Reply: Ethnically Diverse Normative Data for Diffusing Capacity and Lung Volumes

From the Authors:

We thank Dr. Weiner and colleagues for highlighting the dearth of normative data for lung volumes and diffusing capacity in the African American population. Moreover, there is a lack of such data in black and other nonwhite populations worldwide. We agree that this situation poses a significant challenge to physicians and researchers interpreting pulmonary function testing in all minority populations, including those with sickle cell disease (SCD).

As our colleagues stated, the lack of diversity in pulmonary function testing reference standards, particularly for lung volumes and diffusing capacity of lung for carbon monoxide (D_{LCO}), is problematic. The Global Lung Function Initiative reference standards (1) are based predominantly on white subjects. This is the case for all commonly used measures of normative lung function data (including the most commonly used reference standards for plethysmography in children by Rosenthal and colleagues [2]). A 2012 study by Kirkby and colleagues, demonstrating that healthy black children differ from healthy white children of similar height in plethysmography measures, including lower functional residual capacity and total lung capacity (3), highlights the need for these normative data in black subjects. As pulmonary physicians and researchers, we agree that an important clinical and research priority (that includes but is not limited to SCD) is ensuring that the normative data used for interpretation of lung function testing reflects the diversity of populations being evaluated. This will require a commitment to collect lung function data from diverse populations worldwide. In the meantime, investigators evaluating individuals with SCD should be cognizant of the limitations of the current normative values, particularly with respect to lung volumes and D_{LCO}.

Adding to the challenge posed by a lack of a representative population in normative D_{LCO} values, D_{LCO} measurement in people with SCD may be influenced by multiple confounding factors. Chronic pain and other issues affecting chest wall function may inhibit the ability of some patients to attain maximal alveolar volume. The presence of carboxyhemoglobin in the blood can decrease passive diffusion of carbon monoxide (CO) into erythrocytes, leading to an underestimation of D_{LCO}. In contrast, the multifactorial rightward shift of the oxyhemoglobin dissociation curve and release of oxygen to end-organ tissues can leave more hemoglobin binding sites available to bind CO, thus leading to an overestimation of D_{LCO}. D_{LCO} equations correcting for hemoglobin make assumptions regarding pulmonary blood flow that may not be valid in severe anemia. Existing literature reporting D_{LCO} measurements in children with SCD has shown varying results, with one study demonstrating reduced D_{LCO} in 20% of subjects (4) and another study demonstrating increased D_{LCO} in children with SCD compared with race-matched control individuals (5). Studies of adults with SCD have consistently reported reduced D_{LCO} (6–9), although the clinical significance of this reduction in D_{LCO} is unclear (10).

Our workshop report highlighted many gaps in the literature for which more data are needed in sickle cell lung disease (11). We greatly appreciate the authors underscoring the urgent need for normative pulmonary function data from diverse populations. Efforts to increase the participation of individuals from underrepresented groups in normative data collection could benefit not only people with SCD but also many minority populations in both research and clinical settings.

Author disclosures are available with the text of this letter at www.atsjournals.org.

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