LETTER

Does tidal exhaled nitric oxide reflect mucosal airway inflammation in infants?

Exhaled nitric oxide (FE_{NO}) has been proposed as a surrogate of airway inflammation in asthma. The measurement of FE_{NO} may be important to distinguish conditions characterised by eosinophilic inflammation from those which are non-eosinophilic, the former being more likely to respond to steroid treatment. Studies in adults and school-aged children have shown that FE_{NO} levels correlate to some extent with airway mucosal eosinophilia quantified in endobronchial biopsies.[1 2] However, no such studies exist in infants. In this observational study, we assessed whether infants with recurrent respiratory symptoms, in whom bronchoscopy had been undertaken for clinical evaluation, showed evidence of a relationship between mucosal airway inflammation quantified in endobronchial biopsies and levels of FE_{NO} measured during tidal breathing.

The study consisted of 36 infants, aged between 3.4 and 25.9 months, referred for clinical evaluation of recurrent lower respiratory tract symptoms (wheeze, cough and dyspnoea), and who underwent both FE_{NO} measurement and bronchoscopy with an endobronchial biopsy specimen suitable for assessment of inflammatory cells. None had received corticosteroids within 8 weeks of the assessment. The study was approved by the local ethics committee, and written informed consent was obtained from parents. Details of patient characteristics, methods, statistical analyses and results are available as supplementary material online.

During tidal breathing, infants inspired room air with ambient NO <10 ppb, exhaled air was collected with a face mask placed over the infants' mouth and nose, and the fraction of NO was analysed offline with a chemiluminescence analyser ($FE_{NO,TB}$). Using transmission electron microscopy, the numbers of subepithelial eosinophils, neutrophils, mast cells, plasma cells, and lymphomononuclear cells, identified by their ultrastructure, were determined in ultrathin sections obtained from the endobronchial biopsies.[3] As there are no reference data in normal healthy infants, we used an arbitrary classification based on the median count of each cell line (<50th percentile=low; ≥50th percentile=high). Non-parametric tests were used to compare $FE_{NO,TB}$ and biopsy data.

The median $FE_{NO,TB}$ was 15.7 ppb (range 3.0–68.7 ppb). Eosinophils were infrequent and accounted for an average of 0.2% of the total inflammatory cells, without any significant association with $FE_{NO,TB}$. However, in the subgroup of atopic infants (n=15), median $FE_{NO,TB}$ was slightly higher in those with eosinophils in the biopsy (26.7 ppb) than in those without (14.7 ppb, p=0.08). Infants with high counts of neutrophils or plasma cells had significantly lower levels of $FE_{NO,TB}$ (figure 1).

This is the first biopsy study in infants that explores the relationship between $FE_{NO,TB}$ and inflammatory cell phenotypes. We acknowledge the limitation that the sample size of infants in whom endobronchial biopsy was undertaken is small, but ethical considerations render bronchoscopic studies difficult to perform at this age. Techniques to measure FE_{NO} in infants also differ from those used in older children and adults. Sampling of exhaled air during normal tidal breathing with offline measurement of NO is the most practical method, but $FE_{NO,TB}$ may be confounded by variations of tidal flow and ambient as well as upper airway NO.

We conclude that in infants with recurrent respiratory symptoms, measures of $FE_{NO,TB}$ do show associations with components of bronchial mucosal inflammation. However, the paucity of eosinophils in our infant biopsies makes it difficult to ascertain whether there is a relationship between $FE_{NO,TB}$ and mucosal eosinophilia in this age group, as seen in older children and adults with asthma. Only the results in atopic infants favoured an association between FE_{NO} and eosinophils. Thus, although it seems unlikely that $FE_{NO,TB}$ would be a useful predictor of corticosteroid responsiveness in unselected infants with severe recurrent respiratory symptoms, its usefulness in selected infants with recurrent wheeze remains to be studied further.

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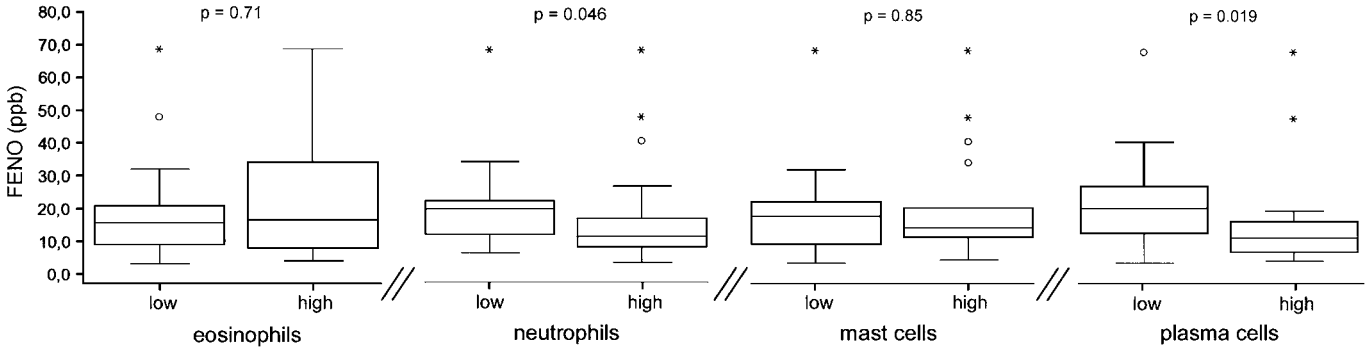

Figure 1 Distribution of exhaled NO levels by the endobronchial cell counts of eosinophils, neutrophils, mast cells and plasma cells. Low=count <50th percentile; high=count ≥50th percentile.