PAPERS AND ORIGINALS

Virological Findings and Blood Gas Tensions in Acute Lower Respiratory Tract Infections in Children

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Summary

Sequential blood gas tensions and pH have been measured in 84 children selected from 486 admitted to hospital during a 15-month period with acute lower respiratory tract infections. Of those selected 73 were treated conservatively and 11 by intermittent positive-pressure ventilation; one infant in the latter group died. Respiratory syncytial virus (R.S.V.) was isolated from 24 out of 62 patients studied and the main pathogen in the most severely affected infants. Statistical analysis showed that age and R.S.V. infection were independent determinants of severity, as reflected by a peak Pco_2 measurement at the height of the illness (age, $P < 0·01$; R.S.V. $0·05 > P > 0·01$).

Introduction

In Britain acute lower respiratory tract infections (bronchitis, bronchiolitis, and bronchopneumonia) are the main respiratory illnesses causing admission to hospital of children under the age of 2 years. When these conditions are considered together as "bronchiolitis" the mortality rate is about 5% (Heycock and Noble, 1956, 1962; Disney *et al.*, 1960) compared with 1-2% in series where the diagnosis "bronchiolitis" is made on stricter criteria (High, 1957; Elderkin *et al.*, 1965; Court, 1973). These deaths usually occur shortly after admission to hospital, and the precise cause is often in doubt.

Since respiratory syncytial virus (R.S.V.) was first isolated from infants with bronchiolitis (Chanock *et al.*, 1961) its importance as an aetiological agent in bronchiolitis and pneumonia in infancy has become well recognized (McClelland *et al.*, 1961; Andrew and Gardner, 1963; Holzel *et al.*, 1963; Elderkin *et al.*, 1965; Loda *et al.*, 1968). It has also been implicated in deaths associated with respiratory tract infections (Gardner *et al.*, 1967; Aherne *et al.*, 1970). The occurrence of arterial hypoxaemia and hypercapnia during the course of these illnesses (Reynolds, 1963; Downes and Striker, 1966; Simpson and Flenley, 1967; Simpson, 1973) has also been noted, yet to our knowledge there have been no reports relating virological findings to measurements or arterial blood gas tensions and pH. We describe here a study done over 15-months on 84 patients with acute lower respiratory tract infections selected from a much larger group ill enough to be admitted to hospital.

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Patients and Methods

From 1 January 1972 to 31 March 1973, 486 children, 351 under 2 years of age, representing 12·0% and 8·7% respectively of all admissions to three general medical wards, were admitted with acute lower respiratory tract infections to the Royal Hospital for Sick Children, Edinburgh. Of these, 84 (17·3%), including 71 (14·6%) aged under 2 years, were judged ill enough to warrant sequential measurements of blood gas tensions and pH. Fifteen of these patients were referred to a two-bedded respiratory care unit opened within the hospital at the start of the period, where 11 were treated with intermittent positive-pressure ventilation (I.P.P.V.) using a mechanical ventilator. The modes of clinical presentation, blood gas findings ,and treatment of these 11 patients are described in our accompanying paper (Simpson *et al.*, 1974).

Virus Studies.—Throat and nasal swabs were obtained for virus isolation from 62 (74%) of the 84 patients in whom blood gas tensions and pH were measured, including 10 of the 11 patients treated by I.P.P.V. The cotton ends of swabs were broken into the same bottle of virus transport medium (Hanks's balanced solution + 0·2% bovine albumin) and transported to the laboratory without delay. Each specimen was well shaken to liberate cells from the swabs. About 0·2 ml of the cell suspension was then inoculated into culture tubes of secondary rhesus monkey kidney and diploid human embryo lung fibroblasts (W.1.38) and incubated on a roller drum apparatus at 33°C. Cultures of HEp2 were also inoculated and incubated stationary at 36°C. Monkey kidney and HEp2 cultures were maintained with twice-weekly changes of medium for three weeks, when if no virus had been isolated a blind passage was made into similar cell cultures for a further week. Inoculated W.I.38 cultures were maintained with twice-weekly changes of medium for three weeks, when if no c to-pathic effect was seen and the cells appeared healthy they were discarded. Monkey kidney cultures were tested for haemadsorption using guinea-pig ervthrocvtes twice weeklv ju t be^c^o^r^e the change of medium. R.S.V. and influenza A virus were identified by the indirect fluorescent antibody technique or by neutralization tests. Diagnostic sera supplied by the Public Health Laboratory Service, Colindale, were used for all identification purposes. Rhinoviruses were identified by their cytopathic effect in W.1.38 cell cultures and by their lability to acid. Paired sera were also studied in six of the patients treated by I.P.P.V.

Analysis of Blood Gas Tensions and pH.—Serial radial or brachial arterial or arterialized capillary blood samples were analysed for oxygen tension Po_2, carbon dioxide tension Pco_2), and pH within five minutes. All measurements were performed in duplicate. The values obtained were corrected for the patient's temperature using the blood gas calculator of Severinghaus (1966). Measurement of Po_2, in arterial samples only, was always first performed with a Radiometer (Clark-type) Po_2 electrode (type E/5046) calibrated with room air before and after each determination. Each day the meter was set to zero with nitrogen. Duplicate measurements had to agree within 2 mm Hg. Arterial or capillary blood Pco_2 was measured with the Severinghaus electrode (type E/5036), the calibrating gases having been alaysed with Haldane apparatus to within $\pm$ 0·02%. The pH was measured with the G297/G2 electrode and PHM27 meter. Duplicate readings were within 0·004 units. Base excess values were derived from the nomogram of Andersen (1963) and related to the patient's haemoglobin level. A correction factor was made for the in-vivo effect of Pco_2 (Severinghaus and Bradley, 1969). Inspired oxygen concentration was measured using a Servomex oxygen analyser calibrated with air and nitrogen (Nunn *et al.*, 1964).

Results

Of the original 486 patients all but one survived. (During the study period an 8-year-old boy was admitted to hospital with fulminating staphylococcal septicaemia and pneumonia. He was also shown to have an influenza A infection. He was not treated in the respiratory care unit and is not included here. Details of his illness are described elsewhere (Habel and Inglis, 1974)).

Virology.—Some 70% of the children were swabbed routinely on admission. R.S.V. was isolated from 109, and in a further three R.S.V. infection was diagnosed from a fourfold or greater rise in antibody titre (actual titres: < 8 → 256; < 8 → 256; < 8 → 64). The overall isolation rate of R.S.V. from specimens obtained from 62 of the 84 children in whom blood gas tensions and pH were measured was 39% (table I). R.S.V. was isolated from six out of 11 infants treated by mechanical ventilation and its aetiological role was confirmed in a further two from serial antibody titre estimations. Other viruses isolated included influenza A (3), rhinovirus (3), adenovirus (2), parainfluenza 2 virus (1), and echovirus (1).

TABLE I—*Virus Isolations in 84 Patients in whom Blood Gas Tensions and pH were measured*

Clinical Category		No. of Patients	No. Sampled	No. of Viruses Isolated		
				R.S.V.	Other*	Total
"Conservative" treatment	>2 yr	13	8	2	1	3
	⩽2 yr	60	44	16	8	24
Mechanical ventilation	⩽2 yr	11	10	6†	1	7
Total		84	62	24	10	34

*Influenza A, rhinovirus, adenovirus, parainfluenza 2 virus, echovirus 22.
†Two additional cases confirmed serologically.

Blood Gas Tensions and pH.—Blood gas tensions and pH measurements in patients breathing air or oxygen according to age are shown in table II. In conservatively treated patients peak severity data relate to the highest measured Pco_2; peak severity data in infants treated by mechanical ventilation correspond to the highest recorded arterial Pco_2 before I.P.P.V. Severe ventilatory failure with Pco_2 values exceeding 65 mm Hg was present in nine of the latter patients.

TABLE II—*Blood Gas Tensions and pH in 84 Patients breathing Air or Oxygen at "Peak" Severity. Results are expressed as means ±S.D. with Ranges shown in Parentheses*

Clinical Category		No. of Patients	pH	PCO₂ (mm Hg)	Base Excess (mEq/1.)
Conservative treatment	>2 yr	13	7·36 ±0·07 (7·26–7·46)	39 ±13 (23-64)	−3·2 ±3·3 (−10·00 to +1·0)
	⩾2 yr	60	7·33 ±0·07 (7·15-7·46)	47 ±12 (22-73)	−1·7 ±3·4 (−8·0 to +6·0)
Mechanical ventilation	⩾2 yr	11	7·21 ±0·10 (6·99-7·37)	77 ±19 (49-120)	+2·8* ±4·9 (−7·5 to +8·7)

*Prior infusion of sodium bicarbonate in four patients.

Effect of Age and R.S.V. Isolation on "Peak" Pco_2.—The most severe degrees of respiratory failure occurred in the early months of life—that is, the age at which R.S.V. was isolated most frequently. To determine the relative contribution of age and R.S.V. infection to the degree of severity of the illness the effect of these variables on peak Pco_2 was assessed statistically by analysis of variance. The results given in tables III, IV, and V show that each was independently significant (age effect, $P < 0·01$; virus effect, $0·05 > P > 0·01$).

TABLE III—*Peak PCO_2* (mm Hg) in R.S.V.-positive and R.S.V.-negative Patients according to Age*

3 Months		6 Months		1 Year		2 Years		>2 Years	
Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.
48	44	45	55	29	54	37		64	48
45	42	43	51	31	54	21		35	35
40	51	38	50	31	65			37	
39	57	36	29	33	57†			38	
54	66	66	68					38	
57	48	43	50					56	
73	55	46	66						
65	83	56							
51	63	50							
48	78								
46	49†								
51	63								
47	69								
65									
85									

*Excludes post-$NaHCO_3$ measurements.
†R.S.V. infection shown serologically.

TABLE IV—*Effect of Age and R.S.V. on PCO_2 (mm Hg)*

	-3 Months		-6 Months		-1 Year		>1 Year		Total	
	Mean	No.	Mean	No.	Mean	No.	Mean	No.	Mean	No.
R.S.V.-negative	54·3	15	47·0	9	31·0	4	40·8	8	46·9	36
R.S.V.-positive	59·1	13	52·7	7	57·5	4	41 5	2	55·8	26
Total	56·5	28	49·5	16	44·3	8	40·9	10	50·6	62

TABLE V—*Analyses of Variance: Unbalanced Design*

Source of Variation	D.F.	Sum of Squares	Mean Squares	F Ratio
Age effect	3	1,897	632	4·68 P<0·01
R.S.V.	1	837	837	6·20 0·05>P>0·01
Interaction (swab and age)	3	858	286	2·12
Error	54	7,312	135	
Total	61	11,265		

Discussion

Our results confirm previous reports of the aetiological importance of R.S.V. in acute lower respiratory tract infections in young children. Of the 71 infants under 2 years of age in the present series 20 had peak P_{CO_2} measurements greater than 60 mm Hg (11 treated conservatively and 9 with I.P.P.V.), and in 14 of these R.S.V. infection was proved. No other virus was isolated from these 14 infants but in one of the remaining six an echovirus 22 was isolated. The extent to which bacteria were primarily involved is uncertain, as most patients had been treated with antibiotics before their admission to hospital. The bacteriological findings in patients treated by I.P.P.V. are described in our accompanying paper (Simpson *et al.*, 1974). Our isolation rate of R.S.V. was higher than that reported by Gardner (1973) in a large hospital-based survey in which the isolation rate was based solely on throat swabs. The highest isolation rates reported, however, were in series in which direct immunofluorescent techniques for the identification of R.S.V. were utilized (Gray *et al.*, 1970; McQuillin *et al.*, 1970). Those workers also obtained higher isolation rates from nasopharyngeal secretions than from throat swabs.

The arterial or arterialized capillary blood gas tensions were in close agreement with those of Downes and Striker (1966) and Downes *et al.* (1968). All the conservatively treated patients recovered though there was some concern about 10 in whom P_{CO_2} peaked between 60 and 73 mm Hg. Four were referred to the respiratory care unit, where with continued treatment including frequent aspiration of nasal and oropharyngeal secretions they improved clinically and the P_{CO_2} returned to normal within several days. Mechanical ventilation was withheld, for despite the P_{CO_2} levels they did not show evidence of impending exhaustion clinically—severe thoracic retractions, decreased-to-absent breath sounds, maximal hyperinflation of the chest, central cyanosis in 40% oxygen, and diminished response to painful stimuli, signs which constitute the clinical criteria suggested by Downes *et al.* (1968) for acute respiratory failure in bronchiolitis. Arterial P_{O_2} exceeded 80 mm Hg in each case while breathing 40-50% oxygen, and P_{CO_2} values exceeding 60 mm Hg were not maintained in any patient for more than a day. In retrospect the decision to withhold ventilation proved correct but previous experience (Simpson and Flenley, 1967; Downes *et al.*, 1968) had suggested that a P_{CO_2} of 65-70 mm Hg in such infants represents the limits to which a conservative approach is justified.

AGE AND "PEAK" P_{CO_2}

Previous investigations have shown (Reynolds, 1963; Simpson and Flenley, 1967) that in patients such as ours, unlike adults with chronic obstructive airway disease, ventilatory failure does not worsen when they are breathing oxygen. We therefore chose P_{CO_2} as the main index of respiratory failure rather than P_{O_2}, as many affected infants were breathing oxygen-enriched air in tents with or without high humidity. The statistical observation that age has a significant effect on P_{CO_2} ($P < 0{\cdot}01$) confirms the clinical impression that infants are more susceptible than older children and adults to hypoxaemia with carbon dioxide retention during the course of acute respiratory illnesses. In pneumonia in adults, for example, hypoxaemia is usually associated with a normal or low P_{CO_2} (Meakins and Davies, 1925).

Anatomical and physiological considerations (mechanical and regulatory) during the period of postnatal lung growth and development may explain in part at least this increased vulnerability. Even in full-term infants lung development is incomplete. The number of alveoli increases after birth in an exponential manner up to the age of 8 years (Dunnill, 1962). During this period there is a 10-fold increase in the number of lung alveoli. Lung surface area increases some 20-fold, which is about the same as the increase in body weight. The metabolism of the infant expressed per kg of body weight exceeds that of the adult, however, which suggests that it has less reserve surface area for added metabolism. Hogg *et al.* (1970) studied the distribution of resistance to air flow in the lungs of infants dying from non-respiratory causes and also in lungs of patients who died of bronchiolitis or cystic fibrosis. They demonstrated the large contribution of peripheral airway resistance to total lower airway resistance in the lungs of infants and young children as compared with adults. In abnormal lungs peripheral airway disease led to clinically recognizable disease in life and death from respiratory failure in the young child; similar lesions went virtually unrecognized during life in the adult.

The tendency to maldistribution of ventilation leading to imbalance of ventilation and perfusion is facilitated by an increased tendency of small airways to close in young children. Mansell *et al.* (1972) found large closing volumes in young children comparable to those found in middle-aged adults. This may be due to incomplete development of elastic tissue, a view supported by physiological data on elastic recoil and also histological studies.

The combination of high peripheral airway resistance, maldistribution of ventilation (perhaps a consequence of small airway closure), and rapid rates of respiration (often 60-100/min, which alone contributes to an increase in the dead space: tidal volume ratio in bronchiolitis) may result in frequency dependence of dynamic compliance and further impairment of gaseous exchange. This phenomenon has been shown in infants with acute bronchiolitis (Krieger, 1964).

R.S.V. AND "PEAK" P_{CO_2}

R.S.V. was isolated most often from patients under the age of 6 months (table III). Our results suggest that infection with this virus is an important determinant of severity quite distinct from age. A word of caution is necessary, however, for in view of our low isolation rate our data may include false-negative results. Further experience is necessary before the observed effect of R.S.V. on peak P_{CO_2} can be regarded as fully proved. This question is important in view of the growing suspicion that immunological factors play a part in the pathogenesis of acute respiratory failure associated with R.S.V. infection in infancy. Chanock *et al.* (1970) suggested that immune mechanisms enhance the virulence of R.S.V. in the early months of life and that there is an interaction of virus and circulating antibody in the lung resulting in the most severe manifestations of the disease (type III reaction). An alternative explanation suggesting a type I immunological reaction was proposed by Gardner *et al.* (1970). At present there is no direct evidence to support either hypothesis. The elucidation of this problem may, however, lead to methods being devised to protect infants in the early months of life.

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Acute Respiratory Failure in Bronchiolitis and Pneumonia in Infancy. Modes of Presentation and Treatment

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Summary

The modes of presentation and the management of acute respiratory failure in 11 infants with severe lower respiratory tract infections (due to respiratory syncytial virus in eight) are described. Progressive respiratory difficulties leading to exhaustion, peripheral circulatory collapse, recurrent apnoeic attacks, or generalized convulsions were the main clinical presentations resulting in severe ventilatory failure. In nine infants preventilation carbon dioxide tensions exceeded 65 mm Hg. It seems likely that the use of intermittent positive-pressure ventilation in these patients contributed to the low mortality rate, less than 0·5%, from such illnesses during the 15-month study period.

Introduction

Every year some 3,000 children in the U.K. die from respiratory tract infection. Many of these deaths occur at home but even in hospital-based series the mortality rate is high (Disney *et al.*, 1960; Heycock and Noble, 1962; Court, 1973). In more than a third of the cases predisposing disease or malformation is present (Court, 1973). Most affected infants respond satisfactorily to oxygen therapy, antibiotics, and general supportive measures. A few develop severe respiratory difficulties, however, and in these mechanical ventilation has been shown to be a major adjunct to treatment (Downes and Striker, 1966; Jones *et al.*, 1968; Phelan *et al.*, 1968). We have attempted to define the latter group with particular reference to its size, the mode of presentation of the illness, and the relation of clinical and blood gas findings. The management of these patients is also described.

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Patients and Methods

Out of 15 infants with bronchiolitis or pneumonia referred to the respiratory care unit of the Royal Hospital for Sick Children, Edinburgh, between 1 January 1972 and 31 March 1973, 11 were treated with intermittent positive-pressure ventilation (I.P.P.V.) using a mechanical ventilator. These infants represent some 3% of all infants under the age of 2 years admitted with acute lower respiratory tract infections during the same period. Their clinical details are given in table I. None had an associated congenital abnormality.

Respiratory distress, most prominent during feeds, and a dry, repetitive cough preceded by a coryzal phase were common initial symptoms; tachypnoea, retractions, and hyperinflation of the chest were the usual findings of the initial examination. Chest signs were bilateral, with areas of consolidation, collapse, or hypertranslucency to *x* rays. Haemoglobin levels ranged from 9 g to 12 g/100 ml and only one patient had a white blood cell count exceeding 15,000/mm³ (case 11, W.B.C. 25,000/mm³; neutrophils 73%, lymphocytes 22%). Serum sodium, potassium, chloride, and urea nitrogen concentrations were within normal limits in the eight patients in whom measurements were made before rehydration. E.C.G. showed no evidence of myocarditis in the nine patients studied at the height of their illness. *Escherichia coli*, *Haemophilus influenzae*, and *Staphylococcus aureus*, isolated in cases 2, 6, and 8 respectively, were the sole bacterial pathogens found in nasal and throat swabs. Coliforms (cases 2, 6, and 10), pneumococci (case 7), and *Pseudomonas aeruginosa* (case 8) were isolated from bronchial secretions obtained at the time of nasotracheal intubation. No organism was isolated from blood cultures. There was evidence of infection with respiratory syncytial virus (R.S.V.) in eight out of 10 infants studied (cases 1, 3, 4 and 7-11; table I). In all cases serum concentrations of IgA IgM, and IgG were within normal limits for age (Stiehm and Fudenberg, 1966).

Two patients were treated with corticosteroids before I.P.P.V. (cases 2 and 11) and five were digitalized (cases 1, 4, 6, 7, and 11). Correction and maintenance of fluid and electrolyte balance was achieved by tube-feeding or parenteral replacement. Intravenous infusion of sodium bicarbonate (8·4%) preceded I.P.P.V. in cases 2, 4, 6, and 8.