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## Exhaled Nitric Oxide Still Alive, Not Laid to Rest

The interrelationships between the fraction of nitric oxide in exhaled air ( $F_{ENO}$ ), eosinophilic airway inflammation and steroid responsiveness, together with the ease with which  $F_{ENO}$  may be measured, have prompted a series of randomized trials designed to confirm that using  $F_{ENO}$  to optimize inhaled corticosteroid (ICS) therapy will improve asthma outcomes (1–3). The latest are reported in this issue of the *Journal* (pages 93–97) (4) and also recently in *The Lancet* (5). Overall, we must accept that, notwithstanding any weaknesses of the various  $F_{ENO}$ -based treatment algorithms, the routine use of  $F_{ENO}$  in this setting does not fulfill earlier expectations. This is disappointing given the enthusiasm generated by proof of concept studies in which induced sputum eosinophilia, for which  $F_{ENO}$  is used as a surrogate marker, was successfully used to guide asthma treatment (6).

It is important to highlight features in these studies that may have resulted in the “negative” outcome for  $F_{ENO}$ . First, there was little left to achieve. In the study by de Jongste and colleagues (4), 151 children with mild/moderate asthma were randomized to have their ICS dose adjusted on the basis of regular home monitoring of  $F_{ENO}$  or symptom scores. Over half of the improvement in symptoms was achieved during the first 6 weeks in both management groups and before significant ICS dose adjustments had occurred. The authors attributed this to frequent monitoring and telephone contacts. Similarly, in the study by Szeffler and colleagues (5), in 546 adolescents, almost all of the improvements in symptoms were dramatically accomplished during the run-in.

These outcomes are welcome; they indicate that using a biomarker, which may not always be available, cannot achieve more than intensive patient support but not that the biomarker has no role.

The studies confirm that using *high*  $F_{ENO}$  levels to prompt an increase in ICS dose and improve asthma outcomes was ineffective. This reflects the lack of specificity for high  $F_{ENO}$  levels: they do not always result from increased airway inflammation (7) even though, in steroid-naïve patients with uncontrolled symptoms, they are predictive of steroid responsiveness (8, 9). However, in both studies (4, 5), the combination of a high symptom score and *low*  $F_{ENO}$  resulted in “no change” in ICS dose: symptoms invariably trumped  $F_{ENO}$  levels. This design weakness means that no meaningful judgment regarding the utility of a low  $F_{ENO}$  can be made from these data. The cup is half empty. The predictive value of a low  $F_{ENO}$  for the absence of eosinophilic airway inflammation has been shown to be high (1), permitting steroid unresponsive symptoms to be differentiated from those which are steroid responsive. This is critically important in the management of individual patients. Further, repeatedly low  $F_{ENO}$  levels have been shown to predict the absence of long-term steroid requirement in children (10), and in adults consistently low values predict a low risk of deterioration in asthma control (9).

In these studies, the majority of participants were children, not adults, and all-comers were enrolled; for these reasons, con-

founding comorbidities were unlikely to be frequent. This reduces the power of these clinical trials to identify the utility of a biomarker where it matters most: in complex asthma. Cluster analysis has shown that in patients whose symptoms and inflammation are discordant rather than concordant, an objective biomarker of inflammation is more likely to be useful (11). In fact, Szeffler and colleagues confirmed that in a subgroup of obese patients (in whom symptoms and airway inflammation are often discordant), the outcomes were improved by using  $F_{ENO}$  (5). There are other patients for whom adjusting the ICS dose may be problematic because of comorbidities (and discordance); examples would be anxiety-overlap, vocal cord dysfunction, rhinosinusitis, or gastro-esophageal reflux. No substantial studies investigating the targeted use of  $F_{ENO}$  have been conducted: they are now required.

Do these studies spell the end for  $F_{ENO}$ ? The answer is no, but not just for the reasons highlighted above. Our lessons ought to be learned from the cardiologists. The use of pro-BNP (brain natriuretic peptide) as a biomarker in cardiac disease is based on its proven diagnostic and prognostic utility. Its value is found in the context of diagnostic uncertainty in the dyspnoeic patient, when low levels provide particularly useful information. Data supporting pro-BNP as a guide to heart failure therapy are much less substantial (12). The same applies to  $F_{ENO}$ . It is understandable, but perhaps unfortunate, that the most rigorous studies to date have focused narrowly on how  $F_{ENO}$  might be used to improve asthma outcomes in relation to ICS treatment. A broader view is required. As in heart failure, the pathophysiology of airway disease is heterogeneous, with many overlap syndromes giving rise to nonspecific symptoms which are only weakly correlated with abnormal lung function.  $F_{ENO}$  measurements shed complementary light on the underlying inflammatory phenotype and, more importantly, on the potential response to antiinflammatory treatment (which is a different question than “How much is required?”) (8). Historically, this has been assessed either by empiric “trials of steroid” or, even more imperfectly, with reference to before/after changes in spirometry (13). Serial or repeated  $F_{ENO}$  measurements in individual patients may provide additional diagnostic as well as prognostic insights (9, 14).

That “asthma is a chronic inflammatory disorder” has been shouted from the rooftops for over 20 years, and the case for assessing airway inflammation in clinical practice has been strongly made (15). Practical issues have impeded the wider use of induced-sputum and exhaled-breath condensate techniques. The standard of proof to support the adoption of  $F_{ENO}$ , which is more accessible, ought to be rigorous but not narrowly focused; otherwise spirometry and diffusing capacity measurements would never have made it! A working party of the American Thoracic Society is currently drawing up guidelines for the clinical use of  $F_{ENO}$  measurements, and we await their statement with interest.

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## Extracellular Superoxide Dismutase Haplotypes and Acute Lung Injury

### Reading into the Genome to Understand Mortality?

Acute lung injury (ALI) and its most severe form, the acute respiratory distress syndrome, are among the most challenging

disease processes that we face in the intensive care unit. The mortality for ALI remains unacceptably high, outstripping the