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Influence of circulating α adrenoceptor agonists on lung function in patients with exercise induced asthma and healthy subjects

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ABSTRACT The influence of circulating noradrenaline (in this context primarily a non-selective α agonist) and the α_1 selective agonist phenylephrine on bronchial tone, blood pressure, and heart rate was studied in eight patients with exercise induced asthma and eight age and sex matched controls. All subjects refrained from taking treatment for at least one week before the trial. The agonists were infused intravenously in stepwise increasing doses of 0.04, 0.085, 0.17, and 0.34 μg/kg a minute for noradrenaline and 0.5, 1.0, 2.0, and 4.0 μg/kg a minute for phenylephrine. At the highest dose the plasma concentration of noradrenaline was about 30 nmol/l, resembling the concentrations found during intense exercise, and that of phenylephrine was about 400 nmol/l. Both agonists caused dose dependent and similar increases in blood pressure in the two groups. Despite clearcut cardiovascular effects (systolic and diastolic blood pressure increased by about 40–50/25–30 mm Hg), neither agonist altered lung function, as assessed by measurements of specific airway compliance (sGaw), peak expiratory flow (PEF), or end expiratory flow rate, in either group. It is concluded that circulating α agonists, whether α_1 selective (phenylephrine) or non-selective (noradrenaline), fail to alter basal bronchial tone in patients with exercise induced asthma or in healthy subjects.

The role of pulmonary α adrenoceptors in asthma is not clear. Inhaled α agonists have usually caused bronchoconstriction in asthmatic patients but not in healthy subjects,[1-3] though a small but significant effect has been shown in some healthy subjects.[4] These in vivo findings are consistent with some in vitro findings that suggest the presence of α adrenoceptor mediated constriction of human airways smooth muscle.[5] Blockade of α adrenoceptors caused bronchodilatation in one study,[6] although this finding was not confirmed by others.[7,8]. Alpha adrenoceptor blocking drugs have also been shown to protect against bronchoconstriction induced by histamine,[9,10] allergen,[11] and exercise,[12] although, again, others have failed to confirm these data.[7,13,14] Thus the findings with α adrenoceptor agonists and antagonists on the airways of normal subjects and asthmatic patients have not been consistent, though some findings suggest that α adrenoceptor stimulation might cause bronchoconstriction.

Whether or not the α adrenoceptor sensitivity of asthmatic patients is different from that of controls is also debated. One study has shown greater α adrenoceptor mediated vascular and pupillary smooth muscle responses in asthmatic patients than in healthy controls.[15] Another study, however, showed that the α_2 adrenergic responses of platelets were similar in asthmatic and in healthy subjects.[16]

The aim of the present study was to investigate pulmonary and cardiovascular responses to circulating α adrenoceptor agonists in asthmatic patients. We studied the effect of intravenous phenylephrine (an α_1 selective agonist) and noradrenaline on the airways, blood pressures, and heart rates of patients with exercise induced asthma and matched healthy controls. Circulating noradrenaline acts mainly as a non-selective[17] α adrenoceptor agonist, as indicated by a lack of effect of β blockade on blood pressure and heart rate responses to infused noradrenaline in man.[18] Noradrenaline has β_1 stimulating properties, but this does not cause bronchodilatation in man.[19] The effects of β_1 selective and non-selective β blockade on responses to infused noradrenaline are very

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Data on control subjects (C) and patients with excercise induced asthma (E)

Subject No	*Age (y)*	*Sex*	*Weight (kg)*	*Height (cm)*	*Basal PEF ($l s^{-1}$)*	*Treatment**
C1	25	M	83	173	8.98	—
C2	28	M	74	186	7.67	—
C3	16	M	72	182	7.77	—
C4	22	M	66	169	9.14	—
C5	32	F	56	175	7.30	—
C6	29	M	73	185	8.03	—
C7	31	M	70	175	11.08	—
C8	23	M	62	184	8.40	—
E1	25	M	85	185	10.60	Terbutaline (MDI)
E2	27	M	86	180	6.93	Terbutaline (MDI)
E3	17	M	74	179	6.10	Salbutamol (MDI)
E4	19	M	65	169	5.78	SCG (spinhaler); terbutaline (tablets) 2.5 mg seasonally twice daily
E5	33	F	53	159	5.25	Terbutaline (MDI)
E6	28	M	70	175	7.51	Terbutaline (MDI); SCG (spinhaler)
E7	36	M	94	183	8.61	Choline theophyllinate (tablets) 135 mg
E8	24	M	83	188	10.08	Terbutaline (MDI)

*As needed, unless otherwise specified.
MDI—metered dose inhalers; SCG—sodium cromoglycate.

similar in man.[18] Thus noradrenaline may be regarded as a non-selective α adrenoceptor agonist in this context. Patients with exercise induced asthma were studied since they develop asthma after physical exertion, when circulating noradrenaline concentrations are increased. In the present study the responses were related to the plasma concentrations rather than to the infused doses of phenylephrine and noradrenaline.

Methods

SUBJECTS

Eight patients with exercise induced asthma and eight age and sex matched healthy control subjects were studied (table). Exercise induced asthma was confirmed by demonstrating a fall in FEV_1 of greater than 15% in a pretrial exercise test on a treadmill. All subjects were non-smokers and took no treatment for at least one week before the trial. The subjects gave their informed consent to participate in the study, which had been approved by the local ethical committee.

MEASUREMENTS

Blood pressure was measured non-invasively with an Automanometer (Electronic Research and Development, Dunedin, New Zealand), which allows measurements to be made blind.[20] Heart rate was monitored by telemetry. Lung volumes, airway resistance, and indirectly specific airway conductance (sGaw) were measured in a constant volume body plethysmograph (PK Morgan Ltd, Chatham, UK), from which flow-volume loops were also recorded. Airway resistance was measured at a panting frequency of about two per second and a flow rate of about $0.5 l s^{-1}$. Functional residual capacity and sGaw were determined as the mean of three measurements. When appropriate, two flow-volume loops (with a difference in PEF of less than 10%) were recorded and the peak flow rate and maximum expiratory flow rates at 50% (MEF_{50}) and 25% (MEF_{25}) of forced vital capacity (FVC) were calculated from the loop with the highest PEF. The mean slope of the flow-volume curve between 50% and 25% of FVC (FEF_{50-25}) was calculated according to the equation

$$\frac{4(MEF_{50} - MEF_{25})}{FVC}$$

All lung function measurements were carried out in the following order: airway resistance, lung volumes, and finally the flow-volume loops. Infusions were given with a Perfusor ED2 pump (B Braun, Melsungen, West Germany) equipped with an accumulator to allow continuous infusions in the closed body plethysmograph.

Catecholamines were analysed according to Hjemdahl *et al.*[21 22] In our laboratory the method has a sensitivity better than 0.05 nmol/l for all three catecholamines (adrenaline, noradrenaline, and dopamine) and has interassay and intra-assay coefficients of variation of about 10% in the 0.1–0.2 nmol/l concentration range and 2–3% above 1–2 nmol/l. A brief description of the phenylephine assay has been given.[23] The full details of the assay are to be published later. In essence, 2 ml of plasma (with orciprenaline 400 pmol added as internal standard) was deproteinised by the addition of 220 μl 3 mol/l perchloric acid. After centrifugation at 15000–20000

g for 20 minutes at 4°C the supernatant was collected and mixed with 2 ml 800 mmol/l boric acid and 80 μmol/l EDTA in 1 mol/l NaOH. The sample was passed through a Sep Pak C_{18} column (Waters Associates). After the column had been washed with distilled water, phenylephrine and orciprenaline were eluted in 5 ml 0.1 mol/l acetic acid and 0.1 mmol/l sodium metabisulphite with 10% methanol. After concentration by lyophilisation the samples were finally suspended in 0.1 mol/l perchloric acid containing 0.1 mmol/l sodium metabisulphite. Liquots of 50–100 μl were analysed by high pressure liquid chromatography with a strong cation exchange column (Nucleosil 10SA, 30 cm) and electrochemical detection. The oxidating potential was +0.95 v. The interassay and intra-assay coefficients of variation for the analysis were 10.6% and 19.1% at 20 nmol/l of phenylephrine and 6.5% and 7.1% at 200 nmol/l. Recovery was 50–60% for phenylephrine and 60–70% for orciprenaline over a large number of determinations. This allowed a correction factor for recovery to be introduced into the calculations.

PROCEDURE

Venous cannulas were inserted into an antecubital vein on each arm (one for sampling and one for infusion) and electrocardiograph electrodes (three leads) and blood pressure cuff were applied. The subjects then rested in the supine position for 20 minutes, which was followed by 10 minutes' rest in the seated position in the body plethysmograph. Basal blood pressures and heart rate were recorded and a 10 ml blood sample was drawn. After two basal measurements (five minutes apart) lung function measurements were performed. Noradrenaline was subsequently infused at four dose rates, increasing stepwise (0.04, 0.085, 0.17, and 0.34 μg/kg a minute), each step being maintained for eight minutes. Blood pressure was recorded each minute for the first five minutes and at eight minutes. The heart rate was monitored continuously. Venous blood samples were drawn four and eight minutes after the start of the infusion and lung function tests were repeated during the last three minutes.

After the noradrenaline infusion subjects rested for two hours. Repeated basal measurements were performed as in the first study and followed by an infusion of phenylephrine at four dose rates (0.5, 1.0, 2.0, and 4.0 μg/kg a minute), each dose rate being maintained for six minutes. Blood pressure and heart rate were recorded each minute and venous blood samples drawn during the last minute. After six minutes the infusion was stopped and lung function tests were repeated. When these had been performed after the highest dose of phenylephrine, 5 mg of salbutamol was inhaled and final lung function tests were performed 10 minutes later. Lung function, blood pressure, and heart rate were related to the phenylephrine concentration six minutes after the start of the infusion.

STATISTICAL ANALYSIS

All results are presented as mean values with standard errors in parentheses. Student's *t* tests for paired or unpaired variates and linear regression analyses were used. A p value of <0.05 was considered significant. The coefficient of variation for sGaw measurements was 12%. When sGaw measurements were repeated in 13 healthy subjects on the same day the second

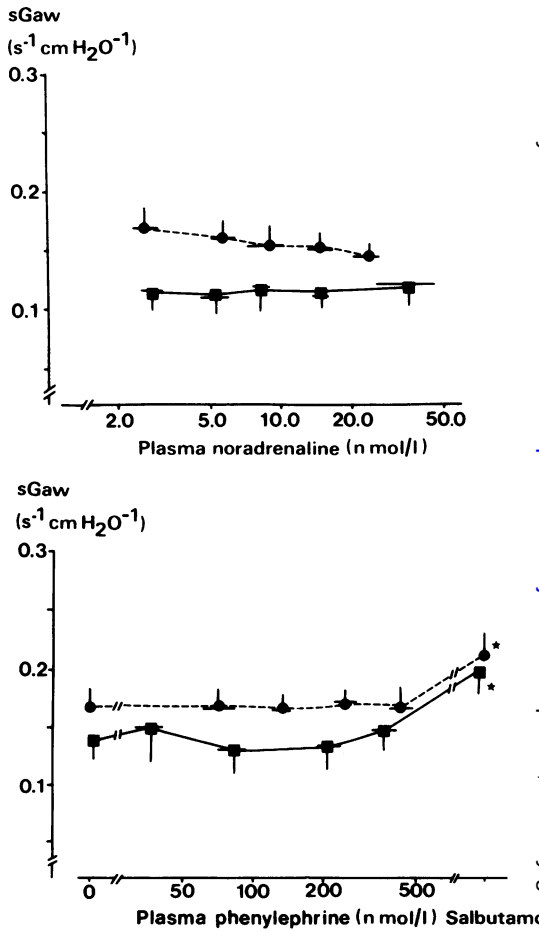

Fig 1 *Effects of increasing plasma concentrations of noradrenaline and phenylephrine on specific airway conductance (sGaw) in control subjects (●---●) and in patients with exercise induced asthma (■——■). The post-salbutamol values were significantly higher than the basal values obtained before the noradrenaline infusion. Bars indicate standard errors. *p < 0.05.*

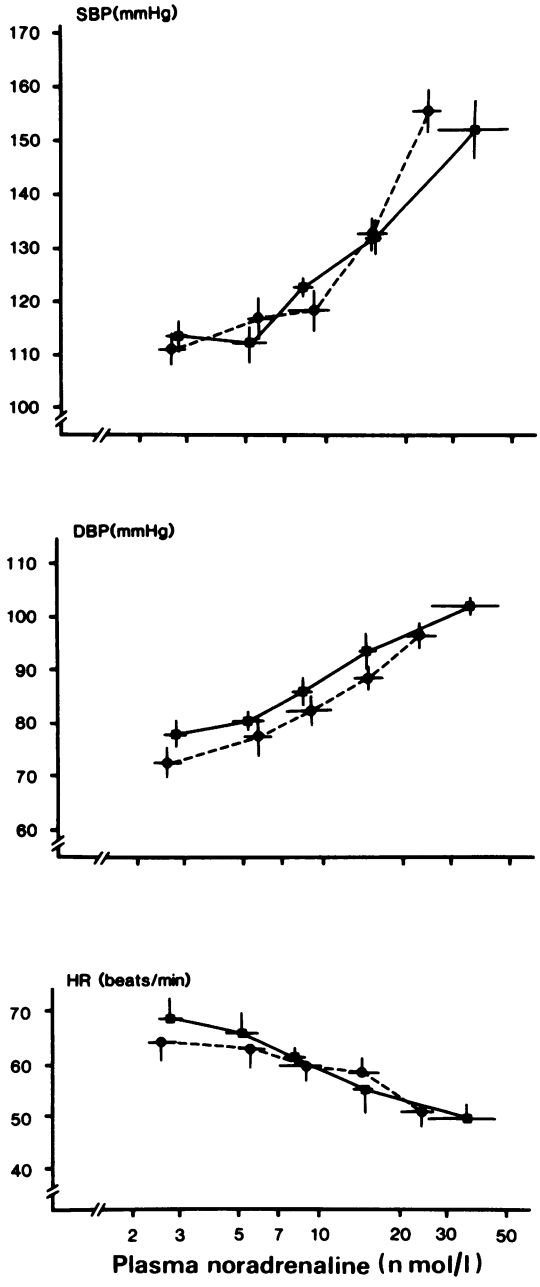

Fig 2 *Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) in control subjects (●---●) and patients with exercise induced asthma (■——■) in relation to the venous plasma noradrenaline concentrations determined before infusion and after eight minutes of infusions at each dose rate. All indices were significantly different from basal values in both groups at the second or third dose rate.*

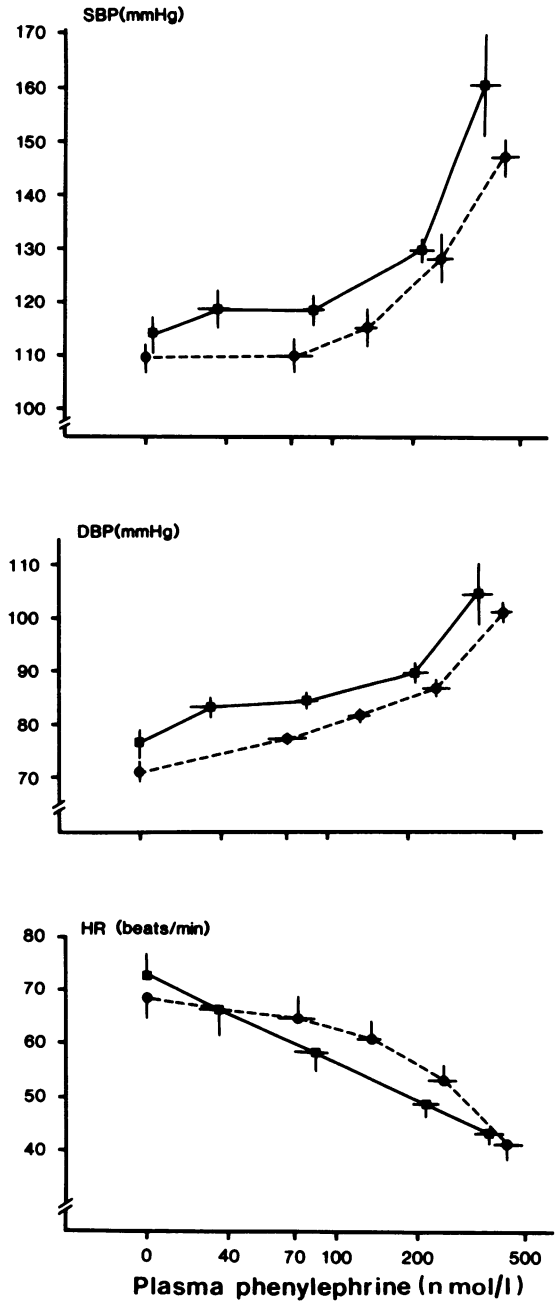

Fig 3 *Effects of increasing plasma concentrations of phenylephrine on systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). All three indices were significantly different from basal values at the first or second dose rate in both groups. ●---● control subjects; ■——■ patients with exercise induced asthma.*

measurement was 1.6% (3.4%) higher than the first (a non-significant difference), suggesting that if the patients behaved in a similar way the probability of detecting a mean decrease in sGaw of more than 15% in the present study was greater than 90%.

Results

All subjects had a baseline PEF of 68% or more of their predicted normal value. In the asthmatic group mean basal sGaw before phenylephrine infusion was slightly higher than basal values before noradrenaline (0.139 (0.022) compared with 0.116 (0.016) s^{-1} cm H_2O^{-1}; $p < 0.05$). None of the other basal lung function measurements differed significantly.

The asthmatic patients had significantly lower basal MEF_{50} before noradrenaline than the control subjects (3.19 (0.30) *v* 4.40 (0.35) $l s^{-1}$; $p < 0.05$) and adrenaline infusions (3.26 (0.33) *v* 4.51 (0.35) $l s^{-1}$; $p < 0.05$). Basal sGaw was significantly lower in the asthmatic patients than in the controls before noradrenaline (0.116 (0.016) *v* 0.17 (0.016) s^{-1} cm H_2O^{-1}; $p < 0.05$), but not phenylephrine (0.139 (0.022) *v* 0.168 (0.016) s^{-1} cm H_2O^{-1}). Basal PEF and FEF_{50-25} showed no significant differences between the two groups.

The plasma concentrations of noradrenaline increased from basal levels of 2.79 (0.25) nmol/l in the asthmatic paitients and 2.63 (0.31) nmol/l in control subjects to 35.5 (10.5) nmol/l and 24.2 (2.6) nmol, respectively, after eight minutes of infusion at the highest noradrenaline dose rate. Similar values were present after four minutes of infusion. Infusion of phenylephrine yielded maximum plasma concentrations of 364 (52) nmol/l in the asthmatic patients and 446 (48) nmol/l in the controls. Hence at the highest doses venous plasma concentrations of noradrenaline were about 50% higher and those of phenylephrine about 20% lower in the asthmatic patients than in control subjects. During noradrenaline or phenylephrine infusion there was no significant change in lung volumes (FRC and FVC), sGaw, or expiratory flow rates (PEF, MEF_{50}, MEF_{25} and FEF_{50-25}) in either group. Inhalation of salbutamol caused a significant percentage increase in mean sGaw in both control and asthmatic subjects (25 (9) and 90 (29): fig 1); but the percentage increases in PEF (2.8 (2.7) and 9.2 (1.7) and MEF_{50} (13.0 (4.5) and 26.5 (4.6) in response to salbutamol achieved significance only in the asthmatic patients.

Blood pressure and heart rate before the infusions did not differ significantly between normal and asthmatic subjects. Systolic and diastolic blood pressure increased and heart rate decreased with increasing doses of both α agonists in normal and asthmatic subjects (figs 2 and 3). There was no significant difference between the groups in the blood pressure response and no correlation between basal heart rate and the decrease in heart rate induced by noradrenaline or phenylephrine in either group. Decreases in heart rate correlated closely with increases in systolic and diastolic blood pressure during both infusions in both groups ($p < 0.01$–0.001).

Discussion

The patients considered themselves to be free from asthmatic symptoms at the time of the study despite a treatment free interval of at least one week before the trial. This was confirmed by high basal PEF values, which were not significantly different from the values of the control group. Nevertheless, more sensitive indicators of larger airways (sGaw) and smaller airways function (end expiratory flow rates) showed slight bronchial constriction in the asthmatic subjects before the study.

In the present study neither circulating noradrenaline, in this context primarily a non-selective α agonist, nor phenylephrine, an α_1 selective agonist, influenced airway function. The plasma concentrations of noradrenaline obtained during these infusions were as high as those seen during heavy exercise,[24] which is the specific stimulus inducing exercise induced asthma. Appreciable changes in heart rate and blood pressure were also observed. Phenylephrine was administered in doses that induced similar cardiovascular responses to those of heavy exercise. Physiologically relevant concentrations of circulating α adrenoceptor agonists do not seem to influence bronchial tone in either patients with exercise induced asthma or controls. The present results do not support the idea[25,26] that high plasma noradrenaline concentrations in connection with exercise are of pathophysiological importance in exercise induced asthma.

Even though we found no bronchial response to circulating α agonists, α adrenoceptors probably do exist in human airways.[1,5] Stimulation of these receptors by inhalation of α_1 agonists, such as methoxamine and phenylephrine, has been shown to induce bronchoconstriction.[1-4] Alpha adrenoceptor antagonists given systemically are capable of preventing asthma induced by histamine[9,10] and allergen[11]. Results obtained with alpha blockers may, however, be related to additional pharmacological properties of these drugs, such as inhibition of histamine or serotonin or direct actions on the smooth muscle,[27] rather than blockade of α adrenoceptors.

If α adrenoceptors are important for the regulation of bronchial tone in man, the present results indicate that they should be activated by locally released noradrenaline. It is not yet clear whether α adrenoceptors

of the human airways are innervated by sympathetic nerves. In dogs α mediated bronchoconstriction in vitro occurs mainly through stimulation of α_2 adrenoceptors, which seem to be innervated.[28] Although the lungs seem to release noradrenaline into plasma,[29] previous efforts to demonstrate sympathetic innervation of the human bronchial smooth muscle have failed.[30 31] Recent findings suggest that there is a sparse adrenergic innervation of bronchial smooth muscle in man,[32 33] in addition to the rich sympathetic innervation of pulmonary blood vessels[31 33] and submucosal glands.[32] The latter nerves are probably the most important source of noradrenaline released from the lungs into the circulation. A spillover effect from nerve endings not directly innervating the bronchial smooth muscle could, however, also result in high noradrenaline concentrations in the vicinity of bronchial smooth muscle in vivo without an extensive direct innervation of the broncial smooth muscle. Since the influence of locally released noradrenaline on human broncial smooth muscle tone in vivo has not been examined, the role of α adrenoceptors in the human airways is still unclear.

All subjects were normotensive and the basal preinfusion blood pressures were similar in the two groups. Noradrenaline and phenylephrine evoked clearcut increases in blood pressure and those responses were similar in the two groups. A previous study of cutaneous blood flow and pupillary responses to phenylephrine provided evidence supporting increased α adrenergic responsiveness in patients with allergic asthma.[15] Although blood pressure is controlled by more complex mechanisms, our results suggest that vascular α adrenoceptor sensitivity was normal in the patients with exercise induced asthma.

In conclusion, we found no alteration of basal bronchial tone during intravenous infusions of α_1 selective (phenylephrine) or non-selective (noradrenaline) α adrenoceptor agonists in patients with exercise induced asthma and no indication of an increased vascular α adrenoceptor sensitivity in these asthmatic patients. Circulating noradrenaline does not seem to be of pathophysiological importance in the development of postexercise bronchoconstriction in exercise induced asthma.

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