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Tracheal aspirate pH is alkaline in pre-term human infants

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ABSTRACT: The pH of sputum and exhaled breath condensate is abnormal in several pulmonary disorders. Though airway pH regulatory proteins may be abnormally expressed in human development, the tracheal aspirate pH of infants born prematurely has not been studied.

Undiluted mid-tracheal aspirate samples were obtained on the first day of life from pre-term (23–30 weeks' gestation) and term (⩾37 weeks' gestation) infants for pH measurement; subsequently, pH was measured on days 7, 14 and 21 from the pre-term infants who remained intubated.

Thirty-five pre-term infants and eight term infants had samples collected on the first day of life. The mean pH of the pre-term infant samples (8.31±0.35) was significantly higher than that of the term infants (7.83±0.39). The pH in pre-term infants' airways fell with prolonged endotracheal intubation; the maximal decrease was of -1.37±0.96 pH units to 6.89±0.77.

Pre-term infants have a higher tracheal aspirate pH than full-term infants, and their airways tend to become more acidic with prolonged mechanical ventilation. The present data demonstrate for the first time that premature infants may have abnormal tracheal aspirate pH.

KEYWORDS: Airway, lung injury, mechanical ventilation, pH, prematurity

Twelve per cent of infants are born prematurely [1]. Despite pre-natal corticosteroid administration, exogenous surfactant use and improved ventilation strategies, 60% of infants born at <28 weeks of gestation develop respiratory distress syndrome (RDS), while ⩽30% of infants born between 28–34 weeks of gestation develop RDS [2].

Recent evidence suggests that abnormal airway pH may be a determinant of lung disease [3–8]. Mature alveolar type-II cells secrete surfactant at low pH (~3–5) [6]. There is a paucity of these cells in the pre-term airway; before alveolarisation occurs, most cells in the distal airway are type-I alveolar cells, which do not produce surfactant. The release of acid from the lamellar bodies of type-II cells would then occur predominantly after 34 weeks. As distal airway lining fluid is cleared proximally by mucociliary clearance, a decrease in distal airway acid production should result in an increase in proximal tracheal aspirate pH. Therefore, it was hypothesised that the tracheal aspirate pH of pre-term infants would be more alkaline than that of term infants. Additionally, under normal conditions, distal airway acid is neutralised by several pH regulatory enzymes [4, 7, 9, 10]. The effectiveness of this pH regulation in the pre-term airway has not previously been studied, though expression of at least one carbonic anhydrase isoform is thought to be decreased in prematurity [9].

METHODS

Pre-term infants (23–30 weeks' gestation) who required endotracheal intubation for respiratory distress were enrolled on the first day of life. Their initial tracheal aspirate pH values were compared with those of term infants (37–42 weeks' gestation) who had no evidence of lung disease, sepsis or other infection, thoracic wall abnormalities, or chromosomal abnormalities, who were not asphyxiated, whose serum pH was in the normal range and who either required endotracheal intubation on the first day of life for nonpulmonary surgery, or had been intubated for prostaglandin- or neurologically induced apnoea. Tracheal aspirates were obtained during routine, clinically indicated endotracheal suctioning without administration of normal saline or airway medications. The samples were all obtained from a mid-tracheal location by inserting a 6 French suction catheter just far enough to protrude 1–3 mm from the tip of an endotracheal tube, which had been documented by chest radiograph to be in a mid-tracheal position. Samples from pre-term infants were obtained within the first 24 h of life, and then weekly during the period of intubation. Samples were obtained ⩾4 h after surfactant

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TABLE 1 Maternal characteristics for pre-term and term infants

	Pre-term	Full-term	p-value
Subjects n	35	8	
Maternal age yrs	26.7±6.2	24.6±5.5	NS
Male:female infant n	15:13	6:2	NS
Gestational age weeks	25.7±1.8 (25; 24–27)	38.9±1.2 (39; 38–40)	<0.001
Birthweight g	787±170 (782; 651–860)	3191±438 (3270; 2827–3450)	<0.001
Pre-natal corticosteroids	2 (1–2)	0	NA
Surfactant doses	1 (1–2)	0	NA
Chorioamnionitis n	11	0	NS

Data are presented as mean±SD, mean±SD (median; interquartile range) and median (interquartile range), unless otherwise indicated. NS: not significant; NA: not available.

administration. Samples were immediately placed in a refrigerator at 4°C, then stored in a freezer at -80°C, and assayed immediately after thawing. pH was measured using a Cardy twin pH meter (Horiba, Kyoto, Japan). The present study was approved by the University of Virginia Human Investigation Committee (Charlottesville, VA, USA).

The Mann–Whitney rank-sum test (for nonparametrically distributed data) and the unpaired t-test (for parametrically distributed data) were used to compare groups, with $p<0.05$ considered to be significant.

RESULTS

Thirty-five pre-term infants and eight term infants had tracheal aspirate samples collected on the first day of life. There were no age differences in maternal characteristics between the pre-term and term infants (table 1). Subsequent tracheal aspirates for pH measurement were available from 31 pre-term infants. Not all of these were available at every time point because of intubation status and clinical indications for suctioning.

The mean tracheal aspirate pH of the pre-term infants (8.31±0.35) was significantly higher than that of the full-term infants (7.83±0.39, p=0.001; fig. 1). Neither therapeutic interventions nor arterial pH would have favoured a more alkaline pre-term airway: 1) all pre-term infants received at least one dose of surfactant (pH 5.5; infants received a median dose of one); and 2) the arterial pH of the pre-term infants was 7.346±0.071, while that of the term infants was 7.415±0.043 (nonsignificant).

Though 30% of the pre-term infants, and none of the term infants, were born after the development of chorioamnionitis, the tracheal aspirate pH of the infants born after chorioamnionitis was not significantly different from that of the other pre-term infants (8.28±0.40 *versus* 8.32±0.31; nonsignificant).

Term infants had been intubated for anaesthesia or for prostaglandin- or neurologically induced apnoea. While it is possible that the causes of apnoea in term infants could also have lowered airway pH, no infants with hypoxic–ischaemic encephalopathy, pneumonia or airway/systemic acidosis were included. Data on maternal asthma, allergy or tobacco use were not available for analysis.

Tracheal aspirate pH fell over time among pre-term infants who required mechanical ventilation for >3 days, with a mean maximal change in pH of -1.37±0.96 (to 6.89±0.77; fig. 1).

DISCUSSION

The tracheal aspirate pH of human neonates has not previously been studied. In the present study, it is reported that pH values for term infants are comparable with those previously reported for adults (~7.8) [4], while those of pre-term infants are significantly higher. This alkalinity of the proximal pre-term airway may reflect immature lung development and the paucity of type-II alveolar cells, resulting in decreased acid secretion by lamellar bodies into the distal airway [6]; distal airway lining fluid moves proximally up the mucociliary escalator. Excessive base production is also possible. The difference is not likely to have resulted from surfactant therapy; the pH of the exogenous surfactant was

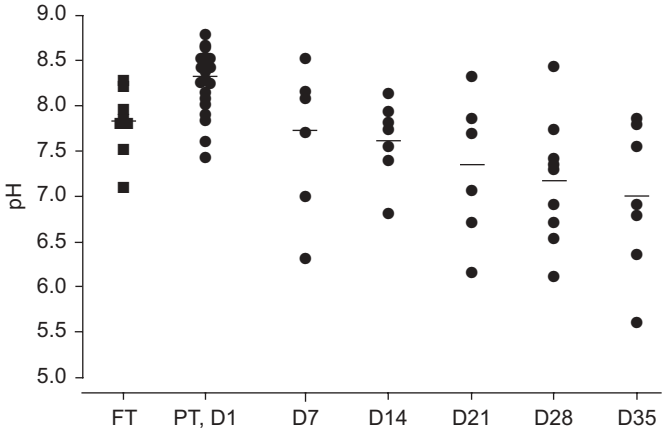

FIGURE 1. Tracheal pH is high in pre-term infants on the first day of life, then decreases. Term infants without lung disease on the first day of life (FT; ■; n=8) were compared with pre-term infants (PT; ●; n=35) endotracheally intubated for respiratory distress on the first day of life (PT, D1). The graph also shows the sequence of pH changes among pre-term infants who required prolonged intubation on subsequent days (day (D)7, n=7; D14, n=8; D21, n=6; D28, n=9; D35, n=7).

~5.5. Similarly, the difference was unlikely to have resulted from differences in arterial pH, as both groups were ventilated and maintained at similar arterial pH. If anything, the arterial pH of the pre-term infants was slightly lower, not higher, than that of the term infants. It is of interest that lower pH in the normal alveolus/distal airway has been proposed (as in the stomach and bladder) to prevent distal airway infection [4]; this process might thus be initially impaired in the pre-term airway. Every effort was made to use uniform suction technique, though it cannot be excluded that the more distal airway was sampled in pre-term infants. Additional studies will be required to firmly establish the cause of this relative alkalinity in the proximal pre-term airway.

Airway acid stress is characteristic of several airways diseases, including asthma and cystic fibrosis [3–5, 7, 8]. Recent evidence suggests that cytokine-mediated inhibition of enzymes that regulate airway epithelial buffering may contribute to airway acidification in these conditions [4, 7, 10]. The present data demonstrate for the first time that prolonged endotracheal intubation can be associated with a fall in tracheal pH. They also suggest that airway pH homeostatic mechanisms may be abnormal or immature in the pre-term airway. Indeed, there are several pH regulatory enzymes in the airway epithelium [7, 9, 10], at least one of which, carbonic anhydrase, may be differentially expressed in the pre-term airway [9]. Taken together, these data suggest the possibility that abnormal pH regulation in the pre-term airway could contribute to the pathophysiology of neonatal lung disease.

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