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Lung function test results in normal infants: A COPSAC sequel

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A report by Bisgaard and coworkers in this issue shows that high body mass index and maternal smoking worsen infant lung function¹. This is a descriptive sequel to a study regarding the effect of neonatal bacterial colonization on subsequent asthma: specifically, the Copenhagen Prospective Study of Asthma in Childhood (COPSAC)² of healthy children born to mothers with current or past asthma. Oddly, this month's sequel has nothing to do with asthma or clinical immunology, except to argue that maternal atopy is NOT a determinant of early childhood lung function or airway reactivity.

The lung function measurement techniques were interesting and informative. However, they were somewhat unusual, even in the rather esoteric world of infant lung function testing. Degree of obstruction was quantified as FEV_{0.5}. After the infant was sedated with chloral hydrate, a well-sealed mask was used to expose the airway to a specific pressure. After a brief pause, the airway was exposed again to the same pressure; and then again a third time. The Hering-Breuer inflation reflex permitted a pause. Then, at the end of the third inspiration, a bladder in a plastic jacket wrapped around the child's chest was rapidly inflated to a fixed pressure, and airway (mask) flow 0.5 seconds after this forced expiration was measured. This procedure was repeated five times. Unlike $\dot{V}_{\max}$ at FRC,^{3,4,5} this technique did not require an FRC measurement and did not require confirmation that flow limitation was achieved based on flow-volume loops: the median value was reported, with no questions asked. Though counterintuitive from the point of view of physiology, the authors report that this technique has been reproducible in their hands^{1,6} and that it might measure flows that are unaffected by variations in chest wall compliance.

The testing for airway reactivity was also a bit unusual. The method described above (FEV_{0.5}) was repeated three times each after sequentially increasing doses of methacholine. The test was stopped at a fixed maximum dose of methacholine, or after there was a 20% fall in FEV_{0.5}. Curiously, however, the dose required for a specific fall in FEV_{0.5} was not the outcome of interest: rather, it was the dose required to cause a 15% drop in the transcutaneously measured oxygen tension (PtcO₂). Of note (Figure 2E in the on-line repository), simple linear regression of the methacholine dose - as is commonly performed in spirometry-based methacholine testing - underestimated the PD₁₅ for PtcO₂ when compared with more elegant, non-linear modeling. This suggests that simple, linear analysis may lead to overestimation of

methacholine reactivity. However, it must be born in mind that capillary pO_2 is in non-linear equilibrium with oxyhemoglobin saturation; and that transcutaneous diffusion of oxygen may not be linear, depending on ambient temperature and other factors. Thus, we do not know if the nonlinearity of $PtcO_2$ response to methacholine would reflect nonlinearity of an airflow obstruction response.

This was a difficult and expensive study to do, and the authors deserve credit. It is the largest study yet of the determinants of lung function in normal infants, and it will be of lasting interest to pediatric pulmonologists. It reports some important findings. First, it shows that infants in the upper quartile for body mass index (BMI) have lower $FEV_{0.5}$ values at 4–6 weeks of age than lighter and longer infants: that is, that increased weight is associated with flow limitation in shorter infants. Further, it confirms that infants born to smoking mothers have lower lung function. It is also of interest that airway reactivity increased significantly with age, though – as the authors note – this will need to be confirmed longitudinally, if possible.

That said, there are a number of things to dislike about this paper. First, the longitudinal outcome of these children is actually known: indeed, long-term follow-up for this cohort has been reported in the context of the late implications of their neonatal upper airway bacterial colonization.² Thus, most of the important questions raised in this paper have probably already been answered, but simply were not reported by the authors. For example: did low $FEV_{0.5}$ or increased airway reactivity predict obstruction, airway reactivity, allergy or asthma symptoms at five years old? Do these data fit with longitudinal studies like those of Martinez⁷ or Sears⁸? Did maternal atopy predict any of these variables at five years old? It is disturbing to have presented in different papers here and there and not analyzed as a whole.

Second, maternal atopy was ascertained only by history: we do not have skin test or IgE data on the mothers. It remains unclear whether objective allergy truly fails to affect neonatal lung function.

Third, though the statisticians on the paper are first rate, the statistical methods are admittedly a bit counterintuitive and derivative. This can have the effect of making the ordinary reader concerned about the real biological relevance of the conclusions. By analogy, it is rather like we are being asked to buy financial derivatives that are difficult to trace back to determine the actual value.

Fourth, there are no control groups of children born to mothers with atopy alone, or to mothers with neither asthma nor atopy.

Perhaps the observation of greatest interest was that infants exposed (by history) to maternal acetaminophen tended to have more airway reactivity. Though this association was driven largely by outliers and will need to be confirmed, it could be consistent with patchy but emerging evidence that the asthma epidemic may be driven by acetaminophen use.^{9,10} The mechanism may involve acidic acetaminophen nitration in the stomach - and/or in the airway, in the context of airway acidification occurring during the infection for which the acetaminophen is being used.^{11,12,13} It would be of interest to know if nitroacetaminophen crosses the placenta, and if the highly reactive subset of infants exposed prenatally to acetaminophen were those who went on to develop allergic asthma. Again, one wishes that all the data had been analyzed and shown. Presumably, the ending is meant to make us anxious to see the next sequel, "Son of COPSAC II."

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