Effects of physical endurance training on the plasma renin-angiotensin-aldosterone system in normal man

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ABSTRACT

The effect of physical endurance training on the plasma renin-angiotensin-aldosterone system was studied in 27 normal sedentary volunteers aged between 20 and 55 years, using a randomized two-period cross-over study design. After 4 months of training (2.5 h/week), peak oxygen uptake and physical working capacity at a heart rate of 130 beats/min were increased by 16% (P<0.001) and 29% (P<0.001) respectively, whereas resting heart rate was decreased by 15% (P<0.001). The plasma noradrenaline concentration and haematocrit were both decreased (P<0.01) after training. For the total group of subjects, the small decreases in plasma renin activity (PRA) and in the plasma concentrations of angiotensin-I, angiotensin-II and aldosterone were not statistically significant. However, the change in PRA during the training period was negatively correlated with the increase in physical working capacity (r = -0.49, P<0.01), suggesting that PRA decreased only in those subjects with the greatest increase in exercise capacity. Also, the change in plasma aldosterone during training was negatively related to the rise in physical working capacity (r = -0.57, P<0.01). Furthermore, the changes in plasma angiotensin-I (r = 0.75), angiotensin-II (r = 0.49) and aldosterone (r = 0.43) during the training period correlated positively with the change in PRA.

It is concluded that physical endurance training, leading to a substantial gain of physical working capacity, suppresses the plasma renin-angiotensin-aldosterone system in normal man.


INTRODUCTION

Cross-sectional studies have shown that plasma renin activity (PRA) is lower in athletes than in untrained subjects (Skipka, Böning, Deck et al. 1979; Fagard, Grauwels, Groeseneke et al. 1985; Lijnen, Hespel, Van Oppens et al. 1986). Findings from longitudinal intervention trials, which investigated the effect of a physical training programme on PRA, are controversial. Some studies report a fall in basal PRA after a period of physical training (Geyssant, Geelen, Denis et al. 1981; Gharib, Vincent, Annat et al. 1981; Vanhees, Fagard, Lijnen et al. 1984; Jennings, Nelson, Nestel et al. 1986), whereas others report no significant change (Convertino, Brock, Keil et al. 1980; Greenleaf, Sciaraffa, Shvartz et al. 1981; Kiyonaga, Arakawa, Tanaka & Shindo, 1985; Nelson, Jennings, Esler & Korner, 1986). None of these intervention studies, however, included the follow-up of a control group; training programmes were qualitatively and quantitatively very different and different types of subjects were studied. Interpretation of the presently available and apparently contrasting results is therefore difficult. As data on the effect of physical conditioning on plasma renin substrate, angiotensin-I and -II, angiotensin-converting enzyme and aldosterone are scarce, firm conclusions concerning the precise effect on physical training on the plasma renin-angiotensin-aldosterone system cannot yet be drawn.

The present study aimed, therefore, to investigate further the effect of physical endurance training on the plasma renin-angiotensin-aldosterone system in normal man.
MATERIALS AND METHODS

Subjects

Fifty military men, aged between 20 and 55 years and with a sedentary occupation, were recruited. Twenty of them were excluded because of overt cardiovascular disease or other medical problems which would contra-indicate physical training because of medication intake, high blood pressure (>160/95), abnormal electrocardiogram (ECG) at rest or during exercise, or excessive amounts of physical activity (sports participation >1 h/week). The remaining 30 subjects were instructed to maintain their dietary, physical activity and other living habits constant throughout the study period and to avoid all medication. During the study, three subjects interrupted the training programme, two due to lack of motivation for the exercise programme and one due to surgical intervention. Ultimately, 27 subjects completed the study (group A, n = 13; group B, n = 14).

Experimental design

Two weeks after preliminary physical and laboratory examinations and after written consent had been obtained, the subjects were randomized into two groups of similar age and weight distribution and underwent baseline laboratory examinations. There were no significant differences observed between the preliminary and baseline values for any of the variables measured; therefore, only the last values were finally used for statistical analyses. Immediately after the baseline laboratory examinations, group A was entered into the training programme which consisted of 48 training sessions of 1-h duration at a frequency of three sessions per week. Subjects who did not accomplish the training programme (48 h) within 16 weeks were asked to continue training until completion of the full programme. During the training period of group A the subjects of group B served as controls. They were repeatedly instructed to maintain their usual amount of physical activity and to retain their normal life-style throughout the control period. All laboratory examinations were repeated at the end of the training (group A) and control (group B) periods. At the end of the training period the subjects of group A were instructed to stop all physical training for a period of 4 months and thus to resume their original sedentary life-style. At the same time the subjects of group B were entered into the training programme and followed the same training protocol as did group A. All laboratory examinations were repeated at the end of the training period in group B and 16 weeks after stopping training in group A.

Training programme

All training sessions were supervised and consisted of successive periods of cycling (25 min), rest (5 min), jogging (15 min), rest (5 min) and finally 10 min of mainly dynamic callisthenics. During bicycle ergometry the external workload was repeatedly adjusted to obtain a heart rate during cycling equal to the sum of resting heart rate and 70% of the increment between resting and maximal heart rate as determined by the laboratory exercise test (Karvonen, Kentala & Muslala, 1957). For the jogging, the subjects were asked to cover a distance as long as individually possible during 15 min; they were encouraged to improve their performance throughout the training programme. The subjects counted their pulse rate by palpation at the start of the session, immediately after and 1 min after cycling and jogging, and immediately after the callisthenics. These pulse rates, together with the distance covered during jogging, were noted in a personal training file.

Laboratory examinations

Blood sampling and biochemical determinations

The subjects collected two 24-h urine samples in the 48 h immediately preceding the days of blood sampling. After an overnight fast the subjects came to the laboratory around 08.30 h. After 10 min of rest in the sitting position, blood pressure was measured by means of a standard mercury column sphygmomanometer. A blood sample (50 ml) was then taken from an antecubital vein. The blood samples were always taken on the same day of the week and at least 65 h after the last training session.

Plasma renin activity (Fyhrquist & Puutula, 1978) and the plasma concentration of renin substrate (Gould, Goodman, De Wolf et al. 1979), angiotensin-I (Lijnen, Amery & Fagard, 1978a), angiotensin-II (Lijnen, Amery, Fagard & Katz, 1978c) and aldosterone (Lijnen, Amery, Fagard & Corvol, 1978b) were measured by radioimmunoassay. Plasma angiotensin-converting enzyme (ACE) was measured spectrophotometrically (Lijnen & Amery, 1978) and plasma noradrenaline determined by high pressure liquid chromatography (Moerman & De Schaepdryver, 1984). Mean interassay variation of the assays of PRA, plasma renin substrate and angiotensin-I averaged 6-7%; mean interassay variation of the assays of plasma angiotensin-II, aldosterone, ACE and noradrenaline averaged 6-4, 5-7, 7-3 and 5-1% respectively.

Exercise testing

On a day different from that of blood sampling and always on the same day of the week, the subjects came to the air-conditioned exercise laboratory, where room temperature was stabilized between 18 and 20 °C.
On arrival their body weight and height were measured and a resting ECG was recorded. The subjects then underwent a graded and uninterrupted maximal exercise test on an electromagnetically braked cycle ergometer (Siemens 380B). The initial workload of 20 Watts was increased by another 20 Watts every minute until exhaustion. Through use of an open circuit method, oxygen uptake (\(\text{VO}_2\)) and CO\(_2\) output (\(\text{VCO}_2\)) were measured continuously. The respiratory gas exchange ratio was calculated as \(\text{VCO}_2/\text{VO}_2\). Heart rate was calculated from the ECG, which was monitored continuously. The external workload (Watt) at which a heart rate of 130 beats/min was achieved (\(\text{PWC}_{130}\)) was noted.

### Statistical analysis

The data were analysed with the conventional method for two-period cross-over trials as described in detail by Hills & Armitage (1979). Two-sample \(t\)-tests were applied to test whether treatment \(\times\) period interactions, and treatment effects were significantly \((P<0.05)\) different from zero. For those variables for which a significant treatment \(\times\) period interaction was found, the training effect was evaluated by comparing the changes from baseline during period one between the two experimental groups by two-sample \(t\)-test. The relationships between the changes in different variables during training were investigated by single (Pearson’s correlation coefficients) and multiple regression analysis (step-up procedure). The dispersion of the data is given by s.d. Before statistical analysis, PRA and plasma concentrations of angiotensin-I, angiotensin-II, aldosterone and noradrenaline were transformed to their logarithms, since only the log distribution was Gaussian; therefore, geometric means and ranges are reported for these variables.

### RESULTS

#### Characteristics of the subjects at the start of the study

Age, systolic and diastolic blood pressure averaged, respectively, 38 ± 10 years, 129 ± 13 mmHg and 88 ± 10 mmHg at the start of the study and were similar in both experimental groups. Body weight was on average 176 ± 7 cm; the subjects of group B were, however, 5.8 cm taller \((P<0.05)\) than those of group A. The urinary baseline excretions of sodium, potassium and creatinine were 142 ± 50, 69 ± 24 and 14.0 ± 3.9 mmol per 24 h in both experimental groups and remained constant throughout the study. For none of the other baseline characteristics of the subjects, which are given in Tables 1 and 2, was a significant difference found between the two groups.

#### Compliance with and intensity of the training programme

Thirteen out of the 27 subjects accomplished the training programme within the prescribed period of 16 weeks. For the other subjects the training period was prolonged by an average of 3.5 weeks (range, 1–16 weeks). Consequently, the average training frequency was 2.5 h/week (range, 1.5–3 h); it was, however, greater \((P<0.01)\) in group B (2.8 h/week) than in group A (2.1 h/week). The exercise heart rates counted during the training sessions were identical in both experimental groups and averaged 146 ± 10 beats/min immediately after cycling, 157 ± 10 beats/min at the end of jogging and 139 ± 12 beats/min after the callisthenics.

#### Body weight, heart rate and exercise capacity (Table 1)

Training significantly decreased body weight \((-1.8\%; P<0.01)\), resting heart rate \((-15\%; P<0.001)\), peak exercise heart rate \((-3\%; P<0.05)\) and the peak respiratory gas exchange ratio \((-3.6\%; P<0.05)\). A significant treatment \(\times\) period interaction was found for peak \(\text{VO}_2\) \((P<0.01)\) and for \(\text{PWC}_{130}\) \((P<0.05)\); based on the observations during the first study period, a significant increase in both variables could, however, be demonstrated after training \((P<0.01)\). When compared with the values immediately before the start of the training period, the training programme had increased peak \(\text{VO}_2\) and \(\text{PWC}_{130}\) by 16 and 29% respectively in the total group of subjects.

#### Biochemical measurements (Table 2)

A significant \((P<0.01)\) decrease in the plasma noradrenaline concentration \((-24\%)\) was observed after training. For haematocrit a significant treatment \(\times\) period interaction was found; during the first period of the study, however, haematocrit was slightly decreased after training in the training group compared with the control group \((P<0.01)\). No significant training effect could be demonstrated on PRA, plasma concentrations of angiotensin-I, angiotensin-II, aldosterone, renin substrate and ACE, or on haemoglobin and erythrocyte count. Also, no significant training effect was found after adjusting PRA for urinary sodium excretion.

#### Regression analysis

As shown in Fig. 1, the changes in PRA \((r = -0.49, P<0.01)\) and plasma aldosterone \((r = -0.57, P<0.01)\) during the training period were significantly correlated to the increase in \(\text{PWC}_{130}\) induced by training. In multiple regression analysis the following variables did not add significantly to the regression equation: age and the changes in body weight, urinary sodium excretion, haematocrit and plasma noradrenaline.
TABLE 1. Body weight, heart rate (HR) and respiratory variables at baseline and at the end of the periods with and without physical endurance training in men of group A (n = 13) and group B (n = 14). Values are means ± s.d.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A</th>
<th>Group B</th>
<th>r values</th>
<th>Treatment × period interaction</th>
<th>Training effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Training</td>
<td>No training</td>
<td>Baseline</td>
<td>No training</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78.5±15.0</td>
<td>78.0±15.3</td>
<td>79.0±15.9</td>
<td>80.1±8.8</td>
<td>80.8±9.5</td>
</tr>
<tr>
<td>Rest recumbent HR (beats/min)</td>
<td>65.2±8.9</td>
<td>57.0±11.0</td>
<td>63.1±8.3</td>
<td>66.2±9.1</td>
<td>66.6±8.8</td>
</tr>
<tr>
<td>Peak HR (beats/min)</td>
<td>172±17</td>
<td>170±14</td>
<td>172±14</td>
<td>173±17</td>
<td>171±15</td>
</tr>
<tr>
<td>Peak VO₂ (ml/min)</td>
<td>2904±689</td>
<td>3299±751</td>
<td>2899±522</td>
<td>3165±482</td>
<td>3228±633</td>
</tr>
<tr>
<td>Peak R</td>
<td>1.15±0.12</td>
<td>1.08±0.07</td>
<td>1.11±0.05</td>
<td>1.15±0.11</td>
<td>1.13±0.05</td>
</tr>
<tr>
<td>PWC₁₃₀ (Watt)</td>
<td>121±28</td>
<td>148±25</td>
<td>132±23</td>
<td>132±36</td>
<td>130±32</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001
VO₂, oxygen uptake; R, respiratory exchange ratio; PWC₁₃₀, physical working capacity at a heart rate of 130 beats/min.

TABLE 2. Biochemical measurements at baseline and at the end of the periods with or without physical endurance training in men of group A (n = 13) and group B (n = 14). Values are means ± s.d. or † geometric means and range (in parentheses)

<table>
<thead>
<tr>
<th>Variable</th>
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<td>Baseline</td>
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<td>No training</td>
<td>Baseline</td>
<td>No training</td>
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<tr>
<td>PRA (nmol/l.h)†</td>
<td>0.72 (0.34–2.10)</td>
<td>0.69 (0.26–1.59)</td>
<td>0.64 (0.28–1.21)</td>
<td>0.80 (0.17–2.09)</td>
<td>1.02 (0.45–2.57)</td>
</tr>
<tr>
<td>PA-I (pmol/l)†</td>
<td>61 (32–93)</td>
<td>76 (33–160)</td>
<td>50 (30–68)</td>
<td>59 (32–116)</td>
<td>79 (35–146)</td>
</tr>
<tr>
<td>PA-II (pmol/l)†</td>
<td>38 (19–79)</td>
<td>38 (17–81)</td>
<td>31 (18–73)</td>
<td>38 (24–65)</td>
<td>43 (28–66)</td>
</tr>
<tr>
<td>PRS (nmol/l)†</td>
<td>102±19 (0.54–2.50)</td>
<td>98±17 (0.53–2.09)</td>
<td>90±15 (1.78–2.22)</td>
<td>96±18 (1.01–3.55)</td>
<td>100±12 (0.53–3.96)</td>
</tr>
<tr>
<td>ACE (U/l)</td>
<td>31.5±7.2 (1.54–3.50)</td>
<td>32.6±9.1 (0.95–2.89)</td>
<td>32.8±8.1 (1.78–2.22)</td>
<td>29.0±10.4 (1.01–3.55)</td>
<td>31.3±10.1 (0.53–3.96)</td>
</tr>
<tr>
<td>PNA (nmol/l)†</td>
<td>2.90 (1.50–5.00)</td>
<td>2.01 (0.95–2.89)</td>
<td>2.96 (1.78–2.22)</td>
<td>2.25 (1.01–3.55)</td>
<td>2.43 (0.53–3.96)</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>45.7±5.02 (4.5–5.02)</td>
<td>45.5±0.2 (4.5–5.02)</td>
<td>46.0±0.2 (4.5–5.02)</td>
<td>47.2±0.3 (1.01–3.55)</td>
<td>49.1±0.3 (0.53–3.96)</td>
</tr>
<tr>
<td>Haemoglobin (mmol/l)</td>
<td>9.5–0.52</td>
<td>9.5±0.50 (9.5–0.52)</td>
<td>9.6±0.47 (9.5–0.52)</td>
<td>9.68±0.56 (1.01–0.58)</td>
<td>10.1±0.58 (0.53–3.96)</td>
</tr>
<tr>
<td>Erythrocytes (10¹²/l)</td>
<td>4.97±0.29</td>
<td>5.25±0.86 (4.5–5.02)</td>
<td>5.02±0.30 (4.5–5.02)</td>
<td>5.21±0.40 (1.01–0.58)</td>
<td>5.42±0.40 (0.53–3.96)</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001
PRA, plasma renin activity; PA-I, plasma angiotensin-I; PA-II, plasma angiotensin-II; PAC, plasma aldosterone; PRS, plasma renin substrate; ACE, angiotensin-converting enzyme; PNA, plasma noradrenaline.
The changes in plasma concentrations of angiotensin-I and angiotensin-II during the training period did not correlate significantly with the change in PWC\textsubscript{130}. The change in PRA during the training period was positively correlated with the change in plasma angiotensin-I ($r=0.75$, $P<0.001$), the change in plasma angiotensin-II ($r=0.49$, $P<0.01$) and the change in plasma aldosterone ($r=0.43$, $P<0.05$).

Amery, 1985) on the plasma renin-angiotensin-aldosterone system were thus to be avoided and, therefore, the blood samples were always taken at least 65 h after the last training session. The training programme proved to have been efficient as evidenced by the observed increase in peak oxygen uptake and physical working capacity and by the decrease in resting heart rate. In spite of this improvement in cardio-respiratory fitness, for the group as a whole, no significant change in PRA was seen. As shown in Fig. 1, the response of PRA to training was very different between subjects; in some subjects PRA decreased during training, but in others no change or even a small increase was observed. Independent of the other important variables determining PRA, these changes in PRA were related to the training-induced gain in physical working capacity. These findings agree with our previously observed negative correlation between maximal aerobic capacity (maximal VO\textsubscript{2}) and PRA in a population of normal male subjects, indicating that those with the highest physical fitness are characterized by the lowest PRA (M'Buyamba-Kabangu, Fagard, Lijnen & Amery, 1985). This seems to be confirmed by cross-sectional studies (Fagard et al. 1985; Lijnen et al. 1986) showing that the PRA in elite long-distance runners is about half that in untrained subjects; the PRA of the latter was similar to the PRA in the sedentary volunteers of the present study before training. Previous short-term longitudinal intervention studies in normal volunteers have reported apparently contrasting results; some studies found a decrease in PRA after a training programme of several months (Geyssant et al. 1981; Jennings, et al. 1986) whereas others did not (Convertino et al. 1980; Greenleaf et al. 1981; Wade, Dresendorfer, O'Brien & Claybaugh, 1981). However, in the latter three studies the training periods were less than 2 weeks and sub-acute effects of exercise were not always excluded with certainty. In accordance with the present data, Jennings et al. (1986) reported that in their sub-set of normal subjects the changes in plasma renin levels after bicycling three times per week for 1 month were very variable and did not reach statistical significance; plasma renin, however, significantly decreased when the subjects trained daily. Short-term longitudinal studies in hypertensive patients did not find an effect of training on PRA (Kiyonaga et al. 1985; Nelson et al. 1986; Urata, Tanabe, Kiyonaga et al. 1987). A study on rats suggests, however, that PRA responds differently to training stimuli in hypertensive than in normotensive animals (Marcus & Tipton, 1985).

Our data show no significant changes in the plasma concentrations of angiotensin-I, angiotensin-II and aldosterone at the end of the training period. However, significant positive correlations were found between the changes in PRA and the changes in plasma

**FIGURE 1.** Relationship between the changes in (a) plasma renin activity (PRA) and (b) plasma aldosterone concentration (PAC) and the increase in physical working capacity at a heart rate of 130 beats/min (PWC\textsubscript{130}) during a period of physical endurance training in men ($n=27$).

**DISCUSSION**

Plasma renin activity in man is affected by a number of environmental factors, among which are acute (Kotchen, Hartley, Rice et al. 1971) and possibly also chronic (Skipka et al. 1979; Gharib et al. 1981; Fagard et al. 1985; Jennings et al. 1986; Lijnen et al. 1986) physical exercise. The aim of the present study was to investigate further the chronic effect of endurance training on the plasma renin-angiotensin-aldosterone system in normal man. Short-term effects of exercise (Costill, Branam, Fink & Nelson, 1976; Lijnen, Hespel, Vanden Eynde &
angiotensin-I, angiotensin-II and aldosterone during the training period, and between the change in plasma aldosterone and physical working capacity. This suggests that in these subjects with the most important training effect, PRA decreased and concomitant decrease in the plasma concentrations of angiotensin-I, angiotensin-II and aldosterone occurred. Previous cross-sectional studies have shown that very well-trained athletes may have normal plasma angiotensin-II or aldosterone concentrations, although their PRA is decreased (Melin, Eclache, Geelen et al. 1980; Gharib et al. 1981; Fagard et al. 1985; Lijnen et al. 1986). Kosunen, Pakarinen, Kuappasalmi et al. (1980), however, demonstrated that, in long-distance runners, PRA and the plasma concentrations of angiotensin-II and aldosterone showed parallel changes over time during the various training periods of the year. In a study by Skipka et al. (1979), PRA tended to be lower in trained than in untrained subjects; this was accompanied by reduced urinary excretion of aldosterone in the former. In hypertensive patients, Kiyonaga et al. (1985) observed no change in PRA after 20 weeks of training, whereas plasma angiotensin-II concentrations were increased. This does not, however, conflict with the present observation since, as discussed above, adaptations of the plasma renin-angiotensin system to training in hypertensive subjects seem to be different from those in normotensive subjects (Marcus & Tipton, 1985). To the best of our knowledge, longitudinal data concerning the effect of training on plasma angiotensin-I and -II in normal man have not been previously published. In healthy volunteers trained during a period of 5 months, no change in plasma aldosterone occurred, although their PRA decreased significantly (Geyssant, Geelen, Denis et al. 1981); the number of subjects in the latter study was, however, small (n = 4).

A decrease in sympathetic tone (Winder, Hickson, Hagberg et al. 1979) and expansion of plasma volume (Oscal, Williams & Hertig, 1968; Greenleaf et al. 1981) could be responsible for the fall in basal PRA induced by training. In the present study the plasma noradrenaline concentration was decreased after training but no correlation could be found between the changes in PRA and plasma noradrenaline during the training period. Plasma noradrenaline, however, only partially reflects sympathetic tone (Floras, Jones, Hassan et al. 1986). Moreover, the catecholamine-stimulated renin release not only depends on sympathetic outflow but also on the sensitivity of the involved adrenoreceptors. The sensitivity of the adrenergic receptors on the juxtaglomerular cells might change during training, independently from an alteration in sympathetic tone; it has indeed been demonstrated that physical training may cause selective enhancement of β-receptor sensitivity in certain tissues but not in others (Svedenhag, Martinsson, Ekblom & Hjedmahl, 1986). Whether training alters the sensitivity of the adrenergic receptors mediating renin release is, however, not known. Blood haematocrit was slightly decreased after training in our subjects. Assuming that the red cell volume remained constant, this could indicate that plasma volume was increased. We found, however, no correlations between the training-induced changes in blood haematocrit or PRA. The lowering of the basal plasma aldosterone concentration during training is probably partially due to the fall in plasma angiotensin-II but possibly also to a direct adaptation of the adrenal gland to adrenocorticotropic hormone (ACTH) stimulation. It has been demonstrated in vitro that ACTH-induced corticosterone release by the adrenal gland of well-trained rats is reduced compared with that of untrained rats (Tharp & Buuck, 1974).

In conclusion, the present data provide evidence that physical endurance training suppresses the plasma renin-angiotensin-aldosterone system only when leading to a pronounced improvement of physical working capacity. The precise mechanism responsible for the suppression of PRA induced by training remains to be elucidated.

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