

## The hormonal response to exercise in asthma

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*The hormonal response to exercise in asthma. J.M. Kallenbach, V. Panz, M.S. Girson, B.I. Joffe, H.C. Seftel.*

**ABSTRACT:** The hormonal responses to exercise of 10 asthmatic patients and 12 normal subjects were compared by studying the changes in the plasma levels of growth hormone, prolactin, adrenocorticotrophic hormone (ACTH) and cortisol induced by treadmill running. The asthmatic patients demonstrated absence of the plasma cortisol response to exercise (peak increment  $-15 \pm 21$  (SEM) vs  $108 \pm 34$  nmol·l<sup>-1</sup> p<0.02). None of these patients were being treated with systemic corticosteroids and there was no difference between the responses of users and non-users of beclomethasone dipropionate. The results suggest the presence of an impaired adrenocortical response to the stress of physical exercise in asthma and indicate the need for detailed evaluation of hypothalamic-pituitary-adrenal function in patients with the disease.

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Physical exercise is associated with a significant rise in the plasma levels of growth hormone, prolactin, adrenocorticotrophic hormone (ACTH) and cortisol. The responses in the levels of both growth hormone and prolactin appear to be, at least in part, alpha-adrenergically mediated [1]. The precise cause of the airway hyperreactivity in bronchial asthma remains undefined and it has been suggested that overactivity of the alpha-adrenergic component of the sympathetic nervous system may be an important pathogenetic mechanism [2].

The possibility that impaired adrenal function may be present in asthmatic patients has long been the subject of speculation [3]. In a recent study we observed that asthmatic patients with "morning dipping" had lower midnight plasma cortisol levels than either those without "dipping" or normal subjects and a greater amplitude of variation in the circadian cortisol rhythm [4]. These findings did not appear to be related to corticosteroid therapy.

The object of this study was twofold: namely, i) to test the hypothesis of alpha-adrenergic overactivity in asthma; and ii) to examine the adrenocortical response to the physiological stress of physical exercise in patients with the disease.

### Subjects and methods

The study was approved by the Committee for Research on Human Subjects of the University of the Witwatersrand. Ten asthmatic patients and 12 normal subjects were studied, all of whom were males. No subject was a trained athlete.

Each asthmatic patient had a long history of the disease. The diagnosis was confirmed in each by the finding of at least one of the following: i) a forced expiratory volume in one second (FEV<sub>1</sub>) less than 70% of the predicted value with at least 20% improvement following the inhalation of a sympathomimetic bronchodilator aerosol; ii) significant bronchial hyperreactivity as manifested by a fall in the peak expiratory flow rate (PEFR) of at least 20% on exercise. The normal subjects had no history of asthma or any other atopic condition. Each had completely normal pulmonary function and a negligible fall in the PEFR on exercise.

Age and pulmonary function data are shown in table 1. The asthmatic patients had a significantly lower FEV<sub>1</sub> and a significantly greater airway resistance and percentage fall in PEFR on exercise than the normal subjects.

Only one patient had been treated with systemic corticosteroids; for a short period some years prior to the study. He and three other patients were using beclomethasone dipropionate aerosol (maximum dose 400 µg·day<sup>-1</sup>; duration of use greater than one year in 3, less than 2 months in one). None was using vasoconstrictor nose drops. All bronchodilator therapy was discontinued at least 7 days, and all other medications at least 24 h prior to the study. The asthmatic patients were all in a stable condition at the time of the study.

Eight of the 10 asthmatic patients gave a history of exercise-induced bronchospasm. As this may itself be a stimulus for increased hormonal secretion both in relation to the work of breathing and by a stress-related effect [5], it was necessary to eradicate this response as completely as possible during the study. Each patient was therefore studied following the administration of

Table 1. - Age and pulmonary function data

	Age <sup>‡</sup> yrs	FEV <sub>1</sub> <sup>+</sup> % predicted	Airway resistance cmH <sub>2</sub> O·l <sup>-1</sup> ·s <sup>-1</sup>	Fall in PEFR on exercise %
Normal subjects (n=12)	20-27(22)	103±3* (85-119)	1.6±0.1*	2±1*
Asthmatic patients (n=10)	17-26(20)	63±2 (54-72)	4.0±0.5	28±5

Values are mean±SEM; <sup>‡</sup> range (median in brackets); <sup>+</sup> mean±SEM (range in brackets); FEV<sub>1</sub>: forced expiratory volume in one second; PEFR: peak expiratory flow rate; \*: normal subjects vs asthmatic patients significantly different (p<0.0005).

anti-asthmatic premedication consisting of salbutamol (200 µg) and disodium cromoglycate (2 mg) administered by aerosol 10 min prior to exercise, resulting in a marked attenuation of the fall in PEFR on exercise (8±3% (SEM) vs 28±5%). As it has been suggested that the cortisol response to exercise may be affected by disodium cromoglycate [6], each normal subject received the same premedication.

Each study was commenced at 0800h following an overnight fast. After arrival at the exercise laboratory the subject was placed in the recumbent position in a quiet room. A 19-gauge, or larger, cannula was immediately inserted into an arm vein and kept patent with a slow infusion of normal saline. Not less than 30 min later blood was sampled through the cannula and this was repeated 15 min later. Immediately after this the subjects ran for 10 min on a treadmill of variable speed and incline during which heart rate was continuously monitored. The incline of the treadmill was progressively increased so that by the end of 7 min the subject had attained estimated maximum heart rate based on the data in the review of FORTUIN and WEISS [7]. This heart rate was then maintained for a further 3 min, following which the subjects were once again placed in the recumbent position.

Blood was sampled immediately, and 5, and 20 min following the completion of exercise. Heart rate and blood pressure were measured prior to each sampling of blood. Aliquots of blood for the determination of the plasma levels of growth hormone, prolactin, ACTH and cortisol were placed into iced tubes and immediately centrifuged. The separated plasma was stored at -20°C until assayed.

#### Biochemical methods

Plasma growth hormone levels were measured by radioimmunoassay (kit supplied by Serono Biodata, Milan, Italy; lower limit of sensitivity 0.2-0.4 ng·ml<sup>-1</sup>).

Plasma prolactin levels were measured by radioimmunoassay (kit supplied by Serono Biodata, Milan, Italy; lower limit of sensitivity 2 ng·ml<sup>-1</sup>).

Plasma ACTH levels were measured by radioimmunoassay (kit supplied by CIS International, St-Quentin-Yvelines, Cedex, France; lower limit of sensitivity 10 pg·ml<sup>-1</sup>).

Plasma cortisol levels were measured by radioimmunoassay (kit supplied by CIS International,

St-Quentin-Yvelines, Cedex, France; lower limit of sensitivity 4 ng·ml<sup>-1</sup>).

#### Statistical analysis

The response to exercise in the plasma level of each hormonal variable was analysed by means of: i) a random coefficients repeated measurements growth model [8] which was restricted to a linear model in view of the relatively small number of time points being analysed; ii) comparison of peak incremental responses which were calculated by subtracting the basal hormone level (arithmetic mean of the values obtained at -15 and 0 min) from the peak level attained following exercise. In the case of decremental hormonal responses, the basal value was subtracted from the highest value obtained following exercise.

Unpaired data were compared by means of the two-tailed Mann-Whitney U test and paired data using the 95% extreme range limits of mean ranks. The significance of the variation in each variable following exercise was assessed within each group using Friedman's two-way analysis of variance.

All data are presented as mean±standard error of the mean.

#### Results

There was no difference between the asthmatic patients and the normal subjects in the heart rate or blood pressure responses at any time in the study (fig. 1).

The plasma growth hormone level varied significantly in both the normal subjects (p<0.0005) and the asthmatic patients (p<0.01) in association with exercise. There was no difference between the responses of the two groups of subjects.

Similarly, while the plasma prolactin level varied significantly in both the normal subjects (p<0.001) and the asthmatic patients in association with exercise (p<0.05), there was no difference between the responses of the two groups.

The plasma ACTH and cortisol responses are shown in table 2. The plasma ACTH level varied significantly in the normal subjects (p<0.02) but not the asthmatic patients in association with exercise. Although the plasma

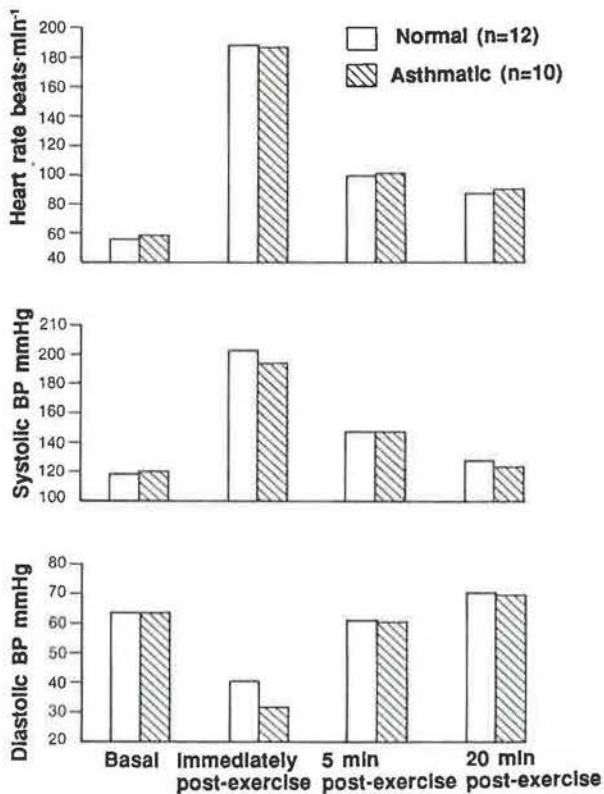


Fig. 1. – Haemodynamic responses to exercise of asthmatic and normal subjects.

ACTH level was significantly lower in the asthmatic patients immediately after exercise ( $p < 0.006$ ) there was no difference between the responses of the two groups when analysed by the two methods used.

The plasma cortisol level varied significantly in both the normal subjects ( $p < 0.02$ ) and the asthmatic patients in association with exercise ( $p < 0.01$ ). In the asthmatic patients the plasma cortisol level was significantly lower than the basal level both immediately and 5 min after

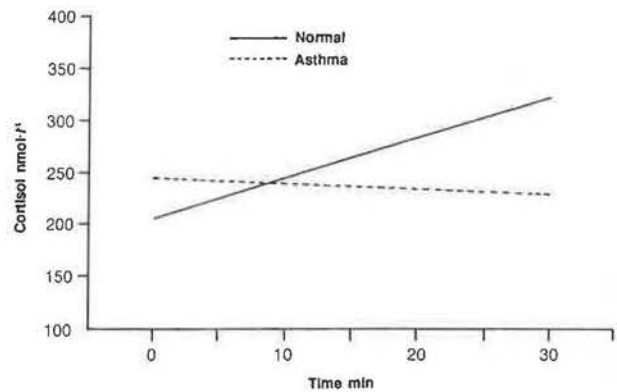


Fig. 2. – Regression lines showing plasma cortisol responses in asthmatic and normal subjects.

exercise ( $p < 0.05$ ), while it was significantly higher than basal in the normal subjects 20 min after exercise ( $p < 0.05$ ). The plasma cortisol level was significantly lower in the asthmatic patients than in the normal subjects 20 min after exercise ( $p < 0.05$ ).

Analysis of the plasma cortisol responses showed: i) the peak incremental response was significantly smaller in the asthmatic subjects ( $p < 0.02$ ); ii) the regression lines obtained yielded the following equations:

$$\text{Asthmatic patients: } y = 244.3 - 0.54 t$$

$$\text{Normal subjects: } y = 205.2 + 3.88 t$$

which differed significantly ( $p < 0.026$ ). The slope of the regression line was significantly greater in the normal subjects ( $p = 0.006$ ) and the intercepts on the y-axis were not significantly different (fig. 2).

The cortisol responses of the individual asthmatic patients are shown in figure 3. There was no significant difference between users and non-users of beclomethasone in the magnitudes of the cortisol or ACTH responses.

Table 2. – Plasma ACTH and cortisol responses to exercise

	Basal	Immediately post-exercise	5 min post-exercise	20 mins post-exercise	Peak increment
ACTH pmol·l <sup>-1</sup>					
Normal subjects (n=12)	27±7	46±13*	29±6	21±5	24±14
Asthmatic patients (n=10)	19±2	19±2	32±9	19±2	15±10
Cortisol nmol·l <sup>-1</sup>					
Normal subjects (n=12)	220±13	219±8	266±20	329±25 <sup>§†</sup>	108±34 <sup>†</sup>
Asthmatic patients (n=10)	272±22	217±18 <sup>§</sup>	211±19 <sup>§</sup>	248±23 <sup>§</sup>	-15±21

Values are mean±SEM; +: normal subjects vs asthmatic patients significantly different ( $p < 0.02$ ); †: normal subjects vs asthmatic patients significantly different ( $p < 0.05$ ); \*: normal subjects vs asthmatic patients significantly different ( $p < 0.006$ ); §: value significantly different from basal ( $p < 0.05$ ); ACTH: adrenocorticotrophic hormone.

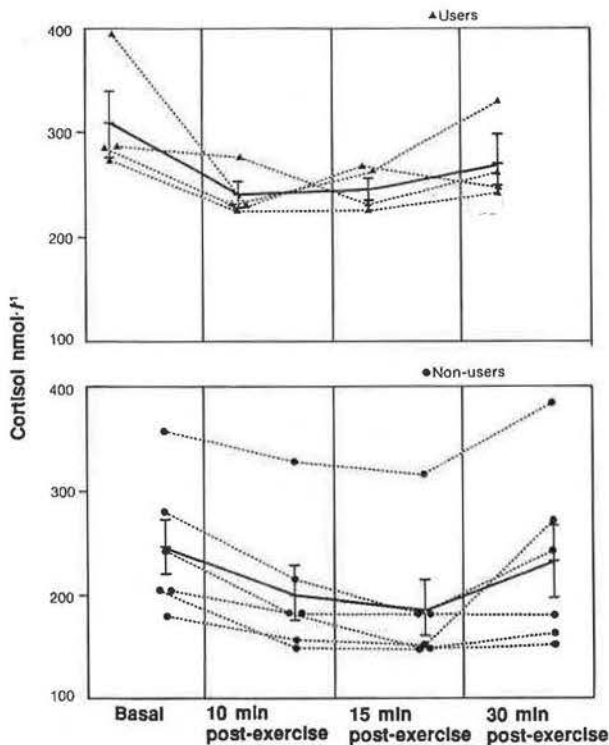


Fig. 3. - Individual (.....) and mean (—) responses ( $\pm$ SEM) of "users" and "non-users" of beclomethasone dipropionate.

### Discussion

The most noteworthy finding in this study was the diminished cortisol response to exercise in the asthmatic patients. Plasma cortisol levels usually rise in association with exercise, with peak levels often occurring in the post-exercise period [9].

The present findings require analysis in the light of corticosteroid therapy in the asthmatic group. Four of the 10 patients had been using inhaled beclomethasone dipropionate (maximum dose  $400 \mu\text{g}\cdot\text{day}^{-1}$ ) until 24 h prior to the study. It has been suggested that children using relatively large doses ( $300\text{--}800 \mu\text{g}\cdot\text{day}^{-1}$ ) may have diminished adrenal responses to insulin-induced hypoglycaemia [10] and metyrapone [11]. However, most studies in both adults and children using the compound show normal hypothalamic-pituitary-adrenal reserve as assessed by the responses to ACTH and metyrapone [12–15] even with doses of  $1,000\text{--}2,000 \mu\text{g}\cdot\text{day}^{-1}$  [16, 17]. From these data and our results (fig. 3), we can virtually exclude the possibility that the present finding was the result of pituitary-adrenal suppression by beclomethasone therapy.

The adrenocortical response to exercise has been shown to be affected by the relationship of the exercise to a meal [18], and to be diminished by chronic training [19]. Neither of these variables could have affected our results. The cortisol response to exercise is also dependent on the workload [20] and on the clearance of glucocorticoid hormones from the circulation [1]. The latter does not differ in asthmatic and normal subjects [21, 22] and

the intensity of exercise, as assessed by the haemodynamic responses, was similar in our two groups of subjects (fig. 1).

Previous studies of the plasma cortisol response to exercise in asthma have yielded markedly conflicting results. HOLMES *et al.* [6] found that plasma corticosteroid levels fell in both asthmatic and normal subjects and attributed this to disodium cromoglycate premedication. JAFFE *et al.* [23] reported a greater rise in plasma cortisol levels in asthmatic than normal subjects on exercise, and suggested that this was due to the stress of exercise-induced asthma. In another report, asthmatic patients exhibited no changes in plasma cortisol levels on exercise [24]. All of these studies used relatively inaccurate methods of plasma corticosteroid determination.

The adrenocortical response to any stressful stimulus is directly mediated by ACTH which is secreted in bursts, followed within 5–10 min by increased cortisol secretion [25]. It is possible that the absent cortisol response in the asthmatic patients was related to the blunted ACTH response observed (table 2).

The secretion of ACTH from the anterior pituitary is stimulated by corticotropin releasing hormone (CRH), a neuropeptide with diverse effects on autonomic function as well as on various aspects of behaviour [26]. The release of CRH in the hypothalamus is itself regulated by a complex mechanism involving cholinergic, serotonergic and adrenergic neurotransmitter neurons [25]. Hypothalamic levels of CRH fail to rise in association with stress in the presence of glucocorticoid therapy [27]. Moreover, in animals surgically-induced hypothalamic lesions result in a diminution of the ACTH response to stress as well as an increase in the amplitude of the circadian ACTH and cortisol rhythms [28]. Particularly in the light of our previous findings [4], it is tempting to postulate that asthmatic patients may have a primary abnormality of hypothalamic function, which may also account for the wide spectrum of autonomic abnormalities which occur in association with the disease [2, 29]. Our results suggest the need for detailed evaluation of hypothalamic-pituitary-adrenal function in asthma.

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*Réponse hormonale à l'effort dans l'asthme. J. Kallenbach, V. Panz, M.S. Girson, B.J. Joffe, H.C.P. Sestel.*

RÉSUMÉ: Les réponses hormonales à l'effort ont été comparées chez 10 sujets asthmatiques et chez 12 sujets normaux, par l'étude des modifications des niveaux plasmatiques d'hormone de croissance, de prolactine, d'ACTH et de cortisol, au cours d'un effort sur tapis roulant. Les patients asthmatiques n'ont eu aucune réponse du cortisol plasmatique pendant l'effort (modification de pointe:  $-15 \pm 21$  (SEM) vs  $108 \pm 34$  nmol/l;  $p < 0.02$ ). Aucun de ces patients n'était traité par les corticostéroïdes systémiques et il n'y avait pas de différence entre les réponses des utilisateurs de dipropionate de beclométhasone et celles des non-utilisateurs. Les résultats suggèrent la présence d'un trouble dans la réponse de la corticosurrénale à l'exercice physique dans l'asthme, et suggèrent qu'une évaluation plus détaillée de la fonction hypothalamo-pituitaire et surrénalienne devrait être conduite chez les patients asthmatiques. *Eur Respir J.*, 1990, 3, 171–175.