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Unraveling restrictive chronic lung disease in sickle cell disease

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A LEADING CAUSE of decreased life expectancy in adults with sickle cell disease (SCD) is acute and chronic lung disease (CLD). CLD historically encompassed both pulmonary fibrosis and pulmonary hypertension;¹ however, we now understand that these are distinct entities that may not necessarily coexist in SCD patients. While the latter has been the subject of thorough investigations that have determined its high prevalence (approximately 10% by right heart catheterization), strong association with chronic hemolytic anemia, and its relevance as a risk factor for early mortality in SCD,^{2–5} the former has not been studied comprehensively in the modern era.

Pulmonary fibrosis is associated with restrictive lung defects on spirometric evaluation. This is a common finding in adult SCD patients, probably as a result of longstanding chronic inflammation of the small airways from recurrent acute chest syndrome (ACS), infections, vascular infarction and extra-pulmonary restriction.^{1,6} Longitudinal changes in lung function have also recently been described in children with SCD, with a study reporting an average loss of approximately 3% of forced expiratory volume in one second per year.^{7,8} Few studies have addressed the pulmonary complications of SCD in sub-Saharan Africa. This is a major area of unmet need, as children with SCD in sub-Saharan Africa are exposed to high rates of pulmonary infectious co-morbidities—predominantly tuberculosis and HIV—expected to exacerbate CLD.⁹

The article by Cook et al. in this issue of the *Journal* has focused on determining lung function abnormalities and symptoms of asthma in a cohort of 25 Malawian children with SCD and comparing it to local and international reference ranges.¹⁰ The authors reported spirometric abnormalities suggestive of restrictive rather than obstructive defects and the prevalence of wheeze to be comparable to a cohort of children without SCD from urban areas. This is surprising given the high prevalence of obstructive lung disease in areas with high household pollution from burning biomass fuel, such as many urban and rural areas in Malawi.¹¹ Cook et al. hypothesize that in the Malawian SCD population, progression to late stage restrictive lung disease may be occurring earlier and more rapidly with various environmental influences acting as disease modifiers. The authors did not report on history of ACS in the study cohort, but it is possible that an increased number of episodes of ACS might be an important predictor of development of restrictive lung disease at an earlier age. In addition, the small sample size greatly limits the analysis of associated co-morbidities.

Despite these limitations, this study provides a useful snapshot of the prevalence of pulmonary function testing abnormalities in an international cohort of pediatric SCD patients. Moreover, it offers the potential to spur further research to develop preventive and therapeutic strategies to alter the pattern of CLD over a larger and varied SCD cohort followed longitudinally. As acknowledged by the authors, a more accurate determination of lung function by provocation testing might be helpful in detecting transient obstructive or even mixed obstructive/restrictive defects. Such studies are required, as asthma has been identified as a significant co-morbidity in SCD and there is growing evidence that a history of ACS in SCD children is a risk factor for reactive airway disease and airway hyper-responsiveness after provocation challenge testing.^{12–14} Although these are studies of associations and they do not establish causality, asthma exacerbations may precipitate vaso-occlusion and ACS by inducing ventilation-perfusion mismatches.¹⁵

In conclusion, this study highlights the importance of restrictive lung impairment in SCD patients, but leaves critical questions unanswered regarding the causes and co-morbidities of interstitial lung disease, as well as the prevalence and role of asthma in SCD outcomes in SCD patients.

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