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Mini-Symposium: Controversies in the Evaluation and Treatment of Sickle Cell Disease

Lung Function in Sickle Cell Disease

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EDUCATIONAL AIMS

The reader will:

- Become familiar with the different patterns of lung function among patients with SCD
- Learn the differences in lung function between adults and children with SCD
- Learn about the possible causes that can explain the discrepancies in the findings of previously published studies

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SUMMARY

Although some of the most severe complications of Sickle Cell Disease (SCD) tend to be acute and severe (e.g. acute chest syndrome, stroke etc.), the chronic ones can be equally debilitating. Prominent among them is the effect that the disease has on lung growth and function. For many years the traditional teaching has been that SCD is associated with the development of a restrictive lung defect. However, there is increasing evidence that this is not a universal finding and that at least during childhood and adolescence, the majority of the patients have a normal or obstructive pattern of lung function. The following article reviews the current knowledge on the effects of SCD on lung growth and function. Special emphasis is given to the controversies among the published articles in the literature and discusses possible causes for these discrepancies.

INTRODUCTION

Sickle Cell Disease (SCD) has many acute and chronic effects on multiple organ-systems [1]. Although it has been over 100 years since the first official description of SCD [2], its effects on lung function did not attract any attention until the 1960–1970s. However, only in the last 10–15 years has there been a systematic study of lung function in SCD coinciding with the increased recognition that the pulmonary complications of SCD are among the top causes of morbidity and especially of mortality [3,4].

PATTERN OF LUNG FUNCTION IN SCD

The early studies of lung function were performed on adult patients and their findings suggested that SCD was associated with a progressive restrictive lung defect [5–10] [Table 1]. In 1970, Wall et al. [11] published the first study of lung function in children with SCD and reported that their lung function was normal. These results were later disputed by Pianosi et al. [12] who reported that, like adults, children with SCD had a restrictive pattern. In the first (and to date the only) study of infants, Koumbourlis et al. [13] reported that the majority of infants with SCD had normal lung function and that the only detectable abnormality was lower airway obstruction and not a restrictive lung defect. These findings were in part supported by the study of Santoli et al. [14] who also reported that some young adults had an obstructive pattern, whereas Leong et al. [15] reported that many of their patients had airway hyperreactivity and reversible lower airway obstruction. Using a different methodology, in which each patient was classified as "normal", "obstructive", or "restrictive" according to pre-specified criteria, Koumbourlis et al. [16] confirmed their findings in infants reporting that over 57% of their patients had normal lung function, 35% had obstructive and only 8% had a restrictive pattern.

During the last decade many more studies have been published with information on the lung function of children and adults with SCD [17–34] [Table 1]. While there is now a general recognition

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Table 1
Studies of Lung Function in Adults and Children with SCD

AUTHORS/YEAR	NUMBER	CONTROLS	PARAMETERS REPORTED
Sproule et al. (1958) [5]	21 Adults (Hb-SS, Hb-SC, Hb-Sβ)		
Femi-Pearse et al. (1970) [6]	6 Adults (Hb-SS)	Historical controls	TLC, RV, FVC
Miller & Serjeant (1971) [7]	28 Adults (Hb-SS)	Historical controls	TLC, FRC, RV, FVC, FEV_1, FEV_1/FVC, DLCO, DLCO /VA
Young & Banks (1976) [8]	9 Adults (Hb-SS)	Historical controls	FVC, FEV_1/FVC, FEF_{25-75}
Miller et al. (1978) [9]	39 Adults (Hb-SS, Hb-SC)	Matched controls	VC, DLCO, DLCO /VA
Wall et al. (1979) [10]	12 Children (Hb-SS)	Matched controls	TLC, FRC, RV, RV/TLC, FVC, FEV_1, FEV_1/FVC, FEF_{25-75}, FEF_{50}
Young et al.(1988) [11]	66 Adults (Hb-SS)	Historical controls	TLC, SVC, FRC, RV, FVC, FEV_1, FEV_1/FVC, FEF_{25-75}, DLCO
Pianosi et al. (1993) [12]	37 Children (Hb-SS, Hb-SC, Hb-Sβ)	Non-matched controls	TLC, RV/TLC,FVC, FEV_1, FEV_1/FVC, DLCO, DLCO /VA
Koumbourlis et al. (1997) [13]	20 Infants (Hb-SS, Hb-SC)	Non-matched controls	FRC, V'maxFRC, Crs, Rrs, tme/tE
Leong et al. (1997) [14]	40 Children	Non-matched controls	TLC, RV/TLC, FVC, FEV_1, FEV_1/FVC, FEF_{25-75}
Santoli et al. (1998) [15]	49 Adults (Hb-SS, Hb-SC, Hb-Sβ)	Historical controls	TLC, FRC, FVC, FEV_1, FEV_1/FVC, FEF_{25}, FEF_{50}, FEF_{25-75}, DLCO, DLCO/VA
Koumbourlis et al. (2001) [16]	63 Children (Hb-SS)	Historical controls	TLC, FRC, RV, RV/TLC, FVC, FEV_1, FEV_1/FVC, FEF_{25-75}
Sylvester et al. (2003) [17]	64 Children (Hb-SS)	Race matched controls	TLC, FRC, RV, FVC, FEV_1, FEV_1/FVC, PEFR
Knight-Madden et al. (2004) [18]	80 Children (Hb-SC)	Race matched controls	FVC, FEV_1, FEV_1/FVC
Hijazi et al. (2005) [19]	28 Children (Hb-SS, Hb-SC)	Matched controls	FVC, FEV1, FEV1/FVC
Vendramini et al. (2006) [20]	26 Adults (Hb-SS, Hb-SC, Hb-Sβ)	Healthy volunteers (not matched)	TLC, FVC, FEV_1, FEV_1/FVC, FEF_{25-75}, DLCO
Klings et al. (2006) [21]	310 Adults	Historical controls	TLC, RV, FVC, FEV_1, FEV_1/FVC, DLCO
Akgul et al. (2006) [22]	48 Adults	Healthy controls	TLC, FVC, FEV_1, FEV_1/FVC, PEFR, DLCO
Sylvester et al. (2006) [23]	40 Children (Hb-SS)	Historical controls	TLC, FRC, RV, RV/TLC, FVC, FEV_1, FEV_1/FVC, PEFR, FEF_{50}, FEF_{75}
Ozbek et al. (2007) [24]	31 Children (Hb-SS)	Historical controls	FVC, FEV1, FEV1/FVC, FEF25-75
Koumbourlis et al. (2004) [25]	13 Children (Hb-SC)	Matched controls with Hb-SS	TLC, FRC, RV, RV/TLC, FVC, FEV_1, FEV_1/FVC, FEF_{25-75}
Field et al. (2008) [26]	79 Children (Hb-SS)	Historical controls	FVC, FEV_1, FEV_1/FVC
McLean et al. (2008) [44]	312 Children (Hb-SS, Hb-SC)	Historical controls	TLC, FVC, FEV_1, FEV_1/FVC, FEF_{25-75}
Strunk et al. (2008) [26]	21 Children	Historical controls	FVC, FEV1, FEV1/FVC
Sen et al. (2009) [27]	31 Adults (Hb-SS)	Matched controls	TLC, FVC, PEFR, FEV_1, FEV_1/FVC, FEF_{25-75}, PEFR, DLCO
Boyd et al. (2009) [28]	102 Children ((Hb-SS, Hb-SC, Hb-Sβ)	Historical controls	TLC, FVC, FEV_1, FEV_1/FVC,
Liem et al. (2009) [29]	78 Children (Hb-SS, Hb-SC, Hb-Sβ)	Historical controls	TLC, FVC, FEV_1, FEV_1/FVC, FEF_{25-75}, DLCO
Cohen et al. (2011) [31]	114 Adults (Hb-SS, Hb-SC)	Historical controls	FVC, FEV_1, FEV_1/FVC
Field et al. (2011) [32]	99 Children (Hb-SS)	Historical controls	FEV_1, FEV_1/FVC
Cohen et al. (2013) [33]	195 Children (Hb-SS)	Historical controls	FVC, FEV_1, FEV_1/FVC, FEF_{25-75}
Intzes et al.(2013) [34]	122 Children (Hb-SS, Hb-SC, Hb-Sβ)	Historical controls	FVC, FEV_1, FEV_1/FVC, FEF_{25-75}

that SCD is not associated with a single pattern of lung function and that certain patients may actually have a normal or obstructive pattern, the disease remains mostly associated with a restrictive pattern especially among adult patients. There are many possible explanations for these discrepancies that are briefly summarized below:

Over-estimation of the prevalence of the restrictive pattern

As virtually all published studies both in adults and in children have shown, patients with SCD tend to have lung volumes that are decreased compared to historical or matched controls. This finding is usually interpreted as indicating the presence of a restrictive lung defect; although the volumes (usually forced vital capacity (FVC) and/or Total Lung Capacity (TLC)) are well within the normal range, thus overestimating the prevalence of a "restrictive" pattern. Interestingly, none of the recent studies, both in adults and children, [15–34] have shown significant decreases in the lung volume similar to those reported before the 1980s [5–10]. This raises the possibility that the restrictive lung defects that were being reported in the past might not have been entirely due to the SCD itself, but due to other factors such as inadequately treated recurrent lung infections, poor nutrition or smoking.

Under-estimation of the prevalence of the obstructive pattern

In many studies, relying exclusively on spirometric data, decreases in the FVC have been interpreted as indicating loss of lung volume. However, a decrease in FVC can be caused by actual loss of lung volume (as is the case in typical restrictive lung defects), or more commonly because of the presence of air-trapping in cases of obstructive lung disease. Another possible error is due to the fact that in many studies (even among the recent ones) the criterion of lower airway obstruction has been based on a low cut-off value in the forced expiratory volume in the first second (FEV_1) irrespective of the lung volume. Like the FVC, the FEV_1 can be low due to actual loss of lung volume or due to lower airway obstruction. Other studies have evaluated the lower airway obstruction on the basis of the ratio FEV_1/FVC, that is certainly a far more accurate index of lower airway obstruction, but it has also two potential drawbacks. The first is that the ratio is age dependent (e.g. a FEV_1/FVC ratio of 85% is abnormally low for a 7-year-old but completely normal for a 17-year-old). Thus, studies that use a specific "cut-off" for the determination of abnormality are likely to over- or underestimate the prevalence of obstruction depending on the age composition of their cohorts [20,21,27,34]. A second possible problem is that a normal FEV_1 or even a normal FEV_1/FVC ratio does not rule out the presence of peripheral airway obstruction that is the first and most common abnormality seen in virtually all obstructive diseases such as asthma or Cystic Fibrosis and in SCD as well [16,28,34].

Differences in the analysis of the data

The single most important cause for discrepancies between the results of the various studies probably has to do with the way that the various investigators have analyzed their data. In the majority of the studies the assessment of the pattern of the lung function has been made on the basis of the mean (±SD) (and occasionally on the z-score) of the patients as a group. As Table 2 illustrates when patients are grouped together, the results are very similar among the various studies showing proportional decrease in all indices suggesting the presence of a restrictive lung defect. A totally different picture emerges from the few studies in which the