Hypoxic and hypercapnic response in asthmatic subjects with previous respiratory failure

ARLENE A HUTCHISON, ANTHONY OLINSKY

From the Department of Thoracic Medicine, Royal Children's Hospital, Melbourne, Australia

ABSTRACT   Three children and two young adults with severe asthma who had frequent episodes of respiratory failure were studied. Isocapnic hypoxia and hyperoxic hypercapnia were produced separately using a rebreathing apparatus. Alveolar carbon dioxide tension and oxygen tension were estimated by continuously sampling expired gases. The three young children had a diminished response to hypoxia but a normal response to hypercapnia when compared to control asthmatic children ($p < 0.05$) or healthy children ($p < 0.05$). The two young adult patients had a normal response to hypoxia but one had a low response to hypercapnia. Studies of parents of these patients suggested that familial factors in part may determine the degree of response to hypoxia. It is suggested that the chance combination of a possibly familial, inappropriate response to hypoxia with severe asthma would lead to a risk of respiratory failure.

The degree of ventilatory response to hypoxia and hypercapnia is controlled, in part, by familial factors. Long distance runners and their non-athletic family members have an abnormally low response to hypoxia.[1] Similarly, healthy offspring of hypercapnic patients with chronic obstructive airways disease have a decreased response to carbon dioxide when compared to offspring of normocapnic patients.[2] In contrast, environmental factors such as long-term residence at high altitude may lead to an acquired blunted response to hypoxia.[3] Diseases causing prolonged hypoxia such as cyanotic congenital heart disease[4] or chronic lung disease[5] may also lead to a diminished response to hypoxia.

Asthmatics as a group have a normal response to hypoxia and hypercapnia.[6 7] In fact, in certain situations, such as adding an external resistive or elastic load, the response as measured by Pm 100 is increased.[6 7] However, an individual patient with a combination of severe asthma and an unrelated, inappropriately low, familial response to hypoxia or hypercapnia could be at a disadvantage during a period of increased airways obstruction and may be at risk of respiratory failure or sudden death. Hudgel and Weil[8] have described a 17-year-old asthmatic who was unusually hypoxaemic and who, with three of four members of the family, had a decreased response to hypoxia.

The purpose of this study was to examine the ventilatory response to hypoxia and hypercapnia in a group of five children and young adults with asthma who had previous episodes of respiratory failure, respiratory arrest, or loss of consciousness. If abnormal ventilatory control was found, it was hoped that study of their parents might reveal any familial factors.

Methods

Subjects were selected on the basis of (1) recurrent episodes of respiratory failure, loss of consciousness, or respiratory arrest attributed to asthma, and (2) sufficient comprehension and neuromotor development to perform repeated pulmonary function tests.

Three older children (aged 10 to 12 years) and two young adults (aged 18 years) who conformed to these criteria were studied. Two had multiple episodes of acute bronchoconstriction and associated loss of consciousness occurring at night usually at home. The others had more than one episode of respiratory failure and one had required a period of mechanical ventilation. Parents of patients with a low response to either carbon dioxide or oxygen were tested. One father was not available for testing and one mother was unable to establish a baseline alveolar carbon dioxide above 30 mmHg because anxiety-provoked hyperventilation made her hypoxic response curve invalid.

Because the normal value for ventilatory response

No reprints of this paper will be available.

to hypoxia is lower in children aged 10 to 12 years[9] but is independent of age in early to middle age adult life,[10] two control groups were used. Seven healthy older children aged 9 to 13 years and 14 healthy adults aged 20 to 40 (three smokers and 11 non-smokers) were studied. All healthy controls had normal spirometry, had never lived at high altitude, and had never undertaken athletic training. Six adolescents with a similar degree of asthma to the patients but with no episodes of respiratory failure were also studied.

The hypercapnic response was measured using the method of Read.[11] The subject breathed room air through a two-way valve (Hans Rudolph pediatric valve) until stable ventilation was reached and then, from the end of expiration the subject rebreathed from a bag filled with a mixture of 50% oxygen, 4% carbon dioxide, and 46% nitrogen. The volume used was the subject's vital capacity plus 1 litre if a child and 1·5 litres if an adult. Tidal volume was measured using a Krogh spirometer attached to a bag in a box. Expired gas was sampled continuously for CO_2 (Beckman LB2) and O_2 (Beckman OM11) and returned to the system to prevent a shifting baseline. Tidal volume, and percentages of CO_2 and O_2 were recorded continuously on an eight-channel recorder (Hewlett Packard 748B). The end-tidal CO_2 level slowly rose by 15 to 20 mmHg over three to five minutes and end-tidal O_2 remained above the subject's baseline level when breathing room air.

Minute ventilation ($\dot{V}E$) was calculated using three to four breaths with a constant end-tidal CO_2 and was expressed as l/minute at ATPS. Minute ventilation was calculated for every 2-3 mmHg change in CO_2 tension and plotted against alveolar CO_2 ($Pa{CO_2}$). (It was assumed that end-tidal CO_2 was approximately equal to $Pa{CO_2}$.) The graph of $\dot{V}E$ vs $Pa{CO_2}$ yielded a staight line with slope S (using least squares method). S is the slope of the line expressed as change in ventilation per unit change in $Pa{CO_2}$,

litres/min/mmHg. The higher S, the greater the response to CO_2.

The hypoxic response was measured according to the method of Rebuck and Campbell[12] using the same circuit. The subject breathed room air through the valve until a stable end-tidal $Pa{CO_2}$ in the normal range of 35-45 mmHg was achieved. At the end of expiration, he or she was switched into the rebreathing bag which contained 23% O_2, 4% CO_2, and 73% N_2. The volume of gas mixture again varied according to the subject's vital capacity. As the subject rebreathed, O_2 was consumed and the end-tidal O_2 dropped progressively from over 100 mmHg to 37-40 mmHg over five to eight minutes. The end-tidal CO_2 tension was maintained at a constant level using a scrubber system consisting of cannisters of soda lime and a Sarns variable cardiac bypass pump.

Tidal volume, expired %CO_2 and %O_2 were continuously recorded on the eight-channel recorder. For the O_2 response curve $\dot{V}E$ was calculated for every 3-4 mmHg change in O_2 tension and a graph of $\dot{V}E$ against PaO_2 yielded the classical curve with

the formula $\dot{V}E = \dfrac{Vo + A}{(PaO_2 - 32)}$ where Vo is the

asymptote for ventilation and A the degree of curvature. A was calculated as described by Byrne-Quinn et al.[9] The larger A, the greater the response to hypoxia.

Subjects performed CO_2 and O_2 response tests in random order with a 10 to 15 minute rest period in between. All subjects with an abnormal hypoxic response had a duplicate test. No caffeinated beverages or theophylline containing medicines were allowed for at least six hours before testing. Spirometry was performed using a nine litre water-filled spirometer. Informed consent was obtained from all subjects and also the parents of subjects who were under 18 years of age.

Table 1   *Control hypoxic and hypercapnic data*

Group	Hypoxic data			
	Number	Age (yr)	$FEV_{1·0}/VC$	S (ATPS)
Healthy adults	14	30 ± 1·9*	80 ± 2·3	105 ± 16·3
Healthy children	5	12 ± 0·4	80 ± 2·6	66 ± 14·2
Control asthmatics	6	14 ± 0·8	58 ± 4·1	95 ± 26·0
Group	Hypercapnic data			
	Number	Age (yr)	$FEV_{1·0}/VC$	S (ATPS)
Healthy adults	7	33 ± 3·7	81 ± 3·3	1·91 ± 0·38
Healthy children	4	13 ± 1·6	90 ± 3·9	1·58 ± 0·50
Control asthmatics	5	14 ± 0·9	57 ± 4·6	1·11 ± 0·11

ATPS = ambient temperature, pressure, saturation.
*Mean ± standard error of the mean.

Table 2 *Patients' and parents' hypoxic and hypercapnic data*

	Age (yr)	Sex	$FEV_{1.0}/VC$	A (ATPS)	PCO_2*	S (ATPS)
			Children and parents			
Patient 1	12	F	43	0	36	0·87
Father	33	M	79	22	38	2·18
Mother	30	F	74	145	41	1·43
Patient 2	12	M	55	35	36	0·62
Mother	36	F	72	111	44	1·05
Patient 3	10	M	63	25	33	0·98
Father	37	M	70	244	42	2·03
Mother	33	F	85	58	40	1·33
			Young adults and parents			
Patient 4	18	M	45	81	36	0·55
Father	54	M	67	173	38	1·36
Mother	50	F	71	—	—	1·23
Patient 5	18	M	31	197	38	1·18

*Subjects baseline PCO_2 at which hypoxic response tested.

Comparisons of A and S between groups were made using Student's unpaired *t* test.

Results

CONTROLS
Mean values for parameters A and S are shown in table 1. As a group, A tended to be lower in the normal children. The value of A for control adolescent asthmatics was not significantly different from healthy subjects. The hypercapnic response, S, tended to be lower in the adolescent asthmatic controls but this did not reach statistical significance. There was no significant difference in the degree of airways obstruction between the patients and control adolescent asthmatics as assessed by spirometry.

PATIENTS
The 10 and 12-year-old patients had a significantly lower response to hypoxia than normal controls of the same age (p = 0·02) or asthmatics (p = 0·04) but the response to CO_2 was not significantly different (table 2).

The two 18-year-old patients had a normal response to hypoxia. Patient 5 also had a normal hypercapnic response while patient 4 had the lowest response to CO_2 of the entire group (controls plus patients). However, because of the wide SD of the measurement, this value was still within 2 SD of the mean (2 SD from the mean for S is − 0·09).

PARENTS
Patients 1 and 3 both had one parent with a value for A well below the mean (figure). In the third patient with a low A, only one parent was available and her response was normal. The parents all had a normal hypercapnic response.

Discussion

Respiratory failure in chronic asthma may not be simply an intolerable increase in airways obstruction but rather failure of the integrated system to assess and adjust to the increasing load. Inappropriate neurochemical response and respiratory muscle fatigue are two examples of possible mechanisms involved in the failure of the total system. In this study, asthmatic patients were selected on the basis
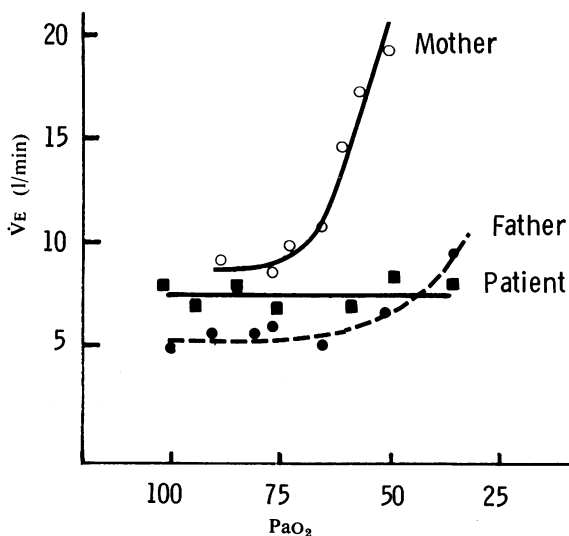

Figure *Graph of minute ventilation ($\dot{V}E$) vs Pao_2 in patient 1 and her parents. The patient had no significant increase in $\dot{V}E$ with increasing hypoxia to a level of 37 mmHg. The father's response appeared to be inappropriately low (A = 22) and the mother's response was appropriate (A = 145).*

of recurrent episodes of respiratory failure or loss of consciousness—that is, a presumptive clinical diagnosis of inappropriate ventilatory control had been made. Of the five, three had an abnormal response to hypoxia and one possibly had a low response to carbon dioxide.

One possible explanation for this decreased ventilatory response is that the patients had severe airways obstruction and were unable to increase their ventilation. This does not appear to be the case. Firstly, each patient with a low response to O_2 showed a normal increase in ventilation with rising CO_2. (The one subject with a low response to CO_2 responded well to O_2.) Secondly, a group of control adolescents with severe airways obstruction but no episodes of respiratory failure demonstrated normal neurochemical control. Finally, other investigations have shown an increased respiratory drive in asthmatics during methacholine-induced bronchoconstriction.[7] Another possible explanation is that the decreased response was acquired because of long-term hypoxia, a situation analogous to high altitude residence. Again this seems unlikely because of the age of the patients: the blunted response in high altitude dwellers is only partial after 10 years of residence and not complete until 20 years.[9] A more likely explanation is that the decreased hypoxic or hypercapnic response and chronic asthma occurred independently. In an interesting study of 19 asthmatics during recovery from severe asthma Rebuck and Read[13] showed that while the majority of their patients increased their hypercapnic response with improvement in their FEV_1, three did not. These three patients showed elevation of arterial CO_2 tension at the time of presentation. Although the studies in the parents of our subjects are not conclusive there is a suggestion of a familial factor in the two families. The number of parents in this study is too small to assess the contribution of environmental and genetic factors. However, Collins *et al*[14] studied 24 pairs of identical and non-identical twins and concluded that hereditary factors influenced the response to hypoxia but not hypercapnia.

If the hypothesis is correct, then the abnormal hypoxic response is familial and antedates the appearance of asthmatic symptoms. However, none of the patients experienced respiratory failure before the age of 8 years. Therefore the presence of an inappropriately low response to hypoxia in an asthmatic does not explain fully the occurrence of respiratory failure. Rather, an associated change in the severity of the airways obstruction may be involved as these episodes are seen in severe chronic asthmatics and their frequency varies as does the disease. In asthmatics, the neurochemical drive and resistive load detection may act synergistically—that is, the

presence of both stimuli results in a greater response than seen in normal subjects exposed to the same stimuli.[7] If resistive load detection is also subnormal in these patients with a low response to O_2, an exacerbation of their airways obstruction could lead to a risk of respiratory failure or sudden death. Why patients with a low hypoxic response and a normal hypercapnic response, which is possibly a more sensitive drive, do not maintain ventilation is not understood.

The present data plus the previous studies on familial effects lead to several speculations. Rather than thinking of neurochemical control as showing a wide range of responses perhaps it would be more helpful to think in terms of appropriate and inappropriate responders. If an inappropriate response were inherited several high risk situations could be envisaged. The chance combination of severe asthma and an inappropriate response would result in a risk of respiratory arrest or sudden death.

References

[1] Scoggin CH, Doekel RD, Kryger MH, Zwillich CW, Weil JV. Familial aspects of decreased hypoxic drive in endurance athletes. *J Appl Physiol* 1978;**44**:464-8.

[2] Mountain R, Zwillich C, Weil J. Hypoventilation in obstructive lung disease: the role of familial factors. *N Engl J Med* 1978;**298**:521-5.

[3] Lenfant C, Sullivan K. Adaptation to high altitude. *N Engl J Med* 1971;**284**:1298-309.

[4] Sorensen CS, Severinghaus JW. Respiratory insensitivity to acute hypoxia persisting after correction of tetralogy of Fallot. *J Appl Physiol* 1968;**25**:221-3.

[5] Bradley CA, Fleetham JA, Anthonisen NR. Ventilatory control in patients with hypoxemia due to obstructive lung disease. *Am Rev Respir Dis* 1979;**120**:21-30.

[6] Cosgrove JF, Neuburger N, Levison H. The ventilatory response to carbon dioxide in asthmatic children, measured by the mouth-occlusion method (P_{M100}). *Pediatrics* 1976;**57**:952-9.

[7] Kelsen SG, Fleegler B, Altose MD. The respiratory neuromuscular response to hypoxia, hypercapnia, and obstruction to airflow in asthma. *Am Rev Respir Dis* 1979;**120**:517-27.

[8] Hudgel DW, Weil JV. Asthma associated with decreased hypoxic ventilatory drive: a family study. *Ann Intern Med* 1974;**80**:622-5.

[9] Byrne-Quinn E, Sodal IE, Weil JV. Hypoxic and hypercapnic ventilatory drives in children native to high altitude. *J Appl Physiol* 1972;**32**:44-6.

[10] Hirshman CA, McCullough RE, Weil JV. Normal values for hypoxic and hypercapnic ventilatory drives in man. *J Appl Physiol* 1975;**38**:1095-8.

[11] Read DJC. A clinical method for assessing the ventilatory response to carbon dioxide. *Aust Ann Med* 1967;**16**: 20-32.

[12] Rebuck AS, Campbell EJM. A clinical method for assessing the ventilatory response to hypoxia. *Am Rev Respir Dis* 1974;**109**:345-50.

[13] Rebuck AS, Read J. Patterns of ventilatory response to carbon dioxide during recovery from severe asthma. *Clin Sci* 1971;**41**:13-21.

[14] Collins DD, Scoggin CH, Zwillich CW, Weil JV. Hereditary aspects of decreased hypoxic response. *J Clin Invest* 1978;**62**:105-10.