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Bronchiolectasis—a complication of artificial ventilation

G SLAVIN,   J F NUNN,   JULIE CROW,   CAROLINE J DORÉ

Abstract

Pulmonary barotrauma associated with artificial ventilation is recognised clinically as pneumothorax, pneumomediastinum, or subcutaneous emphysema. Eleven patients who died in the intensive therapy unit after artificial ventilation were found at necropsy to have pronounced bronchiolectasis, which was associated with a greatly increased physiological dead space during life. The condition was best predicted by the maximum level of positive end expiratory pressure and the duration of application of positive end expiratory pressure. The clinical course of the lesion in survivors is not known.

Further detailed studies are needed, but it is suggested that high levels of positive end expiratory pressure should be used with caution.

Introduction

The lungs may be damaged by artificial ventilation with intermittent positive airway pressure. Pulmonary barotrauma from this cause has been defined as the development of pneumothorax, pneumomediastinum, or subcutaneous emphysema,[1] to which has been added tension lung cyst[2] and hyperinflation of a lung or lobe.[3] The incidence of the first three conditions is 10% and the use of positive end expiratory pressure up to 1 kPa has been claimed not to increase the risk.[1] More recently, Cullen and Caldera[4] reported a much lower incidence of these forms of pulmonary barotrauma, which can be causally related to artificial ventilation.

Such definitions of pulmonary barotrauma may be too restricted, however, and we have recently observed at necropsy a pronounced dilatation of terminal and respiratory bronchioles, producing a condition like honeycomb lung in patients who were artificially ventilated and in whom high levels of airway pressure were used. The histological appearances will be described in detail elsewhere. We have attempted in this paper to determine the relation of bronchiolectasis to the circumstances of artificial ventilation.

Materials and methods

Patients—The study was retrospective and based on 11 consecutive necropsies of patients who died in the intensive therapy unit after artificial ventilation. No patients were excluded. All except case 3 (inactive pulmonary tuberculosis with fibrosis of both upper lobes) were free of appreciable primary pulmonary disease on admission to hospital but subsequently required artificial ventilation for respiratory failure associated with the causes listed in table I. In most cases, pulmonary complications developed before or during artificial ventilation such that intrapulmonary shunting (10-60%) required an increase in the inspired oxygen concentration (over 95% in four cases). Positive end expiratory pressure (0·4-2·3 kPa) was used in seven patients.

Pathology studies—At necropsy the lungs were fixed in inflation either by gaseous formaldehyde[5] or, in two cases, by instillation of liquid formalin. The maximum inflation pressure using gaseous formaldehyde was 3 kPa. After fixation the lungs were examined macroscopically and cut into 1 cm slices. Multiple blocks (average 12 blocks/case) were taken from each lung and 4 μm paraffin sections were stained with haemotoxylin and eosin. Selected blocks were stained with connective tissue stains. Each section was examined independently by two pathologists, both unaware of the duration and manner of artificial ventilation carried out during life. The degree of bronchiolectasis was assessed semiquantitatively on a scale 0 (normal) to 4 and the views of the two observers aggregated by summation of the individual scores to give an aggregate score ranging from 0 to 8. In no case did individual assessments of the same patient differ by more than one grade and in nine cases the scores were identical.

Statistics—The bronchiolectasis score was related to variables characterising the circumstances of the artificial ventilation using stepwise multiple regression analysis and Kendall's rank correlation.

Relation of bronchiolectasis to pulmonary dead space—Formal measurement of pulmonary physiological dead space was not undertaken during artificial ventilation but an approximate and indirect estimate of the ratio of dead space to tidal volume (V_D/V_T) is provided by the product of minute volume and arterial P_{CO_2} (1 kPa), which equals CO_2 production (ml/min) $\times 0·1/(1-V_D/V_T)$. To allow for variations in CO_2 production, we standardised the product for body weight, age, sex, and body temperature. The normal value for the

Northwick Park Hospital and Clinical Research Centre, Harrow, Middlesex HA1 3UJ

G SLAVIN, FRCPGLAS, FRCPATH, head, section of histopathology
J F NUNN, PHD, FFARCS, head, division of anaesthesia
JULIE CROW, BSC, MRCPATH, senior registrar, section of histopathology
CAROLINE J DORÉ, BSC, member of scientific staff, division of computing and statistics

TABLE I—*Details of 11 patients who died during artificial ventilation**

Case No	Age	Sex	Diagnosis on admission	Cause of respiratory failure	Duration of artificial ventilation (days)		Inflation pressure/PEEP during last four days of artificial ventilation (kPa)				Bronchiolectasis score†	Highest inspired O₂ (%)	Latest intra-pulmonary shunting (%)
					Total	PEEP							
1	82	F	Bleeding from polyp of colon	Cardiac arrest	0·4	0	3/0				0	50	16
2	67	M	Myocardial infarction	Pulmonary oedema	3	2	2·8/0·5	2·6/0·5	2·7/0		2	80	50
3	64	M	Inactive pulmonary tuberculosis and fibrosis	Ventilatory failure	10	5	2·5/0·5	2·2/0·5	2·3/0·5	2·5/0·5	3	100	50
4	24	F	Volvulus small bowel	Bacteraemic shock	17	6	6·4/2·2	6·2/2·1	6·5/2·3	6·2/2·3	8	77	45
5	17	F	Crohn's disease	Tetanus	31	16	3·8/0·5	3·8/0·5	3·8/0·5	3·8/0·5	6	100	60
6	19	F	Pre-eclamptic toxaemia	Mendelson's syndrome	6	0	3/0	2·7/0	2·4/0	2·4/0	0	35	10
7	37	M	Multiple fractures	Flail chest	10	3	4/0·6	4/0·6	4·5/0·5	4/0	2	80	25
8	77	M	Strangulated umbilical hernia	Leaking aortic aneurysm	8*	0	3/0	3·4/0	3/0	3/0	0	50	30
9	42	M	Fractured tibia	Pulmonary oedema ? delayed Mendelson	31	29	5·8/1·0	5·8/1·0	6/1·0	6/1·0	7	100	60
10	57	M	Fractured ribs and skull	Flail chest	5	5	3·2/0·4	3·2/0·4	3·6/0·4	3·4/0·4	4	100	40
11	9	F	Fractured femur and skull	Medullary coning	4	0	3·5/0	2·2/0	2·6/0	2·6/0	0	40	15

*Case 8 died 22 days after cessation of artificial ventilation.
†Assessed semiquantitatively on scale 0 (normal) to 4 by two observers, giving aggregate of 0 to 8.
PEEP = Positive end expiratory pressure.

product (for a 70 kg man at 37°C) is about 36 rising to about 120 for a V_D/V_T ratio of 80%. Data from case 11 were incomplete and have been omitted.

Results

Clinical evidence of barotrauma—During life, eight patients had no evidence of pulmonary barotrauma according to the conventional definition cited above. One patient (case 4) showed radiological evidence of surgical emphysema of mediastinum and chest wall and the pneumomediastinum was confirmed at necropsy. No surgical cause existed for this. In case 7 there was radiological evidence of a small pneumothorax on the first and second days of artificial ventilation. Since there was also a haemothorax, it is reasonable to attribute this to the multiple fractured ribs. Radiological evidence of a small pneumothorax the day after weaning from artificial ventilation was found in case 9. There was no surgical cause for this. No patient had radiological evidence of bronchiolectasis or any clinical signs that could be attributed to it.

Pathological features of bronchiolectasis—In the mildest form (scored as 1 on the 0-4 scale) the changes were manifested simply as a relative dilatation of the terminal and respiratory bronchioles in comparison with the adjacent alveolar spaces. In cases showing a greater degree of change the bronchioles were increasingly distorted in shape so that the angles formed by their branching and the openings of the alveolar ducts were obliterated as the spaces were progressively more ballooned. Many of these bronchiolar spaces reached a diameter of several millimetres (fig 1) and were easily visible on examining the histological sections with the naked eye. In these spaces the lining was of cuboidal bronchiolar epithelium. Dilatation of the alveolar ducts was associated with bronchiolectasis in the more severe cases but the bronchiolectasis was the predominant lesion. In the severest degree of change the bronchiolectasis was accompanied by an interstitial emphysema with the formation of even larger air spaces within the interstitial tissue and also seen about the bronchiovascular bundles (fig 2). When these
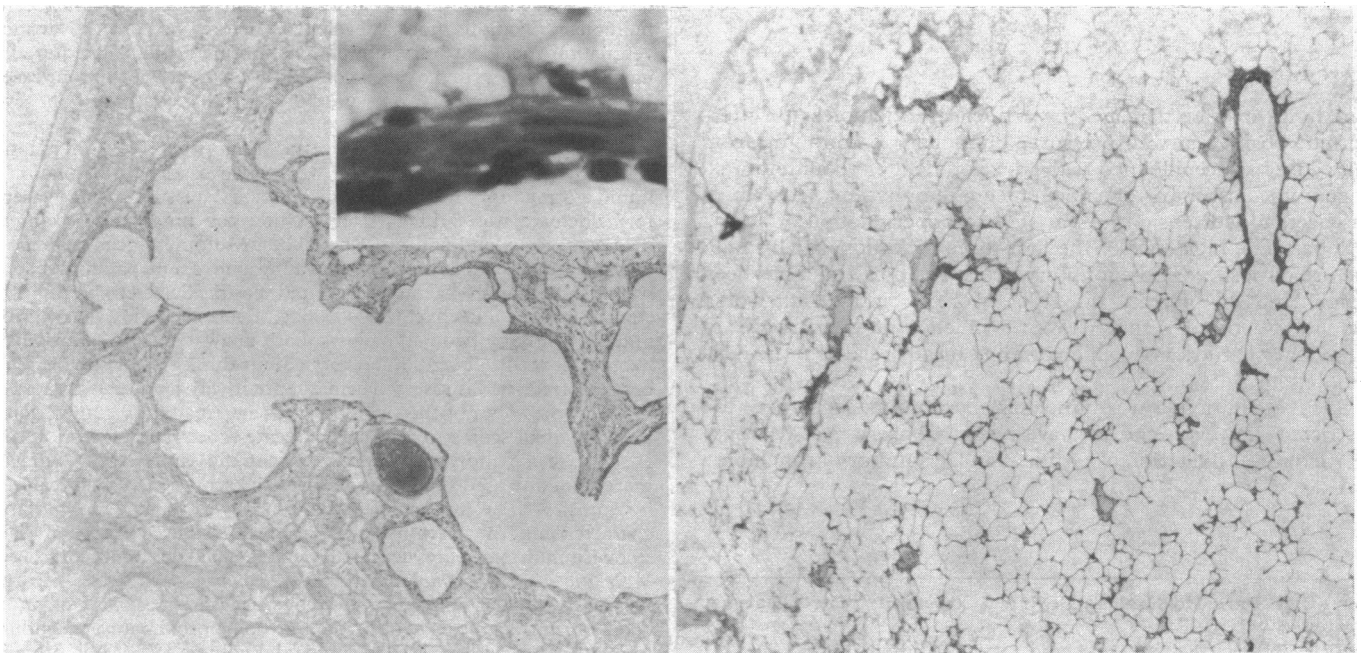

FIG 1—Left—Histological section from patient who received artificial ventilation with positive end expiratory pressure. Bronchiolar dilatation is seen in subpleural region: adjacent alveoli are not dilated. Inset: bronchiole lining ×650. Right—Subpleural region in patient who received artificial ventilation without positive end expiratory pressure.
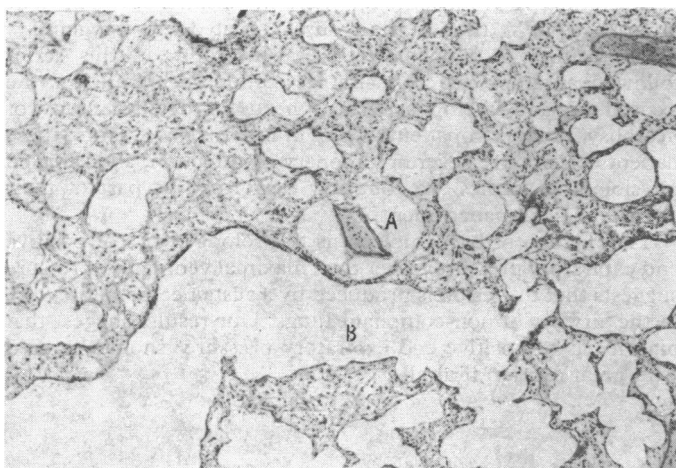Haemotoxylin and eosin ×22·5 (original magnification).

FIG 2—Histological section showing dilated bronchiole (B) surrounded by exudate-containing alveoli: interstitial air (A) surrounds blood vessel.
Haemotoxylin and eosin ×56 (original magnification).

changes were extreme and many of the surrounding alveolar spaces were collapsed, the combination of dilated bronchioles and interstitial spaces (up to 3 mm in diameter) with adjacent collapse gave rise to a picture that could be recognised on the gross lung slices.

Relation of bronchiolectasis to pulmonary inflation—Stepwise multiple regression was performed from measures of the circumstances of artificial ventilation to enable us to predict the degree of bronchiolectasis. Table II shows the correlations between the variables with the degree of bronchiolectasis. Apart from age, the variables are all highly correlated with the degree of bronchiolectasis. The highest correlation is with positive end expiratory pressure (r=0·84, p<0·01) and the highest partial correlation holding positive end expiratory pressure constant is with duration (r=0·85, p<0·01). None of the partial correlations holding both positive end expiratory pressure and duration of positive end expiratory pressure constant is statistically significant (p>0·05). The appropriate multiple regression equation is: degree of bronchiolectasis=0·395+2·88 positive end expiratory pressure (kPa)+0·166 duration (days). Observed degree of bronchiolectasis is plotted against the value predicted from this equation in figure 3. The adequacy of the model was investigated by constructing a normal plot of the residuals and by plotting the residuals against the predicted values and each dependent variable selected. The multiple correlation coefficient is 0·958, 91·8% of the variability in the degree of bronchiolectasis score can be explained by the regression equation. In view of the small size of the sample and the non-parametric nature of the bronchiolectasis score the variable selection was confirmed by calculating rank correlation coefficients. Kendall's rank correlation showed that the best single variable was duration of positive end expiratory pressure (0·896) and, holding duration constant, positive end expiratory pressure had the highest partial rank correlation (0·366).

Relation of bronchiolectasis to pulmonary dead space—Figure 4 shows a strong correlation between the product (minute volume times arterial PCO_2) and the degree of bronchiolectasis in the 10 patients for whom data were available (r=0·90; p<0·001). On the assumption that there was no systematic increase in CO_2 production in the patients with bronchiolectasis, this would indicate that the physiological dead space was considerably increased in these patients.

TABLE II—*Correlations and partial correlations with bronchiolectasis score*

	Correlation with bronchiolectasis score	Holding PEEP constant	Holding PEEP and duration of PEEP constant
Duration artificial ventilation	0·79*	0·82*	0·27
Maximum inflation pressure	0·76*	0·23	−0·48
Maximum PEEP	0·84*		
Duration PEEP	0·75*	0·85*	
Highest inspired O_2 (%)	0·75*	0·77*	0·65
Latest intrapulmonary shunting (%)	0·80*	0·78*	0·56
Age	−0·29	−0·14	−0·07

*p<0·01.
PEEP = Positive end expiratory pressure.

Discussion

Recognition of pulmonary barotrauma resulting from artificial ventilation has hitherto been indirect and confined to changes such as the demonstration of extrapulmonary air in the form of pneumothorax, pneumomediastinum, or subcutaneous emphysema,[1] lung tension cysts,[2] or hyperinflation of lung or lobe.[3] We are unaware of any previous attempts to relate histological changes in the lung to artificial ventilation in adults, though such changes are recognised in the lungs of artificially ventilated infants with respiratory distress syndrome.

Two fundamental problems beset investigation. Firstly, the requirement for artificial ventilation with positive end expiratory pressure implies that there is already severe lung disease that will tend to obscure the diagnosis of any effects due to positive end expiratory pressure itself. Secondly, the patients have life-threatening conditions and it would be unacceptable to apply the principles of a randomised controlled trial since nothing may be allowed to override the judgment of the clinician. We were therefore constrained to undertake a retrospective survey based on the observation of pronounced dilatation of the distal airways in relation to artificial ventilation in adult patients.

Bronchiolectasis occurred in each patient in whom positive end expiratory pressure was used. Its severity correlated well with the level of pressure and it was not seen in those patients in whom positive end expiratory pressure was not used. It also correlated with the duration of positive end expiratory pressure. The degree of bronchiolectasis was highly predictable from the highest pressure and its duration (fig 3). Neither of these factors was found by Kumar et al[1] to be related to pulmonary barotrauma, defined by them as pneumothorax, pneumomediastinum, or subcutaneous emphysema.
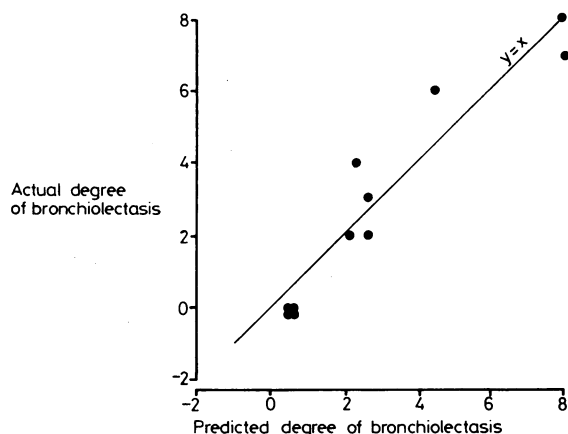

FIG 3—Actual degree of bronchiolectasis as function of degree predicted from multiple regression equation (see text). Line of identity is shown.

Bronchiolectasis has not been recognised in life in patients with barotrauma but Johnson and Altman[6] describe the radiological appearances of vesicular rarefaction (cystic changes) as manifestations of interstitial emphysema due to positive end expiratory pressure and these changes could in part be ascribed to bronchiolectasis. The clinical course of the lesion in survivors is not defined, though many patients have recovered from periods of artificial ventilation with positive end expiratory pressure. The type and extent of the lesion and the associated intra-alveolar changes, however, suggest that full resolution is unlikely and that residual changes are likely to persist.

The functional importance of bronchiolectasis is difficult to determine because the high inflation pressures and positive end expiratory pressures were used only when pulmonary function was already compromised and it was difficult to maintain a satisfactory arterial PO_2 because of intrapulmonary shunting (table I). There is no histological evidence to suggest that

bronchiolectasis per se would increase intrapulmonary shunts, though destruction of the pulmonary capillary bed might possibly cause pulmonary hypertension with opening of arteriovenous shunts, as shown by Niden and Aviado after pulmonary embolisation.[7] It is reasonable to believe, however, that there would be a major increase in the pulmonary dead space since the volume of the terminal conducting air passages is substantially increased relative to gas-exchange tissue. An association between bronchiolectasis and dead space is clearly shown in fig 4 and it seems probable that the relation is causal.

It is unlikely that the use of high inspired concentrations of oxygen is a factor in the development of bronchiolectasis. Comparisons of ventilation with air and oxygen were made in a series of patients with irreversible head injury.[8] At necropsy no differences in histological appearances of the lung were seen
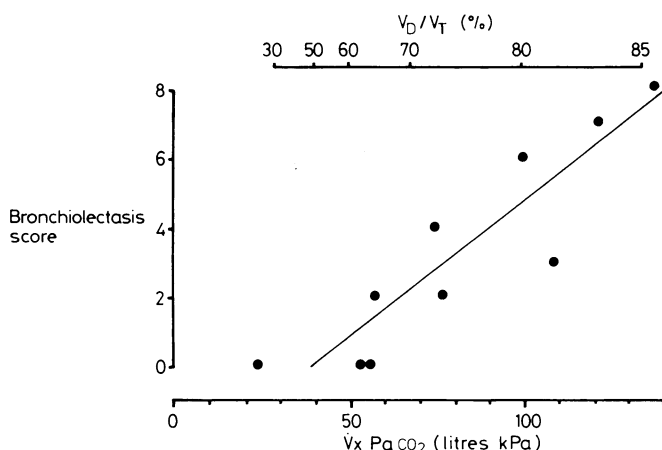
between the two groups, though there was a small but significant increase in V_D/V_T ratio in the group ventilated with oxygen.

Recognition of bronchiolectasis at necropsy in this series followed an improved but simple fixation technique for the excised lungs.[5] It emphasises the need for detailed study of necropsy findings in patients dying in intensive care units; these patients often have severe pulmonary dysfunction, and detailed physiological studies are routinely performed as part of their normal clinical management.

The relation of bronchiolectasis to prolonged rise of positive end expiratory pressure rather than maximal ventilatory pressure suggests that the lesion is produced by a sustained basal pressure in the airways of non-compliant lungs. Our results suggest that high levels of positive end expiratory pressure[9] should be used with great caution if at all.

FIG 4—Observed degree of bronchiolectasis in relation to product of minute volume (V) and arterial carbon dioxide pressure ($Paco_2$) (indirect estimate of pulmonary dead space). Linear regression line is shown $y = -2.86 + 0.0754x$. Value for ratio of dead space to tidal volume (V_D/V_T) assumes basal carbon dioxide output (normal value less than 50%). Data for 10 patients.

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SHORT REPORTS

Adverse reaction to ipratropium bromide

Ipratropium bromide, an anti-cholinergic compound, is increasingly finding a place in the management of reversible airway obstruction. I report here three cases in which the drug appeared to cause an increase in obstruction.

Case reports

Case 1—A 64-year-old atopic man with asthma aggravated by aspirin who was showing a partial but decreasing response to corticosteroids was admitted for assessment. Peak expiratory flow rate stabilised at 270 l/min before and 320 l/min after administration of nebulised salbutamol 20 mg four-hourly while he was taking prednisolone 10 mg a day and theophylline. Nebulised ipratropium bromide 100 μg was added immediately after the salbutamol. His morning peak expiratory flow rate became unrecordable before and 160 l/min after both salbutamol and ipratropium. At other times the peak expiratory flow rate was about 240 l/min before and 280 l/min after both bronchodilators, remaining at 90 l/min and 100 l/min on the next two mornings. Compared with the period when salbutamol alone was taken peak expiratory flow rate fell by a mean of 32% before and 26% after bronchodilators. Ipratropium was stopped on the third day, and peak expiratory flow rate returned to previous levels after 24 hours. He was challenged with ipratropium eight days later after a period of stable readings and a similar fall was seen.

Case 2—A 42-year-old woman with atopic asthma, who had been controlled

satisfactorily with a peak expiratory flow rate of over 400 l/min, had been less stable over the previous three months while taking prednisolone 12 mg a day, with a peak expiratory flow rate of about 300 l/min. She was taking salbutamol 200 μg four-hourly by metered dose inhaler, and ipratropium bromide 40 μg was added by the same route. On two occasions she had an immediate increase of wheeze lasting for 15 minutes. She was so apprehensive about the effects of the ipratropium that she was unwilling to undergo formal challenge.

Case 3—A 58-year-old atopic man, who had smoked intermittently until recently, consistently demonstrated eosinophilia. He gave a long history of wheeze and breathlessness, with a peak expiratory flow rate of about 240 l/min before and 280 l/min after administration of salbutamol 200 μg regularly five times a day by metered dose inhaler. He was also taking prednisolone 9 mg a day and beclamethasone dipropionate 150 μg five times a day. After a stable baseline recording had been obtained for one week at home he was started on ipratropium 40 μg taken five times a day by metered dose inhaler after the salbutamol. Peak expiratory flow rate fell progressively for four days to 110 l/min before and 160 l/min after both bronchodilators (figure). Ipratropium bromide was discontinued on the eighth day and progressive recovery occurred over the next 48 hours.

Comment

Although ipratropium bromide was introduced for use in patients with bronchitis who might have a reversible element in their obstruction, it has also been used in asthma.[1] As the potential response is extremely difficult to predict from clinical features it should probably be tried in all patients in whom satisfactory control has not been obtained with other bronchodilators.[2 3] My experience would support