Original Article

Respiratory alkalosis and associated electrolytes in long-term ventilator dependent persons with tetraplegia

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Study design: A pilot case control study of the acid-base and electrolyte status in 30 long-term ventilator-dependent (LTVD) and 30 self ventilating persons with tetraplegia.

Objectives: To assess the extent of respiratory alkalosis and screen for associated hypokalaemia, hypomagnesaemia and/or hypophosphataemia.

Setting: Medically stable persons with tetraplegia under the long-term care of the Southport Spinal Injuries Centre, England.

Methods: Blood gases and electrolytes were sampled from 30 control patients with tetraplegia and from 30 patients having been LTVD for more than 12 months.

Results: All the blood gas measurements in the LTVD group lay outside both the reference range and the 95% confidence intervals (CI) of the control group: pH 7.46 (0.06); PCO₂ 3.46 (1.1) kPa; bicarbonate 18.3 (3.8) and base excess –3.2 (2.8) mmol/l; PO₂ 13.8 (2.8) kPa (means and standard deviations). The serum potassium, magnesium, phosphate, and sodium means lay within the reference ranges but the potassium, phosphate and calcium were at or below the 95% CI of the control values. One patient on part-time ventilatory support having less bicarbonate compensation had low serum electrolytes during ventilation.

Conclusion: There was no evidence of biochemical jeopardy from long-term mechanical hyperventilation although acutely administered hyperventilation has the potential to cause falls in serum potassium, magnesium and phosphate and so caution should be exercised in part-time ventilated persons. The full range of electrolytes should be assayed during stabilisation in LTVD and periodically thereafter. Hyperventilation helps to maintain good oxygenation in LTVD persons with paralysis and normal lungs.

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Introduction

The condition of ventilator dependency may arise as a consequence of acute lung injury and multi-organ failure, as the end-stage of chronic pulmonary disease or as a result of neuromuscular weakness. Whereas the lungs are grossly pathological in the former categories, commonly there is no fundamental pulmonary defect in the latter group except in so far as there is a tendency towards atelectasis and lower respiratory tract infections as a consequence. There is now a solid body of evidence that large volume-ventilation

and high pressures may be damaging to the diseased lung and, as a consequence, intensive care practice is to avoid the exacerbation of the acute lung injury by limiting the inspiratory plateau pressure to <35 cmH₂O¹ and the tidal volume to less than 6 ml/kg²; in such circumstances permissive hypercapnia is well tolerated if oxygenation can be maintained.

The prerogatives in the management of ventilator dependency in high tetraplegia are different. There is commonly an uncuffed tracheostomy tube with an associated insufflation leak – especially marked during sleep – necessitating ventilator settings which administer mechanical hyperventilation even with added dead space.³ A similar approach is taken by other

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centres experienced in the management of tetraplegic respiratory failure and it has been shown that ventilating with at least 20 ml/kg and an interposed dead space can hasten the slow wean of tetraplegic patients on short-term ventilatory support.⁴ Despite the addition of a breathing system with dead space it is often difficult to avoid a degree of respiratory alkalosis in patients with paralysis and low metabolic rates. Persons with tetraplegia may on occasion have episodes of dizziness which can usually be attributed to postural hypotension, autonomic hyperreflexia with hypertension or hypoglycaemia. Although acute hypocapnia can be associated with symptomatic cerebral vasoconstriction, blood flow is usually restored after 24 h even though bicarbonate elimination only partially restores the cerebrospinal fluid pH to normal.^{5,6}

It is possible to overlook the array of potential electrolyte shifts associated with respiratory alkalosis although Haldane first noted significant hypophosphataemia in 1924⁷ and it has been described more recently.^{8,9}

Serum potassium, magnesium and calcium may be affected by pH swings though the direction of change remains controversial.^{10–13} There is no research to indicate whether or not the long-term ventilator-dependent person is prone to such electrolyte abnormalities separate from the effects of tetraplegia *per se*. The pilot study was undertaken to help validate the technique of mechanical hyperventilation for long-term ventilator-dependent persons.

Methods

Study population

Thirty subjects with tetraplegia who constituted the control group had arterial blood sampled for blood gases, sodium, potassium, phosphate, total calcium and magnesium, creatinine and albumin. They were selected from among medically stable outpatients and inpatients who were undergoing rehabilitation.

Thirty patients with long-term ventilatory dependency (LTVD) were identified who had already been stabilised for domiciliary ventilation at the Southport Spinal Injuries Centre. All but seven were already living in the community, the majority having had high spinal cord damage, but two patients had motor neurone disease, one Duchenne muscular dystrophy, and one had slowly progressive neuro-muscular weakness of unknown aetiology. The patients had been dependent upon respiratory support for between 1 to 30 years, but their present pattern of ventilation had been set at this centre in all cases and had last had blood gases reviewed between 1 and 40 months previously (mean 17.6). All 30 patients had a tracheostomy tube without a cuff and were having assisted respiration with room air. Fourteen were full time mechanically ventilated (FTV), four had full time bilateral phrenic nerve stimulation (FTPNS), five had

diaphragmatic pacing during the day-time with positive pressure ventilation at night (PTPNS), and seven breathed independently in the day time with mechanical ventilation at night (PTV). Mechanical ventilation was delivered in a pressure limited mode to allow for insufflation leaks using either the LP10, Companion 2801, Breas 501 + pressure limiting valve, or PLV100. The overall level of ventilation had originally been set according to oxygen and carbon dioxide variability during waking and sleeping. The ability to speak clearly had also been a factor influencing the settings. As a general policy, patients had a considerable dead space amounting to a volume of at least 200 ml in an attempt to minimise hypocapnia. Young children and patients with known electrolyte disorders were excluded and patients had to be normothermic and were asked not to use a bronchodilator for 2 h before the time of blood sampling. The study had local ethical committee approval as a pilot study.

Sampling and analysis

Arterial blood was sampled from the patient awake and in the supine position, and those patients who had two modes of breathing had a second sample taken after at least an hour had elapsed from the change in ventilatory mode to allow for a new steady state. Eleven patients were visited at home both as a clinical follow-up and for the purpose of this study. Two and a half millilitres of blood were collected in a syringe with only enough heparin to fill the dead space,¹⁴ and blood for the remaining biochemical analysis was collected separately into Vacutainer bottles. The samples of the hospital-based patients could be analyzed immediately whilst those from home visits were plunged into ice, which slows down the rate of change of gas tensions by 90%,¹⁵ and then transported within 45 min to the local hospital laboratory for subsequent arterial blood gas and electrolyte analysis. The laboratories analyzed total magnesium and total calcium corrected for albumin content.

Data processing

The investigation focused upon the periods of maximum ventilation when patients were fully awake so the control values could then be compared with values from all 30 ventilated patients when potentially at their most alkalotic. The values from the PTV group and the PTPNS group obtained during mechanical ventilation were combined with those from the continuously supported groups (FTV, and FTPNS). The acid-base data were plotted on scattergrams, differentiating the values for the part-time ventilated group from the rest of the respiratory-assisted group. Descriptive statistics, including 95% confidence intervals, for two groups of 30 subjects were derived using SPSS 9.0. Boxplots are used to demonstrate ranges of values which are otherwise not highlighted by the 95%

CI. Student's *t*-test was limited to assessing the difference in electrolyte values between the two groups, and to assess for possible significance within LTVD subgroups since the study was a pilot study.

Results

Blood gases

The average age in the control group was 40 years (range 19–66) and three patients were female. The average age in the LTVD group, also with three females, was 43.6 years (range 15–73). The blood gas means in the control group, tabulated in Table 1, were within the normal range except for five, all over 45 years of age, who had reduced oxygen tensions (7.8–10.0 kPa). The measurements in the LTVD group all lay outside the reference range and outside the 95% CI of the control group (Table 2). Fifty per cent of LTVD patients had oxygen tensions above the normal range and 30% between 10 and 12 kPa so that the mean was 13.8 compared with 11.8 kPa in the controls ($P=0.001$). As the carbon dioxide drops below the normal range with increasing alveolar ventilation, the oxygen tension rises to surprisingly high values, being over 17 kPa in 20% of the LTVD persons.

The mean carbon dioxide for the 30 ventilated persons was 3.5 kPa (range 2.0–5.5), whereas the mean pH of 7.47 was only just outside the normal range. This reflects the degree of bicarbonate compensation within the group as reflected in a mean actual bicarbonate (AB) of 18.3 mmol/l and a base excess (BE) of -3.2 mmol/l.

Subgroup analysis

The four patients with full-time phrenic pacing had a mean PCO_2 of 3.8 and pH of 7.42. The five who

alternated between mechanical ventilation and phrenic nerve stimulation were slightly more alkalotic when ventilated (pH 7.47 vs 7.42) though the difference in PCO_2 was not significant (3.1 vs 3.6 kPa).

The seven part-time ventilated patients (PTV) had a PCO_2 swing from 5.5 kPa, when breathing independently, to 4.0 kPa when being ventilated with a corresponding pH change from 7.36 to 7.47. The mean bicarbonate in this group during ventilation was normal at 21.4 mmol/l and as a result three patients had the most extreme pH values of any ventilated patients, the highest being 7.60 with a PCO_2 of 3.1 kPa. The PTV patients are marked separately for clarity from the remainder of the LTVD group in the scattergrams of pH vs PCO_2 (Figure 1).

Electrolytes

The means of creatinine in the control and LTVD groups were 69.5 and 63.3 mmol/l, albumins 40.2 and 39.3 g/l and sodium 137.4 and 137.2 mmol/l respectively. Low sodium values of between 126 and 133 mmol/l which were obtained in five control and seven ventilated subjects were not consistently related to any other biochemical changes. The electrolyte values of primary interest are shown in Tables 3 and 4.

The mean potassium of 3.9 mmol/l was statistically, but not clinically, significantly lower in the ventilated group ($P=0.05$). These are displayed together with carbon dioxide tensions in Figure 2. Though the mean values in the part-time ventilated group were unchanged between breathing independently and being ventilated, the potassium dropped from 3.4 to 3.1 in patient 54 which was the lowest value in the whole series.

There was no significant difference in magnesium between the two groups. The lowest individual control value was 0.66 mmol/l, whilst the lowest LTVD value was 0.64, again in patient 54 when being ventilated compared with 0.72 self ventilating.

The mean phosphate levels were not different between the two groups though the LTVD value of

Table 1 Blood gas measurements in 30 self-ventilating tetraplegic patients

	Mean	SD	95% CI	Normal	Units
PO_2	11.8	1.79	11.2–12.4	12.0–13.3	kPa
pH	7.40	0.02	7.39–7.41	7.32–7.45	
PCO_2	4.62	0.4	4.5–4.8	4.6–6.0	kPa
AB	22.0	2.9	20.9–23.0	20–32	mmol/l
BE	-1.7	0.1	-2.3 – -1.1	-2.0 – $+2.0$	mmol/l

Table 2 Blood gas measurements in 30 tetraplegic patients having ventilatory support

	Mean	SD	95% CI	Normal	Units
PO_2	13.84	2.8	12.8–14.8	12.0–13.3	kPa
pH	7.46	0.06	7.44–7.48	7.32–7.45	
PCO_2	3.46	1.1	3.08–3.84	4.6–6.0	kPa
AB	18.34	3.8	17.0–19.7	20–32	mmol/l
BE	-3.24	2.8	-2.2 – -4.2	-2.0 – $+2.0$	mmol/l

Relation between pH and PCO_2 in LTVD persons and controls

Figure 1 Relation between pH and PCO_2 in LTVD persons and controls

Table 3 Serum electrolyte concentrations in 30 self-ventilating tetraplegic patients

	Mean	SD	95% CI	Normal	Units
K	4.11	0.48	3.94–4.28	3.5–5.2	mmol/l
Mg	0.81	0.08	0.78–0.84	0.7–1.0	mmol/l
PO ₄	1.14	0.19	1.07–1.21	0.8–1.5	mmol/l
Ca	2.39	0.10	2.35–2.43	2.20–2.60	mmol/l
alb	40.2	3.6	38.9–41.5	35–45	g/l

Table 4 Serum electrolyte concentrations in 30 tetraplegic patients having ventilatory support

	Mean	SD	95% CI	Normal	Units
K	3.89	0.36	3.76–4.02	3.5–5.2	mmol/l
Mg	0.79	0.08	0.76–0.82	0.7–1.0	mmol/l
PO ₄	1.07	0.23	0.99–1.15	0.8–1.5	mmol/l
Ca	2.29	0.12	2.25–2.33	2.20–2.60	mmol/l
alb	39.3	4.0	37.9–40.7	35–45	g/l

Figure 2 Potassium and carbon dioxide means, ranges and 25–75th Centiles

1.07 mmol/l was at the 95% CI of the controls. The lowest individual value in the control group was 0.69 mmol/l and the lowest value in the ventilated group was 0.67 yet again in patient 54, having dropped from 0.87 when breathing independently. The mean adjusted total calcium was significantly lower in the ventilator-assisted group at 2.29 mmol/l ($P=0.001$). The fall in calcium in the PTV subgroup was from 2.32 to 2.27 mmol when those seven patients were being mechanically ventilated, and in this case the value in patient 54 whose calcium was already low when self-ventilating actually rose when ventilated.

Discussion

Population

Though there are just over 100 patients in the UK with ventilator-dependency and tracheostomy, only some of

these have spinal cord damage and their ventilatory management may differ between centres. Therefore it was necessary to include different subsets of patients from a single centre and to include those using phrenic nerve pacing. Whilst this is more physiological than mechanical ventilation, uncontrolled passive recoil on expiration impairs continuous speech and so many of the patients also have a large tidal volume setting by way of partial compensation. Those patients using phrenic pacing in the day and positive pressure ventilation at night tended nevertheless to be more alkalotic when receiving positive pressure ventilation and it was deemed reasonable therefore to include the PTPNS mechanical ventilation sample for the group analyses.

The subgroup which may deserve more detailed future study comprises those patients who breathe independently for part of the day (PTV). Their blood samples showed that there is a greater tendency towards respiratory alkalosis when reconnected to the ventilator though it should be remembered that once those patients fall asleep there would again be a reduction in ventilation associated with the insufflation leak.

Sampling

Previous work has shown that the ventilated patient with spinal cord injury has a rise in carbon dioxide during sleep. For example the mean carbon dioxide tension of 10 patients awake was 3.2 kPa compared with 3.9 asleep.¹⁶ The same study also demonstrated a degree of variability of carbon dioxide during continuous measurements such that the range of carbon dioxide tensions in a particular patient (no. 8) were 3.4–5.8 kPa. The degree of variability of carbon dioxide tension overall tends to be less when awake.

Whereas the occasional patient with intercostal activity and diaphragm paralysis may have a drop in carbon dioxide in the transition from waking to sleeping, none of the five non-spinal cord damage cases in the present study had this particular pattern. The present procedure of sampling blood with the patient awake was therefore justified since this was likely to represent the greatest degree of alkalosis even though there would still be hour-to-hour and minute-to-minute variability.

A minimum volume of heparin sufficient to fill the dead space was added to the syringe since it is recognised that when the heparin concentration in the syringe exceeds 15% there is a decrement in apparent carbon dioxide tension, and so also for pH at a dilution of 25%.¹⁴ At such a heparin dilution, the oxygen tension will nevertheless only be 0.8 kPa higher so that significant heparin dilution cannot account for the surprisingly high PO₂ tensions encountered in the ventilated group. Similar oxygen tensions were reported in previous studies.^{3,16}

A further consequence of the need to gather data from a relatively small pool of patients was the need to

study some patients at home, particularly those whose residence was far from the spinal centre and who were not due for formal follow-up for some time. This meant that some blood gas samples were therefore measured in different laboratories and though not ideal, personal delivery of these samples packed in ice ensured insignificant change due to blood metabolism. Usually the electrolytes were analyzed at base hospital.

Acid-base and electrolytes

The bicarbonate and base excess values demonstrate a degree of metabolic compensation for chronic respiratory alkalosis except in those part-time ventilated patients who were also hyperventilated. Nevertheless, compensation in the larger group was incomplete so it was possible to compare pH and other measurements between the control and LTVD groups. Statistically, the most significant difference between the control and LTVD groups lay in the total calcium even though the latter mean value of 2.29 mmol/l still lay within the reference range. In a published case report, the calcium actually rose in association with acute correction of respiratory acidosis⁹ and in voluntary hyperventilation.¹⁷ The study by Mostellar¹³ showed no change in calcium in volunteers during acute respiratory alkalosis, though during acute metabolic alkalosis there was a fall in calcium from 2.38 to 2.18 mmol/l in association with a pH rise from 7.41 to 7.59. Hafen studied healthy subjects during voluntary hyperventilation from pH 7.39 to 7.51 and demonstrated a rise in total calcium from 2.39 to 2.57, with no change in the ionized fractions.¹² The total magnesium was also unchanged but the ionized fraction fell significantly from 0.54 to 0.50, and the free fraction from 0.68 to 0.61 mmol/l. In the same study the phosphate also fell from 1.29 to 0.86 mmol/l whilst the potassium rose.

The variable reported results in relation to magnesium and potassium could be related to the opposing effects of α and β adrenoreceptors,^{18–20} the former of which appear to inhibit cellular uptake whilst the latter promote it, as during β agonist therapy for acute asthma.²¹ Though falls in both magnesium and potassium were documented in the latter study unfortunately no blood gas changes were reported, for an improvement in pH in response to treatment might in itself have shifted potassium. The patient under anaesthesia, when the sympathetic system is at least partly suppressed, probably resembles the tetraplegic more closely than the hyperventilating volunteer, and so one would anticipate that the direction of change of these electrolytes in spinal cord damage would also be to fall with a rise in pH. Indeed the fall to subnormal values in potassium, magnesium and phosphate – but not calcium – in patient number 54 in the present study when he changed from independent breathing to controlled breathing confirm that it is indeed possible to induce such electrolyte shifts in tetraplegic patients by acute respiratory acid-base changes. It is unknown

whether the person with tetraplegia will have denervation supersensitivity to the potassium- and magnesium-lowering β -adrenergic effect of salbutamol. However, we were careful to ensure this medication was not taken at the time of the study. Calcium was unaffected in the studies of adrenergic agents by Sorensen.²⁰

The mean sodium concentrations in each group were the same, but five in the control group and eight in the ventilated group had values lower than 132 mmol/l, the lowest in the control group being 126 and in the ventilated group 128. The low sodium values did not appear to be related to any other biochemical findings. Whilst these findings had been unsuspected in the patients in question, as a group, persons with tetraplegia are also prone to profound hyponatraemia.²²

Hyperventilation

Ever since Morch and Saxton noted that polio patients in 1956 were more settled with high capacity respiration (sic),²³ the technique of mechanical hyperventilation in association with the use of uncuffed tracheal tubes evolved empirically with the observation that the patients were better oxygenated both when awake and during sleep, and complained less of dyspnoea. It is difficult to measure such patients' actual tidal volume, which furthermore is quite variable, and no attempt has been made to estimate the range of minute ventilation in the present study. Suffice to say that a number of patients were being ventilated with machines such as the LP10 on stroke volume settings of 2.2 l in conjunction with the pressure limiting valve. In these circumstances, the measurable inspired volumes typically ranges from 1.5 to 2 l. The dead space usually amounted to about 200 ml with variable rebreathing.

The clinical observation that the transition to independence from oxygen enriched air in a paralysed ventilated patient is hastened by the use of large tidal volumes may be explained by the findings of studies of patients under anaesthesia. The microatelectasis theory is now disproved whereas it has long been known that there is a fall in functional residual capacity (FRC) to below closing volume (CV) on induction of anaesthesia necessitating oxygen enrichment of the inspired mixture. The drop in FRC is now believed to be due to the loss of intercostal muscle tone under anaesthesia even without muscle relaxation.²⁴ Measures to increase FRC such as application of positive end-expiratory pressure (PEEP) are sometimes successful, and less commonly, intermittent sigh breaths.²⁵ Harvey and Ellis studied the effect of continuous positive airways pressure (CPAP) in acute tetraplegia and demonstrated that the FRC could be increased by the application of PEEP but only for so long as the PEEP was being applied.²⁶ Technical difficulties precluded measurements of CV in these tetraplegic patients. It is not possible to apply PEEP in

the presence of an uncuffed tracheal tube, although a retard can prove helpful in this regard.

Imaging of the diaphragm under general anaesthesia has demonstrated impairment of excursion of the dependent portion of the diaphragm consequent upon the change from diaphragmatic respiration to isocapnic positive pressure ventilation with muscle relaxation. This leads to regional ventilation/flow mismatch and could contribute to atelectasis formation.²⁷ Rehder and colleagues showed that the impaired uniformity of dependent lung ventilation in the supine and especially lateral positions under relaxant anaesthesia can however be ameliorated by ventilating with a tidal volume of 60% as opposed to 10% of the total lung capacity.²⁸ Continuous ventilation at this volume might be deleterious whereas, in contrast, periodic large volume inflation of the lung has been shown to stimulate surfactant secretion.²⁹ Another experiment which provided biologically variable ventilation to pigs for 7 h of anaesthesia showed preservation of pulmonary function in contrast to those pigs which had a constant 10 ml/kg tidal volume ventilation.³⁰ These situations are more analogous to that of the patient with an uncuffed tracheal tube and though a longitudinal study of oxygen tension was not carried out in the present study, there is no suggestion of a progressive deterioration of oxygenation except as might occur with aging. Self-ventilating persons with restrictive ventilatory impairment are recognised to develop irreversibly progressively stiffer lungs over the longer term and this is thought to be due to changes in lung elasticity, so that maintaining a generous tidal volume in ventilated tetraplegics may in fact also help maintain their lung compliance.³¹

From the point of view of the tetraplegic person without an active cough mechanism, the greater the lung volume on inspiration, the greater the recoil on expiration. This favours clearance of secretions together with vigorous manual 'bagging' with a 1.6 l self-inflating bag and provision of an assisted cough and postural drainage, and these elements are regarded as our standard practice for the clearance of pulmonary secretions of long-term ventilator-dependent persons.

Circulatory effects of alkalosis

Whilst it is recognised that cerebral vasoconstriction is a rather short-lived effect of hypocapnia, less is known of the effect on cardiac output. On the one hand, carbon dioxide on its own is a myocardial depressant, whereas in the intact mammal a rise in carbon dioxide is associated with release of catecholamines which stimulate the heart and circulation. Prys-Roberts and colleagues³² investigated the effect on cardiac output in three groups of volunteers under anaesthesia at different levels of carbon dioxide but in whom the mean intrathoracic pressure was maintained identical to eliminate a pressure effect on venous return. Whilst

there was no difference in pulse or blood pressure, the systemic vascular resistance (and so venous return and cardiac output) was greater the higher the carbon dioxide tension and this was thought likely to be mediated by catecholamines. The tetraplegic patient, on the other hand, may behave differently, and variations of the mean intrathoracic pressure with ventilation is likely to have at least as great an effect.

Conclusions

Whilst there were slight reductions in means of serum potassium, phosphate and total calcium associated with chronic compensated respiratory alkalosis compared with the self-ventilating tetraplegics, the values remained within the normal range. Taken together with previous studies showing excellent oxygenation from mechanical hyperventilation with an uncuffed tracheal tube and an interposed dead space, the results in this pilot study do not indicate significant biochemical derangements when patients are hyperventilated intermittently with tidal volumes of up to 2 l though the extended range of electrolytes should be monitored routinely. More caution should be exercised in those patients who only have nocturnal ventilation.

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