

## SHORT REPORT

## Nasal potential difference increases with gestation in moderately preterm neonates on the first postnatal day

E A Gaillard, N J Shaw, H L Wallace, N V Subhedar, K W Southern

*Arch Dis Child Fetal Neonatal Ed* 2005;90:F172–F173. doi: 10.1136/adc.2004.054494

At birth the mammalian airway switches from liquid secretion to absorption, an important mechanism in lung liquid clearance. Airway ion transport was examined on the first postnatal day in 38 moderately preterm infants (29–36 weeks gestation). The absorptive airway ion transport capacity was well developed regardless of respiratory condition and there was little capacity for  $\text{Cl}^-$  secretion.

The fetal airway actively secretes  $\text{Cl}^-$  into the lung lumen.<sup>1</sup> During birth,  $\text{Na}^+$  absorption, largely mediated through the epithelial sodium channel (ENaC), becomes the predominant airway ion transport process and remains so throughout postnatal life.<sup>1</sup> This switch from a secretory to an absorptive airway epithelium plays a major role in the clearance of lung liquid in the transition to postnatal air breathing.<sup>2,3</sup>

Extreme prematurity is associated with increased lung liquid content and reduced ENaC mediated  $\text{Na}^+$  absorptive airway ion transport.<sup>4</sup> There are no airway ion transport data in moderately preterm infants.

We performed nasal potential difference (PD) measurements in 38 moderately preterm infants on the first postnatal day to characterise their airway ion transport characteristics.

The study was designed to test two hypotheses: (a) increased gestational age is associated with greater ENaC mediated  $\text{Na}^+$  transport; (b) moderately preterm infants with respiratory disease have reduced ENaC mediated  $\text{Na}^+$  absorption.

## METHODS

The study was approved by the Liverpool Health Authority Local Ethics Committee. A single investigator (EAG) performed nasal PD measurements using a perfusion protocol suitable for neonates.<sup>5</sup> We determined (a) stable maximal baseline PD, (b) the change in PD after perfusion with amiloride ( $10^{-4}$  M), an ENaC inhibitor ( $\Delta\text{amil}$ ), and (c) the change in PD after perfusion with a zero  $\text{Cl}^-$  solution containing amiloride ( $\Delta\text{zeroCl}^-$ ).

## Statistical analysis

A multiple stepwise regression model was constructed and tested for normal distribution, homoscedasticity, linearity, and independence of error terms to examine the relation between the primary outcome measure (stable maximal baseline PD) and predictor variables (gestation, birth weight, sex, requirement for mechanical ventilation at time of study, oxygen requirement at time of study, presence or absence of antenatal steroids, vaginal or caesarean section delivery). In addition, relations between these variables and the secondary outcomes ( $\Delta\text{amil}$  and  $\Delta\text{zeroCl}^-$ ) were examined. Analysis was performed using SPSS 10.0 (SPSS Inc, Chicago, Illinois,

USA). For comparisons between groups, the Mann-Whitney U test was used.

## RESULTS

Thirty eight infants (25 male) between 29 and 36 weeks gestation were recruited (median birth weight 1873 g (range 615–3095)). A valid regression model showed a higher magnitude of PD with increasing maturity. Birth weight was also associated with stable maximal baseline PD but less strongly than gestational age. This variable was therefore removed from the regression model. In addition, high stable maximal baseline PD was associated with male sex, mechanical ventilation at the time of study, and caesarean delivery (table 1; adjusted  $r^2 = 0.45$ , SE of the estimate 9.81) but not with antenatal steroids and requirement for supplemental oxygen. Overall median stable maximal baseline PD was  $-32.5$  mV (range  $-14$  to  $-69$ ). After perfusion with amiloride, the PD fell by a median of 80% (range 43–100). There was no relation between any of the nasal PD variables and the time that the measurement was made (median age 14.5 hours (range 2–24)).

In a second regression model (adjusted  $r^2 = 0.38$ ; SE of the estimate 10.22), the secondary outcome measure,  $\Delta\text{amil}$ , was significantly greater in male infants ( $\beta = -0.44$ ;  $p < 0.005$ ), and in those who were mechanically ventilated ( $\beta = 0.43$ ;  $p < 0.01$ ), but was not associated with gestation ( $\beta = 0.31$ ;  $p = 0.06$ ).

The median capacity for  $\text{Cl}^-$  secretion ( $\Delta\text{zeroCl}^-$ ) on the first postnatal day was  $-5$  mV (range 6 to  $-29$  ( $n = 36$ )). There was no association between stable maximal baseline PD and  $\Delta\text{zeroCl}^-$ . None of the predictor variables (gestational age, sex, mechanical ventilation at time of study, mode of delivery) were related to  $\Delta\text{zeroCl}^-$ .

## DISCUSSION

Under normal circumstances a large proportion of the airway liquid is cleared at birth with a steady decline thereafter over several days.<sup>1</sup> Extremely preterm infants, especially those with respiratory distress, have reduced lung liquid absorptive capacity<sup>4</sup> and increased lung liquid content.<sup>6</sup> This is the first report of airway ion transport processes in moderately preterm infants, and our findings are consistent with a previous study showing a relation between absorptive airway ion transport and gestation.<sup>4</sup> Our moderately preterm infants, especially those born at 34–36 weeks gestation, had higher PDs than well term infants recently reported by our group (fig 1).<sup>5</sup> Whether this represents a compensatory mechanism to clear increased lung liquid content warrants clarification. Our data are also consistent with reports of increasing ENaC expression and distribution in the developing lung.<sup>7</sup>

Although these data are generated by measurements in the proximal airway, these results probably represent distal ion

**Abbreviations:** ENaC, epithelial sodium channel; PD, potential difference

**Table 1** Predictor variables affecting maximal stable baseline potential difference

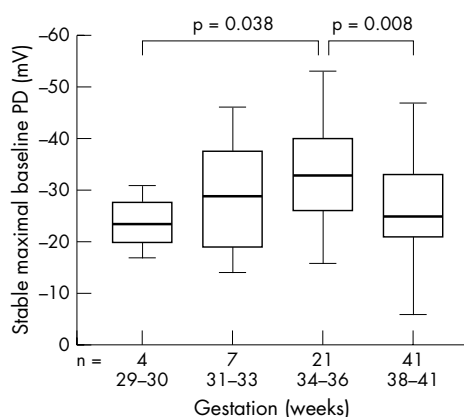
| Variable                                | Regression coefficient (95% CI) (SE) | Standardised regression coefficient (s) | p Value |
|---|--------------------------------------|---|---------|
| Mechanical ventilation at time of study | -16.5 (-26.3 to -6.8) (4.8)          | -0.46                                   | 0.002   |
| Gestation (weeks)                       | -2.0 (-3.9 to -0.1) (0.9)            | -0.32                                   | 0.038   |
| Male sex                                | 10.6 (3.5 to 17.6) (3.5)             | 0.38                                    | 0.004   |
| Caesarean delivery                      | 5.4 (1.1 to 9.7) (2.1)               | 0.35                                    | 0.015   |

transport processes. That these infants have a well developed absorptive airway ion transport capacity is supported by the sizeable response to amiloride (median, 80% reduction in PD). Barker *et al*<sup>5</sup> reported smaller responses but used a less concentrated amiloride solution ( $10^{-5}$  M).

The median capacity for  $\text{Cl}^-$  secretion in our cohort was -5 mV. Taken together these results suggest that, in moderately preterm infants, the airway is predominantly absorptive with little capacity for  $\text{Cl}^-$  secretion on the first postnatal day.

Our second hypothesis, that infants with neonatal respiratory disease have reduced absorptive airway ion transport capacity, was not supported by the high PDs found in mechanically ventilated infants. None of these infants had severe lung disease and all were breathing room air spontaneously on the third postnatal day. Gowen *et al*<sup>8</sup> reported high PDs in term infants with transient tachypnoea of the newborn on the first postnatal day compared with a healthy control group. After three days, PD in these infants had returned to levels seen in well term infants in the first 24 hours after birth. Although counter intuitive, these findings may represent a compensatory mechanism for increased lung liquid in those infants on the first postnatal day.

Our results suggest a difference in airway ion transport between male and female infants. It is difficult to explain how the higher PDs in male infants relates to reported differences in respiratory outcome.



**Figure 1** Stable maximal baseline potential difference (PD) for infants not mechanically ventilated ( $n = 32$ ) at the time of nasal PD measurement stratified for gestational age groups. Box and whisker plot, where the box represents the median and interquartile range and the whiskers represent the range. Infants born at 34–36 weeks gestation had significantly greater stable maximal baseline PD on the first postnatal day than infants born at 29–30 weeks gestation (Mann-Whitney) and term infants previously reported by our group.<sup>5</sup>

The residual PD after perfusion with amiloride was higher in preterm than term infants,<sup>5</sup> as was the increase in PD after perfusion with a zero  $\text{Cl}^-$  solution. These differences were small and do not suggest that increased capacity for  $\text{Cl}^-$  secretion in preterm infants is clinically significant, but further studies are needed to clarify this finding.

In summary, this is the first study to report a significant relation between ENaC mediated  $\text{Na}^+$  absorption and gestation in moderately preterm infants. Our data suggest these infants have well developed absorptive airway ion transport capacity on the first postnatal day.

## ACKNOWLEDGEMENTS

We thank the families who supported this project. We are indebted to Dr Pierre Barker, University of North Carolina at Chapel Hill, for his continuing help and advice and to Dr Gill Lancaster for statistical advice. We would also like to thank the staff on the neonatal intensive care unit and the midwives at Liverpool Women's Hospital for their support.

## Authors' affiliations

**E A Gaillard, N J Shaw, N V Subhedar**, Liverpool Women's Hospital, Neonatal Unit, Crown Street, Liverpool L8 7SS, UK

**H L Wallace, K W Southern**, Institute of Child Health, University of Liverpool, Royal Liverpool Children's Hospital, Alder Hey, Liverpool L12 2AP, UK

Funding: EAG was supported by the Liverpool Women's Hospital 'Newborn Appeal'. HLW was supported by the Medical Research Council, UK.

Competing interests: none declared

Correspondence to: Dr Gaillard, Respiratory Unit, Royal Liverpool Children's Hospital, Eaton Road, Liverpool L12 2AP; gaillard@liv.ac.uk

Accepted 2 September 2004

## REFERENCES

- Strang LB. Fetal lung liquid: secretion and reabsorption. *Physiol Rev* 1991;**71**:991–1016.
- Hummeler E, Barker P, Gatzky J, *et al*. Early death due to defective neonatal lung liquid clearance in alpha-ENaC-deficient mice. *Nat Genet* 1996;**12**:325–8.
- O'Brodovich H, Hannam V, Seear M, *et al*. Amiloride impairs lung water clearance in newborn guinea pigs. *J Appl Physiol* 1990;**68**:1758–62.
- Barker PM, Gowen CW, Lawson EE, *et al*. Decreased sodium ion absorption across nasal epithelium of very premature infants with respiratory distress syndrome. *J Pediatr* 1997;**130**:373–7.
- Gaillard EA, Shaw NJ, Wallace HL, *et al*. Airway ion transport on the first postnatal day in infants delivered vaginally or by elective cesarean section. *Pediatr Res* 2003;**54**:58–63.
- DeSa DJ. Pulmonary fluid content in infants with respiratory distress. *J Pathol* 1969;**97**:469–78.
- Smith DE, Otulakowski G, Yeger H, *et al*. Epithelial  $\text{Na}^+$  channel (ENaC) expression in the developing normal and abnormal human perinatal lung. *Am J Respir Crit Care Med* 2000;**161**:1322–31.
- Gowen CW, Lawson EE, Gingras J, *et al*. Electrical potential difference and ion transport across nasal epithelium of term neonates: correlation with mode of delivery, transient tachypnea of the newborn, and respiratory rate. *J Pediatr* 1988;**113**:121–7.



## Nasal potential difference increases with gestation in moderately preterm neonates on the first postnatal day

E A Gaillard, N J Shaw, H L Wallace, et al.

*Arch Dis Child Fetal Neonatal Ed* 2005 90: F172-F173  
doi: 10.1136/adc.2004.054494

---

Updated information and services can be found at:  
<http://fn.bmj.com/content/90/2/F172.full.html>

---

*These include:*

### References

This article cites 8 articles, 3 of which can be accessed free at:  
<http://fn.bmj.com/content/90/2/F172.full.html#ref-list-1>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Topic Collections

Articles on similar topics can be found in the following collections

[Child health](#) (992 articles)  
[Infant health](#) (591 articles)  
[Neonatal health](#) (636 articles)

---

### Notes

---

To request permissions go to:  
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:  
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:  
<http://group.bmj.com/subscribe/>