

Sudden death in asthma

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SUMMARY Two girls with asthma died suddenly in autumn-winter 1985. On clinical criteria, both had been classified as moderately severe asthmatics, had shown a stabilised disease course, and had complied with antiasthmatic medication. By chance, lung function, bronchial reactivity, and subjective perception of lung function impairment had been assessed five and a half months and one month before death, respectively. For comparative purposes, we measured lung function and bronchial reactivity in a reference group of 37 children who had asthma of the same clinical severity and who were taking the same medication. In comparison with this reference group the index subjects showed a high degree of bronchial reactivity, incomplete recovery of function after bronchodilation, and appreciably reduced perception of severe lung function impairment. Regular assessment of lung function, bronchial reactivity, and perception of breathlessness might help to identify the patient who is prone to a fatal attack of asthma.

Childhood asthma is a major health problem, but updated concepts improve the therapeutic approach to the disease.^{1 2} Nevertheless, there are still some children and adolescents who die of asthma, and many of these deaths occur suddenly.^{3–8} While there are organised attempts to identify these patients,⁹ such endeavours are hampered by the current lack of the objective data that are needed for identification of the subgroup at risk. There are only a few published lung function measurements from paediatric patients with asthma who later died suddenly^{3 5}; so far, no observations on the bronchial reactivity of these patients have been reported.

We have previously studied the practical value of cold air challenge for measuring bronchial reactivity in children,^{10 11} and now try to assess bronchial reactivity by this method once a year in all our patients with asthma of at least moderate severity. In autumn-winter 1985, two of our patients died suddenly at home, five and a half months and one month after this functional assessment, respectively. The present study reports measurements of lung function and bronchial reactivity in these two index patients and in a reference group with asthma of comparable severity.

Patients and methods

CASE 1

This girl died suddenly at the age of 14.8 years. She

had been attending the local asthma clinic for the last two and a half years. Her case history showed extrinsic asthma beginning in the second year of life, three emergency hospital admissions, one hypsensitisation course with pollen antigen, and various courses of medication. In the year preceding death her asthma had appeared well stabilised by combined medication with an inhaled β_2 sympathomimetic, a topical steroid, and a sustained release theophylline preparation. She attended school regularly and was able to participate in various physical activities. On clinical criteria her asthma was graded to be of moderate severity (grade three on a scale from one to four); her compliance with medication was considered to be good. A one week peak flow protocol, recorded nine months before death, showed moderately wide diurnal variations and night dipping; subsequently her evening dose of the sustained release theophylline was increased, and two puffs of the bronchodilator aerosol were recommended, when waking up at night because of asthma symptoms.

Assessment of lung function and bronchial reactivity was performed five and a half months before death. In addition, the concentration of serum theophylline, and the presence of specific IgE antibodies to 12 common allergens were determined by fluorescence polarisation immunoassay and a radioallergosorbent assay (RAST), respectively (Abbott and Pharmacia Diagnostics). The concentration of

serum theophylline was 84.4 $\mu\text{mol/l}$, and specific IgE to seven allergens was found positive.

The girl was last seen in the clinic two months before death. Her asthma appeared well stabilised, and spirometry showed moderate expiratory airflow obstruction; her medication regimen was not altered. Death occurred at home at 0.15 hours in a September night; there were no preceding symptoms of a viral infection, allergen exposure, or asthma exacerbation. The sister, sleeping in the same room, observed that the patient had become restless while still being asleep, then had got up from the bed and collapsed. Resuscitation efforts by family members were unsuccessful, and a local physician pronounced her dead 45 minutes later. In compliance with a request by the parents no post-mortem examination was performed.

CASE 2

This girl died suddenly at the age of 9.4 years. She had attended the local asthma clinic for the previous four years. Her case history showed extrinsic asthma beginning in the fourth year of life and one emergency hospital admission. In the last year of life her asthma had appeared well stabilised by a combined medication with an inhaled β_2 sympathomimetic, a topical steroid, and a sustained release theophylline preparation. She lived with her divorced mother, attended school regularly, and was able to participate in physical activities at school and at a dancing class. On clinical criteria her asthma was graded to be of moderate severity (grade three on a scale from one to four), and her compliance with medication was considered to be satisfactory.

Assessment of lung function and bronchial reactivity was done one month before death. At this time the serum concentration of theophylline was 81.0 $\mu\text{mol/l}$; antibodies to six of 12 allergens were found by RAST. After this investigation she was instructed how to use a peak flow meter at home and was asked to record her peak expiratory flow rate twice a day and when having symptoms. This was, however, only done for the next five days and was subsequently neglected.

Death occurred at home around 7.00 hours on a November morning. The girl had suffered from a common cold for five days and had told her mother at 6.30 hours that she did not want to go to school because of feeling tired and short of breath. The mother found her lifeless on the floor of her room at about 7.15 hours. After emergency transport to a local hospital, she was pronounced dead on admission. Postmortem examination showed hyperinflated lungs with extensive mucus plugging of the peripheral airways.

REFERENCE GROUP

We recruited patients from the local asthma clinic, who were older than 8 years of age, and suffering from asthma of comparable clinical severity, and who were taking the same antiasthmatic medication as the index patients (β_2 sympathomimetic by metered dose inhaler, topical steroid, sustained release theophylline). This resulted in a reference group of 37 patients (28 boys, nine girls) with a mean age of 11.8 years (range 8.3 to 15.2).

ASSESSMENT OF LUNG FUNCTION AND BRONCHIAL REACTIVITY

Measurements in index and reference group patients were part of a routine programme and followed the same protocol. Informed consent by patients and parents was a prerequisite for all measurements. Functional assessment was done in a stable clinical condition twice within 10 days. Patients arrived at 9.00 hours, rested for 30 minutes, and then had baseline lung function testing.

At the first visit patients then inhaled a sympathomimetic β_2 bronchodilator (salbutamol, 0.02 ml of the 0.5% solution per kg of body weight) from a jet type nebuliser (Inhalierboy). Fifteen minutes after bronchodilator inhalation lung function testing was repeated.

Before the second visit, the sustained release theophylline medication was withheld for four days and the sympathomimetic for 12 hours. After baseline lung function testing, patients underwent a standardised cold air challenge according to a method described previously,¹⁰ administered by a commercially available heat exchanger (RHES, Jaeger), which was set to apply absolutely dry air with a temperature of -10°C . Each challenge consisted of four minutes of isocapnic hyperventilation at 75% of maximal voluntary ventilation. The response was assessed by lung function testing three minutes after the termination of the cold air challenge. In addition, the patients were asked before and after the cold air challenge to score their subjective feeling of chest tightness as 'none', 'mild', 'moderate', or 'severe'.

Pulmonary function tests for baseline determinations and for measuring the responses were done on a pneumotachygraph spirometer (Pneumotest Junior, Jaeger). The patients performed several forced vital capacity manoeuvres, which were recorded in form of a maximum expiratory volume time and flow volume curve. Forced expiratory volume in the first second (FEV_1) and maximum expiratory flow at 25% remaining vital capacity ($\dot{V}_{\text{max}25}$) were measured and expressed as percent of predicted normal values.^{12 13}

Thus the investigation resulted in two baselines,

Table Lung function and bronchial reactivity measurements. Results are % predicted

	Case 1		Case 2		Reference group (n=37)			
	FEV ₁	\dot{V}_{max25}	FEV ₁	\dot{V}_{max25}	FEV ₁		\dot{V}_{max25}	
					Mean (SD)	Range	Mean (SD)	Range
Baseline 1	84	55	35	22	89 (12)	40–111	64 (22)	16–115
Baseline 2	52	20	26	16	85 (15)	38–120	56 (23)	18–97
Functional optimum	91	67	82	61	96 (11)	73–126	84 (26)	31–151
Functional minimum	34	12	27	13	61 (20)	16–95	30 (17)	3–67
Range of reactivity	57	55	55	48	35 (18)	6–72	55 (24)	15–107

one measurement after the bronchodilator and one after the cold air challenge. These measurements were then interpreted according to a previously described concept of 'functional dimensions'.¹¹ Dimension one is baseline lung function. The second dimension is the level of function after bronchodilator medication, termed 'functional optimum'. Dimension three is a 'functional minimum', defined as a reproducible minimum function at maximum response to a standardised cold air challenge. The 'range of reactivity' is the distance from optimum to minimum.

Furthermore a 'perception score' was calculated for the pulmonary function tests before and after cold air challenge by multiplying the baseline and the post cold air challenge measurements (in percent predicted) with the subjective perception. For this purpose, a value of 1 was assigned to 'no', 2 to 'mild', 3 to 'moderate', and 4 to 'severe chest tightness'. Thus a low perception score stems from the combination of a low lung function measurement and underperception.

Results

Lung function from index patients and the reference group are compared in the table. Baseline function was better at the first visit—that is, on full treatment—than at the second visit—that is, without preceding bronchodilator medication. The second baseline measurements of case 1 were in the lower part and those of case 2 below the reference range. After the β_2 bronchodilator (functional optimum), both index patients normalised their FEV₁, but failed to completely normalise their \dot{V}_{max25} ; thus they compared with the lower half of the reference range. After cold air challenge (functional minimum), both index patients showed a pronounced further increase of expiratory airflow obstruction and thus compared with the lower end of the reference range. The resulting range of reactivity (distance optimum to minimum) of the two

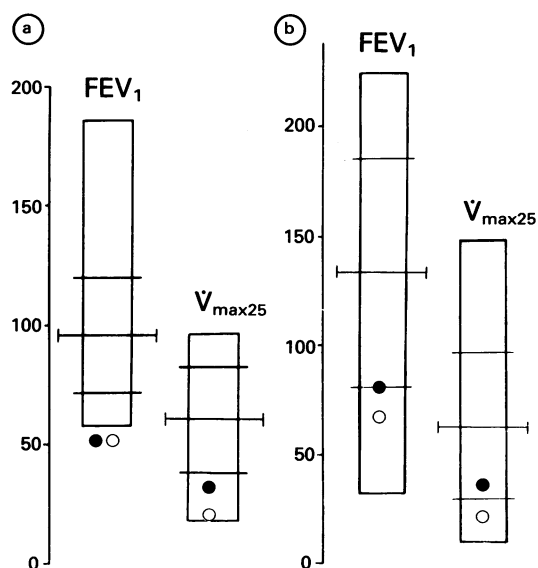


Figure Perception score. The whole range of reference group values is given by the vertical bars; mean (SD) is indicated. Case 1=○; case 2=●. (a) Second baseline measurement (before cold air challenge); (b) minimum function measurement (after cold air challenge).

index patients was in the middle of the reference range for \dot{V}_{max25} , and in the upper part of the reference range for FEV₁. For all lung function situations assessed, both index patients as well as the reference group showed a tendency towards more obstruction in \dot{V}_{max25} , than in FEV₁.

The perception score assessed at baseline and the functional minimum is shown in the figure. Both index patients were below or at the lower end of the reference range for both functions.

Discussion

This study shows that two patients, who subse-

quently died suddenly, when compared with a reference group with asthma of identical clinical severity and medication, were characterised by an average or above average range of reactivity, which, however, was associated with a lower level of lung function. This was expressed by a tendency towards impaired baseline lung function, by incomplete normalisation after bronchodilator medication, and by severely compromised lung function after cold air challenge. Furthermore, both index patients showed a reduced perception of lung function impairment.

The case histories of the two index patients appear similar to previous descriptions of sudden asthma deaths.^{3-5 7 8 14-16} Most likely, these sudden and fatal attacks are caused by a severe narrowing of intrathoracic airways; postmortem findings are characterised by mucus plugging of the peripheral bronchi.^{3-5 14 17} Sudden death should be distinguished from other forms of asthma mortality, which might be caused by: (a) pulmonary or cardiac disorders or complications that went undetected before death; (b) toxic side effects of excessively overused antiasthmatic medication; and (c) prolonged exacerbations (status asthmaticus) resulting in death despite some therapeutic efforts.^{5 6 8 16 18} Unsuspected pathology, especially tension pneumothorax, is unlikely in our two patients, but cannot be definitely excluded for case 1. Abuse of adrenergic aerosols can be excluded for causing the death of case 1, and remains a somewhat unlikely causative factor for the death of case 2. It therefore appears reasonable to assume that both index cases are true examples of 'sudden death in asthma'.

Anyone who attempts to reduce the mortality from such sudden and potentially fatal attacks faces the problem of identifying the patient at risk.⁹ This task is related to the more general question of how to assess the severity of a disorder that is characterised by large variations in functional impairment.¹⁹ Both index patients in the present study showed a functional profile of high bronchial reactivity in addition to impaired baseline function. Any obstructive airway reaction will sooner become life threatening, if it starts from an already compromised lung function level. Lung function and airway reactivity measurements in two patients do not suffice for a general explanation of sudden death in asthma: nevertheless, our observations suggest, that repeated assessments of bronchial reactivity might be helpful for identification of the fatality prone patient.

In many cases of fatal asthma the life threatening character of the disorder had not been perceived or acknowledged by patients, parents, or physicians.^{4-7 15 16 18 20} Correspondingly, the present

study suggests that an appreciable subjective underperception of lung function impairment could be an important risk factor. Previous studies on adult asthma patients have shown wide interindividual variations in the perception of airway obstruction; furthermore, blunted perception tends to correlate with high bronchial reactivity and thus will occur in more severely diseased patients.^{21 22} Consequently, different longitudinal courses of variable airway obstruction could translate through different perception into similar case histories. This is illustrated by the present study, where all patients of the reference group had the same clinical severity grading but showed wide interindividual variations in their functional dimensions. The resulting clinical problem is how to identify those severely diseased patients who have adapted their life style to variable airway obstruction and therefore present with a seemingly benign case history.¹⁹ Occasional lung function measurements cannot be used as a reliable yardstick for assessing disease severity, as lung function may change from hour to hour, day to day, or week to week.¹⁹ Longitudinal peak flow recordings might be more meaningful for assessing the severity of a variable disorder and furthermore, they may gradually lead the patient towards a more accurate self assessment.^{7 14 20} Peak flow recordings done during the day, however, might miss nocturnal deteriorations in lung function; this 'night dipping' might have some relevance for asthma mortality.^{4 6 14}

Another potentially promising approach is suggested by the present study. Repeated assessments of lung function and bronchial reactivity could be complemented by the patient's self assessment of airway obstruction. Objectively measured physiological data, related to the patient's subjective score, could identify the 'poor perceivers' among the paediatric asthma population. This subgroup could then receive special diagnostic and therapeutic attention and a close longitudinal monitoring of clinical and physiological variables. Whether the combination of appreciable airway hyper-reactivity and severe underperception of airflow obstruction does indicate the necessity for a treatment with systemic steroids remains speculative. Other authors suggested that the therapeutic use of systemic steroids could have prevented some sudden deaths.^{3-6 14} At present, any comparative discussion of different treatment strategies for the fatality prone asthma patient remains a speculative one.

The present study employed FEV₁ and end expiratory flow for characterising large and small airway obstruction respectively.²³ In both index patients and in the reference group as well, $\dot{V}_{\max 25}$ was found more compromised than FEV₁. Further-

more, in neither of the index patients was $\dot{V}_{\max 25}$ normalised after the bronchodilator. Correspondingly, another report on bronchodilator induced lung function changes in children who later died of asthma showed incomplete or absent responses for forced mid expiratory flow rates.⁵ These observations correlate with the concept of childhood asthma as a disease of the small airways.^{24 25} Inclusion of small airway related lung function measurements into the evaluation of paediatric asthma patients might be useful for better characterising disease severity.

In conclusion, we observed pronounced airway hyper-reactivity and severe underperception of air-flow obstruction in two children with asthma who later died suddenly. These two observations do not suffice for a general explanation of sudden death in childhood and adolescent asthma. They do, however, suggest that repeated assessments of airway reactivity, complemented by the patient's subjective scoring of breathlessness, might be a promising approach towards better defining those children prone to sudden death from asthma.

References

- Pearlman DS. Bronchial asthma. A perspective from childhood to adulthood. *Am J Dis Child* 1984;138:459-66.
- König P. Asthma: a pediatric pulmonary disease and a changing concept. *Pediatr Pulmonol* 1987;3:264-75.
- Mellis CM, Phelan PD. Asthma deaths in children - a continuing problem. *Thorax* 1977;32:29-34.
- Rubinstein S, Hindi RD, Moss RB, Blessing-Moore J, Lewiston NJ. Sudden death in adolescent asthma. *Ann Allergy* 1984;53:311-8.
- Kravis LP, Kolski GB. Unexpected death in childhood asthma. A review of 13 deaths in ambulatory patients. *Am J Dis Child* 1985;139:558-63.
- Carswell F. Thirty deaths from asthma. *Arch Dis Child* 1985;60:25-8.
- Sears MR, Rea HH, Fenwick J, et al. Deaths from asthma in New Zealand. *Arch Dis Child* 1986;61:6-10.
- Kravis LP. An analysis of fifteen childhood asthma fatalities. *J Allergy Clin Immunol* 1987;80:467-72.
- Strunk RC. Workshop on the identification of the fatality-prone patient with asthma: summary of workshop discussion. *J Allergy Clin Immunol* 1987;80:455-7.
- Zach MS, Polgar G, Kump H, Kroisel P. Cold air challenge of airway hyperreactivity in children: practical application and theoretical aspects. *Pediatr Res* 1984;18:469-78.
- Zach MS, Polgar G, eds. Cold air challenge of airway hyperreactivity in children: dose-response interrelation with a reaction plateau. *J Allergy Clin Immunol* 1987;80:9-17.
- Polgar G, Promadhat V. *Pulmonary function testing in children: techniques and standards*. Philadelphia: WB Saunders, 1971:186.
- Zapletal A, Samanek M, Paul T. Upstream and total airway conductance in children and adolescents. *Bull Eur Physiopathol Respir* 1982;18:31-7.
- Bateman JRM, Clarke SW. Sudden death in asthma. *Thorax* 1979;34:40-4.
- Stableforth D. Death from asthma. *Thorax* 1983;38:801-5.
- Benatar SR. Fatal asthma. *N Eng J Med* 1986;314:423-8.
- Reid LM. The presence or absence of bronchial mucus in fatal asthma. *J Allergy Clin Immunol* 1987;80:415-6.
- Nguyen MT, Patterson K, Sly RM. Causes of death from asthma in children. *Ann Allergy* 1985;55:448-53.
- McNicol KN, Williams HB. Spectrum of asthma in children - I. clinical and physiological components. *Br Med J* 1973;iv:7-11.
- Cushley MJ, Tattersfield AE. Sudden death in asthma: discussion paper. *J R Soc Med* 1983;76:662-6.
- Rubinfeld AR, Pain MCF. Perception of asthma. *Lancet* 1976;i:882-4.
- Burdon GW, Juniper EF, Killian KJ, Hargreave FE, Campbell EJM. The perception of breathlessness in asthma. *Am Rev Respir Dis* 1982;126:825-8.
- Hyatt RE, Rodarte JR, Mead J, Wilson TA. Changes in lung mechanics: flow-volume relations. In: Macklem PT, Permutt S, eds. *The lung in the transition between health and disease*. New York: Marcel Dekker, 1979:73-112.
- Zapletal A, Motoyama EK, Gibson LE, Bouhuys A. Pulmonary mechanics in asthma and cystic fibrosis. *Pediatrics* 1971;48:64-72.
- Hill DJ, Landau LJ, McNicol KN, Phelan PD. Asthma - the physiological and clinical spectrum in childhood: respiratory function studies in its assessment. *Arch Dis Child* 1972;47:874-81.

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Commentary

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Much has been written about the shortcomings in the care of asthmatics who have died in this country. The British Thoracic Association's review identified only 10 of 90 asthmatics in whom death was considered unavoidable.¹ It would be impossible, however, to test whether management is more deficient in those who die than in asthmatics in general because of the difficulty in recruiting controls from the same practice. Carswell, in a review of 30 deaths in children, concluded that inadequate management had probably contributed to many of these deaths.² Twelve of the 30 children had never attended hospital. Speight and colleagues in 1983 highlighted the problem of underdiagnosis and undertreatment of childhood asthma³; one wonders what overall effect educational programmes have since had in addressing this very serious problem. Two American studies of asthma deaths in children drew attention to the unsatisfactory psychosocial profiles of many of the patients and their families, which resulted in erratic treatment.^{4 5} It is difficult to compare the American experience with that in Britain because of