Eur J Pediatr (1999) 158: 42–45 © Springer-Verlag 1999

S. M Tibby · I. U. Cheema · D. Sekaran · M. Hatherill · I. A. Murdoch

Use of permissive hypercapnia in the ventilation of infants with respiratory syncytial virus infection

Received: 22 June 1998 / Accepted in revised form: 25 August 1998

Abstract We wished to retrospectively evaluate the effects of permissive hypercapnia (PHY) on barotrauma, mortality and length of stay when applied to ventilated infants with respiratory syncytial virus (RSV) bronchiolitis. Nineteen control infants with RSV induced respiratory failure were treated with conventional ventilation (April 1991–January 1994), after which time PHY was adopted as unit policy. A further 28 infants were then treated with PHY (January 1994–April 1996). Demographic and physiological data were collected from admission, and outcome variables including length of stay, barotrauma and mortality were recorded. The PHY group showed a significantly higher mean pCO_2 (7.6 vs 5.2 kPa), a lower mean pH (7.34 vs 7.40), and a reduction in maximal peak inspiratory pressures (25 vs 30 cmH_2O). Mortality, barotrauma, use of neuromuscular blockade and nosocomial infection did not differ between groups. There was a trend towards increased length of ventilation in the PHY group (median 7 vs 5 days).

Conclusion Based on this retrospective data we can show no benefit for the use of permissive hypercapnia as a ventilatory strategy in this patient group. A prospective randomised controlled trial is warranted to accurately assess the outcome variables and cost implications of this strategy.

Key words Bronchiolitis · Permissive hypercapnia · Respiratory syncytial virus

Abbreviations *ARDS* acute respiratory distress syndrome · *CV* conventional ventilation · *OI* oxygenation index · *PHY* permissive hypercapnia · *PICU* paediatric intensive care unit · *PRISM* paediatric risk of mortality · *RSV* respiratory syncytial virus

Introduction

Acute viral bronchiolitis in infancy accounts for a significant number of paediatric intensive care unit (PICU) admissions during the winter months [17, 22], with respiratory syncytial virus (RSV) remaining the most important pathogen [1]. Despite the development of various preventative [6] and early treatments [18], little exists in the way of therapeutic options once the infant is mechanically ventilated.

Furthermore, it has been suggested that mechanical ventilation itself may cause additional lung damage as a consequence of high inflationary pressures and large tidal volumes producing regional overdistension [4, 13]. Permissive hypercapnia (PHY) has been suggested as a lung protective ventilatory strategy for adult patients with the acute respiratory distress syndrome (ARDS) [10]. PHY is a strategy that allows for a degree of hypercapnia providing the arterial pH does not fall below a pre-set minimal value; it may be utilised in combination with a degree of permissive hypoxaemia

I. A. Murdoch (✉) · S. M. Tibby · I. V. Cheema
D. Sekaran · M. Hatherill
Department of Paediatric Intensive Care, 9th floor,
Guy's Tower, Guy's Hospital, St Thomas Street,
London SE1 9RT, UK,
Tel.: +44-171-955 2564, Fax: +44-171-955 2563

(usually arterial haemoglobin oxygen saturation above 85%) in an effort to minimise mean airway pressure and hence barotrauma. As a result of increasing evidence from the adult literature [11, 14], this strategy was adopted as part of the treatment regime for ventilated infants with bronchiolitis in our PICU from September 1994 onwards. Our impression has been that this has resulted in longer patient stay without an appreciable decrease in barotrauma or mortality. Given that the number of infants with severe RSV bronchiolitis is likely to increase with the improving survival rate of extremely low birth weight infants, such a strategy may have potential cost implications for future practice. With this in mind we wish to report our experience with the use of PHY on ventilated infants with RSV, to analyse retrospectively its impact in terms of the primary endpoints of pH, pCO_2 and peak ventilator pressure, the secondary endpoints of mortality, length of stay and barotrauma and thus to ascertain if enough evidence is present to warrant a prospective study.

Patients and methods

Guy's PICU is a 16 bed, combined cardiac and general tertiary referral PICU, currently admitting approximately 800 patients per year. A total of 47 RSV positive (direct immunofluorescence on nasopharyngeal aspirates) mechanically ventilated infants were retrospectively identified between April 1991 and April 1996. Demographic and physiological data were collected from admission. Chronic lung disease was defined as supplemental oxygen requirement at 30 days of age. Physiological data included Paediatric Risk of Mortality (PRISM) scores, ventilator settings, daily mean pH and pCO_2 values and oxygenation indices (OI).

OI is defined as: mean airway pressure (cmH_2O) $\times$ FIO_2/arterial pO_2 (mmHg).

All infants were ventilated in pressure-controlled, time-cycled mode on Sechrist IV-100B or Draeger Babylog ventilators. During the period April 1991 to September 1991 19 patients were ventilated conventionally (CV). PHY was introduced as unit policy after this time, with 28 infants receiving this mode of ventilation between September 1994 and April 1996. Management guidelines in CV and PHY are outlined in Table 1. No rigorous extubation criteria were enforced during either period. Extubation was usually performed on clinical grounds irrespective of the blood gas values and generally required an FiO_2 of less than 0.5, a mean airway pressure less than 10 cmH_2O, and a ventilator rate of less than 10 breaths/min.

All patients were nasogastrically fed as soon as practicable (usually within 6 h from admission) and fluid restricted to 65–75% of normal maintenance requirements. Patients were sedated with morphine (20–40 μg/kg/h) and chloral hydrate (30–50 mg/kg 4-hourly as required). Neuromuscular blocking agent use was also recorded and length of usage was calculated on patients who received these agents for more than 24 h (this was to exclude patients who only received blockade for their initial intubation period). Incidence of nosocomial infection, defined as culture positive broncho-alveolar lavage in the presence of central temperature >38.5°C and pulmonary infiltrates on chest X-ray was also noted. Barotrauma was defined as either pneumothorax or pneumomediastinum on chest X-ray.

Exclusion criteria included neuromuscular disorders, uncorrected congenital heart disease and the suspicion of raised intracranial pressure. The following statistical tests were used: for parametric data unpaired *t*-tests (with Welch's approximation if unequal variances were present), for non-parametric data the Mann-Whitney test, and Chi-squared and Fisher's Exact tests for categorical outcome data. In all cases statistical significance was set at $P < 0.05$ level.

Results

Patients were well matched between groups for demographic data, presence of chronic lung disease and severity of illness as measured by both PRISM and worst OI (Table 2). No children with corrected congenital heart disease were seen. Daily average pH and pCO_2 values were calculated for each patient, and then averaged over each patient's ventilated days. Data in Table 3 represent the overall mean pH and pCO_2 values for the respective patient groups.

The PHY group, as expected showed both a significantly higher mean pCO_2 and a lower mean pH, with a reduction in maximal peak inspiratory pressures (Table 3). Despite this there were no appreciable differences in mortality and barotrauma between groups. There was a non-significant trend towards longer du-

Table 1 Ventilatory management guidelines for ventilated RSV infants. (*PEEP* positive end expiratory pressure; *PIP* peak inspiratory pressure)

	Conventional ventilation	Permissive hypercapnia
Oxygen saturation	≥88%	≥88%
pCO_2	4–6 kPa	No specified limit if pH adequate
pH	7.30–7.45	>7.25
PEEP (cm H_2O)	5	5
PIP	To achieve above goals	Minimum to achieve above goals
Ventilator rate	Low rate, long expiratory time	Low rate, long expiratory time

Table 2 Demographic data for CV and permissive hypercapnia (PHY) groups. *CLD* chronic lung disease

Variable	CV (n = 19)	PHY (n = 28)	P value
Age (months)[1]	2.5 (1.1–3.0)	2.4 (1.0–7.0)	0.57
Gestational age (weeks)[1]	35 (32–40)	33.5 (29–39)	0.26
Males:females	13:6	23:5	0.46
CLD	3	4	1.0
PRISM Score	12 (10–15)	11 (8–13)	0.12
Worst OI	12 (10–27)	13 (10–25)	0.76

[1] median (interquartile range)

Table 3 Outcome data and ancillary therapies for CV and PHY groups. (ECMO extracorporeal membrane oxygenation, *NM* neuromuscular, *PIP* peak inspiratory pressure)

Variable	CV ($n = 19$)	PHY ($n = 28$)	P value
$paCO_2$ (kPa)*	5.2 (0.50) range: 4.5–6.5	7.6 (1.4) range:5.7–11.9	<0.0001˜
pH*	7.40 (0.04) range: 7.33–7.52	7.34 (0.04) range:7.23–7.41	<0.0001
Highest PIP* (cm H_2O)	30 (5.1) range: 22–40	25 (4.2) range:16–37	0.001
Ventilated days#	5 (3–6.5) range: 1–18	7 (4–10.3) range:1–15	0.13
PICU days#	7 (5.5–9.0) range: 2–20	8 (5–12) range:2–17	0.39
Mortality	1	0	0.4
Barotrauma	1	0	0.4
NM blockade >24 h	11	13	0.38
NM blockade (days)#	3 (3–5)	5 (4–7)	0.22
Nosocomial infection	2	2	1.0
Nitric oxide	0	5	0.14
ECMO	1	2	1.0

* mean (standard deviation); #median (interquartile range); ˜t test using Welch's approximation

ration of ventilation (7 vs 5 days) amongst the PHY group.

Discussion

PHY, or "controlled hypoventilation" was first described in the setting of status asthmaticus in 1984 by Darioli and Perret [3]. Advocacy for its use in ARDS subsequently appeared in the early part of this decade [11, 14] as a progression from animal models demonstrating the damage inflicted on lungs by overdistension [9, 13]. Until now PHY has been predominantly applied to adult patients with ARDS/acute lung injury, i.e: conditions associated with marked inhomogeneity of lung mechanics. A similar situation may exist in infants with bronchiolitis, where variable degrees of air trapping may co-exist with significant interstitial pneumonitis [7, 15]. Thus, the same ventilatory strategy may be applicable to this group of infants.

Our results have failed to show any improvement in outcome through the use of PHY. There was a trend towards increased length of ventilation in the PHY group (7 vs 5 days), a finding which has recently been demonstrated prospectively in adult trauma patients with ARDS [5]. Although retrospective, our patient groups were well matched. Associated conditions such as nosocomial pneumonia and ancillary therapies such as neuromuscular blockade, which have been shown to lengthen days of ventilation [25], were seen in similar numbers in both groups. A potential shortcoming of this study exists in the use of nitric oxide amongst several PHY patients. Although this did not reach statistical significance ($P = 0.14$), there may have been a clinically significant effect. However, if this is so, it is fair to assume that nitric oxide would allow adequate oxygenation to be achieved at lower mean (and peak) airway pressures resulting in an exaggeration of the pressure differences between groups, along with barotrauma reduction (type 1 errors) but not necessarily length of ventilation. Nonetheless, use of this modality would need to be tightly controlled in any prospective study.

Reports on the use of PHY in children to date have been retrospective, and in the setting of burns with ARDS [20, 21], and congenital diaphragmatic hernia [26], however all have yielded encouraging results. To the authors' knowledge, the only other published study looking at the use of PHY exclusively in RSV infants has demonstrated quite different findings from ours. Reda et al [19] have retrospectively shown a significant reduction in barotrauma (7% vs 26%) and length of ventilation (11.5 vs 15 days) in the PHY group, without a significant change in mortality. However several important differences exist between their control group and the one in the present study. Our control patients were younger (2.5 vs 5 mths), with a reduced mortality (5% vs 10%), lower incidence of barotrauma (5% vs 26%) and a shorter length of ventilation (5 vs 15 days). More importantly, no information is given regarding use of ancillary therapies such as neuromuscular blockade, incidence of nosocomial infection, and whether the CV group received any standardisation in method of ventilation. This makes direct comparisons between the two studies extremely difficult and highlights one of the limitations of retrospective studies.

Concerns have been raised regarding potential untoward effects resulting from PHY. Effects of hypercapnia on various organ systems are extremely complex and show individual variation. It has been shown that acute hypercarbia can impair myocardial contractility [23]. Although the resulting intracellular acidosis is an acute and potentially reversible phenomenon [2], it is possible that the effects may be more pronounced under conditions of reduced inotropy [16]. Respiratory acidosis may worsen pulmonary hypertension through pulmonary arteriolar vasoconstriction [24] which is particularly pertinent to the sub-group of patients with bronchiolitis and chronic lung disease. The increase in intracranial pressure from hypercapnia is well known and may occur chronically [8]. In addition, it has been demonstrated in an animal model that PHY alone does not eliminate ventilator induced lung injury [12].

Given the potential disadvantages of PHY in this patient group and the disparate findings from two small

retrospective studies, a prospective, randomised controlled trial of sufficient size would be necessary to accurately assess what is still a novel therapy in RSV bronchiolitis. Based on our data, with a power of 80% with an α value of 0.05, a 50% reduction in either mortality or barotrauma would require sample sizes of 945, clearly an unachievable goal. However, a 2 day reduction in length of ventilation would need 66 patients in each group. Given the potential cost implications, this study is warranted before an as yet unproven therapy becomes common practice.

References

1. Boeck KD (1996) Respiratory syncytial virus bronchiolitis: clinical aspects and epidemiology. Monaldi Arch Chest Dis 51:210–213
2. Cardenas VJ, Zwischenberger JB, Tao W, Nguyen P-DJ, Schroeder T, et al (1996) Correction of blood pH attenuates changes in hemodynamics and organ flow during permissive hypercapnia. Crit Care Med 24:827–834
3. Darioli R, Perret C (1984) Mechanical controlled hypoventilation in status asthmaticus. Am Rev Resp Dis 129:385–387
4. Dreyfuss D, Basset G, Soler P, Saumon G (1985) Intermittent positive-pressure hyperventilation with high inflation pressure produces pulmonary microvascular injury in rats. Am Rev Respir Dis 132:880–884
5. Gentilello LM, Anardi D, Mock C, Arreola-Risa C, Maier RV (1995) Permissive hypercapnia in trauma patients. J Trauma 39:846–853
6. Groothius JR, Simoes EAF, Levin MJ, et al (1993) Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. N Engl J Med 329:1524–1530
7. Hall CB (1992) Respiratory syncytial virus. In: Feigin RD, Chery JD (eds) Textbook of pediatric infectious diseases, 3rd edn. Saunders, Philadelphia, pp 1633–1656
8. Hargreaves DM (1990) Hypercapnia and raised cerebrospinal fluid pressure. Anesthesia 45:1096–1097
9. Hernandez LA, Peevy KJ, Moise AA, Parker JC (1989) Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. J Appl Physiol 66:2364–2368
10. Hickling HG, Henderson SJ, Jackson R (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 16:372–377
11. Hickling HG, Walsh J, Henderson S, Jackson R (1994) Low mortality rate in adult respiratory distress syndrome using with low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 22:1568–1578
12. Hickling KG, Town IG, Epton M, Neill A, Tie A, Whitehead M, et al (1996) Pressure-limited ventilation with permissive hypercapnia and minimum PEEP in saline-lavaged rabbits allows progressive improvement in oxygenation, but does not avoid ventilator-induced lung injury. Intensive Care Med 22:1445–1452
13. Kolobow T, Moretti MP, Fumagalli R, Mascheroni D, Prato P, Chen V, et al (1987) Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. Am Rev Respir Dis 135:312–315
14. Lewandowski K (1996) Permissive hypercapnia in ARDS: just do it? Intensive Care Med 22:179–181
15. Miller RR (1988) Viral infections of the respiratory tract. In: Thurlbeck WM (ed.) Pathology of the lung. Thieme, New York, pp 157–159
16. Orchard C, Kentish J (1990) Effects of changes of pH on the contractile function of cardiac muscle. Am J Physiol 258:C967–C981
17. Rakshi K, Couriel JM (1994) Management of acute bronchiolitis. Arch Dis Child 71:463–469
18. Randolph AG, Wang EEL (1996) Ribavirin for respiratory syncytial virus lower respiratory tract infection: a systematic overview. Arch Pediatr Adolesc Med. 150:942–947
19. Reda Z, Maggi JC, Torero L, Fam H, Chin T (1997) Permissive ventilation reduces morbidity in respiratory syncytial virus induced respiratory failure. Crit Care Med 25 [Suppl.1]:A215
20. Reynolds EM, Ryan DP, Doody DP (1993) Permissive hypercapnia and pressure-controlled ventilation as treatment of severe adult respiratory distress in a pediatric burn patient. Crit Care Med 21:944–947
21. Sheridan RL, Kacmarek RM, McEttrick MM, Weber JM, Ryan CM, Doody DP, et al (1995) Permissive hypercapnia as a ventilatory strategy in burned children: effect on barotrauma, pneumonia and mortality. J Trauma 39:854–859
22. Stretton M, Ajizian SJ, Mitchell I, Newth CJL (1992) Intensive care course and outcome of patients infected with respiratory syncytial virus. Pediatr Pulmonol 13:143–150
23. Tang WC, Weil MH, Gazmuri RJ, Bisera J, Rackow EC (1991) Reversible impairment of myocardial contractility due to hypercarbic acidosis in the isolated perfused rat heart. Crit Care Med 19:218–224
24. Viitanen A, Salmenpera M, Heinonen J (1990) Right ventricular response to hypercarbia after cardiac surgery. Anesthesiology 73:393–400
25. Willson DF, Jiao J-H (1997) Improved oxygenation after discontinuing neuromuscular blockade. Intensive Care Med 23:214–217
26. Wilson JM, Lund DP, Lillehei CW, Vacanti JP (1997) Congenital diaphragmatic hernia – a tale of two cities: the Boston experience. J Pediatr Surg 32:401–405