Commentary: Heterogeneity of respiratory disease in children and young adults with sickle cell disease

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Sickle cell disease (SCD) affects 300 000 children born worldwide annually. While classically thought of as a genetic haemoglobinopathy, complications impact nearly every vascular bed leading to progressive organ damage and accelerated mortality. Pulmonary complications of SCD are among the most common causes of morbidity and mortality and affect every structure of the lungs. Abnormal pulmonary function is often one of the earliest indicators of lung disease, yet our understanding of the clinical significance of this finding is poor.

Prior studies suggest several consistent themes: (1) while most children with SCD have lung function within the normal range,[1 2] spirometry is, on average, reduced compared with healthy children[3]; (2) the most common abnormality in children with SCD is an obstructive ventilatory defect, observed in 15%–20%[1 2]; (3) lung function declines to a varying extent with increasing age[4 5]; (4) by adulthood, >70% have developed restrictive lung disease often with a reduced diffusion capacity and oxygen desaturation on ambulation.[6] It is not clear what, if any, treatment prevents this progression and as such, the clinical utility of pulmonary function testing in SCD is unclear.

In *Thorax*, Lunt *et al*[7] applied a novel clustering strategy using clinical and biomarker data to clarify the different patterns of lung function abnormalities observed in 114 patients with SCD aged 5–27 years. Individuals in cluster 1 had moderate to severe anaemia, an elevated pulmonary capillary blood volume (PCBV) (attributed to an anaemia-related increase in cardiac output), mixed obstructive/restrictive physiology with increased respiratory system resistance and hypoxia. Those in cluster 2 were older with restrictive lung disease and reductions in diffusion capacity. Cluster 3 consisted of mainly younger patients with baseline obstruction, bronchodilator reversibility (reflective of airway hyper-responsiveness) and elevated serum lactate dehydrogenase (LDH) levels, suggestive of increased haemolysis. The authors noted that obtaining PCBV, diffusion capacity and LDH reliably predict cluster membership with 90% accuracy. Pathophysiologically, this clustering technique supports the emerging concept that the mechanism of airway obstruction in SCD may be specifically related to the haemoglobinopathy. The pattern observed in cluster 1 suggests that increased airway obstruction and resistance reflects extrinsic small airway compression by increased pulmonary vascular engorgement and this may mediate abnormal gas exchange. The airway hyper-reactivity observed in cluster 3 is suggestive of a haemolysis-related dysregulated inflammation aetiology.[8 9] These data suggest that SCD-directed treatments such as hydroxyurea, and potentially, curative therapies may reverse airway obstruction.

The clinical significance of pulmonary function abnormalities in SCD has long been challenging for clinicians. The 2014 National Institutes of Health guidelines for the management of SCD do not recommend their routine assessment as it is unclear that knowledge of lung function impacts clinical outcomes.[10] While many questions remain unanswered, the current study is among the first to associate pulmonary function abnormalities with clinical phenotypes that may warrant distinct intervention strategies. Further research is needed to evaluate the significance of these abnormalities longitudinally and the impact of treatment on the reduced functional capacity, cardiopulmonary disease and early mortality observed in adults with SCD.

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