANP (41–45), while progressive rehydration preventing a decrease in body fluids causes a more pronounced increase in ANP (44). We assume that an ample supply of isotonic drinks during the marathon together with the fairly warm environmental temperatures (46) resulted in a moderate body fluid loss in our study population.

What is the purpose of the observed prominent increase in ANP during prolonged exercise? Electrolyte loss and reduced blood pressure caused by ANP can hardly be expected to improve the hemodynamic stability of a runner. Adrenocortical steroids may counterbalance these negative effects, decreasing urinary fractional excretion of sodium (47). Prolonged exercise, such as competing in a marathon, even causes anti-diuresis (48) probably due to the marked increase in adrenocortical steroids (2, 11, 49–51) concomitantly with sympathoadrenal activation (52).

However, ANP may influence fluid regulation by shifting fluid from the intra- to the extravascular space (53). Receptors for natriuretic peptides in human sweat glands (54) might indicate a meaningful role for these peptides in the regulation of core temperature. A clearly positive and specific effect of ANP during prolonged exercise could be a potent stimulation of lipolysis in adipose tissue (55–57). Thus ANP may help to compensate the immense and limiting energy demand during long-distance running by elevating circulating free fatty acids (58).

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