Eur Respir J 2012; 39: 1256–1273
DOI: 10.1183/09031936.00173011

LETTERS

Stitching and switching: the impact of discontinuous lung function reference equations

To the Editors:

In order to distinguish the effects of lung disease from those of normal growth and development, lung function is expressed in comparison with reference data, with forced expiratory volume in 1 s (FEV_1) commonly being presented as % predicted. FEV_1 % pred has been identified as being of prognostic value in cystic fibrosis (CF), such that an FEV_1 of $<30\%$ pred or rapid decline to that level should prompt referral to a transplant centre [1]. Subsequent monitoring of FEV_1 % pred after lung transplantation is also important for monitoring graft function and is required to detect any signs of rejection or onset of bronchiolitis obliterans syndrome (BOS), a disease defined as a fall in FEV_1 of $>20\%$ from baseline determined by the average of two measurements made $\geqslant 3$ weeks apart. Continuing to monitor FEV_1 % pred after the development of BOS has also been shown to provide important insight into the patient's prognosis and therapeutic options [2].

Given that FEV_1 % pred plays such a key role in the clinical management of a child with CF or any child who has undergone lung transplantation, it is imperative to ensure that it is measured and interpreted accurately. Although guidelines for standardised measurement of spirometry have been developed for both adults [3] and children [4], the decision on which spirometry reference equation to use, amongst the plethora available [5], varies widely. This situation is further complicated by the fact that until recently published equations, and, hence, those incorporated into commercial spirometry devices, only incorporated certain age ranges, thereby necessitating a combination of different equations when undertaking serial measurements commencing in childhood.

In the UK, the British Thoracic Society currently recommends the equations of ROSENTHAL *et al.* [6] for children aged 4–18 yrs, and the European Coal and Steel Community (ECSC) equations for adults [7], whereas various different combinations are recommended by other international respiratory societies. These recommendations mean that as a child turns 18 yrs of age and moves into adult care, a change in reference equations is required. The extent to which this may introduce bias in predicted values and, hence, in clinical interpretation of results is not generally appreciated, especially as many manufacturers ''stitch'' equations representing different age groups together so that the user is presented with apparently seamless predictions, with no overt warning at periods of transition.

The magnitude of such potential errors can be illustrated by an 18-yr-old male with CF who had been undergoing regular serial spirometry measurements after lung transplantation. His progress post-transplant in 2007 (aged 14 yrs) had been generally good, with only one instance of severe respiratory compromise (January 2011, aged 17 yrs). On that occasion, his FEV_1 fell to 1.44 L (57% pred), from the usual baseline of ~2.0 L (~80% pred according to ROSENTHAL *et al.* [6]). After appropriate prompt investigation and treatment, his FEV_1 returned to 2.09 L (82% pred). On his next visit to the lung function laboratory in April 2011, aged 18 yrs, he recorded a FEV_1 of 58% pred, which would be deemed consistent with a significant illness (similar to that seen 3 months previously). However, during clinical review, it was noted that the patient had no other symptoms of respiratory compromise and claimed to be well. It was also noted that, although the patient's FEV_1 % pred had decreased dramatically (fig. 1a), his absolute FEV_1 was 2.13 L, which was consistent with his stable baseline (fig. 1b). The apparent decline in lung function was, therefore, not a reflection of any clinical change, but simply an automated, internal switching between paediatric and adult reference equations by the spirometry software. The magnitude of error when calculating the apparent change in predicted FEV_1 was such that, had the underlying cause not been rapidly identified, an urgent admission and invasive evaluation would have been triggered.

The magnitude of observed differences when switching between paediatric and adult reference ranges are most dramatic when using paediatric equations that do not include age (such as those of ROSENTHAL *et al.* [6]) in height-restricted subjects. Since many children with lung disease have some degree of growth restriction [9], the potential underestimation of predicted (and, hence, overestimation of % pred) values means that the incident reported here could frequently occur in other patients. Furthermore, it is increasingly recognised that the use of the ECSC equations in adults is not without its problems [10].

With the recent introduction of all-age reference equations [8], such scenarios could easily be avoided. These equations provide smoothly changing curves to describe the transition between childhood and adulthood, and eliminate the arbitrary break points which occur when using different equations over different ranges of age or height (fig. 1c). These equations represent the largest collation of healthy spirometry data published to date, but are currently limited to the Caucasian population and, despite recent incorporation into some commercially available spirometers (see www.lungfunction.org for details), are still not widely available for use in clinical laboratories. Recent work by the American Thoracic Society/Asian Pacific Society of Respirology/European Respiratory Society Task Force to Establish Improved Lung Function Reference Values to extend the all-age spirometry reference equations to an even wider age range (3–90 yrs) and other ethnic groups offers the means to overcome problems relating to switching between equations in the near future. However, for these to have any practical impact in clinical laboratories, rapid incorporation into commercial equipment and endorsement by the relevant professional bodies internationally will be essential.

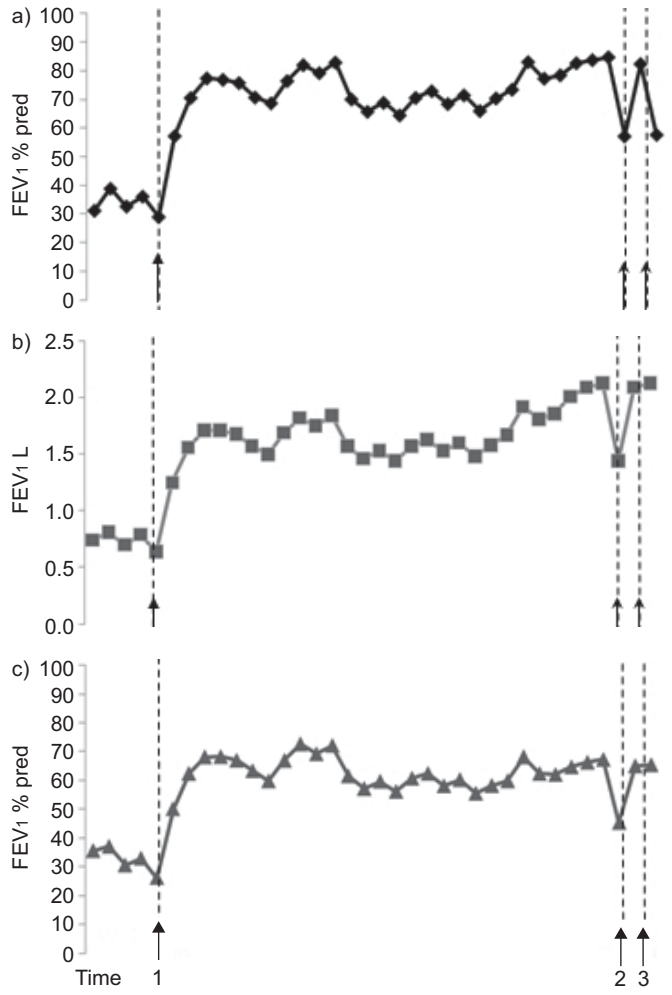

FIGURE 1. Serial measurements of forced expiratory volume in 1 s (FEV_1) in a young male with cystic fibrosis lung disease. a) FEV_1 % predicted (% pred) as reported by the equipment (ROSENTHAL *et al.* [6] paediatric equation for ages 6–17.9 yrs and adult equations of the European Coal and Steel Community [7] for >18 yrs of age). b) Absolute values of FEV_1. c) FEV_1 % pred using the all-age reference equations of STANOJEVIC *et al.* [8]. The data points represent serial FEV_1 measurements prior to and following lung transplantation. The first vertical dashed line (time 1) indicates time of lung transplantation at 14 yrs of age, after which there was marked improvement in lung function, which was consistently maintained until the second dotted line (time 2; 17 yrs 9 months of age), where there was a drop in lung function associated with an acute respiratory infection that was successfully treated. The third dotted line (time 3) indicates the patient's 18th birthday and the switch between paediatric and adult equations, resulting in an apparent dramatic reduction of lung function on the last test occasion, which was not accompanied by any change in clinical status. Inspection of absolute values (b) confirmed that level of lung function had in fact been maintained over the last two test occasions. Use of the all-age equations (c), which provide a smooth transition from early childhood to old age, allowed accurate interpretation of the results.

The responsibility to ''treat the patient and not the numbers'' should always remain with the clinical staff. Nevertheless, given the potentially serious clinical implications of ''stitching and switching'' reference equations, there is an urgent need to change international recommendations regarding such practices and to ensure that appropriate equations, to avoid such errors, are readily implemented in commercially available equipment to facilitate their widespread use in both clinical practice and research applications.

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Statement of Interest: None declared.

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DOI: 10.1183/09031936.00173011