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Pulmonary function in thalassaemia major and its correlation with body iron stores

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Summary

This study compared pulmonary function tests (PFTs) with cardiac, pancreatic and liver iron in 76 thalassemia major (TM) patients. Restrictive lung disease was observed in 16%, hyperinflation in 32%, and abnormal diffusing capacity in 3%. While no patients met Global Initiative for Chronic Lung Disease criteria for airways obstruction, there were indicators of small airways disease and air trapping. PFTs did not correlate with somatic iron burden, blood counts or haemolysis. Restrictive lung disease was associated with inflammation. We conclude that TM patients have pulmonary abnormalities consistent with small airways obstruction. Restrictive disease and impaired diffusion are less common.

Keywords

Iron overload; pulmonary function; thalassaemia; magnetic resonance imaging; lung disease

Introduction

Pulmonary function is abnormal in thalassemia major (TM) patients, but a consistent spectrum of disease has not been observed. Although changes in pulmonary function have been attributed to iron overload, those that examined the link between somatic iron stores

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Tom Coates recruited subjects, and reviewed the paper.

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and pulmonary function had varying conclusions. Furthermore, no study has evaluated the correlation between cardiac iron- a possible proxy measure for long-term iron overload and adherence to chelation therapy- and pulmonary function in TM patients (Noetzli *et al*, 2008).

The primary aim of this study was to relate pulmonary function abnormalities to short term (liver) and long term (cardiac) iron control. The second aim was to characterize the pulmonary phenotype of a large, North American TM cohort, including lung volume corrected metrics of flow restriction and diffusing capacity.

Methods

Seventy-six patients with TM were studied between August 2005 and May 2009 as part of the Early Detection of Iron Cardiomyopathy in Thalassemia (EDICT) study. All patients had received >8 transfusions per year for at least 7 years. All had pulmonary function tests (PFT's), magnetic resonance imaging (MRI) scans of the heart and liver, and blood tests completed within 7 days of each other, though most were within 24 h. All tests were performed 7–10 days after the previous transfusion.

Patients completed PFT's in the Children's Hospital Los Angeles Pulmonary Physiology Lab using the Vmax 6200 and Vmax Spectra 6200 systems (Viasys, Cardinal Health, Dublin, OH). Spirometry, lung volumes, single breath nitrogen washout curve, and single breath diffusing capacity of the lung for carbon monoxide were obtained. To standardize flow rates for varying patient size and lung volumes, the maximal expiratory flows at 80% total lung capacity (TLC) ($V_{max80\%}$), 70% TLC ($V_{max70\%}$), and 60% TLC ($V_{max60\%}$) were calculated by dividing the flow rates by TLC (Cooper *et al*, 1977).

Abnormal forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), 25%–75% forced expiratory flow ($FEF_{25\%-75\%}$), and TLC results were defined as percent predicted less than 80 percent (Cotes 1979). Airway obstruction was diagnosed using Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: $FEV_1 < 80\%$ predicted and $FEV_1/FVC < 70\%$. Restrictive lung disease was defined as TLC <80% of predicted. Hyperinflation was defined as residual volume (RV)/TLC ratio >120% of predicted. Non-uniform distribution of ventilation was determined by an increased (>2.5% N_2/l) slope of phase III of the single breath nitrogen washout curve. Diffusing capacity of the lung for carbon monoxide was corrected for the patient's alveolar volume and haemoglobin according to the method of Cotes (1979) with an abnormal result defined as $D_{LCOsb} < 4$ ml/mmHg/min/l.

Patients had blood drawn for complete blood count, lactate dehydrogenase, N-terminus pro-brain natriuretic protein (NT-proBNP), ferritin, and high sensitivity C-reactive protein (hs-CRP). MRI scans of the heart and liver with cardiac $R2^*$ measurements were performed according to validated techniques (Wood *et al*, 2005). Hepatic iron concentration (HIC) was calculated using liver $R2$ and $R2^*$ measurements as described (Wood *et al*, 2005).

All statistical analysis was performed using JMP Statistical Discovery Software (SAS, Cary, NC). Two-tailed Student's T-test was used to compare percent predicted values to population norms. Linear regression was performed to determine correlations between pulmonary function with body iron and age. Bonferroni correction was applied to reduce type I error. A correction factor of four was used for body plethysmography and spirometry but no correction for phase III nitrogen or diffusing capacity testing.

Results

There were 37 males and 39 females. Mean age of the patients was 25.6 ± 8.8 years, range 11.8–48.4 years. Patients were heavily iron overloaded- mean liver iron 13.2 mg/g dry weight liver (normal < 2 mg/g) and serum ferritin 3,127 $\mu\text{g/l}$. Patients had been transfused and chelated for most of their life. Mean cardiac $R2^*$ was 98.8 Hz, indicating significant cardiac iron overload (abnormal >50Hz). Females were an average of 4.3 years older ($p=0.03$) but cardiac $R2^*$, liver iron, and ferritin were comparable among the sexes.

As a group, TM patients exhibited significantly abnormal predicted mean values of all volumetric and flow data than population norms ($p<0.0001$ by one sample T-test). Figure 1 shows the percentage of individual patients who had abnormal PFT's. $\text{FEF}_{25\%-75\%}$ was low in 61% (mean $95.2\% \pm *$). The next most common abnormalities were low FEV_1 (mean $81.4\% \pm *$), high $N2$ delta (mean $* \pm *$), low FVC (mean $85.2\% \pm *$), and increased RV/TLC ratio (mean $112.6\% \pm *$). These findings suggest small airway obstruction. However, no patient met GOLD criteria for airway obstruction. All V_{max} values were in the normal range in children and adolescents where norms are available.

Restrictive lung disease was found in only 16% of patients and none had concomitant obstructive lung disease when examining V_{max} values. Restrictive lung disease was associated with inflammation, as TLC correlated with hs-CRP ($r=-0.31$, $p=0.01$). Moreover, restrictive disease occurred in 10 of 32 patients with hs-CRP value > 1 ($p=0.002$) compared with only 2 of 40 patients with hs-CRP < 1.0.

Only 2.7% of patients had decreased diffusing capacity of the lung for carbon monoxide after correction for lung volume and haemoglobin. The diffusing capacity declined weakly with age ($r=-0.36$, $p=0.002$). No correlation was observed between $\text{adjD}_{\text{LCOsb}}/V_{\text{A}}$ and any of the pulmonary function or physiological variables.

There were no significant gender differences in PFT's. No significant relationship was observed between PFT's, body iron stores (HIC, cardiac $R2^*$, serum ferritin), haemoglobin, haematocrit, platelet count, or lactate dehydrogenase (as a surrogate for haemolysis). Only three patients smoked (ranging from 2 to 10 pack years), therefore no meaningful differences could be obtained between smokers and non-smokers.

Several age-normalized measures of pulmonary function (Table 1) worsened with age, indicating faster declines than the general population. Changes in $V_{\text{max}80/70/60\%}$ and $\text{adjD}_{\text{LCOsb}}/V_{\text{A}}$ reached statistical significance while downward trends were observed in FEV_1 , FVC, VC and TLC. $V_{\text{max}60\%}$, a measure of small airways flow corrected for total lung volume, declined 50% faster with age than $V_{\text{max}70\%}$ or $V_{\text{max}80\%}$ (measures of medium and larger airways flow) consistent with progressive small airways impairment.

Table 1 also summarizes the contribution of inflammation. Lung volume metrics (FVC, VC, TLC, FEV_1 , and MVV) decreased more strongly with hs-CRP than with age. On multivariate stepwise linear regression analysis, age was retained as a weak independent predictor for FVC, VC, and TLC.

Discussion

We found that patients with TM have pulmonary function abnormalities mostly consistent with small airway disease, characterized by relative hyperinflation (RV/TLC) in 32%, decreased $\text{FEF}_{25\%-75\%}$ in 61%, and non-uniform distribution of ventilation in 44%. Khong *et al.* (2003) used high resolution inspiratory/expiratory chest computerized tomography (CT) to document air trapping consistent with small airways obstruction. Air trapping scores

were correlated with FEV₁, FEV₁/FVC, and FEF_{25%-75%} (Khong *et al*, 2003). On autopsy, iron was concentrated in bronchiolar epithelial and mucous glands. Haemosiderin-laden macrophages are present in bronchoalveolar lavage, often in quantities similar to those observed in idiopathic pulmonary haemosiderosis, as well as lymphocytic infiltrates suggestive of alveolitis (Cooper *et al*, 1980; Priftis *et al*, 2006). Taken together, these findings suggest diffuse small bronchiolar and patchy alveolar inflammation and obstruction.

A much smaller subset of patients had pure restrictive lung disease (16%), with normal volume-corrected flow metrics (Vmax_{80%/70%/60%}). The aetiology of restrictive disease is unclear but was most strongly correlated with hs-CRP. Restrictive disease is common in systemic inflammatory diseases but often accompanied by fibrosis. Some prior reports have found fibrosis on CT or biopsy in TM patients (Freedman *et al*, 1990; Zakyntinos *et al*, 2001) while others have not (Cooper *et al*, 1980; Tai *et al*, 1996). Enlarged livers or spleens could theoretically limit lung expansion but we found no association between liver and lung volumes.

A few of our findings are discordant with previous work. The relatively small fraction of true restrictive disease is concordant with our prior work and a few others, but contrary to a larger body of evidence (Grisaru *et al*, 1990; Khong *et al*, 2003; Piatti *et al*, 2006; Tai *et al*, 1996). However, our patients were all well-transfused, had begun chelation early in life, and covered a broad range of ages, all factors that might influence the relative distribution of obstructive and restrictive disease.

We also found that patients exhibited normal diffusing capacity when normalized to both alveolar volume (D_Lco_{sb}/V_A) and haemoglobin, as described previously (Hoyt *et al*, 1986; Keens *et al*, 1980). Many papers cite decreased D_Lco_{sb}, corrected for haemoglobin, but do not correct for differences in lung volume (Cooper *et al*, 1980; Freedman *et al*, 1990; Khong *et al*, 2003; Tai *et al*, 1996). In these instances, restrictive lung disease or borderline low volumes would result in the observance of abnormally low D_Lco_{sb} that may be normal if corrected for lung volume. Our finding suggests that pulmonary vascular density is preserved in well-transfused TM patients, consistent with their low prevalence of pulmonary hypertension (Aessopos *et al*, 2004).

The clinical significance of pulmonary disease in TM remains unclear. Thalassaemia patients do not complain of ventilatory limitations and have adequate breathing reserve on cardiopulmonary exercise testing. The restrictive component of the disease is mild and progresses slowly with age (Piatti *et al*, 2006). However, with improved access to iron chelation and monitoring, thalassaemia patients can expect a near normal lifespan and these “mild” changes may become more limiting.

In summary, TM patients have pulmonary abnormalities most consistent with small airways obstructive disease and mild restrictive lung disease. Hyperinflation was found in about a third of our patients, non-uniform distribution of ventilation (another marker for small airways obstruction) in almost a half of our patients, and true restrictive lung disease in only about one sixth of our patients. Lung volumes and expiratory flow rates decreased slowly with age, consistent with an insidious inflammatory process. We speculate that iron deposition in the lungs from transfusion-related iron overload is a mechanism in disease progression but that other factors, such as iatrogenic cyclic anaemia and ineffective erythropoiesis, may play a role in chronic airway inflammation.

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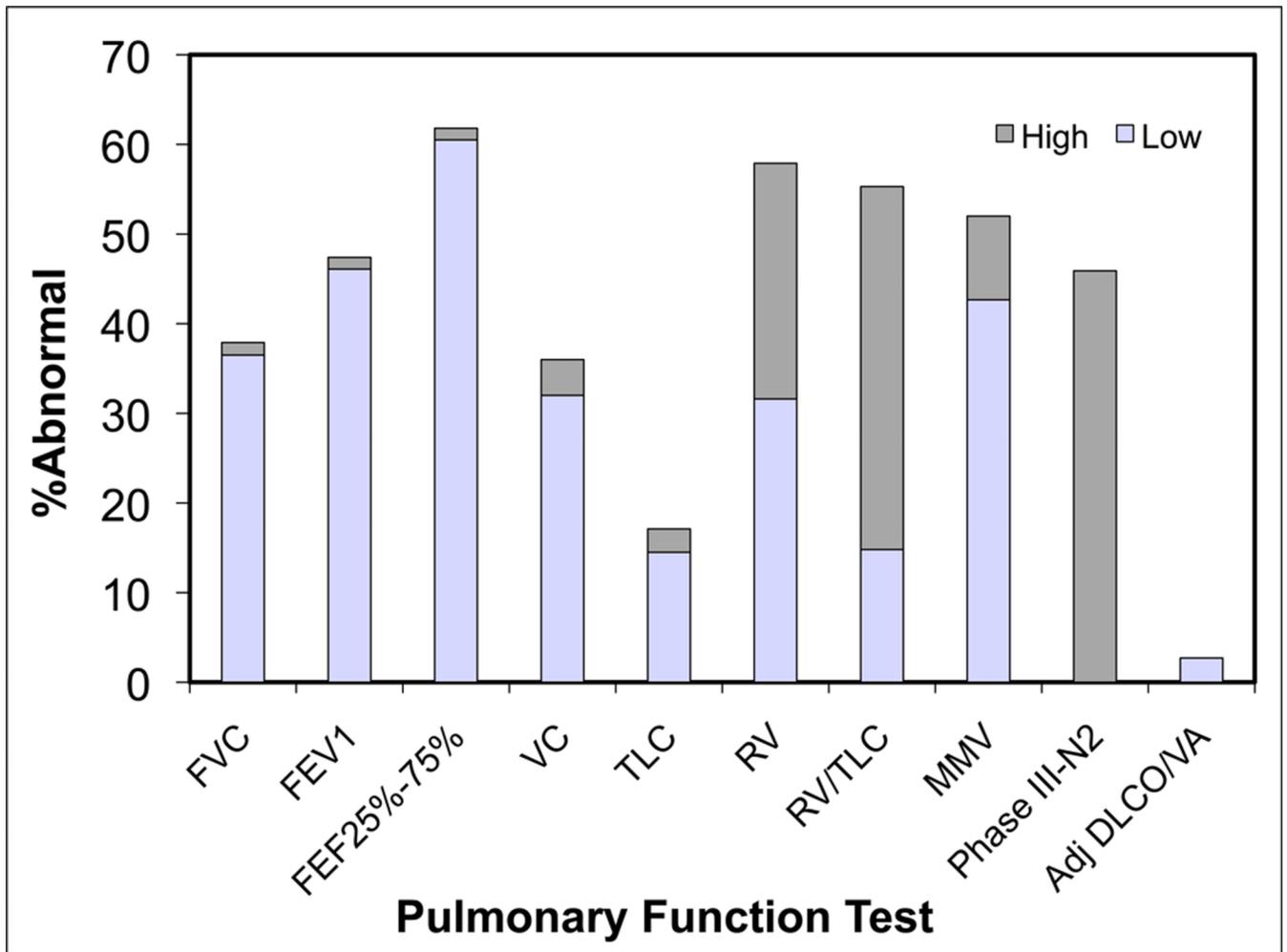


Figure 1.

The percentage of patients with abnormal pulmonary function tests.

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; FEF25-75, 25%–75% forced expiratory flow; VC, vital capacity; TLC, total lung capacity; RV, residual volume; MVV, maximum voluntary ventilation; Phase III-N₂, phase III of the single breath nitrogen washout curve; Adj DLCO/VA, diffusing capacity of the lung for carbon monoxide corrected for alveolar volume

Table 1

Statistically significant correlations between pulmonary function tests, age, and inflammation.

	Age		hs-CRP	
	r	p	r	p
Vmax _{60%}	-0.51	0.0001*	-0.10	0.39
Vmax _{70%}	-0.41	0.0003*	-0.05	0.68
Vmax _{80%}	-0.36	0.003*	-0.06	0.63
adj D _L co _{sb} /VA	-0.352	0.006*	0.10	0.40
FEF _{25-75%}	0.26	0.022	-0.07	0.55
FVC	-0.29	0.01	-0.36	0.002*
VC	-0.25	0.04	-0.31	0.007*
TLC	-0.22	0.05	-0.30	0.010*
RV	0.19	0.10	-0.10	0.42
FEV ₁	-0.19	0.10	-0.30	0.009*
MVV	-0.10	0.40	-0.36	0.002*
Phase III N ₂	0.09	0.41	0.15	0.22
PEF	0.05	0.64	-0.09	0.54
RV/TLC	0.01	0.90	0.03	0.78

* indicates significance after Bonferroni correction.

hs-CRP, high sensitivity C-reactive protein; Vmax_{60%}, 70%, 80%, maximal expiratory flows at 60%, 70% and 80% total lung capacity (TLC); adj D_Lco_{sb}/VA, diffusing capacity of the lung for carbon monoxide corrected for alveolar volume; FEF_{25%-75%}, 25%-75% forced expiratory flow; FVC, forced vital capacity; VC, vital capacity; RV, residual volume; FEV₁, forced expiratory volume in 1 second; MVV, maximum voluntary ventilation; Phase III N₂, phase III of the single breath nitrogen washout curve; PEF, peak expiratory volume.