Respiratory Physiology & Neurobiology 222 (2016) 6–10

Contents lists available at ScienceDirect

Respiratory Physiology & Neurobiology

journal homepage: www.elsevier.com/locate/resphysiol

Lung function, transfusion, pulmonary capillary blood volume and sickle cell disease

Alan Lunt[a,b], Emily McGhee[a], Polly Robinson[a], David Rees[c], Susan Height[c], Anne Greenough[a,b,*]

[a] Division of Asthma, Allergy and Lung Biology MCR Centre for Allergic Mechanisms in Asthma, King's College London, UK
[b] National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St. Thomas' NHS Foundation Trust and King's College London, UK
[c] Department of Paediatric Haematology, King's College Hospital NHS Foundation Trust, London, UK

ARTICLE INFO

Article history:
Received 30 July 2015
Received in revised form
10 November 2015
Accepted 10 November 2015
Available online 22 November 2015

Keywords:
Sickle cell disease
Lung function abnormalities
Pulmonary capillary blood volume
Transfusion

ABSTRACT

Lung function abnormalities occur in children with sickle cell disease (SCD) and may be associated with elevated pulmonary blood volume. To investigate that association, we determined whether blood transfusion in SCD children acutely increased pulmonary capillary blood volume (PCBV) and increased respiratory system resistance (Rrs5). Measurements of Rrs5 and spirometry were made before and after blood transfusion in 18 children, median age 14.2 (6.6–18.5) years. Diffusing capacity for carbon monoxide and nitric oxide were assessed to calculate the PCBV. Post transfusion, the median Rrs5 had increased from 127.4 to 141.3% predicted ($p < 0.0001$) and pulmonary capillary blood volume from 39.7 to 64.1 ml/m2 ($p < 0.0001$); forced expiratory volume in one second ($p = 0.0056$) and vital capacity ($p = 0.0008$) decreased. The increase in Rrs5 correlated with the increase in PCBV ($r = 0.50$, $p = 0.0493$). Increased pulmonary capillary blood volume may at least partially explain the lung function abnormalities in SCD children.

1. Introduction

Sickle cell disease (SCD) is one of the commonest inherited disorders worldwide; approximately 250,000 children are born with homozygous SCD per year (Piel et al., 2013). The majority of children with SCD in developed countries can expect to survive to adulthood (Quinn et al., 2010), but may then suffer severe pulmonary morbidity including hypoxia and pulmonary hypertension (Powars et al., 1988). Restrictive and obstructive lung function abnormalities are common. Restrictive lung disease is associated with increasing age (Sylvester et al., 2004; MacLean et al., 2008) and obstructive defects can occur even in young children with SCD (Koumbourlis et al., 2001, 1997). Hence, it is important to understand the etiology of such abnormalities; mechanistic insights are necessary to better inform therapy to hopefully prevent SCD pulmonary complications. A number of researchers have suggested that asthma is responsible for impaired lung function and respiratory symptoms in SCD, but the evidence is conflicting. A high prevalence of asthma in children with SCD has been reported in one study (Knight-Madden et al., 2005), but not in others (Bernaudin et al., 2008; Boyd et al., 2004). In addition, the response to bronchial challenges in SCD patients, such as cold air, exercise, or methacholine has been variable ranging from no response (Chaudry et al., 2014) to 78% of those tested having a positive response (Ozbek et al., 2007).

Furthermore, whereas some studies have shown a high response rate to bronchodilator therapy in SCD children compared to controls (Knight-Madden et al., 2005; Koumbourlis et al., 2001), others have shown no significant difference in the response rates of SCD children compared to that of controls (Sylvester et al., 2004).

An alternative explanation for the impaired lung function is increased pulmonary capillary blood volume due to chronic anemia resulting in a raised cardiac output and increased vascular recruitment and distension (Batra et al., 2002; Chaudry et al., 2011; Delclaux et al., 2005; Femi-Pearse et al., 1970; Lunt et al., 2014; Wedderburn et al., 2014). Indeed, we have demonstrated children with SCD have increased pulmonary capillary blood volume compared to controls, which was associated with airway obstruction and correlated with respiratory system resistance

* Corresponding author at: Neonatal Intensive Care Centre, 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, London, SE5 9RS, UK. Fax: + 44 20 3299 8284.
E-mail addresses: alan.lunt@nhs.net (A. Lunt), emily.mcghee@kcl.ac.uk (E. McGhee), polly.robinson@gmail.com (P. Robinson), david.rees2@nhs.net (D. Rees), sue.height@nhs.net (S. Height), anne.greenough@kcl.ac.uk (A. Greenough).

http://dx.doi.org/10.1016/j.resp.2015.11.006
1569-9048/

Table 1
Lung function and pulmonary capillary blood volume results before and after transfusion.

	Pre-transfusion	Post-transfusion	% Change from baseline[a]	*P*
Rrs5	127.4 (88.9–207.8)	141.3 (96.1–234.1)	10.7 (−3.6–22.0)	<0.0001
Rrs20	119.4 (78.2–187.5)	136.8 (80.5–191.9)	4.8 (−16.7–43.2)	0.0332
R5–R20[a] (kPa/l/s)	0.145 (0.00–0.420)	0.165 (0.01–0.541)	0.03 (−0.10–0.29)[b]	0.0082
Xrs5	119.6 (49.7–201.0)	133.4 (65.0–281.2)	28.5 (−18.2–69.8)	0.0023
f_{res}	112.7 (60.7–178.9)	118.7 (72.4–190.5)	6.3 (−21.1–49.0)	0.0665
AX[a] (kPa/L)	0.795 (0.05–3.820)	0.850 (0.13–5.130)	40.7 (−52.7–200.0)	0.0052
FEV_1	84.4 (66.2–139.6)	79.4 (63.5–132.9)	−4.9 (−20.5–8.6)	0.0056
VC	94.2 (73.7–142.1)	90.72 (60.5–144.0)	−5.5 (−9.8–6.1)	0.0008
FEV_1:VC	91.2 (73.0–105.3)	92.7 (74.5–112.8)	2.6 (−12.0–17.5)	0.2462
$FEF_{25–75}$	69.9 (34.4–122.5)	62.5 (30.3–111.5)	−8.9 (−55.8–45.6)	0.0483
DLCO	74.8 (57.5–106.1)	90.2 (61.4–114.3)	12.0 (1.0–37.7)	<0.0001
KCO	71.1 (58.1–94.2)	90.4 (60.8–108.5)	19.2 (4.6–49.1)	<0.0001
TLC	92.2 (71.6–135.1)	–		
RV	90.1 (61.7–104.3)	–		
RV:TLC	105.1 (87.4–134.8)	–		
DLCOc	88.3 (76.0–122.6)	–		
KCOc	86.8 (75.1–109.3)	–		
PCBV/BSA[a] (ml/m^2)	39.7 (25.3–63.6)	64.1 (33.4–129.3)	43.3 (14.1–108.2)	<0.0001

[a] The results are expressed as median (range) and percent predicted for height except where indicated.
[b] Indicates absolute change.

(Wedderburn et al., 2014). Similarly in adults, vascular changes on high resolution computed tomography (HRCT) (increased segmental pulmonary artery diameter and total cross-sectional area of all pulmonary vessels less than 5 mm in diameter (CSA < 5mm%), correlated with reductions in lung function (Lunt et al., 2014).

Experimental increases in thoracic blood volume have been shown to produce reductions in lung function and an increase in respiratory system resistance. For example, rapid saline infusion has been shown to produce a significant decrease in dynamic lung volumes as assessed by spirometry in healthy adults (Collins et al., 1973; Muir et al., 1975), as well as in patients with left ventricular failure (Puri et al., 1999). In addition, Lorino et al. found that the inflation of pneumatic trousers in healthy subjects caused an increase in respiratory system resistance as assessed by impulse oscillometry (Lorino et al., 1994). Recently Bihari et al. (2015) demonstrated that in healthy subjects, infusion of 0.9% saline caused a significant increase in respiratory system resistance at 5 Hz as assessed by impulse oscillometry. Such studies have not been performed in SCD children, but some SCD children receive blood transfusions as part of their routine care. Blood transfusions have been shown to result in transient increases in cardiac output (Duke et al., 1964). Routine blood transfusions in SCD children would then allow investigation of the acute effect of fluid loading on lung function and further add to the understanding of the etiology of pulmonary function impairment in SCD children The aim, therefore, of this study was to test the hypothesis that blood transfusion would result in an acute increases in pulmonary capillary blood volume and respiratory system resistance and reductions in spirometry in children with SCD. Such data would further aid the understanding of the pathophysiology of lung function abnormalities in SCD children.

2. Methods

Children homozygous for sickle cell haemoglobin (HbSS) undergoing regular blood transfusion at King's College Hospital NHS Foundation Trust, London were recruited. Only children of seven years of age or greater were recruited as they were likely to be able to complete all the lung function tests. The study was approved by the King's College Hospital NHS Foundation Trust Research Ethics Committee and parents gave informed, written consent for their child to take part. Impulse oscillometry, spirometry and pulmonary capillary blood volume were measured before and immediately after transfusion. In order to further characterise the lung function of the patients, static lung volumes were measured before transfusion. The volume of packed red cells (PRCV) administered to each patient was determined using the following formula: PRCV (mls) = patient weight (kg) × change in haemoglobin to be achieved (g/dl) × transfusion factor of (4–5 $ml.kg^{-1}/g.dl^{-1}$), in order to achieve a target haemoglobin concentration of 13.5 g/dl. All transfusions were administered over approximately four hours.

2.1. Lung function assessments

Spirometry, gas transfer for carbon monoxide and body plethysmography were performed. The forced expiratory volume in one second (FEV1) vital capacity (VC), ratio of FEV1 to VC (FEV1/VC), forced expiratory flow between 25 and 75% of VC (FEF25–75), transfer factor for carbon monoxide (DLCO), transfer factor adjusted for alveolar volume (KCO), total lung capacity (TLC), residual volume (RV) and the ratio of RV to TLC (RV:TLC) were assessed according ATS/ERS guidelines. The highest forced vital capacity result obtained from spirometry and the slow vital capacity from the DLCO manoeuvre were reported as VC. Results were expressed as the percentage predicted for height using an ethnic-specific reference range for spirometry and Caucasian reference data for gas transfer and body plethysmography (Quanjer et al., 2012; Rosenthal et al., 1993). Respiratory system resistance

(Rrs) was also measured using impulse oscillometry. Rrs was measured before the other lung function tests and a resistance at 5 Hz (Rrs5) was used in order to assess both distal and proximal changes in lung function. Respiratory system resistance at 20 Hz (Rrs20), the frequency dependence of resistance (R5–R20), the respiratory system reactance at 5 Hz (Xrs5), the resonant frequency (fres) and the area under the reactance curve between resonant frequency and 5 Hz (AX) were also recorded. For all IOS indices the whole-breath values were reported. All measurements were performed using a commercially available lung function system (Jaeger MasterScreen IOS, Carefusion Ltd., Basingstoke UK).

The Rrs5, Rrs20, Xrs5, and fres results were expressed as the percent predicted for height using the reference range of Nowowiejska et al., 2008. Raw values were reported for R5–R20 and AX as predicted values are not available for these indices for the age range of the children studied. For IOS indices, the mean of two measurements for Rrs5 and Rrs20 were reported for each measurement the two results were within 5% of each other.

Patients were diagnosed with an obstructive abnormality if their FEV1:FVC was less than the lower limit of normal (LLN)