

Lungs in thalassaemia major patients receiving regular transfusion

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Lungs in thalassaemia major patients receiving regular transfusion. D.Y.H. Tai, Y.T. Wang, J. Lou, W.Y. Wang, K.H. Mak, H.K. Cheng. ©ERS Journals Ltd 1996.

ABSTRACT: Progressive tissue iron deposition from multiple blood transfusions is common in beta-thalassaemia and pulmonary iron deposition may result in parenchymal damage. The objectives of this study were to: 1) determine the predominant pulmonary dysfunction in patients with thalassaemia major; and 2) demonstrate that parenchymal disease, if present, is at the level of the alveolocapillary membrane.

Fourteen thalassaemia major patients (13 nonsmokers) receiving regular blood transfusion and without any history of chronic respiratory disease were recruited. Pulmonary function tests and echocardiography were performed before the scheduled transfusions. Three patients with the most restricted lung function were selected for high resolution computerized tomography (CT) of the lungs.

One patient had an obstructive pattern with a forced expiratory volume in one second as percentage of forced vital capacity (FEV₁/FVC) of 71%. Four patients demonstrated a restrictive pattern, as defined by total lung capacity (TLC) less than 80% predicted with normal FEV₁/FVC%. Twelve patients had pulmonary transfer factors for carbon monoxide (T_{L,CO}) below 80% pred, even after correction for the anaemia, indicating parenchymal disease. Eight of these 12 patients had alveolocapillary membrane defect, as demonstrated by a gas transfer factor of the pulmonary membrane (T_m) less than 80% pred. Mean resting arterial oxygen saturation was 95±2 (range 92–98)%. Eleven patients had oxygen desaturation of 5% or more during exercise on a bicycle ergometer, consistent with interstitial lung disease. There was no clinical or echocardiographic evidence of heart failure. Percentage predicted TLC was inversely correlated with age (r=-0.547; p=0.043). Both percentage predicted TLC and T_{L,CO} were not correlated with iron burden or desferrioxamine ratio. High resolution CT in the three selected patients showed no evidence of pulmonary fibrosis.

We conclude that thalassaemia major patients have a predominant restrictive lung dysfunction with pulmonary parenchymal disease and alveolocapillary membrane block. The restrictive and interstitial lung disease could not be accounted for by iron loading or pulmonary fibrosis in our patients.

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In beta-thalassaemia major (TM), there is abnormal haemoglobin synthesis which results in decreased oxygen delivery to the tissues, ineffective erythropoiesis, and iron overload [1]. To improve the oxygen carrying capacity of the blood, patients receive regular transfusions. However, this may result in generalized iron loading, such as in the heart, liver, endocrine organs and lungs [2]. Iron deposition in the lungs has been observed on postmortem examination of patients receiving multiple blood transfusions [3, 4]. Pulmonary iron deposition may result in parenchymal damage.

FACTOR *et al.* [2] have documented pulmonary parenchymal disease in patients with TM [2], and other investigators have observed a restrictive defect [5, 6]. In contrast, other studies have concluded that an obstructive pattern is more common [7, 8].

This study was, therefore, conducted to determine the predominant lung dysfunction in patients with TM, and to demonstrate that parenchymal lung disease, if present, is at the level of the alveolocapillary membrane.

Methods

Patients

Patients were enrolled from the Department of Paediatrics, Tan Tock Seng Hospital, Singapore. The anthropometric and prestudy data are as shown in table 1. All patients had TM requiring regular blood transfusion at 4 weekly intervals. However, only four patients (Nos. 4,

Table 1. – Anthropometric and prestudy data of all patients

Pt No.	Age yrs	Sex	Height cm	Weight kg	Hb g·dL ⁻¹	Iron burden g·kg ⁻¹ BW	DFO ratio
1	9	M	130	23.0	7.9	0.58	0.270
2	10	F	128	26.1	7.3	0.35	0.380
3	10	F	130	23.0	8.8	0.74	0.290
4	11	M	137	27.0	8.7	0.62	0.018
5	13	M	142	34.5	8.4	0.98	0.390
6	13	M	146	34.0	8.6	1.02	0.420
7	13	F	147	36.4	8.4	0.94	0.011
8	14	F	130	28.5	10.2	0.98	0.330
9	15	F	153	40.0	9.4	0.88	0.430
10	18	M	147	36.0	6.8	1.04	0.320
11	18	M	158	41.0	9.3	0.89	0.320
12	19	F	155	37.5	9.7	1.13	0.013
13	20	F	156	48.2	8.8	0.87	0.014
14	21	M	167	45.0	8.1	0.90	0.510
Median	14		147	35.3	8.7	0.90	0.320
Mean	15		145	34.3	8.6	0.85	0.265
SD	4		12	7.9	0.9	0.21	0.175

Pt: patient; M: male; F: female; Hb: haemoglobin; DFO: desferoxamine; BW: body weight.

7, 12 and 13) were on regular chelation therapy, which consisted of nightly subcutaneous desferoxamine (DFO) injection five times a week, at a dose of 50 mg·kg⁻¹ body weight (BW).

There were 8 Chinese and 6 Malays. None had a history of chronic respiratory disease. Some patients complained of exertional dyspnoea but no abnormal respiratory signs were detected. All patients but one (No. 11) were life-long nonsmokers. Two patients (Nos. 10 and 11) on L-thyroxine replacement for hypothyroidism were clinically and biochemically euthyroid at the time of the study. Eight patients (Nos. 5, 6, 8, 9 and 11–14) had splenectomy, and of these, only two were compliant with penicillin prophylaxis for pneumococcal infection. Except for two patients (Nos. 5 and 8), there was no increased propensity to recurrent chest infection in the other splenectomized patients. Hepatomegaly was found in all patients. All of the patients were clinically stable and not in overt cardiac failure, and none were seropositive for the human immunodeficiency virus at the time of the study.

The lifetime transfusional iron burden (g·kg⁻¹ BW) was calculated based on the estimate that each unit of packed cells provided 167 mg of iron [9]. The cumulative amount of DFO was determined based on the medical records. The DFO ratio, as described by BRITTENHAM [10], was used to correct the transfusional iron burden for chelation therapy received:

$$\text{DFO ratio} = \frac{\text{total transfusional iron load (g)}}{\text{cumulative DFO (g)}}$$

Procedures

All the pulmonary function studies were performed on the day prior to scheduled transfusion by two technicians, according to the recommended standards [11].

The Wright peak flow meter was used to measure the peak expiratory flow rate (PEFR). Spirometry was measured by a dry rolling-seal spirometer (SensorMedics 2450). The best of at least three technically acceptable

values for PEFR, forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), maximum mid-expiratory flow rate (MMEFR) and flow-volume curves were selected. Functional residual capacity (FRC), residual volume (RV) and total lung capacity (TLC) were measured by body plethysmography (SensorMedics 6200) and expressed in litres corrected for body temperature, atmosphere pressure and saturation with water vapour (BTPS).

The transfer factor of the lungs for carbon monoxide (*T*_{L,CO}) was measured by the single-breath technique of OGIIVIE *et al.* [12], as modified by JONES and MEADE [13] (SensorMedics 6200 Autobox DL) and corrected for haemoglobin (Hb) concentration [14]. The gas mixture used to estimate *T*_{L,CO} contained 0.3% methane (CH₄), 0.3% acetylene (C₂H₂), 0.3% carbon monoxide (CO), 21% oxygen (O₂) and the balance nitrogen (N₂). The carbon monoxide transfer coefficient (*K*_{CO}) was computed according to the equation of KROGH [15]. The carbon monoxide back pressure was not corrected because it was negligible in nonsmokers [16, 17].

The gas transfer factor of the alveolocapillary membrane (*T*_m) and capillary volume (*V*_c) were estimated according to the methods of ROUGHTON and FORSTER [16]. The patient performed two single-breath *T*_{L,CO} measurements after breathing 60% oxygen for 10 min. Various workers have used wash-in periods of 3 min [18], 5 min [17], 7 min [19] and 20 min [20]. The initial test gas mixture comprised 0.3% CH₄, 0.3% C₂H₂, 0.3% CO, 60% O₂ and the balance N₂. A wash-out of 5 min was allowed between measurements [17].

The above sequence was then repeated after a 10 min interval [18], this time measuring *T*_{L,CO} at 21% O₂. The test gas mixture comprised 0.3% CH₄, 0.3% C₂H₂, 0.3% CO, 21% O₂ and the balance N₂. The *T*_{L,CO} at higher oxygen concentration was performed first to minimize back pressure from CO-Hb, as less CO is absorbed at higher oxygen tension [18, 21, 22]. The coefficients of variation for *T*_{L,CO} and alveolar volume (*V*_A) had to be less than 5% and for *T*_m and *V*_c they had to be less than 10% to be accepted [21].

The pulmonary function results were expressed as percentages of predicted normal values [22–26] (table 2).

Table 2. – Reference sources for the predicted norms

Respiratory function	Age yrs	First author	[Ref]
FEV ₁	9–21	ROSENTHAL	[23]
FVC			
PEFR			
MMEFR	9–21	NGIAM	[24]
TLC	9–21	ROSENTHAL	[25]
RV			
FRC			
VC			
T _{L,CO}	9–21	ROSENTHAL	[25]
KCO			
T _m	8–16	COTES	[26]
	17–21	BUCCI	[22]
V _c	8–16	COTES	[26]
	17–21	BUCCI	[22]

FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; MMEFR: maximum mid-expiratory flow rate; TLC: total lung capacity; RV: residual value; FRC: functional residual capacity; VC: vital capacity; T_{L,CO}: transfer factor of the lungs for carbon monoxide; KCO: carbon monoxide transfer coefficient; T_m: gas transfer factor of the pulmonary membrane; V_c: capillary volume.

Progressive exercise tests were conducted on a cycle ergometer (Siemens EM 840). The initial workload was 10 W, and was increased by 10 W every minute until exhaustion. Oxygen saturation (Sp_o₂) was monitored by pulse oximetry (SensorMedics Sat-Trak™).

Three patients with the worst restrictive lung function (Nos. 10, 13 and 14 Table 1), as measured by the lowest TLC percentage predicted × T_{L,CO} percentage predicted were selected for high resolution computed tomography (HRCT).

Two-dimensional echocardiography was performed prior to transfusion.

The chest radiographs were graded by a radiologist and a respiratory physician independently, without any knowledge of the medical history or clinical findings using the International Labour Office (ILO) classification [27].

Statistical analysis

The sigmastat package (Jandel Scientific, San Rafael, CA, USA) was used for data analysis. The results are reported as mean±SD and median value. Correlation analysis was performed using Pearson's product moment correlation coefficient. A result was considered significant when the p-value was less than 0.05.

Results

The results are summarized in tables 3 and 4. One patient (No. 8) had an obstructive pattern with FEV₁/FVC of 71% (table 3). Her MMEFR (37% pred) was also the lowest in this study sample. She did not have any past or familial history of asthma and was a nonsmoker. Interestingly, 6 months later, she developed bronchial asthma while awaiting blood transfusion. She was also prone to recurrent chest infection which, in retrospect, could have been asthmatic attacks.

Table 3. – Spirometry results of all patients

Pt No.	FEV ₁ % pred	FVC % pred	FEV ₁ /FVC %	PEFR % pred	MMEFR % pred
1	84	75	95	114	73
2	105	98	95	136	103
3	91	90	89	81	76
4	96	84	97	132	98
5	98	93	87	129	81
6	70	69	86	96	61
7	102	96	93	92	81
8	70	86	71	105	37
9	92	90	89	100	55
10	74	67	93	98	68
11	93	84	93	126	102
12	58	52	98	91	100
13	89	81	95	105	98
14	66	56	98	82	98
Median	90	84	93	102	81
Mean	85	80	91	106	81
SD	15	14	7	18	20

For definitions see legends to tables 1 and 2.

Four patients (Nos. 6, 10, 12 and 14) demonstrated a restrictive pattern, as defined by TLC below 80% pred with normal FEV₁/FVC (table 4). Twelve patients had T_{L,CO} below 80% pred, even after correction for Hb concentration, indicating parenchymal disease. Eight of these 12 patients were found to have alveolocapillary membrane defect (T_m <80% pred).

The mean resting arterial oxygen saturation was 95±2% (range 92–98%). Six patients had Sp_o₂ of 95% or less. During exercise on a bicycle ergometer, 11 patients desaturated by 5% points or more, suggesting interstitial lung disease [28, 29].

Age was significantly correlated with iron burden (r=0.630; p=0.016). Percentage predicted TLC was inversely correlated with age (r=-0.547; p=0.043). Percentage predicted TLC did not correlate with iron burden (r=-0.177; p=0.546) or DFO ratio (r=-0.215; p=0.461).

Percentage predicted T_{L,CO} and percentage predicted T_m were not correlated with age (r=-0.446; p=0.010 and r=-0.154; p=0.599, respectively), iron burden (r=-0.189; p=0.517; and r=-0.035; p=0.905, respectively) or DFO ratio (r=-0.051; p=0.864; and r=0.051; p=0.864, respectively).

Percentage predicted T_m only correlated with percentage predicted T_{L,CO} (r=0.674; p=0.008). There was no correlation with percentage predicted KCO (r=0.431; p=0.124) or percentage oxygen desaturation with exercise (r=0.236; p=0.417).

There was no significant relationship between resting oxygen saturation and iron burden (r=-0.209; p=0.473). Percentage arterial oxygen desaturation with exercise did not correlate with percentage predicted T_{L,CO} (r=0.136; p=0.64) or percentage predicted T_m (r=0.236; p=0.417).

The absolute agreement with regard to profusion on the chest radiographs between the two observers was 86%. This compares very favourably with the figures reported by other investigators [30]. One patient was scored 1/1, three patients obtained a grading of 0/1, and seven patients had 0/0. The two observers differed in the two remaining patients who were graded 0/1 and 0/0 by the radiologist, and 0/0 and 0/1, respectively, by the respiratory physician.

Table 4. – Results of pulmonary function tests and ejection fraction for all patients

Pt No.	FRC*	RV*	TLC*	VC*	TLCO*	KCO*	T _m *	V _c *	Sp _o 2 %	Desat %	EF %
1	85	112	91	79	61	100	36	84	96	7	65
2	89	89	85	84	66	89	43	72	97	8	61
3	118	138	88	85	71	88	89	46	98	11	55
4	77	65	81	87	77	92	103	48	93	3	61
5	96	96	87	84	59	70	74	37	95	21	61
6	99	106	75	65	83	111	81	75	98	15	75
7	107	123	100	102	74	74	84	82	93	14	59
8	132	166	104	79	65	77	67	82	92	4	57
9	95	93	84	82	86	98	119	86	97	9	64
10	80	136	73	49	25	42	40	110	96	6	74
11	35	78	88	92	60	76	83	110	96	16	60
12	72	103	73	57	63	43	40	183	94	9	53
13	78	129	81	64	56	77	71	61	94	15	57
14	53	75	60	55	55	88	54	124	97	2	68
Median	87	105	84	80	64	82	73	82	96	9	61
Mean	87	107	84	74	64	80	70	86	97	10	62
SD	25	28	11	15	15	20	25	38	8	6	7

*: results expressed as percentage of predicted; Sp_o2: oxygen saturation measured by pulse oximetry; Desat: oxygen desaturation on exercising on an ergometer; EF: ejection fraction. For further definitions see legend to table 2.

There was no evidence of interstitial lung fibrosis on the HRCT in the three selected patients with the worst restrictive impairment. No cardiac dysfunction was detected on echocardiography (Table 4).

Discussion

Restrictive lung function abnormality with pulmonary parenchymal disease was the most striking observation documented in this study. Interstitial oedema is an unlikely cause of the pulmonary dysfunction observed [2, 6], as none of the patients had any clinical or echocardiographic evidence of heart failure. Our findings are consistent with those of FACTOR *et al.* [2], COOPER *et al.* [5] and LUYT *et al.* [31]. What is unique in our study is that we showed that the parenchymal disease is at the level of the alveolocapillary membrane, using T_m measurements. Although T_m (and V_c) measurements are difficult to achieve and there was a wide scatter of values, there was nevertheless a statistically significant correlation with TLCO measurements in our patients. Arterial oxygen desaturation on exercise provided further evidence of a pulmonary parenchymal disease [28]. Surprisingly, arterial oxygen desaturation on exercise did not correlate with any measurement of CO transfer through the lungs. However, other factors such as decreased lung transit time, decreased ventilation-to-perfusion (V'/Q') ratio, decreased lung compliance and low mixed venous oxygen tension may play a role [28, 29].

Arterial hypoxaemia at rest has been commonly observed in patients with TM [5, 7]. Six of 14 patients had an Sp_o2 of 95% and below compared with 28 of 29 patients in the study by FACTOR *et al.* [2]. We found that percentage predicted TLC was inversely correlated with age but not iron burden or DFO ratio. LUYT *et al.* [31] reported no correlation between pulmonary dysfunction and patient's age or iron burden, whereas FACTOR *et al.* [2] reported an inverse relationship of percentage predicted TLC with age, iron burden and DFO ratio. He suggested that the duration of iron overload may be more important

in this disease than the actual amount of iron provided through transfusions.

CAPPELL *et al.* [4] found massive accumulation of haemosiderin in alveolar phagocytes in the perivascular and supporting framework of the lungs in postmortem studies of one of five cases of transfusion siderosis. This was also observed by WITZLEBEN and WYATT [3] and COOPER *et al.* [5]. However, there was no increase in fibrous tissue in the lungs [4–6]. Some authors [2, 5] have suggested that a process related either to the intrinsic disease or to the frequent transfusion therapy may have interfered with the rapid alveolar growth in the first 8 yrs of life [32, 33].

WARD and REMICK [34] suggested that the generation of free hydroxyl radicals from iron deposition may promote tissue damage, but LUYT *et al.* [31] were unable to find a causal relationship between free radical production and tissue damage in the lungs. Another paper postulated the facilitation of tissue damage by certain microorganisms which are iron-dependent [35]. Iron deposition in the airway lining may cause intrinsic airway obstruction [7, 8].

Immunological mechanisms may also contribute to these abnormalities. SANTAMARIA *et al.* [36] demonstrated that in patients with pre-existing bronchial hyperreactivity, transfusion may trigger bronchoconstriction 24 h afterward. FREEDMAN *et al.* [37] reported a pulmonary syndrome of sudden onset within 5–9 days of receiving DFO infusions. This syndrome, probably mediated by immunoglobulin E (IgE) hypersensitivity reaction, was characterized by cough, tachypnoea, hypoxaemia, restrictive pulmonary dysfunction, and diffuse interstitial pattern on chest roentgenograms. Hence regular transfusions and intravenous DFO therapy may result in progressive pulmonary impairment.

Minor abnormalities were observed on the chest radiographs in our study. The chest roentgenogram is relatively insensitive for detecting early fibrotic changes in the lungs or assessing its severity. In a pooled series of patients with interstitial lung disease, nearly 10% had normal chest radiographs, although most had abnormal spirometry, reduced TLCO or abnormal exercise test [38].

Exclusion of underlying fibrosis in our study is based mainly on negative HRCT findings in three of the most affected patients. This does not entirely rule out parenchymal fibrosis in the other patients. The absence of fibrosis is consistent with postmortem findings of TM patients conducted previously [5, 6].

In conclusion, restrictive lung disease with alveolo-capillary membrane block is the predominant pulmonary dysfunction in thalassaemia major. We were unable to show that the deposition and prolonged accumulation of iron played a major role in the pathogenesis of the pulmonary disease. Furthermore, fibrosis could not be demonstrated in the lungs by radiographic methods. Further studies are required to study the cause-and-effect relationship of frequent blood transfusions and intravenous desferrioxamine and to explain the functional and radiographic abnormalities from the morphological viewpoint.

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