Pathophysiological analysis of hypoxaemia during acute severe asthma

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SUMMARY Blood gas measurements obtained during 35 episodes of acute, severe asthma in 19 children were analysed. Arterial carbon dioxide tension (P_{aCO_2}) was mean (SD) 5.7 (1.2) kPa and the arterial oxygen tension (P_{aO_2}) was 7.7 (1.1) kPa. Hypoxaemia was severe ($P_{aO_2} \leq 7.9$ kPa) on 19 occasions, was present alone (type I) on eight of these, and was associated with hypercapnia (type II) on 11. The P_{aO_2} was similar in both the type I and type II subgroups, but P_{aCO_2} was significantly higher in the type II and the alveolar-arterial oxygen tension difference was significantly higher in the type I subgroup. Classification of acute respiratory failure into these two types proved useful in understanding the pathophysiology of acute, severe asthma. Type I failure, conventionally regarded as a precursor of type II, itself caused severe, critical hypoxaemia.

Acute severe asthma is a medical emergency, and the importance of blood gas measurement has been widely recognised.^{1,2} So far, however, knowledge of blood gas disorders during acute, severe asthma has been almost exclusively obtained from experience in adults,^{3,4} and reports on children have been limited.⁵⁻⁷

Recently, the pathophysiological classification of acute respiratory failure into hypoxaemic respiratory failure (type I) and hypoventilatory failure (type II) has been postulated,^{8,9} but the clinical and theoretical usefulness of this classification in children with acute, severe asthma has never been discussed fully. We examined blood gas disorders in asthmatic children in terms of the arterial oxygen and carbon dioxide tensions and the alveolar-air equation, and discuss two physiological causes of profound hypoxia in acute severe asthma—alveolar hypoventilation and ventilation perfusion inequality (V/Q mismatch).¹⁰

Patients and methods

Thirty five acute asthmatic attacks in 19 children (9 boys and 10 girls) aged from 4 to 19 years (mean (SD), 11.4 (3.2) years) were analysed. On every occasion, orthopnoea, weakness of respiratory sounds, and speech disturbance were seen, and the clinical score of McKenzie⁷ was always above six/nine. On 30 occasions, the attack occurred at home. Arterial blood samples were taken on admis-

sion to hospital (in 26) or within several hours of admission (in four)—whenever respiratory failure was first suspected clinically. In five children the attack occurred during a hospital stay—for parentectomy in three and steroid withdrawal in two. In all cases, patients were treated with xanthine compounds (orally or intravenously, or both) and β stimulants (orally only, if possible) before sampling.

Heparinised arterial blood was drawn from the radial artery before oxygen and alkali were given. All blood samples were analysed for arterial oxygen tension (P_{aO_2}), arterial carbon dioxide tension (P_{aCO_2}), and arterial pH immediately after sampling. An ABL2 Acid-base laboratory (Radiometer Corporation, Copenhagen) was used for analysis. The normogram of Siggaard-Andersen¹¹ was used to evaluate the acid base status. The point of sampling was assumed to be a steady state, and the alveolar-air equation⁸ was used for further analysis.

The alveolar-arterial oxygen tension gradient (A-a D_{O_2}) was then calculated by subtraction.

$$A-aD_{O_2} = P_{IO_2} - \frac{P_{aCO_2}}{R} - P_{aO_2}$$

where P_{IO_2} =oxygen tension of inspired gas and R=respiratory quotient.

Because patients included in this study were breathing room air only at the time of sampling the P_{IO_2} was assumed to be 19.9 kPa. In this study, R is assumed to be 0.85.¹²

The P_{aCO_2} is known to be a direct reflection of the adequacy of alveolar ventilation¹³ and we regarded a P_{aCO_2} of more than 5.9 kPa as an indicator of alveolar hypoventilation.¹⁴ Although the calculated A-a DO_2 has a limited value (as discussed above) it was regarded as an indicator of ventilation/perfusion inequality because more accurate measurement techniques were impossible to perform during most critical asthmatic episodes.

Statistical analysis was performed using Student's *t* test and the Person correlation coefficient was calculated.

Results

Arterial oxygen tension and arterial carbon dioxide tension. In 33 measurements out of 35, the P_{aO_2} was less than 9.3 kPa, and in 19 it was less than 7.9 kPa. Hypercapnia (P_{aCO_2} more than 5.9 kPa) was seen on 13 occasions. The P_{aO_2} was mean (SD) 7.7 (1.1) kPa and the P_{aCO_2} was 5.7 (1.2) kPa. One patient required mechanical ventilation during three attacks of asthma. All patients recovered.

Arterial pH and the logarithmic arterial carbon dioxide tension. These are shown in Fig. 1. The normogram of Siggaard-Andersen was employed. In 16 episodes the P_{aO_2} was above 7.9 kPa. Ten (63%) patients did not have acid base disorders, two had a mild metabolic acidosis, and two had a

respiratory alkalosis. Interestingly, two in this group had a respiratory acidosis, one of whom had a combined respiratory and metabolic acidosis (details are shown in Table 1).

In 19 episodes the P_{aO_2} was below 7.9 kPa and acid base disorders were more severe and variable. Only four (21%) patients did not experience acid base disorders. Eleven had a respiratory acidosis, two of whom had a combined respiratory and metabolic acidosis. These two required mechanical ventilation. Four patients had a respiratory alkalosis, associated with metabolic acidosis in one. Metabolic acidosis was seen in a total of six (17%) patients.

Pathophysiological analysis of the cause of the hypoxaemia. The relation between P_{aO_2} and P_{aCO_2} was used for further analysis and the A-a DO_2 was calculated by the equation given above (Fig. 2). As

Table 1 Blood gas measurements in two asthmatic patients with hypercapnia ($P_{aCO_2} \geq 5.9$ kPa) and $P_{aO_2} > 9.3$ kPa

Case no	Sex	Age (yrs)	P_{aCO_2} (kPa)	P_{aO_2} (kPa)	A-a DO_2 (kPa)	pH
1	M	11	6.8	9.6	2.3	7.219
2	F	10	5.9	9.6	3.2	7.356

Conversion—SI to traditional units: 1 kPa=7.5 mmHg.

Fig. 1 Log P_{aCO_2} in relation to pH showing acid base status.

Open circles= $P_{aO_2} \leq 7.9$ kPa; closed circles= $P_{aO_2} > 7.9$ kPa.

I=acute respiratory acidosis.

II=acute respiratory alkalosis.

III=chronic respiratory acidosis.

IV=acute base deficit.

V=chronic base deficit.

Fig. 2 Correlation between P_{aCO_2} and P_{aO_2} .

The solid line indicates the regression ($P_{aCO_2} = -0.49 P_{aO_2} + 9.5$, $r = -0.46$). Open circles= $P_{aCO_2} < 5.9$ kPa; closed circles= $P_{aCO_2} \geq 5.9$ kPa.

expected there was a significant inverse correlation between P_{aO_2} and the P_{aCO_2} , but the correlation coefficient was smaller ($r=-0.46$) than previously reported ($r=-0.75$, Simpson *et al*⁵ and $r=-0.61$, Downes *et al*).⁶ The differences in patient selection may be responsible for this discrepancy, because our series included the most severely affected patients only.

In Table 2, episodes associated with (type II) and without (type I) hypercapnia (P_{aCO_2} more or less than 5.9 kPa) are analysed separately. In episodes without alveolar hypoventilation (without hypercapnia), the P_{aO_2} was significantly inversely correlated with the A-a Do_2 but not the P_{aCO_2} , but in patients who experienced alveolar hypoventilation, however, the P_{aO_2} was significantly inversely correlated with the P_{aCO_2} but correlated only roughly with the A-a Do_2 .

Physiological causes of the severe hypoxaemia. In 19 episodes, the P_{aO_2} was below 7.9 kPa—11 were accompanied by the hypercapnia, and eight were not. As shown in Table 3, patients with severe hypoxaemia were divided into two subgroups: (1) type I, severe hypoxaemia without hypercapnia (hypoxaemic respiratory failure); and (2) type II, severe hypoxaemia with hypercapnia (hypoventilatory failure). The P_{aO_2} was comparable in both groups but the P_{aCO_2} was significantly higher, the arterial pH significantly lower in the type II group,

and the A-a Do_2 was significantly higher in the type I patients.

Discussion

The progression of the arterial blood gas disorders that occurs in acute severe asthma has been described as a uniform process. In the early stage, the usual manifestations are hypocapnia due to hyperventilation and hypoxaemia due to ventilation/perfusion inequality (mismatch). The hypocapnia is accompanied by a raised pH, respiratory alkalae-mia.^{1 15} With progression, the work of breathing exceeds the capacity of the respiratory 'pump', and alveolar hypoventilation develops, resulting in retention of CO_2 and ultimately acidaemia.^{1 15} Ventilation/perfusion inequality (increase in A-a Do_2) is considered to result in hypercapnia only late in the disease.

Although the finding of an acute respiratory acidosis is considered to be a danger signal,¹⁶ no reliable guides to the P_{aCO_2} value or rapid clinical deterioration are known,^{5 16} and the value of the widening A-a Do_2 as a predictor of forthcoming hypercapnia and rapid clinical deterioration has not been fully investigated. Thus, some questions remain. Firstly, whether the pattern of progression to hypercapnia and severe hypoxia of asthmatic patients is individual or uniform, and secondly, whether or not the increased A-a Do_2 value is a predictor of the forthcoming hypercapnia.

In the present study, two different patterns of progression of blood gas derangement have emerged: hypoxaemic respiratory failure and hypoventilatory failure. In the former (type I), the hypoxaemia is caused by a wide and increasing (6.6 kPa or more) A-a Do_2 value without alveolar hypoventilation, and in the latter (type II), the hypoxaemia is caused by a relatively mild but increasing (5.3 kPa or less) A-a Do_2 , and coexisting alveolar hypoventilation. It was observed that hypoventilation could occur even in the most mildly hypoxaemic patients, with a small A-a Do_2 value (Table 1).

The above observations suggest that the pattern of progression of blood gas disorders in acute, severe asthma is not uniform. All patients may develop hypoventilation ultimately, but the point at which this occurs may be different. Some patients may tolerate a considerably large ventilation/perfusion inequality, and others may not. Thus, the value of A-a Do_2 is not a predictor of forthcoming hypercapnia: furthermore not only patients with hypercapnia (type II) but those with the normo- or hypocapnia (type I) may suffer a critically severe hypoxaemia. In the present study, no episodes associated with type I failure required mechanical

Table 2 Correlations between P_{aO_2} and P_{aCO_2} /A-a Do_2 during episodes of hypoxaemia with (type II) and without (type I) hypercapnia

Correlation	Type I (n=22) ($P_{aCO_2}<5.9$ kPa)	Type II (n=13) ($P_{aCO_2}\geq 5.9$ kPa)
P_{aCO_2}	$r=-0.07$ (NS)	$r=-0.81$ ($P<0.005$)
A-a Do_2	$r=-0.78$ ($P<0.001$)	$r=-0.64$ ($P<0.05$)

NS=not significant.

Table 3 Blood gas measurements and mean age in 19 asthmatic children with severe hypoxaemia ($P_{aO_2}\leq 7.9$ kPa) with (type II) and without (type I) hypercapnia

	Type I (n=8)	Type II (n=11)
Age (yrs)		
Mean (SD)	11.1 (3.3)	11.1 (3.2)
P_{aCO_2} (kPa)	4.8 (0.7)*	7.1 (0.8)*
P_{aO_2}	6.9 (0.7)	6.9 (1.0)
A-a Do_2	7.4 (0.7)*	4.6 (0.7)*
pH	7.436 (0.047)*	7.294 (0.044)*

* $P<0.01$.

ventilation, but the severity of the hypoxaemia was not different between these two groups (Table 3).

In conclusion, the classification of acute respiratory failure into hypoxaemic respiratory failure (type I) and hypoventilatory failure (type II), is considered to be useful in understanding the pathophysiology of acute, severe asthma in childhood. Although hypoventilatory failure is known to be relatively rare in adults,^{4,12} it seems more common in children.⁷ In these two groups with respiratory failure in acute severe asthma, the difference in airways resistance, the responsiveness to different mediators,¹⁷ the ventilatory control (hypoxic and hypercapnic response),¹⁸⁻²⁰ and many other pathophysiologic factors should be studied further.

Conclusion

Two different patterns in the progression of arterial blood gas disorders in children with acute, severe asthma have emerged. In type I, a large and widening A-aDo₂ was considered to be the sole mechanism behind the severe hypoxaemia, and in type II, a limited but widening A-aDo₂ and coexisting alveolar hypoventilation were deemed to be the causative mechanisms. I speculate that type I failure is not always merely the first stage of the type II disorder. Even in type I failure, critically severe hypoxaemia was not uncommon. Some patients may tolerate considerably large ventilation/perfusion inequality, and others may not. The pathophysiological basis of the difference between these two groups needs to be investigated further.

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Received 21 February 1985