RESEARCH PAPER

# Pulmonary Dysfunction in Transfusion-Dependent Thalassemia and Response to Intensive Chelation Therapy

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**Objectives**: To evaluate pulmonary functions in children with transfusion-dependent thalassemia, and its reversal (lung dysfunction) using intensive intravenous chelation with desferrioxamine (DFO) (4 weeks). **Methods**: This descriptive study enrolled 77 children with transfusion-dependent thalassemia. Pulmonary function test (PFT) and iron load (serum ferritin (SF) & T2* MRI of heart and liver) were done. PFT included spirometry, total lung capacity (TLC) by helium dilution test and diffusion capacity by carbon monoxide (DLCO). Follow-up PFT was available for 13 children with moderate to severe lung dysfunction given intravenous DFO. **Results**: 50 (68.8%) patients had lung dysfunction, most commonly diffusional impairment (48; 96%), and reduced TLC (11; 22%); and none had obstructive pattern. 9 (81.8%) patients with restrictive defect had moderate to severely deranged DLCO. PFT and T2* MRI values were inversely correlated with serum ferritin. Among 13 patients receiving intensive chelation for 4 weeks, significant improvement was noticed in forced expiratory volume in one minute/ forced vital capacity ratio (ΔFEV1/FVC) ($P$=0.009), ΔDLCO ($P$=0.006) and ΔSF ($P$=0.01). **Conclusions**: Pulmonary dysfunction is common in children with multi-transfused thalassemia, and routine screening by PFT needs to be part of the management guidelines.

**Keywords**: *Desferrioxamine, Iron, Hemosiderosis, Pulmonary function tests.*

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Pulmonary dysfunction is being increasingly recognized as one of the sequelae affecting a large proportion of patients with transfusion-dependent thalassemia (TDT)[1-5]. The mechanisms of lung injury in TDT include complications of regular blood transfusions and chronic hypoxia, pulmonary hemosiderosis, pulmonary hyper-tension as well as associated cardiac dysfunction. Restrictive lung injury has been reported as a common pattern of lung dysfunction in TDT in a few previous studies [1,2], although obstructive [3] and diffusional impairment [4,5] have also been described as other patterns of lung injury.

Intensive chelation therapy (ICT) using intravenous desferrioxamine (DFO) is an effective treatment for reversal of cardiac dysfunction in TDT [6,7]. However, the role of the same in reversing lung damage has not been studied. This study was done to evaluate the pattern of pulmonary dysfunction in patients with transfusion-dependent thalassemia, and its reversal using ICT with DFO.

## METHODS

This descriptive study was conducted after institutional ethics committee clearance at the thalassemia day care center of a public tertiary care hospital in Delhi, between November, 2017 and April, 2019. We included children older than 7 years with TDT, who were registered at our center and had been receiving regular blood transfusions and chelation therapy as per institutional criteria. We excluded patients with acute respiratory infections, pulmonary tuberculosis, HIV infection, congestive cardiac failure and history of smoking. Informed written consent was obtained from parents (in case of minor participants) or participants aged ≥18 years.

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Taking the prevalence of restrictive lung dysfunction in patients with TDT as 70% [1,5] with 15% relative precision and 95% confidence level, a sample size of 74 was calculated.

A detailed history and physical examination were recorded for all participants. Details like age at which transfusions were started, number of blood transfusions received, annual blood requirement over the preceding one year (mL/kg), and details of chelation therapy were recorded. Mean pretransfusion hemoglobin over the preceding one year was computed from records. Chest radiograph was performed to rule out any infection and evidence of interstitial lung disease.

All participants underwent pulmonary function tests (PFTs) that included spirometry, total lung capacity (TLC) and diffusion capacity (DLCO) (Benchmark-PK Morgan device); best of three technically acceptable values was used. These tests were performed in the respiratory laboratory of Vallabh Bhai Patel Chest Institute, Delhi, by a single technician under the supervision of a respiratory specialist for all patients. Spirometry measured forced expiratory volume in first one second of expiration (FEV1) and forced vital capacity (FVC). Helium dilution technique and carbon monoxide diffusion technique were used to measure TLC and DLCO of patients, respectively. DLCO measurements were adjusted for the degree of anemia. PFT values were compared with predicted values (for age, sex and height) and expressed as percentage of predicted normal values. Reference standards for Indian children [8] were used for interpretation of predicted values for spirometry indices. For interpretation of predicted values of DLCO and TLC, standards given by American Thoracic Society [9] were used. PFT was reported as normal, restrictive, obstruc-tive, or diffusional impairment. Restrictive disease [10] was defined as reduction in TLC to less than 80% and diffusional impairment [10] as a reduction in DLCO to less than 80%. Obstructive pattern [9] was defined as decrease in ratio of FEV1 and forced vital capacity (FVC) to a value below 80%; grading of severity of obstructive lung dysfunction was done based on the percentage of FEV1 of the predicted normal value.

Iron load assessment of participants was done by serum ferritin levels (chemiluminescence immunoassay method), and cardiac and hepatic $T_2$*MRI. Cardiac and hepatic hemosiderosis were estimated using $T_2$*MRI (GE Signa HD XTh 1.5 Tesla Vol MR). Patients were categorized into four groups based on their $T_2^*$MRI results according to following cut-off points: hepatic hemosiderosis: normal >6.3 milliseconds (ms), mild 6.3-2.7 ms, moderate 2.7-1.4 ms and severe <1.4 ms; and cardiac hemosiderosis was classified as normal >20ms, mild 12-20 ms, moderate 8-12 ms and severe <8 ms [11].

Deranged lung function was described as follows: DLCO <40% of predicted – severe dysfunction, 40-59% - moderate dysfunction, and 60-79% mild dysfunction. Restrictive pattern was categorized as mild – 70-79%, moderate – 60-69% and severe <60% of predicted TLC. Obstructive pattern was categorized as mild – 70-100%. moderate – 60-69% and severe <60% of predicted $FEV_1$. Children with moderate to severe dysfunction were administered ICT (daily IV DFO, 40 mg/kg infused over 6 hours, with mid-infusion 2 mg/kg oral vitamin C) for four weeks duration, along with their usual chelation therapy. PFT and serum ferritin levels were repeated after four weeks of ICT to ascertain improvement.

*Statistical analysis*: Data were entered in Microsoft Excel file and analyzed using SPSS Version 20.0. Wilcoxon-signed rank test was used to evaluate improvement in PFT following intervention. We estimated Spearman rank correlation coefficient between PFT and iron status as measured by serum ferritin, $T_2$*MRI of heart and liver. *P* value <0.05 was considered as significant.

## RESULTS

We enrolled 77 patients with TDT (73 β-thalassemia major, one heterozygous sickle cell-β thalassemia, and three heterozygous Hb Eβ-thalassemia) aged 7 years - 30 years (83% aged <18 year, 58.4% males). As per age-appropriate criteria (<18 years) [12], 61 (95%) had normal BMI, three had thinness, while none had severe thinness. Similarly, for age >18 years (*n*=13), 8 had normal BMI, two had mild thinness, and one had moderate thinness, as per standard criteria [15]. The mean (SD) pre-transfusion hemoglobin and the annual blood requirement was 8.6 (0.4) g/dL and 239.6 (32.9) mL/kg/year, respectively. All participants were receiving iron chelation therapy. Eight patients were receiving deferasirox (DFX) alone, and 18 deferiprone (DFP) alone; with 51 receiving combinations of chelating drugs (DFP+DFX, 29; DFO+DFP, 13; DFO+DFX, 8; DFO+DFP+DFX, 1). The median (IQR) SF of the study participants was 2735 (2735-4470.5) mg/dL.

The PFT and serum ferritin values were available for all 77 patients but results of T2*MRI of heart and liver were available for only 40. Pulmonary dysfunction was noticed in 50 (64.9%) participants. Diffusional impairment alone was detected in 39 patients, restrictive defect alone was seen in 11 patients, while nine patients had both. Diffusional impairment was severe in three patients and moderate in 18 patients. The patient with heterozygous sickle cell-β thalassemia had mild impairment of diffusional capacity. Amongst the participants with restrictive lung dysfunction, nine patients had mild decrease, and one each had moderate and severe reduction in TLC. None of the participants had obstructive defect. The mean (SD) FEV1/FVC, TLC and DLCO were 101 (6.4), 96.1 (13.0) and 73.1 (21.8), respectively. No child had FEV1/FVC <80% of predicted; whereas, 11 and 48 children had <80% predicted values for TLC and DLCO, respectively.

Chest radiographs were unremarkable in all patients, and echocardiography revealed impaired left ventricular ejection fraction (LVEF) in one child. None of the patients had evidence of pulmonary hypertension on echocardiography. Amongst 40 children in whom T2* MRI was done, hepatic iron overload alone was seen in 22 (55%) participants, and 16 (40%) of them had impaired PFT. Both cardiac and hepatic iron overload was seen in 11 participants and 8 of them had impaired PFT; seven

participants did not have evidence of cardiac or hepatic iron overload on T2* MRI but three of them had impaired PFT. There was inverse correlation present between all pulmonary function indices ($P$>0.05). Serum ferritin had low but significant correlation with cardiac iron overload ($r$ = -0.33, $P$=0.04) but not with hepatic iron load (r =- 0.27, $P$=0.10) (**Table I**).

Of the 17 patients given ICT, post-ICT PFT results were available only for 13 (76.5%) patients (1 non-compliant, 3 refused for repeat PFT). The median (IQR) serum ferritin of these 13 patients decreased significantly after ICT [2634 (2318-4386) vs 2177 (1691.5-3330.5) mg/dL; $P$=0.016]. There was also a significant improve-ment in PFT after four weeks of ICT (**Web Table I**, **Fig. 1**).

**Table I Correlation Between Pulmonary Function Tests, T2*MRI Values and Serum Ferritin in Children With Transfusion Dependent Thalassemia ($N$=40)**

| *Parameter* | *Hepatic T2* MRI values* | *Cardiac $T_2$* MRI values* | *Serum ferritin* |
|---|---|---|---|
| FEV1 | 0.13 | 0.05 | -0.07 |
| FVC | 0.08 | 0.08 | -0.07 |
| FEV1/FVC | 0.15 | -0.11 | -0.06 |
| TLC | 0.32 | 0.14 | -0.04 |
| DLCO | 0.10 | -0.14 | -0.008 |

*Values are in Pearson correlation coefficients (r). All [a]P>0.05. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEV1/FVC: forced expiratory volume in one second to forced vital capacity; TLC: total lung capacity; DLCO: single breath diffusing capacity of the lung by carbon monoxide. [a]Spearman rank correlation coefficient used to estimate P value.*

## DISCUSSION

We found diffusional impairment to be the most common pattern of lung dysfunction in TDT patients. A much lower prevalence of the diffusional impairment (3%) and a higher prevalence of restrictive dysfunction (16%) was reported by Sohn, et al. [3]. These differences may have been due to differences in race, or because they adjusted the diffusion capacity values for alveolar volumes, which is a non-standard practice [10] and only preferred when there is large lung volume reduction due to pneumonectomy.

Restrictive lung disease in TDT as measured by decreased TLC has been reported in 35-79% of patients with thalassemia [1,2]. The lower incidence of restrictive lung disease in present study group could be due to adequate chelation of registered patients in our centre since an early age. The difference may also have been due to different parameters used to define restrictive lung pattern; while Boddu, et al. [1] used spirometry parameters to define restrictive lung dysfunction, we used TLC. A much higher incidence of restrictive dysfunction as reported by Arora, et al. [13] could be due to inclusion of diffusional impairment as part of restrictive defect, whereas most of the researchers attribute diffusional defect to be due to parenchymal damage rather than restrictive defect. Absence of obstructive defect in this study is similar to 3.2% having obstructive defect from another cohort from Delhi [5]. Obstructive lung dysfunction has been described in a few other studies [3] as the most common pattern depending on decrease in FEV 25%-75% values, which again, is not a recommended method for spirometry reporting [9].

We did not find a significant correlation between TLC and DLCO although majority of patients with restrictive defect also had diffusional impairment. This lack of statistical significance may be explained by a lesser number of patients with restrictive defect in our study group. We believe that most of our patients were detected early as pulmonary diffusion defect was seen in the majority while reduced lung volume was seen only in a few patients. Unless, intervened at early stage, it is possible that several of them might develop restrictive pattern in future.

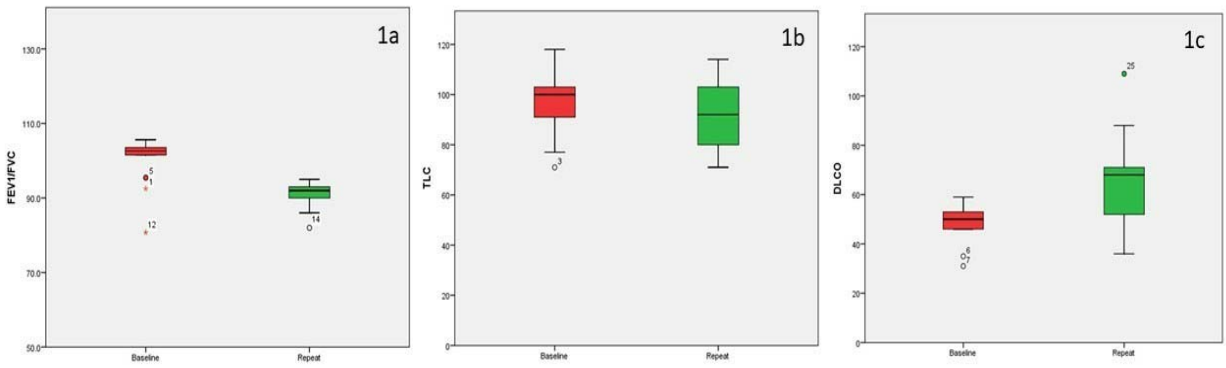


**Fig. 1** Effect of intensive intravenous chelation therapy with desferrioxamine on lung function tests ($n$=13). *a*) Change in FEV1/FVC; *b*) Change in TLC; *c*) Change in DLCO.

**WHAT THIS STUDY ADDS?**

- Diffusional impairment was the most common pulmonary dysfunction seen in children with transfusion-dependent thalassemia.
- The pulmonary dysfunction did not correlate with cardiac or hepatic iron load as measured by T2*MRI.

The use of intravenous DFO has been shown to cause life-threatening pulmonary syndrome in patients with TDT receiving prolonged intravenous infusion (lasting more than 24 hour) [14]. A dose-dependent toxicity (>10 mg/kg/h) has also been suggested [14] as a possible mechanism. In this study, we infused DFO intravenously over 4 hours without any untoward effect in any patient. The number of patients treated with ICT was small and follow-up PFT were not available for almost a quarter of these, which suggests the need for confirmation with a larger sample.

Our results suggest early diffusional impairment in TDT and its reversibility by intensive chelation therapy in a few patients. We suggest considering annual screening for pulmonary dysfunction in patients with TDT.

*Ethics clearance*: Institutional Ethics Committee for Human Research, UCMS; No. IEC-HR/2017/32/97 dated Oct 17, 2017.
*Contributors*: SG: conceptualized the study; NP, PD,RK: were involved in data collection; RK: provided laboratory support; PD,NP: drafted the manuscript; SG,RK: provided critical input. All authors approved the final manuscript and are accountable for the manuscript.
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**Web Table I Effect of 4-Week Intensive Chelation Therapy (ICT) With Intravenous Desferrioxamine in Multi-transfused Children with Pulmonary Dysfunction (*N*=13)**

| *Parameters* | *Before ICT* | *After ICT* | *P value* |
|---|---|---|---|
| FEV1 (%) | 78.3 (69.2-84.2) | 78 (70.5-89.5) | 0.07 |
| FVC (%) | 77.1 (67.1-81.7) | 78 (69-85.5) | 0.34 |
| FEV1/FVC | 102.6 (98.5-104) | 92 (89-93.5) | 0.009 |
| TLC (%) | 100 (88.5-103.5) | 92 (78.5-108.5) | 0.23 |
| DLCO (%) | 50 (46-53) | 68 (50-76) | 0.006 |

*Values in median (IQR). [a]P<0.01. FEV1: forced expiratory volume in one second; FVC: forced vital capacity; FEV1/FVC: forced expiratory volume in one second to forced vital capacity; TLC: total lung capacity; DLCO: single breath diffusing capacity of the lung by carbon monoxide.*

*[a] Wilcoxan-signed rank test was used to estimate p value*