An unexpected ending: brain death following acute severe asthma

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ABSTRACT

A 56-year-old woman presented to our hospital with acute severe asthma. As a consequence of severe refractory airflow limitation, moderate hypercapnia ensued for several days. Unexpectedly, the patient died as a result of brain stem herniation, in the absence of hypoxaemia, arterial hypotension or an intracranial mass lesion. We discuss the mechanisms that may have precipitated severe intracranial hypertension resulting in brain death, and the possible methods to detect and avoid such a devastating consequence.

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Although the mortality of asthma has decreased in recent years,[1] acute asthma remains a significant clinical challenge. For severely affected patients requiring mechanical ventilation, the management priorities are ensuring adequate oxygen delivery, while minimising iatrogenic harm. To curtail dynamic hyperinflation, standard ventilatory management mandates the delivery of modest tidal volumes at low rates and with long expiratory times.[2,3] An inherent consequence is hypercapnia, but the "permissible" limits are somewhat arbitrary and not consistently defined.[4-6] Although modest hypercapnia is generally not considered deleterious, the combination of significant hypercapnia and elevated intrathoracic pressure simultaneously promotes cerebral vasodilatation and impairs venous drainage. This may result in generalised cerebral oedema and clinically significant intracranial hypertension, in the absence of an otherwise more conspicuous attributable mechanism, such as hypoxia related to severe asthma or following a period of cardiorespiratory arrest.

We report a patient with severe acute asthma who, while undergoing "protective" mechanical ventilation, unexpectedly developed generalised cerebral oedema, culminating in central herniation and brain death.

Clinical record

A 56-year-old woman with a history of asthma presented with an acute exacerbation of the illness. Her medical history was otherwise unremarkable. Triggers for her asthma were known to include multiple environmental agents. On this occasion, symptoms developed rapidly after exposure to household paint. The patient self-administered salbutamol with a metered-dose inhaler, but the symptoms progressed, and an ambulance was immediately sought.

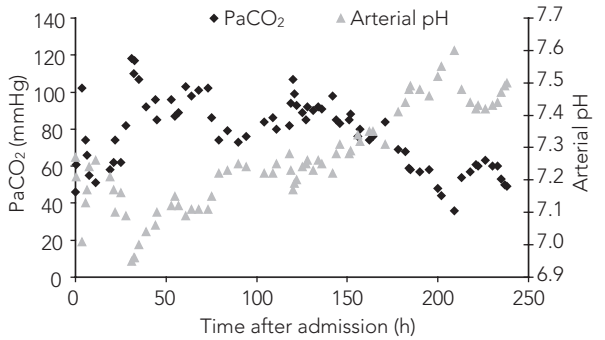
The ambulance service found the patient in severe respiratory distress, with a respiratory rate of 40 per min, and able to speak only with single words. Aliquots of intramuscular adrenaline (to a total of 1 mg) were administered during transfer to hospital. The patient remained conscious and was haemodynamically stable. Oxygen saturation remained above 94% while she received supplemental oxygen by face mask.

On arrival at our hospital, the diagnosis of acute severe asthma was evident. Severe respiratory distress persisted, with diffuse wheeze present on chest auscultation. Chest x-ray revealed hyperinflation of the lungs without focal abnormality. Initial arterial blood gas analysis revealed hypercapnic acidosis (P_{O_2}, 141 mmHg; P_{CO_2}, 62 mmHg; and pH, 7.21). Immediate therapy was initiated with salbutamol by continuous nebulisation, adrenaline (5 μg/min by intravenous [IV] infusion), magnesium sulfate (5 mmol IV bolus), and hydrocortisone (100 mg IV bolus).

However, as the patient was becoming increasingly fatigued, and respiratory arrest was pending, we performed endotracheal intubation after induction of anaesthesia with ketamine (1.5 mg/kg) and suxamethonium (1 mg/kg). Sedation was maintained with a midazolam–fentanyl infusion, and mechanical ventilation was initiated in a volume-controlled mandatory mode. Initial settings were: respiratory rate, 8 per min; tidal volume, 500 mL; inspiratory to expiratory time (I : E) ratio, 1 : 4; and applied positive end-expiratory pressure (PEEP), 0 mmHg. Inspiratory flow was provided in a decelerating fashion, with peak flow rates > 100 L/min. This yielded peak airway (Ppk) and plateau (Ppl) pressures of 40 cmH_2O and 25 cmH_2O, respectively.

Blood gas analysis at this time revealed severe hypercapnic acidosis (P_{O_2}, 141 mmHg; P_{CO_2}, 102 mmHg; and pH, 7.00). Airflow limitation and dynamic hyperinflation were evident clinically, by visualisation of the flow–time ventilator waveform, and by the presence of systolic pressure variation up to 40 mmHg (systolic arterial pressure remained > 90 mmHg without vasopressor support). Intrinsic PEEP measured by an expiratory hold manoeuvre was only 8 cmH_2O, although this measurement can underestimate

Figure 1. Arterial carbon dioxide tension and pH in a patient with acute severe asthma



Hypercapnia > 80 mmHg was present for 6 days.

true intrinsic PEEP because of small-airway closure during expiration.[3]

Treatment was continued with salbutamol, by both continuous nebulisation (10 mg/h) and IV infusion (10–20 μg/min); hydrocortisone (200 mg IV four times daily); ketamine (8 mg/h) and magnesium (2 mmol/h) infusion; and intermittent use of neuromuscular blockade. Bronchospasm remained refractory to these measures, with Ppk of 40–45 cmH_2O and Ppl of 25–30 cmH_2O. Significant hypercapnia persisted for several days, peaking at 118 mmHg. Metabolic compensation to pH 7.35 occurred over 6 days (Figure 1). Haematological and biochemical parameters are shown in Table 1.

Intravenous magnesium and salbutamol were weaned by Day 4, and ketamine by Day 5, with salbutamol continuously nebulised until Day 8. By this time, the severe bronchospasm had resolved, allowing weaning to pressure-support ventilation. Until then, haemodynamic stability had been maintained, and no other organ failure had developed. At no time was arterial hypoxaemia documented; the maximum F_{IO_2} required to afford a P_{O_2} greater than 80 mmHg was 0.6.

However, on Day 9 of admission, the patient suddenly developed severe arterial hypertension (mean arterial pressure, 140–150 mmHg), associated with atrial fibrillation and rapid ventricular rate. Within several hours, hypotension requiring vasopressor support developed, followed by the onset of apnoea, with absence of brain stem reflexes (corneal, oculocephalic, and pupillary responses to light), and polyuria consistent with diabetes insipidus. This constellation of signs suggested severe intracranial hypertension with central herniation. Computed tomography revealed diffuse cerebral oedema with sulcal effacement, loss of grey–white matter differentiation, and compression of basal cisterns. Brain death was later declared following the demonstration of absent intracranial blood flow by nuclear scintigraphy.

Postmortem examination revealed severe brain swelling with uncal notching, and grooving and necrosis of the cerebellar tonsils. Microscopy revealed widespread petechial haemorrhages in the white matter of the cerebral hemispheres, cerebellum and brain stem, with relative preservation of the cerebral cortex. There was no histological evidence of diffuse anoxic encephalopathy. These findings were interpreted as secondary to a primary process of raised intracranial pressure. The lungs showed histological changes consistent with asthma, including bronchiolar smooth muscle hyperplasia and hypertrophy, mucous gland hyperplasia, and patchy chronic inflammation.

Discussion

Like many other developed countries in the past decade, Australia has seen a decline in both the absolute number and proportion of patients with acute severe asthma who

Table 1. Haematological and biochemical results, by day of hospital admission

Parameter	1	2	3	4	5	6	7	8	9
Haemoglobin (g/L)	136	120	119	105	95	92	88	83	81
Platelet count ($\times 10^9$/L)	262	214	180	149	146	141	138	122	126
White cell count ($\times 10^9$/L)	9.36	16.7	17.6	9.63	7.39	9.82	11.5	14.3	19.0
Serum concentrations									
Sodium (mmol/L)	139	143	144	149	153	151	155	152	153
Potassium (mmol/L)	5.8	4.6	5.2	3.8	3.8	6.0	6.1	6.3	4.6
Chloride (mmol/L)	107	115	115	116	116	117	118	111	107
Bicarbonate (mmol/L)	28	22	29	33	37	40	42	41	45
Urea (mmol/L)	5.8	6.2	8.1	9.2	13.7	19.4	17.8	17.9	17.4
Creatinine (μmol/L)	80	76	89	78	77	85	74	76	61
Magnesium (mmol/L)	0.94	1.21	1.93	2.44	1.85	1.80	1.68	1.56	1.51

are admitted to intensive care units.[1] Moreover, the mortality of patients who require mechanical ventilation has significantly improved.[1] The cornerstone of modern ventilatory management is to prevent iatrogenic harm, with minimisation of barotrauma and dynamic hyperinflation. Typically, this involves the delivery of relatively low tidal volume ventilation at low frequencies, with low I : E ratios and judicious use of external PEEP. Inevitably with this approach, most patients develop alveolar hypoventilation, typically to target plateau pressures < 30 cmH_2O and intrinsic PEEP < 15 cmH_2O. This strategy is undisputed, especially given the historical context, with many patients dying from iatrogenic cardiovascular or barotraumatic complications when mechanical ventilation was targeted at near-normalisation of arterial CO_2 tension. An ongoing debate surrounds the "permissible" limits for hypercapnia. Authoritative reviews recommend a target of 80–90 mmHg, but also recognise the potential importance of the rate of rise of CO_2 tension.[2-5]

It is common experience that patients with severe asthma tolerate severe hypercapnia without apparent detriment. Yet, although normoxic hypercapnia is generally well tolerated, there remains the potential, at least in particular circumstances, for adverse effects, including the development of intracranial hypertension. Purportedly, simultaneous cerebral vasodilatation (from hypercapnic acidosis) and impaired venous drainage (from raised intrathoracic pressure) have been associated with severe intracranial hypertension in patients with acute asthma. Several reports have documented this, at least as a transitory phenomenon, with supportive clinical and radiological evidence. Focal neurological deficits (unilateral fixed, dilated pupil),[7] quadriparesis,[8] and generalised cerebral oedema[9] associated with intracranial hypertension (quantified with extradural pressure monitoring) have all been described in asthmatic patients with severe exacerbations.

To our knowledge, this is the first described case of asthma to be complicated by brain death in the absence of an obvious diffuse insult, such as prolonged severe hypoxia or hypotension. We find it plausible to attribute the development of cerebral oedema and intracranial hypertension directly to the mechanisms elucidated above. Disturbingly, this occurred with levels of hypercapnia that would not usually be regarded as malignant. The manner of our patient's death was unexpected, particularly given the absence of overt cardiovascular instability or hypoxaemia. Presumably, other mechanisms contributed. These may relate to the rate of rise of CO_2 tension or an intrinsic susceptibility to the cerebral effects of hypercapnia, including effects on autoregulation of cerebral blood flow, and the failure of local adaptive mechanisms that usually occur with exposure to sustained hypercapnia. Any idiosyncrasy of our patient in this regard was not predicted. An intriguing, if not ironic, observation is the temporal association of evolving brain stem death with resolution of the underlying illness. Perhaps such sustained hypercapnia, with normalisation of cerebrospinal pH, "reset" the cerebral vasculature response to CO_2,[10,11] so that the relatively rapid decline in CO_2 tension as the bronchoconstriction resolved further compromised the patient with "inappropriate" vasoconstriction, which was particularly deleterious in the setting of established cerebral oedema and intracranial hypertension.

Confounding this analysis are the possible effects of the administered agents, such as magnesium and salbutamol, on cerebral haemodynamics. In animal models, magnesium infusion has shown cerebral vasodilator properties,[12,13] but in a study of human volunteers, no effect was seen on middle cerebral artery blood-flow velocity or cerebral vascular reactivity to CO_2.[14] The cerebral vasculature has a rich adrenergic nerve supply; both endogenous catecholamines[15] and infused salbutamol[16] have been associated with cerebrovascular dilatation. Furthermore, ketamine, which was administered to our patient at subanaesthetic doses for 5 days, has complex effects on cerebral haemodynamics. Although early studies associated ketamine anaesthesia with increased cerebral oxygen consumption, cerebral blood flow and intracranial pressure,[17,18] these conclusions have been more recently challenged.[19,20] Rather, a review of the literature demonstrates that, even in patients with brain injury, ketamine is not associated with a rise in intracranial pressure if co-administered with γ-aminobutyric acid receptor agonists.[20] The significance of such possible contributions, particularly given the likelihood of additive or synergistic effects, is difficult to resolve in a single case.

The particulars of this case may have significant implications for the management of patients with severe asthma. Intracranial hypertension can be a potential complication of this disease, particularly in patients who require mechanical ventilation and have severe dynamic hyperinflation. Reaching a balance between the competing interests of minimising transpulmonary inflation pressures, avoiding barotrauma, maintaining haemodynamic stability, and protecting cerebral function is difficult. In these cases, where arterial CO_2 tension remains high, monitoring of intracranial pressure might help direct a safer balance of therapeutic interventions. Interventions might include lowering the permissible hypercapnic threshold with a more aggressive ventilatory strategy and use of adjunctive therapies (eg, volatile anaesthetic agents), and extracorporeal CO_2 elimination. Our patient's death painfully illustrates the complex, clinical challenge of acute severe asthma, where the optimal treatments remain elusive.

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