CLINICAL RESEARCH

Circulating catecholamines in acute asthma

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Abstract

Plasma catecholamine concentrations were measured in 15 patients (six male) aged 14-63 years attending the casualty department with acute severe asthma (peak expiratory flow 27% (SEM 3%) of predicted). Nine patients were admitted and six were not. The plasma noradrenaline concentration, reflecting sympathetic nervous discharge, was two to three times normal in all patients and was significantly higher in those who required admission compared with those discharged home (mean 7·7 (SEM 0·6) v 4·7 (0·5) nmol/l (1·3 (SEM 0·1) v 0·8 (0·08) ng/ml); $p < 0.001$). Plasma adrenaline concentration, however, was not increased in any patient. This surprising failure of the plasma adrenaline concentration to increase during the stress of an acute attack of asthma was unexplained and contrasts with the pronounced rise in plasma adrenaline and noradrenaline concentrations in acute myocardial infarction, heart failure, and septicaemia.

The failure of plasma adrenaline concentration to increase in acute asthma is unlikely to be explained by adrenal exhaustion, but it may be another example of impaired adrenaline secretion in asthma.

Introduction

Adrenaline has been used as a bronchodilator since early this century,[1] and it is still the first line treatment for acute severe asthma in many countries. Investigation of the role of endogenous adrenaline in the regulation of airway smooth muscle tone has become possible only with the recent development of sensitive and specific assays.[2 3]

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β Adrenoceptor antagonists exacerbate bronchoconstriction in asthmatic patients, suggesting that their airway β receptors are normally under tonic stimulation. In the absence of a functional sympathetic innervation to bronchial smooth muscle in man[4] it has been suggested that endogenous circulating adrenaline activates these airway β receptors.[5] Plasma catecholamine concentrations in resting stable asthmatic subjects are normal,[6] however, and probably too low to account for resting β adrenergic tone. There is no information about sympathoadrenal activation during acute exacerbations of asthma, when endogenous catecholamines would be expected to be recruited to promote bronchodilatation in the same way that adrenaline and noradrenaline act to stimulate the failing heart[7] or counteract the cardiovascular changes of septicaemic shock.[8] We report the first measurements of plasma adrenaline and noradrenaline concentrations during the stress of acute severe asthma.

Patients and methods

We studied 15 patients aged 14-63 years (mean 31) who attended the casualty department with acute exacerbations of asthma. In all the diagnosis of asthma was established on the basis of a history of reversible airflow obstruction and a documented >20% improvement in forced expiratory volume in one second (FEV_1) or peak expiratory flow rate (PEF), either spontaneously or after salbutamol. Six of the patients were male, and 11 were atopic on skin prick testing with common antigens. Nine of the patients required admission on clinical criteria (group 1) and six (group 2) did not. All patients were taking regular inhaled β_2 agonists, 12 took inhaled steroids, two took regular cromoglycate, and four took oral theophyllines. None had taken oral steroids within the past month, and none received aminophylline or any other drug before blood sampling. All made an uneventful recovery.

Heart rate was measured by 30 second radial pulse count, and blood pressure by sphygmomanometry, and pulsus paradoxus was determined in duplicate. PEF was measured using a Wright peak flow meter. Arterial blood gas values and pH were determined when clinically indicated.

After initial assessment an intravenous cannula was sited and oxygen (24-60%) administered through a facemask while a solution of a β_2 agonist (salbutamol 5 mg) was prepared for nebulisation. At that stage, with the patient semirecumbent, a 3 ml blood sample—that is, in addition to the clinical sample (15 ml)—was drawn into a heparinised tube on ice, the plasma being separated within 15 minutes and stored in duplicate at −80°C until assay. Consent to remove the extra 3 ml of blood was obtained verbally in each case. Patients were reassessed 15-30 minutes after nebuliser treatment and a decision

made regarding hospital admission and further management as an inpatient or outpatient. Arterial blood gas tensions were measured if admission was recommended. Results were expressed as the arterial to alveolar oxygen tension ratio (a:A_{O_2}), which allows comparison between patients receiving differing inspired oxygen concentrations.[9] Plasma catecholamine concentrations were measured by a double isotope enzymatic technique, which is specific and has a sensitivity of 0·05 nmol/l (0·01 ng/ml) and an intra-assay coefficient of variation of 10%.[3]

Results are expressed as means and standard error of the mean (SEM). Statistical tests included paired and unpaired *t* tests and the Mann-Whitney U test.

Results

The mean initial heart rate was 120 (SEM 4)/min and initial PEF 22% (SEM 3%) of predicted in group 1 compared with 100 (8)/min and 36% (7%) of predicted in group 2 (fig 1). Mean systolic blood pressure was significantly higher in the patients who were admitted (128 (SEM 4) mm Hg) than in those in group 2 (108 (7) mm Hg) ($p < 0·02$). Mean pulsus paradoxus was 27 (SEM 4) mm Hg in group 1 compared with values of 0 to 15 mm Hg in group 2. After nebulised salbutamol the mean PEF was 34% (3%) of predicted in group 1 compared with 56% (9%) of predicted in group 2. Patients in the admission group were significantly more ill than the others as judged by higher heart rate ($p < 0·02$), lower PEF after salbutamol ($p < 0·03$), and the degree of pulsus paradoxus ($p < 0·01$). Nevertheless, the initial PEF was not significantly different and the duration of the acute attack, which ranged from four hours to several days, did not differ in the two groups. Arterial blood gas values measured in eight of the nine patients who were admitted (one refused) disclosed hypoxaemia in five and a low a:A_{O_2} ratio in seven (mean 0·59 (SEM 0·06)), indicating impaired gas exchange in these patients.

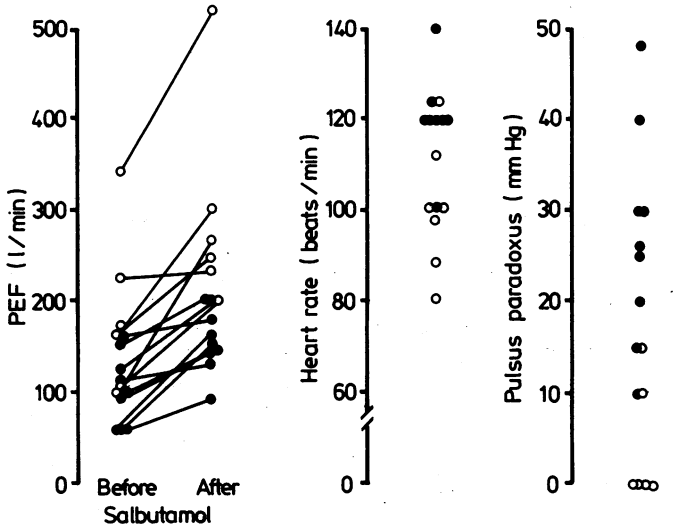

FIG 1—Initial measurements of PEF before and after nebulised salbutamol 5 mg, heart rate, and pulsus paradoxus on presentation in patients in group 1 (●) and group 2 (O).

Plasma noradrenaline concentrations were noticeably increased in all patients (fig 2). The mean concentration was 7·74 (SEM 0·59) nmol/l (1·31 (SEM 0·10) ng/ml) in group 1 and 4·67 (0·47) nmol/l (0·79 (0·08) ng/ml) in group 2. It was significantly higher in patients who required admission than in those who did not ($p < 0·001$). Plasma adrenaline concentrations, however, were not raised in either group: the mean value was 0·23 (SEM 0·04) nmol/l (0·04 (SEM 0·007) ng/ml) in group 1 compared with 0·27 (0·09) nmol/l (0·05 (0·016) ng/ml) in group 2. Normal values in our laboratory for seated subjects range from 1·0 to 5·0 nmol/l (0·17 to 0·85 ng/ml) for noradrenaline and from 0·2 to 1·0 nmol/l (0·04 to 0·18 ng/ml) for adrenaline. In several studies in 43 resting stable asthmatic subjects (FEV_1 >70% of predicted) we have determined the mean noradrenaline concentration as 2·78 (0·12) nmol/l (0·47 (0·02) ng/ml) and mean adrenaline concentration as 0·29 (0·04) nmol/l (0·05 (0·007) ng/ml). These plasma catecholamine concentrations do not differ from those in normal subjects.[6] Plasma adrenaline concentrations in these acute asthmatics were at the lower end of the range that we have measured in normal or in asthmatic subjects.

There was no significant correlation of plasma catecholamine concentrations with PEF, heart rate, systolic blood pressure, pulsus paradoxus, or blood gas tensions.

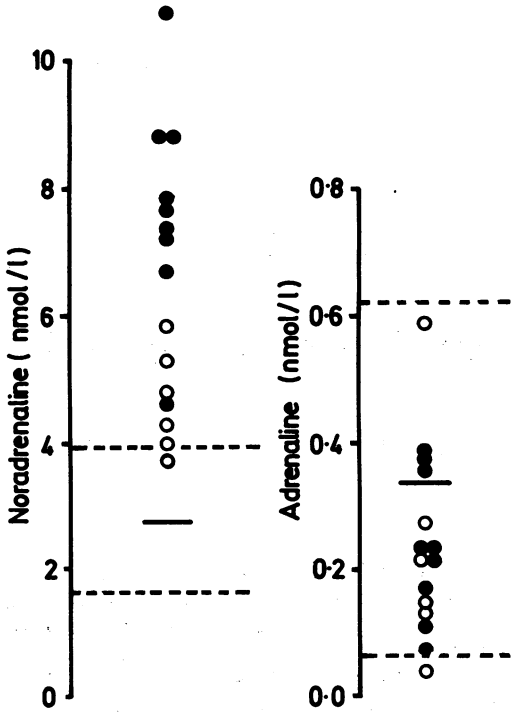

FIG 2—Plasma noradrenaline and adrenaline concentrations on presentation in patients in groups 1 (●) and 2 (O). Horizontal bars and dashed lines represent mean and SEM of values from 43 patients with stable asthma and FEV_1 >70% of predicted.

Conversion: SI to traditional units—Noradrenaline: 1 nmol/l≈0·17 ng/ml. Adrenaline: 1 nmol/l≈0·18 ng/ml.

Discussion

Plasma noradrenaline represents the synaptic overflow from sympathetic postganglionic nerves and may reflect the degree of sympathetic activation. In 15 patients with acute severe asthma seen in the casualty department plasma noradrenaline concentrations were raised twofold to threefold compared with values in stable asthmatic or normal subjects. These concentrations in acute asthma are comparable to those found under conditions of acute stress, such as surgery, hypoglycaemia, septicaemia, or myocardial infarction.[2 10] This increase is compatible with activation of the sympathetic nervous system, which is readily apparent in patients with acute asthma and is reflected by raised systolic blood pressure and heart rate. It may be related to respiratory muscle work and the use of accessory respiratory muscles. Infusion studies, however, indicate that these circulating concentrations of noradrenaline are unlikely themselves to modulate airway tone significantly,[11] though minimal effects on blood pressure might be anticipated.[12]

Adrenaline is secreted by the adrenal medulla and, unlike noradrenaline, functions as a circulating hormone with potent actions on β_2 adrenergic receptors, mediating metabolic effects[2 13] and modulating airway calibre.[11] Plasma adrenaline concentration is raised in acute stress, and in acute myocardial infarction peak increases of 17-fold were found associated with 3·4-fold rises in plasma noradrenaline.[10] In heart failure, septicaemia, and hypoglycaemia increased adrenaline secretion has obvious beneficial actions in supporting the circulation and mobilising carbohydrate metabolism. It is doubly surprising that adrenaline concentrations failed to rise in acute severe asthma. Not only

is there the failure to respond to the stress of severe, possibly life threatening, bronchoconstriction but in acute severe asthma it would be expected that all possible dilator mechanisms would be recruited. Adrenaline is the most potent endogenous bronchodilator and yet circulating concentrations remained in the low normal range—well below those necessary to produce bronchodilatation in asthma.[11]

This surprising failure to increase plasma adrenaline concentration might be explained by exhaustion of adrenaline production by the adrenal gland, by an impairment of release, or possibly by an increased clearance of adrenaline from the circulation. Depletion of adrenaline is extremely unlikely, as the duration of the asthmatic attack in some of these patients was only a few hours and increased adrenaline secretion in myocardial infarction is known to persist for over 12 hours.[10] Clearance of adrenaline from the circulation is rapid[13] and does not appear to be increased, certainly not in patients with stable asthma.[19] Impairment of adrenaline release may be a more likely explanation of our findings, as there is other evidence for this in asthma. Although plasma catecholamine concentrations in stable asthma are normal,[6] there is evidence of reduced adrenaline excretion in response to mental stress[14] and also a blunted rise in noradrenaline and a block of the normal increase in circulating adrenaline on treadmill exercise of asthmatic compared with control subjects.[15 16] Impaired catecholamine release is partial, however, since more profound stimuli such as hypoglycaemia[17] or more strenuous exercise[18] or histamine infusion[17] produce a normal plasma catecholamine response in asthma. Previous β adrenergic bronchodilator treatment is unlikely to explain the low adrenaline concentrations, since large oral doses of salbutamol have no effect on plasma adrenaline values.[19]

When acute bronchoconstriction is induced experimentally by isocapnic hyperventilation,[15] exercise,[15 16] propranolol,[20] or antigen bronchoprovocation[21] there is a similar failure to increase circulating adrenaline concentrations, though this would be expected to alleviate airway narrowing.

In this study of acute severe asthma plasma noradrenaline concentrations were increased as anticipated but, though adrenaline secretion as a bronchodilatator mechanism would be expected, there was a surprising failure of the plasma adrenaline concentration to increase. This may be due to impaired secretion of adrenaline in asthma, although the mechanism remains uncertain.

References

1 Solis-Cohen S. The use of adrenal substance in the treatment of asthma. *JAMA* 1900;**34**:1164-6.
2 Cryer PE. Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. *N Engl J Med* 1980;**303**:436-44.
3 Brown MJ, Jenner DA. Novel double-isotope technique for the enzymatic assay of plasma catecholamines permitting high precision, sensitivity and sample capacity. *Clin Sci* 1982;**61**:591-8.
4 Nadel JA, Barnes PJ. Autonomic regulation of the airways. *Annu Rev Med* 1984;**35**:451-67.
5 Barnes PJ. Endogenous plasma adrenaline in asthma. *Eur J Respir Dis* 1983;**64**: 559-63.
6 Barnes PJ, Ind PW, Brown MJ. Plasma histamine and catecholamines in stable asthmatic subjects. *Clin Sci* 1982;**62**:661-5.
7 Francis GS, Goldsmith SR, Ziesche SM, Cohn JN. Response of plasma norepinephrine and epinephrine to dynamic exercise in patients with congestive heart failure. *Am J Cardiol* 1982;**49**:1152-6.
8 Benedict CR, Grahame-Smith DG. Plasma noradrenaline and adrenaline concentrations and dopamine-beta-hydroxylase activity in patients with shock due to septicaemia, trauma and haemorrhage. *Q J Med* 1978;**47**(NS):1-20.
9 Gilbert R, Keighley JF. The arterial/alveolar oxygen tension ratio. An index of gas exchange applicable to varying inspired oxygen concentrations. *Am Rev Respir Dis* 1974;**109**:142-5.
10 Karlsberg RP, Cryer PE, Roberts R. Serial plasma catecholamine response early in the course of clinical acute myocardial infarction: relationship to infarct extent and mortality. *Am Heart J* 1981;**102**:24-9.
11 Berkin KE, Inglis GC, Ball SG, Thomson NC. Role of physiological concentrations of catecholamines in the control of airway calibre in asthmatic patients. *Thorax* 1984;**39**:697.
12 Silverberg AB, Shah SD, Haymond MW, Cryer PE. Norepinephrine: hormone and neurotransmitter in man. *Am J Physiol* 1978;**234**:252-6.
13 FitzGerald GA, Barnes P, Hamilton CA, Dollery CT. Circulating adrenaline and blood pressure: the metabolic effects and kinetics of infused adrenaline in man. *Eur J Clin Invest* 1980;**10**:401-6.
14 Mathe AA, Knapp P. Decreased plasma free fatty acids and urinary epinephrine in bronchial asthma. *N Engl J Med* 1969;**281**:234-8.
15 Barnes PJ, Brown MJ, Silverman M, Dollery CT. Circulating catecholamines in exercise and hyperventilation induced asthma. *Thorax* 1981;**36**:435-40.
16 Warren JB, Keynes RJ, Brown MJ, Jenner DA, McNicol MW. Blunted sympathoadrenal response to exercise in asthmatic subjects. *Br J Dis Chest* 1982;**76**:147-50.
17 Ind PW, Brown MJ, Barnes PJ. Sympathoadrenal responses in asthma. *Thorax* 1983;**38**:702.
18 Larssen K, Hjemdahl P, Martinsson A. Sympathoadrenal reactivity in exercise-induced asthma. *Chest* 1982;**82**:560-7.
19 Barnes PJ. Adrenergic mechanisms in asthma. Oxford: University of Oxford, 1982. (DM thesis.)
20 Ind PW, Barnes PJ, Durham SR, Kay AB. Propranolol-induced bronchoconstriction in asthma: beta-receptor blockade and mediator release. *Am Rev Respir Dis* 1984;**129**:A10.
21 Ind PW, Causon RC, Barnes PJ. Plasma catecholamines in acute severe asthma and antigen-induced bronchoconstriction. *Clin Sci* 1984;**67**:34-5P.

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Serial estimation of serum angiotensin converting enzyme activity during and after pregnancy in a woman with sarcoidosis

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Abstract

Serum angiotensin converting enzyme activities were estimated during pregnancy and the puerperium in a woman with sarcoidosis and a series of normal women.

In the patient with sarcoidosis angiotensin converting enzyme activity was raised during pregnancy, particularly at 21 weeks' gestation, yet she remained well with no symptoms to suggest relapse of sarcoidosis.

Serum angiotensin converting enzyme activity may not be of value in monitoring sarcoidosis activity during pregnancy.

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Introduction

Serum angiotensin converting enzyme activity has been studied extensively in patients with sarcoidosis and has been used both as a diagnostic test and in assessing the activity of the disease.[1] Serum activities tend to be high in acute disseminated disease when corticosteroid treatment has been withheld.[2] Sarcoidosis