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Need for Healthy Control Subjects when Assessing Lung Function in Infants with Respiratory Disease

Awareness of the relevance of early life events to lung health in adults, and the need to identify and treat lung disease before changes become irreversible in children with chronic respiratory conditions such as cystic fibrosis (CF), has led to a resurgence of interest in infant respiratory physiology. Following recommendations from the ATS/ERS Task Force on infant pulmonary function testing (IPFT) (1), commercially available equipment has been developed. While potentially facilitating the use of IPFTs as outcome measures in studies such as that described in the current issue of the *Journal* (2) (pp. 1387–1397), this increased availability presents challenges as to how and when such tests should be used.

The study by Davis and coworkers addresses several significant issues relating to the future use of IPFT as objective outcome measures in multicenter clinical trials of young children with CF, including feasibility, repeatability and required sample size (2). One hundred infants with CF, recruited from 10 centers across the United States, were studied on up to four occasions, with repeated measures after 1 month in a subset. Significant decrements in pulmonary function were observed in infants with CF when compared with historical control subjects. Changes were most marked for plethysmographic lung volumes, whereas, in contrast to previous reports (3, 4), forced expiratory flow-volume (FEFV) outcomes from the Raised Volume Technique discriminated poorly. Based on acceptability rates, variability, and the potentially large sample sizes required to detect reasonable treatment effects, the authors concluded that IPFT do not yet appear ready to be used as primary efficacy endpoints for multicenter clinical trials, particularly at inexperienced sites.

This was a large and important study that was generally well conceived and executed by a group of leaders in CF care and IPFT. The authors are to be congratulated on the rigorous training and quality control applied across centers. However, interpretation of their findings is hampered by one major flaw in the study design: the lack of a prospective control group. The inability to recruit control subjects was attributed to failure by the relevant Institutional Research Boards (IRB) to give permission to sedate healthy infants, on the grounds that sedation represents "more than minimal risk and that the research would be of no benefit to a healthy child."

Opinion on the ethics of children participating in clinical research continues to evolve (5–11). The former view that only research that is of therapeutic benefit to the infant is acceptable has been replaced by an acknowledgment of the importance of noninterventional studies and the benefits they bring to infant health and well being, a position that shifts the debate to considerations around "benefit" and "harm," and the quantification of "negligible" and "minimal" risk. Clinical trials are held to be the gold-standard approach to defining the therapeutic evidence base, yet in a randomized trial, where the aim is to demonstrate one treatment to be superior to another, one randomized group will *de facto* receive less or even no therapeutic benefit.

Should healthy children be sedated for research reasons? The minimal risk of occasional oral sedation in healthy infants in the doses administered for IPFT is evidenced by the thousands of healthy babies that have participated in such studies without adverse effect, apart from occasional emesis or short-lived disturbance of sleep (12). Indeed, during the past 5 years, at least 36 publications from three continents, including two centers in the USA, have reported IPFT results from healthy sedated infants.

The risk of adverse effects from sedation rises in those born preterm (13) or with respiratory problems, in whom special precautions have always been advocated (14). Before infants with respiratory disease are recruited into clinical research studies, it is imperative that the study design is sound, conclusions will be robust, and the benefits, whether on a population or individual basis, will be tangible. Unfortunately, this has not always been the case where IPFTs are

involved. Lack of prospective control subjects or appropriate reference data with which to distinguish the effects of growth and development from those of disease (15) have limited interpretation of at least 50% of studies published in this field over the past 5 years. Poor study design, inappropriate methods, equipment and quality control, insufficient sample size and lack of knowledge about within-subject repeatability, within- and between-tests (without which it is impossible to interpret the effects of any intervention), have also limited the usefulness of many studies.

When faced with the decision of the IRB, Davis and colleagues may have decided that they could rely on the reference equations they selected (16, 17), since they had personally been instrumental in developing these. However, the equations used to interpret plethysmographic lung volumes were only based on 22 children studied on 35 occasions, whereas at least 300 subjects may be required to avoid bias and estimate between-subject variability reliably (18). Reference equations for FEFV parameters were based on a much bigger sample size (17), but, as for plethysmography, were derived from children studied using equipment developed "in-house" rather than the commercially available device used in the actual study. Using a different commercial device can lead to serious misinterpretations (19).

By providing an honest and critical appraisal of the limitations of their study, Davis and coworkers have made an important contribution to the field of IPFT. Their data will hopefully help fuel discussions as to how best to address these issues. It is reassuring that the Canadian Healthy Infant Longitudinal Development Study will undertake serial PFTs using the same device in around 750 normal infants over the next few years, though difficult to understand why such a study is considered ethical in Canada, but not across the border. Once available, these normative data may facilitate more meaningful interpretation of the current multicenter study, but will not be able to address issues of inter-center differences, nor substitute for the current need to study healthy infants in all centers that intend undertaking IPFT for research or clinical purposes. As demonstrated in this study by Davis and colleagues, the complexities and subtleties of IPFT are such that, even with thorough training and ongoing supervision, equipment cannot simply be placed in inexperienced laboratories with the expectation that reliable results will be forthcoming.

Anyone who has recruited to infant studies knows that considerable time is required to explain the study. Nevertheless, in our experience, parents that consent generally find the experience interesting and rewarding and frequently return to participate in longitudinal studies that stretch well beyond infancy (19, 20). The wealth of knowledge that now exists regarding the early determinants of lung function, origins of adult lung disease, and impact of CF, prematurity, and wheezing disorders on the developing lung would not have been possible without studies in healthy infants. Unless such studies continue, both the research and clinical utility of IPFT will be severely curtailed. We suggest that IRBs ask the following questions when considering the sedation of healthy infants for IPFT research. Have alternative approaches been considered? Is the study design sound? Will the study improve clinical care? Are the investigators competent? Are the facilities suitable for infants? Have parents been fully informed? If the answers are all in the affirmative, surely the opportunity to improve the care of infants with lung disease should be welcomed?

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Will the Genes Responsible for Familial Pulmonary Fibrosis Provide Clues to the Pathogenesis of IPF?

In this issue of the *Journal*, van Moorsel and colleagues (pp. 1419–1425) report findings of surfactant protein C (*SFTPC*) mutations in a cohort of patients with idiopathic interstitial pneumonia (IIP) from The Netherlands (1). While *SFTPC* mutations have previously been reported in association with familial forms of interstitial lung disease (ILD), this manuscript has two prominent findings important to the pulmonary community. First, approximately 10% of individuals within their adult IIP cohort had a family history of ILD, illustrating that familial disease represents a significant contribution overall. Second, they found that 25% of their adult patients with familial pulmonary fibrosis (FPF) had mutations in *SFTPC*, a rate far higher for a single gene than any other cohort reported to date.

FPF, or familial interstitial pneumonia (FIP), is identified when two or more members of a family have an IIP (2, 3). Previous reports from Marshall and colleagues in the United Kingdom (4) and Hodgson and colleagues in Finland (5) suggested that 0.05–2.2% and 3.3–3.7% of their idiopathic pulmonary fibrosis (IPF) cases, respectively, had a familial basis. In contrast, our experience revealed that approximately 19% (9/47) of individuals who received lung transplant for IPF by 2003 had a family history of ILD (2). Here, van Moorsel and colleagues found that approximately 10% of their IIP cohort had FPF. Where the exact percentage for overall cases of IIP lies is not yet known, but it probably depends not only on patient characteristics, but characteristics of the evaluating clinic as well. Nevertheless, this study highlights the importance of a detailed family history when evaluating an individual with ILD. Routinely educating every patient with IIP about a possible genetic basis may boost their awareness to detect other family cases.

Over the past several years, there has been hope that identifying genetic links to FPF will lead to improved understanding of the pathogenesis of IPF to suggest future therapeutic targets. To date, genetic mutations in four well-described genes have been reported: *SFTPC* (6, 7), surfactant protein A2 (*SFTPA2*) (8), telomerase reverse transcriptase (*TERT*), and telomerase RNA component (*TERC*) (9, 10). A fifth gene, *ELMOD2*, has been associated with FPF by linkage in a Finnish cohort (11), but the role of this gene remains largely undefined.

SFTPC mutations have been linked to both pediatric and adult forms of FPF in multiple reports (6, 7). Of these mutations, those in the carboxy-terminal region are the best characterized. With these mutations, pro–surfactant protein C cannot be folded normally in the endoplasmic reticulum (ER) of the type II alveolar epithelial cell (AEC), leading to ER stress and activation of the unfolded protein response (UPR) (12). ER stress can lead to increased AEC apoptosis (12), which may be one mechanism by which carboxy-terminal *SFTPC* mutations lead to lung fibrosis. Interestingly, ER stress and UPR activation have been noted in lung tissue from individuals with non-*SFTPC* mutation pulmonary fibrosis (both familial and sporadic) (13, 14), suggesting that these pathways may be important in IPF pathogenesis and that *SFTPC* mutation–associated FPF may serve as a paradigm for understanding sporadic IPF. In contrast, the I73T mutation (isoleucine to threonine substitution), and likely other mutations in this region, does not appear to induce ER stress (12), but does result in altered intracellular trafficking with localization to an endosomal compartment (15), likely leading to type II AEC dysfunction. In their study, van Moorsel and colleagues noted two previously unreported *SFTPC* mutations, while the I73T mutation, the most commonly reported *SFTPC* mutation, was observed in three families (1). Their observation that approximately 25% of their FPF cohort had disease explained by *SFTPC* mutations is a far greater percentage than noted by other investigators, a finding that could reflect aspects of the genetic background specific to the Dutch population.

The identification of *SFTPC* mutations raised speculation that mutations in the genes for the other surfactant proteins might be found in FPF. Such was the case with *SFTPA2*, when in 2009 Wang and colleagues reported mutations in two families in a cohort of 59 (8). Interestingly, the first family in which they identified a disease causing *SFTPA2* mutation not only had individuals with ILD but also individuals with bronchoalveolar cell carcinoma.

In 2007, two groups reported cases of FPF associated with mutations in two genes from the telomerase complex, *TERT* and *TERC* (9, 10). Both groups demonstrated that these mutations were associated with telomere shortening, a potential mechanism by which they led to lung fibrosis. Subsequently, both groups demonstrated that even in the absence of telomerase mutations, sporadic IPF is associated with telomere shortening in peripheral blood leukocytes as well as lung epithelial cells (16, 17), further illustrating that pathways involved in familial disease may also have specific roles in sporadic IPF.

The idea that gene variations which exhibit a disease-modifying effect rather than a direct causative impact has been explored by multiple investigators, but the analysis of common polymorphisms in candidate genes has had mixed results (2). Recently, however, the finding that mutations in ATP-binding cassette transporter A3 (*ABCA3*) could not only cause pediatric ILD, but modify severity of *SFTPC* mutation associated pediatric ILD (18), raised questions about whether *ABCA3* mutations might be present in adult FPF either as a disease-causing or -modifying gene. However, in this article, van Moorsel and colleagues found no association between *ABCA3* variations and their noted *SFTPC* mutations or with their cases of FPF in general (1). Nevertheless, given their relatively small FPF cohort, *ABCA3* still remains an attractive target for other studies.

Together, the genes with known mutations related to FPF suggest important potential features of IPF pathogenesis. First, the presence of *SFTPC* and *SFTPA2* mutations implicates the

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