Sympathoadrenal Reactivity in Exercise-induced Asthma*

Kjell Larsson, M.D.; Paul Hjemdahl, M.D.; and Arne Martinsson, M.D.

The possibility that sympathoadrenal activity is altered in asthma was examined in eight patients with a history of exercise-induced asthma (EIA), eight matched patients with nonexercise induced asthma (NEIA), and eight matched healthy control subjects. No medication was allowed for at least one week before examination. In a pretrial exercise test diagnosis of EIA was confirmed and each individual’s work capacity (\(V_{\text{O}_2}\) max) was determined. The trial consisted of an ortostatic test and a standardized exercise test at 80 to 90 percent of \(V_{\text{O}_2}\) max on a treadmill. The trial exercise test caused a decrease in FEV\(_1\), in EIA patients only, whereas measurements of Sgaw revealed a significant but less pronounced postexercise bronchoconstriction in NEIA-patients as well. Basal plasma catecholamine levels were similar in all groups. Noradrenaline and adrenaline levels were approximately doubled by the ortostatic test and increased approximately ten-fold following exercise, with no differences between the groups. Plasma cAMP levels were approximately doubled by the exercise test. In the EIA patients there was an inverse correlation between increases in plasma cAMP and decreases in Sgaw. Our study does not support earlier claims that exaggerated catecholamine response to exercise causes postexercise bronchoconstriction by \(\alpha\)-adrenoceptor stimulation in EIA. Differences in study results appear to have methodologic explanations.

It is well known that \(\beta\)-adrenoceptor blockade may cause bronchoconstriction\(^1\) and that \(\beta_2\)-adrenoceptor stimulation induces bronchodilation in patients with bronchial asthma. There is also evidence for the existence of \(\alpha\)-adrenoceptors in human airways,\(^2,8\) the stimulation of which may induce contraction of human bronchial smooth muscle.\(^4\) Conversely, \(\alpha\)-adrenoceptor blockade may counteract or reduce bronchoconstriction provoked by allergen,\(^5\) exercise,\(^6,7\) or histamine.\(^2,8,9\) Hence, adrenergic mechanisms seem to be important for the regulation of bronchial tone in patients with bronchial asthma. This raises two questions. First, is the liberation of endogenous adrenergic agonists altered, \(ie\), is sympathoadrenal reactivity altered in asthmatic patients? Second, is there an altered adrenergic receptor sensitivity in asthma, as suggested by Szentivanyi?\(^2,10\)

Sympathoadrenal reactivity in asthma has not been the subject of intense investigation. However, some studies have shown that patients with exercise-induced asthma (EIA) obtain higher plasma levels of noradrenaline during work than healthy control subjects.\(^11-14\) The conclusion of these studies has been that postexercise bronchoconstriction is the result of \(\alpha\)-adrenoceptor stimulation caused by an excessive production of endogenous noradrenaline.

Since there are limitations with regard to patient selection, standardization of antiasthmatic treatment, and standardization of the experimental procedures in the above-mentioned studies, we attempted to study these problems further. The present report concerns sympathoadrenal reactivity in asthmatic patients with a history of EIA and in patients with nonexercise-induced asthma (NEIA).

**Material and Methods**

Sixteen asthmatic patients and eight healthy control subjects participated in the study. The patients were divided into two groups, one with a history of EIA and one with a history of NEIA. The healthy control subjects (group C) had no history of asthma or any other allergic manifestation. All subjects were nonsmokers, and the three groups were matched with regard to sex and age (Table 1).

Each subject was studied on two occasions, separated by less than two months. On the first occasion a pretrial exercise test was performed on a treadmill to define the maximal work capacity of each individual. During this exercise test, the maximal ventilation (\(V_{\text{E}}\)) and the maximal oxygen uptake (\(V_{\text{O}_2}\)) were measured. The exercise was submaximal during the first five minutes, after which the work was increased stepwise until exhaustion. Before, immediately after, and 5, 10, and 20 minutes after this exercise test, FEV\(_1\), VC and VC were measured with a Vitalograph. Subsequently, 160 µg of isoproterenol (Isoproterenol, ACO, Sweden) was inhaled from a pressurized aerosol, and five minutes later a final spirometric measurement was performed. This pretrial exercise test was used to confirm the existence of exercise-induced bronchoconstriction and to predict the work level at which the experimental exercise test should be performed. Exercise-induced asthma was defined as a decrease in FEV\(_1\) of more than 15 percent when compared with basal preexercise values.

On the second occasion all subjects had been without

---

*From the Department of Pharmacology, Karolinska Institutet, and the Department of Clinical Physiology, Thoracic Clinics, Karolinska Hospital, Stockholm, Sweden.

This study was supported by the Swedish National Society Against Heart and Chest Diseases and by the Swedish Medical Research Council, Proj No 5930.

Manuscript received February 25; revision accepted June 10.

Reprint requests: Dr. Hjemdahl, Department of Pharmacology, Karolinska Institutet, Box 60-400, S-104 01 Stockholm, Sweden
any kind of medication for at least seven days. Thoracic gas volume (TGV), airways resistance (Raw), and, from this, specific airways conductance (Sgaw) were measured in a volume-constant body plethysmograph. The mean values of ten initial measurements at the subject's functional residual capacity (FRC) were calculated. The subjects then received a venous cannula, after which they rested in the supine position for 25 minutes. After this rest, two venous blood samples (10 ml) were collected at five-minute intervals, and heart rate, blood pressure, and lung function were measured. Blood pressure was measured with a conventional arm cuff; the diastolic pressure was defined as the point where the Korotkoff sounds were muffled. This procedure was repeated after another five minutes of rest, after which an orthostatic test was performed. Heart rate and blood pressure were measured in the recumbent position, immediately after standing, and after four and eight minutes in the upright position. At the end of the orthostatic test, a venous blood sample was collected, and measurements in the body plethysmograph and the Vitalograph were repeated. Thereafter, an exercise test was performed on the treadmill at a submaximal work level (90 percent of maximal \( V_{O_2} \)) during eight minutes. The breathing frequency was registered during the last minute of exercise and heart rate was continuously monitored by ECG. Following this exercise test, venous blood samples were collected at 0, 5, and 25 minutes. Plethysmographic measurements were made at 6, 11, and 26 minutes after exercise and \( FEV_1 \) and VC were measured immediately thereafter.

Venous blood was collected in ice-cooled centrifuge tubes containing EDTA (10 mM final concentration). The samples were centrifuged in the cold, and plasma was subsequently stored at -80°C. Plasma samples were later analyzed for contents of adrenaline, noradrenaline, and dopamine (by HPLC with electrochemical detection according to Hjemdahl et al.\textsuperscript{15}), glycerol\textsuperscript{16} and cAMP.\textsuperscript{17} The catecholamine assay sensitivity was better than 0.05 nM for all three catecholamines using 2 ml of plasma. The inter- and intra-assay coefficients of variation in the assay were 2 to 3 percent for noradrenaline (at basal levels of 1 to 2 nM) and 9 to 12 percent for adrenaline and dopamine (at basal levels of 0.1 to 0.2 nM, less at higher levels).

On the days of the exercise tests the patients were supposed to be in a free interval of their disease. Therefore, the basal \( FEV_1 \) was not allowed to differ more than 10 percent between the two occasions. Statistical evaluation was performed by three-way analysis of variance. Results are presented as mean values ± SEM.

This study was approved by the Ethical Committee of Karolinska Institutet, Stockholm.

### RESULTS

At the time of the two exercise tests the relative humidity was 22 to 45 percent and the ambient temperature 22 to 24.5°C, as determined in 24 of the 48 experiments.

### Prettrial Examination

Basal preexercise values for \( FEV_1 \) and VC were similar in the three groups, and all were within 75 percent of the predicted values. All patients with a history of EIA had decreases in \( FEV_1 \) of more than 15 percent following the prettrial exercise test.
whereas none in the NEIA group or the C group did (Fig 1A). In the EIA group there was no tendency toward recovery during the first 20 minutes after this maximal exercise test. Isoprenaline inhalation reestablished basal FEV₁ values in all individuals (Fig 1A). There was no significant difference between the basal preexercise FEV₁ and the value recorded after inhalation of Isoprenaline in any patient or control subject, indicating absence of bronchoconstriction in the basal state.

There was no significant difference between the three groups with regard to maximal VO₂ (Fig 2). VE at the end of the exercise was greatest in the EIA group (118.9 ± 13.2 L/min) and smallest in the NEIA group (104.2 ± 14.9 L/min). However, this difference was not statistically significant. There was no correlation between the degree of postexercise bronchoconstriction and the maximal VE in the asthmatic patients.

**Trial Examination**

The basal preexercise FEV₁ and VC did not differ from the basal values in the pretrial examination in any of the three groups (TEIA = 0.99, TNEIA = 0.93, rC = 0.99 for FEV₁), indicating that the patients were also in a free interval at the time of the trial examination. No subject had a basal FEV₁ of less than 75 percent of the predicted value. Following the submaximal treadmill exercise test, FEV₁ decreased to less than 85 percent of preexercise values in six of the EIA patients but in none of the others. The postexercise recovery of the EIA patients was faster than after the pretrial testing, but was not complete within 25 minutes after exercise (Fig 1B). All subjects completed the eight minute exercise test, with the exception of two patients in the EIA group who discontinued exercise after a shorter time than eight minutes (3'15'' and 6'') due to dyspnea. Of
exercise Sgaw or FRC between the groups or between the two basal measurements in the same subject. Basal Raw at FRC exceeded 100 percent of the predicted value in three patients, all of whom belonged to the NEIA group, but did not exceed 125 percent of the predicted value in any patient. The postexercise Sgaw decreased to less than 65 percent of basal preexercise values in all EIA patients and in three of the NEIA patients, but in none of the control subjects (Fig 1C). Two patients in the NEIA group had a slight postexercise fall in FRC of less than 5 percent compared with basal preexercise values. All other subjects in this study had a postexercise increase in FRC (Fig 3).

One patient in each asthma group and two subjects in the C group could not complete the orthostatic test due to vasovagal reactions. Two of these individuals fainted. There were no statistically significant differences in mean arterial pressure at rest in the supine position or during standing when comparisons were made between the three groups. The mean increases in heart rate during standing were 10 to 20 beats/min in all three groups. The C group had slightly lower heart rates than the two patient groups. The basal plasma catecholamine levels were: noradrenaline, 1.36 ± 0.20 nM; adrenaline, 0.07 ± 0.01 nM; and dopamine, 0.12 ± 0.04 nM in the C group. The basal catecholamine levels did not differ between the groups and there were no differences between the two resting samples. Noradrenaline and adrenaline levels were approximately doubled during the orthostatic test, while dopamine levels were unchanged (Fig 4). There was no difference between the groups with regard to plasma catecholamine reactivity in connection with the orthostatic test.

The trial exercise test increased plasma noradrenaline by a factor of 11.9 (range 10.8 to 13.5) and plasma adrenaline by a factor of 10.2 (6.1 to 12.7), when calculated on all subjects participating in the study. Maximal catecholamine levels were obtained immediately after exercise. These were: noradrenaline, 14.72 ± 1.35 nM; and adrenaline, 0.83 ± 0.24 nM in the C group. There were no statistically significant differences between the groups with regard to maximal concentrations or maximal increases of noradrenaline and adrenaline obtained after exercise (Fig 4). There was no significant difference in dopamine levels at rest or following exercise. The increase in dopamine tended to be greatest in the NEIA group and smallest in the C group, in which the maximal concentration was 0.21 ± 0.05 nM. The difference, however, was not statistically significant. The catecholamine levels were normalized 25 minutes after exercise, as there was

Figure 2. Maximal ventilation (VE), maximal oxygen uptake (VO2), and maximal heart rate in pretrial maximal exercise test. Mean values (±SEM) from eight subjects in each group.

Figure 3. Percent change in functional residual capacity (FRC) after submaximal exercise test. Each point represents mean values (± SEM) from eight subjects.

all patients in the EIA group, one of these patients had the highest noradrenaline level (27.02 nM), and the other patient had the highest adrenaline level (1.40 nM) immediately following exercise.

There was no significant difference in basal pre-
were in active concentrations respectively. When the trial exercise test was 179 ± 6, 171 ± 3, and 172 ± 3 beats/min in the EIA, NEIA, and C groups, respectively.

The baseline plasma level of cAMP was 16.7 ± 0.9 nM and of glycerol was 60 ± 5 μM in the C group. There was no difference between the groups regarding these levels. Cyclic AMP levels were unchanged after the orthostatic test and were doubled following exercise (Fig 5). The glycerol concentrations rose slightly during standing and were about doubled to a maximal value five minutes after exercise. There was no significant difference between the groups with regard to plasma levels of cAMP and glycerol at rest or increases in connection with the orthostatic test or the exercise test.

When plasma levels of catecholamines, cAMP, and glycerol were correlated with VO₂ or Sgaw, no correlation was found, with the exception of a negative correlation between the postexercise increase in cAMP and decrease in Sgaw in the EIA group (r = 0.77). Thus, the more pronounced the postexercise bronchoconstriction, the less plasma cAMP increased following exercise (Fig 6). There was a positive correlation between the increase in plasma levels of cAMP and adrenaline in the C group (r = 0.81, p < 0.05) and in the whole population (r = 0.48, p < 0.05). Apart from this, no correlation was found between the exercise-induced changes in plasma levels of the substances analyzed.

**DISCUSSION**

EIA is usually defined as a postexercise decrease in FEV₁ of 15 percent or a decrease in Sgaw of 35 percent compared with basal preexercise values. In the present study, all asthmatic patients had postexercise bronchoconstriction, but the severity of this reaction varied. When using a less sensitive parameter, such as FEV₁, to evaluate bronchial tone, the postexercise measurements of the NEIA patients did not differ from those of the C group. With the more sensitive plethysmographic method of detecting airways obstruction, a significant increase in postexercise bronchial tone was found also in the NEIA group. Thus, the C group had no postexercise decrease of Sgaw, while the NEIA patients responded with a postexercise decrease of Sgaw which was about half as pronounced as that found in the EIA group. Hence, postexercise bronchoconstriction...
levels
16.0

Downloaded From: http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21321/ on 06/26/2017

FIGURE 6. Relationship between increases in plasma cyclic AMP (ΔcAMP) during exercise test and postexercise decreases in airways conductance (Sgaw) in the EIA group (n=8).

seems to be a general phenomenon in asthma and not restricted to the subgroup of asthmatic patients with clinical symptoms of EIA.

In this study there was no difference in the catecholamine response to orthostatic provocation or exercise when comparisons between asthmatic patients and healthy control subjects were made. The adrenaline levels in the EIA patients were similar to those of the C group after exercise. Thus, this degree of bronchoconstriction does not seem to be a potent stimulus for adrenaline secretion. Several earlier studies of sympathoadrenal activity in bronchial asthma have shown enhanced plasma noradrenaline levels during exercise in patients with EIA compared with healthy control subjects and patients with NEIA. The conclusion of these studies has been that the exaggerated noradrenaline response causes bronchoconstriction by α-adrenoceptor stimulation.11-14 Two studies, however, found no difference in postexercise noradrenaline levels when comparing EIA patients with healthy control subjects,18,19 and one study found lower levels in EIA patients.20 The discrepancies in results and conclusions of these different studies may be related to differences in patient selection, treatment, analytical methodology, and standardization of experiments.

We have attempted to define our patients and control subjects and to standardize the exercise tests. The HPLC method used for determining plasma catecholamines in this study has a good sensitivity and selectivity and has been validated against radioenzymatic methodology.15 In earlier studies patients have not always been very well defined,18,20 and in some studies there are signs of bronchoconstriction in the basal state.18,20 In most of these studies the plasma catecholamine concentrations have been analyzed by fluorometric methods. The exceptions are the studies of Reinhart et al12 and Barnes et al,20 which employed radioenzymatic methods. Several of these earlier studies report high basal plasma catecholamine levels or small increases in plasma noradrenaline or both following exercise. Plasma adrenaline levels also increased little18,14 or not at all11,13,19 following exercise. Barnes et al20 found a clear-cut increase of plasma adrenaline in healthy control subjects following exercise, but no increase in asthmatic patients. There is thus a discrepancy with regard to the catecholamine reaction following exercise in our study and these previous studies, since we found low basal plasma catecholamine levels and clear-cut increases in both noradrenaline and adrenaline following exercise.

A limitation of the present and earlier studies of the catecholamine response to exercise is the possibility that sympathetic activity is unevenly distributed. There may be increases in sympathetic activity to the bronchial smooth muscle in EIA without a generalized increase in sympathetic activity, which would be reflected in elevated plasma catecholamine levels. However, our results lend no support to the above-mentioned claims of an exaggerated plasma noradrenaline response to exercise in EIA.

Prolonged treatment with β2-agonists may influence the results of studies on asthmatic patients, since it is well known that a continuous stimulation of the β-adrenoceptor reduces its sensitivity to further stimuli.21 Thus, the sensitivity to endogenous β-adrenoceptor agonists, especially the β2-agonist adrenaline, may also be reduced. In earlier studies the medication was withdrawn 8 hours,18 12 hours,20 or 72 hours19 before the exercise tests, or was not specified. In our study no treatment was allowed for at least one week before the test to preclude any possible effect of drug treatment on the results. It has been shown that the number of β-adrenoceptor binding sites on lymphocytes is normalized seven days after the discontinuation of β2-agonist treatment.22 Holgate et al23 have stated that seven to ten days is required for the normalization of β-adrenoceptor sensitivity in the lungs of healthy volunteers following treatment with β2-adrenoceptor agonists. Furthermore, most of our patients had only symptomatic treatment before this medication-free week, and it is therefore very unlikely that drug treatment influenced the results of our study. The drawback of our nontreatment requirement, of course, is that only patients with mild asthma who could be without treatment for this period were
studied. Thus, our results may not apply to severe cases of asthma.

One interesting finding was a negative correlation between postexercise bronchoconstriction and increases in plasma cAMP following exercise in the EIA group. A blunted plasma cAMP response to exercise in EIA patients has been reported by others.20,24 It is not known by which mechanism plasma cAMP is increased by exercise, but endogenously produced adrenaline may be important. Adrenaline is a potent stimulus for plasma cAMP increases in the dog28 and in man.29 The plasma cAMP elevating effect of adrenaline seems to be linked to β2-adrenoceptor stimulation.28 Correlations between increases in adrenaline and increases in cAMP have been shown after surgery27 and exercise (present results). Since the plasma adrenaline response of the EIA patients to exercise was not reduced, it is possible that their β2-adrenoceptor sensitivity is reduced. Preliminary results of studies of plasma cAMP responses to isoprenaline and β2-adrenoceptor sensitivity of lymphocytes are consistent with this hypothesis.28 The β2-adrenoceptor sensitivity of bronchial smooth muscle, however, has not been studied in EIA patients.

The pathophysiology underlying EIA is not fully known. Recent studies have shown that the energy loss caused by humidification and warming of the inhaled air is correlated to the degree of postexercise bronchoconstriction in asthmatic patients.29 In the present study the ambient temperature and humidity was relatively stable on the occasions when the subjects were monitored. The V̇e during exercise tended to be greatest in the EIA group and smallest in the NEIA group, although this difference was not statistically significant. Since the energy cost of humidifying and warming inhaled air is correlated with the magnitude of ventilation,30 it is possible that asthmatic patients without a history of EIA tend to maintain a lower V̇e during exercise to minimize the energy loss from the airway mucosa. This hypothesis requires further investigation.

In conclusion, the results of the present study indicate that not only patients with symptoms of EIA but also other asthmatic patients obtain increases in bronchial tone following exercise. We found no evidence in favor of altered sympathoadrenal reactivity in EIA or NEIA. The possibility of a reduced β2-adrenoceptor sensitivity in EIA patients is subject to further investigation in our laboratory.

ACKNOWLEDGMENTS: We sincerely thank assistant professor Alf Holmgren, head of the Department of Thoracic Clinical Physiology, Karolinska Hospital, for advice and laboratory facilities. Assistant professor Bengt S. Nilsson, Department of Thoracic Medicine, Karolinska Hospital, gave us valuable advice and encouragement during the planning of this study. The expert assistance of Maud Dale-skog is gratefully acknowledged.

REFERENCES

1 McNeil RS. Effect of a β-adrenergic-blocking agent, propranolol, on asthmatics. Lancet 1964; 2:1101-02
5 Patel KR, Kerr JW. Effect of an alpha-receptor blocking drug, thymoxamine, on allergen induced bronchoconstriction in extrinsic asthma. Clin Allergy 1975; 5:311-16
10 Szentivanyi A. The beta adrenergic theory of the atopic abnormality in bronchial asthma. J Allergy 1968; 42:203-32
18 Anderson SD, Pojer R, Smith ID, Temple D. Exercise-related changes in plasma levels of 15-keto-13,14-dihydro-prostaglandin F₂α and noradrenaline in asth-
24 Hartley JPR, Davies CJ. Plasma cyclic nucleotides in exercise induced asthma. Thorax 1978; 33:668
29 Chen WY, Horton DJ. Heat and water loss from the airways and exercise-induced asthma. Respiration 1977; 34:305-13