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Lung function in allogeneic bone marrow transplantation recipients

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ABSTRACT: In order to investigate the incidence of pulmonary function complications following bone marrow transplantation (BMT), 17 patients with leukaemia and 8 with aplastic anaemia were sequentially assessed over a one year period. Before BMT, all the patients were free of respiratory symptoms and had both normal chest X-ray and routine lung function tests. However, 5 patients disclosed airway hyperreactivity. Aplastic anaemia patients had significantly lower haemoglobin-adjusted diffusing capacity for carbon monoxide (DLCO) than those with leukaemia, a finding significantly related to the lower haemoglobin values shown in the former individuals. Following BMT there were transient mild to moderate reductions in DLCO and static lung volumes; moreover, patients with leukaemia had lower DLCO than those with aplastic anaemia. Fourteen of the 25 patients had ventilatory defects, including 10 individuals with bronchial hyperresponsiveness. Post-BMT lung function changes were transiently accompanied by mild to moderate symptoms of respiratory disease in most of the patients.
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Allogeneic bone marrow transplantation (BMT) is being increasingly and successfully used in the treatment of various severe haematological disorders [1, 2]. However, a number of serious and potentially fatal complications have emerged following BMT, irrespective of the presence or absence of graft-*versus*-host disease (GVHD) [3, 4]. Most prominent among these are pulmonary complications, namely restrictive lung disease associated with interstitial pneumonitis [5]. In addition, there is increasing evidence to support the view that obstructive lung disease can also be present in BMT recipients, usually associated with GVHD [4, 6–13].

Following the observation of a fatal necrotizing obliterative bronchiolitis shortly after BMT [10], we had repeatedly noticed various patterns of both subclinical and clinical lung function abnormalities in BMT patients. These findings led us to investigate the incidence of lung function impairment in these patients. The present study results in part from a comprehensive screening programme to assess the incidence of respiratory function complications following BMT. The preliminary data collected from BMT recipients during one year in our institution are reported here.

Methods

Patients

Over a period of eighteen months, 32 patients received 33 allogeneic BMT from first degree relatives (twice in a single patient). Three patients were not included because they were too young to co-operate and 4 others died shortly after BMT. Of the remaining 25 patients reported on here there were 17 females and 8 males, aged 24±2 yrs (SEM) (table 1). Thirteen were nonsmokers, 10 mild smokers (6.5±1.7 pack-yrs) and 2 exsmokers. Marrow transplantation was undertaken in 16 patients for acute leukaemia, in 8 for severe aplastic anaemia, one of them with an associated nocturnal haemoglobinuria, and in one for chronic myelogenous leukaemia. All donors were HLA-identical, mixed lymphocyte culture negative siblings. Before BMT, all leukaemic patients were conditioned with cyclophosphamide (120 $mg \cdot kg^{-1}$ body weight) plus total body irradiation (10 Gy) with lung shielding at 8 cGy (dose-rate ranging from 5.85–8 $cGy \cdot min^{-1}$). Three of the 8 patients with aplastic anaemia were conditioned with cyclophosphamide alone (200 $mg \cdot kg^{-1}$), while the other 5 received the same dose of the drug plus thoracoabdominal irradiation (total dose of 6 Gy with the dose-rate ranging from 53–73 $cGy \cdot min^{-1}$) with lung shielding. Prophylaxis against GVHD was made with a standard methotrexate regimen in 23 patients. Two patients, one with aplastic anaemia and another with chronic myelogenous leukaemia, received cyclosporin A. Oral consent was obtained from all the participants in accordance with the ethical standards of the Clinical Research Committee from the Hospital Clinic-Universitat de Barcelona.

Table 1. – Clinical data of bone marrow transplantation recipients (n=25)

Patient	Sex	Age yrs	Smoking habits pack-yrs	Haematological disease	GVHD Day	Present situation	Follow-up period Day
1	M	14	Non	ALL (L_2)	-	D	360
2	M	22	Yes (14)	AA	Ac (II) (24)	A	390
6	F	8	Non	AA	Ac (II) (60) Cr (I) (210)	A	390
7	M	12	Non	ANLL (M_2)	Ac (II) (12) Cr (II) (75)	D	210
9	F	16	Non	ANLL (M_4)	-	A	390
10	M	20	Yes (6)	AA	Cr (II) (55)	A	390
11	M	23	Yes (9)	AA	Cr (I) (75)	A	390
12	M	30	Yes (7)	AA	-	A	300
13	M	35	Non	ANLL (M_1)	Ac (III) (14)	D	30
15	M	37	Ex (9)	ANLL (M_2)	Ac (IV) (16)	D	30
16	M	28	Non	ANLL (M_1)	Ac (IV) (34)	D	45
17	F	10	Non	ANLL (M_5)	Ac (II) (30) Cr (I) (45)	A	390
18	F	25	Yes (3)	ANLL (M_4)	Ac (IV) (40)	D	60
20	M	24	Non	AA	Ac (IV) (38)	D	60
21	M	44	Non	ANLL (M_5)	Ac (IV) (27)	D	30
22	F	40	Non	AA (PNH)	Ac (I) (45)	D	90
23	F	11	Non	ANLL (M_2)	Ac (I) (20)	D	90
24	F	31	Yes (10)	AA	Ac (IV) (45)	D	90
26	M	24	Yes (3)	ALL (T-cell)	Ac (II) (45) Cr (I) (90)	A	390
27	M	24	Yes (7)	ANLL (M_3)	Ac (II) (45) Cr (II) (90)	A	390
28	M	31	Yes (5)	ANLL (M_1)	Ac (III) (20) Cr (II) (100)	D	180
29	M	32	Ex (16)	ANLL (M_4)	Ac (III) (30) Cr (II) (60)	A	390
30	M	9	Non	ALL (unknown)	-	D	120
31	F	24	Non	ANLL (M_5)	-	A	390
32	M	39	Yes (1)	CML	Ac (II) (13)	D	45

ALL: acute lymphoblastic leukaemia; AA: aplastic anaemia; ANLL: acute non lymphocytic leukaemia; CML: chronic myeloid leukaemia; PNH: paroxysmal nocturnal haemoglobinuria; GVHD: graft-*vs*-host disease; Ac: acute, (I) mild, (II) moderate, (III) moderate-severe, (IV) severe; Cr: chronic, (I) mild, (II) moderate, (III) severe; D: dead; A: alive.

Procedures

Pulmonary evaluation was sequentially carried out before the conditioning regimen for BMT, and each 30 days during the first trimester, and then each trimester following BMT (the day of bone marrow infusion was called "day 0"). In the event of any unexpected clinical complication, this evaluation was supplemented as needed. Lung function tests were performed as follows:

a) single-breath carbon monoxide diffusing capacity (D_{LCO}) (Transfer Model A, PK Morgan) with correction for anaemia [14];

b) thoracic gas volume (Vtg) and airway resistance, expressed as specific conductance (sGaw), using a constant-volume body plethysmograph (Body-Pneumotest, E Jaeger) [15], inspiratory capacity (IC) and vital capacity (VC) (Pulmonary System, HP 47804A, Hewlett-Packard) and residual volume (RV) being calculated from Vtg;

c) forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and maximal flow rates at 50 and 75% of FVC ($MEF_{50\%}$ and $MEF_{75\%}$, respectively) (HP 47804A);

d) arterial blood gases were measured using an IL-1302 and the alveolar-arterial O_2 difference ($P(A\text{-}a)O_2$) was calculated according to the simplified form of the alveolar gas equation ($P_{AO_2}=P_{IO_2}-P_{ACO_2}/R$), where P_{AO_2} and P_{ACO_2} are the oxygen and carbon dioxide alveolar partial pressures, respectively, P_{IO_2} is the inspired O_2 partial pressure, and R corresponds to the exchange respiratory ratio (0.8);

e) an abbreviated methacholine challenge test (one breath of 25 $mg \cdot ml^{-1}$ followed by 4 additional breaths of 25 $mg \cdot ml^{-1}$) after first inhaling control saline solution, according to PARKER *et al.* [16].

Before BMT, all adult lung function tests except sGaw

were expressed as a percentage of our own predicted values [17, 18]; for children, we used those of CASAN [19] for forced spirometry, those of POLGAR and PROMADHAT [20] for static lung volumes, and those of the Intermountain Thoracic Society for DLCO and carbon monoxide transfer coefficient (KCO) [21]. Methacholine (MTH) responsiveness was considered positive when FEV_1 fell from baseline by 16% after 1 breath or 20% after 4 breaths. These percentage falls correspond to x±2 sd values after a methacholine challenge test, from 115 subjects selected from 860 healthy nonsmokers [22]. Only $P(A\text{-}a)O_2$ values measured before transplantation are reported. After BMT, ventilatory abnormalities were defined as follows: obstructive ventilatory pattern (FEV_1 below 85% and FEV_1/FVC ratio below 90% of pre-BMT values, and/or abnormal (positive) MTH hyperresponsiveness); restrictive ventilatory pattern (FVC below 85%, FEV_1/FVC ratio above 100% and total lung capacity (TLC) below 90% of pre-BMT values), and, mixed ventilatory pattern (similar abnormal percentages, but without the aforementioned criteria for obstructive or restrictive pattern). In our laboratory these percentages for FVC and FEV_1 represent a five-fold increase in their respective intra-individual coefficients of variation; for those of TLC they are twice as high.

Statistics

Both paired and unpaired Student's t-tests, Mann-Whitney's test and Fisher's exact test were used for statistical analysis when appropriate. Bonferroni's correction for the level of significance was used when multiple comparisons were carried out. To investigate the influence of the type of haematological disease (aplastic anaemia *versus* leukaemia) on haemoglobin-adjusted DLCO values measured before BMT, a stepwise multiple regression analysis was carried out. Height, age, weight, sex, haemoglobin (Hb) and type of disease were treated as covariables while actual DLCO was considered as the dependent variable, *i.e.*;

$$DLCO = a \cdot height + b \cdot age + c \cdot weight + d \cdot sex + e \cdot Hb + f \cdot disease + g$$

Both the level of significance (p values) and the amount of variability (r^2) explained by each covariable included in the regression were taken into account to analyse the results.

Results

Pulmonary manifestations before BMT

Before marrow transplantation all the patients were free of respiratory symptoms and had both normal chest physical examinations and chest X-ray films. One patient (Case 6) had whooping cough when she was 5 yrs old and another (Case 17) had asymptomatic asthma. Overall, static and dynamic lung volumes were well preserved and none of the patients showed ventilatory abnormalities (table 2). Five patients (Cases 1, 9, 17, 18, and 30) had bronchial hyperreactivity, as defined by an abnormal methacholine responsiveness, and three others (Cases 15, 28 and 32) an FEV_1/FVC ratio lower than 70% (66% each) the interpretation of which remains uncertain. Although mean DLCO was within normal limits, fourteen individuals had values below 80% predicted (range 65–79%); mean KCO was slightly reduced (79% predicted). Mean $P(A\text{-}a)O_2$ was also within the normal range, but eight patients displayed abnormally high values (>3.3 kPa (25 mmHg); range 3.4–5.4 kPa).

Except for a significantly lower FEV_1, presumably without physiological significance, patients with leukaemia had lung function tests within the normal range. In contrast, patients with aplastic anaemia had both DLCO and KCO values below 80% predicted. As a result, the latter group showed a significantly lower DLCO, differences in KCO just failing to reach significance (p=0.059). Likewise, haemoglobin was significantly lower in the aplastic anaemia group. In contrast, mean $P(A\text{-}a)O_2$ values were not significantly different from each other. As regards DLCO, the cumulative r^2 shown after introducing each covariable in the stepwise multiple regression analysis was as follows: height, 0.56; sex, 0.66; and Hb, 0.70. Accordingly, the amount of variability explained by each of these covariables was 56, 10 and 4%, respectively. The type of haematological disorder did not provide any further reduction in DLCO variance, such that the r^2 fell from 0.7 to 0.69 when this covariable was added to the regression analysis; instead, haemoglobin concentration played a significant role. No differences were shown when patients where grouped according to sex, age (younger and older than 20), smoking habits, or clinical outcome.

Pulmonary manifestations following BMT

Twenty of the 25 patients developed acute and/or chronic GVHD (proven by skin biopsy) of different degrees of severity: eleven had an acute form, two a chronic one, and the remaining seven both forms. All but two patients with acute GVHD and all but one with both acute and chronic GVHD underwent regular treatment with steroids. In addition, six patients received azathioprine and two others anti-thymocytic globulin. At the end of the follow-up, eleven patients had survived. Pulmonary causes of death (8 patients) were interstitial pneumonitis, either idiopathic (2) or secondary to cytomegalovirus (2), and bacterial (2) or fungal (2) lung infections. Extrapulmonary causes (6 patients) included a gastrointestinal disorder related to GVHD (3), generalized sepsis (1), and recurrence of the haematological disease (2).

Table 3 shows the mean actual values for all lung function tests for those patients who were included over the follow-up period. Whereas both DLCO and KCO fell significantly early after transplantation (day 30), static lung volumes were reduced at day 120 (FVC, TLC and VC were diminished by 10% and IC by 20% of pre-BMT values). Except for a significant fall in IC (to 2.7 *l*, p<0.006) alone at day 60, by days 60 and 90 all

Table 2. – Pre-transplantation lung function tests for all the participants grouped according to their haematological disorder (mean±SEM)

		All n=25	Leukaemia n=17	p	Aplastic anaemia n=8
Age	yrs	25±2	24±3		25±3
(range)		(8–44)	(9–44)		(8–40)
FVC	%	103±2	101±2		107±4
FEV_1	%	97±2	95±2	<0.03	103±3
FEV_1/FVC	%	80±2	80±2		82±2
$MEF_{50\%}$	%pred	88±4	85±5		95±7
$MEF_{75\%}$	%pred	66±4	64±5		72±7
Vtg	%pred	103±4	102±4		105±9
IC	%pred	101±3	101±4		103±3
VC	%pred	102±2	101±2		106±4
RV/TLC	%	26±1	26±1		27±3
sGaw	$l \cdot s^{-1} \cdot kPa^{-1}$	1.5±0.1	1.6±0.1		1.3±0.2
DLCO	%pred	81±3	85±3	<0.02	73±3
KCO	%pred	79±3	83±3		73±3
$P(A\text{-}a)O_2$	kPa	2.9±0.3	2.8±0.3		3.1±0.4
Hb	$mmol \cdot l^{-1}$	7.4±0.3	8.3±0.3	<0.0001	5.7±0.2

p values refer to differences between each haematological disease. FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; $MEF_{50\%}$, $MEF_{75\%}$: maximal expiratory flow when 50% and 75% of FVC remains to be exhaled, respectively; Vtg: thoracic gas volume; IC: inspiratory capacity; VC: vital capacity; TLC: total lung capacity; sGaw: specific airways conductance; DLCO: diffusing capacity for carbon monoxide; KCO: carbon monoxide transfer coefficient; $P(A\text{-}a)O_2$: alveolar-arterial oxygen tension difference; Hb: haemoglobin concentration.

Table 3. – Mean±SEM of pre-BMT lung function tests before and after transplantation (n=12)*

		Pre-BMT	Day 30	Day 120	Day 210	Day 300	Day 390
FVC	l	4.2±0.4	4.0±0.4	3.6±0.5 p<0.006	3.7±0.5 p<0.001	3.8±0.5	3.7±0.5
FEV_1	l	3.5±0.3	3.3±0.3	3.0±0.4	3.1±0.4	3.1±0.4	3.1±0.4
FEV_1/FVC	%	84±2.1	84±1.9	83±4.0	82±4.3	80±4.4	80±4.7
$MEF_{50\%}$	$l \cdot s^{-1}$	4.6±0.5	4.6±0.6	4.2±0.6	4.3±0.6	4.2±0.6	4.3±0.7
$MEF_{75\%}$	$l \cdot s^{-1}$	2.0±0.3	2.1±0.3	1.8±0.4	1.9±0.3	1.7±0.4	1.8±0.4
Vtg	l	2.5±0.3	2.5±0.3	2.5±0.2	2.7±0.3	2.9±0.3	2.8±0.3
IC	l	2.9±0.3	2.6±0.3	2.3±0.4 p<0.002	2.7±0.4	2.7±0.4	2.3±0.4 p<0.007
TLC	l	5.4±0.6	5.2±0.6	4.8±0.6 p<0.0001	5.3±0.7	5.6±0.6	4.9±0.6
VC	l	4.1±0.5	4.1±0.5	3.7±0.6 p<0.004	3.9±0.5	3.9±0.5 p<0.002	3.6±0.6
RV/TLC	%	25±2.0	23±1.8	27±3.5	26±3.0	32±3.6	30±5.0
sGaw	$l \cdot s^{-1} \cdot kPa^{-1}$	1.6±0.1	1.6±0.1	1.8±0.3	2.4±0.6	1.6±0.3	1.7±0.3
DLCO	$mmol \cdot min^{-1} \cdot kPa^{-1}$	8.0±0.7	6.9±0.6 p<0.001	7.4±0.8	7.9±0.8	8.7±0.8	8.4±1.0
KCO	$mmol \cdot min^{-1}$	1.8±0.1	1.6±0.1 p<0.005	1.6±0.1	1.6±0.1	1.8±0.1	1.8±0.1

*: n may differ for some variables; p values refer to differences between pre-BMT measurements and their respective days; BMT: bone marrow transplantation. For other abbreviations see legend to table 2.

lung volumes (not shown in the table) were close to day 30 values. The reductions in IC, TLC and VC at day 390 are probably related to the smaller number of patients (n=9) performing these lung function tests. By contrast, all the variables reflecting central and peripheral airflow limitation and/or air trapping remained essentially unchanged over the whole period of study. Alternatively, significant mild differences were observed in DLCO in leukaemic patients compared to those with aplastic anaemia at day 90 (86 *vs* 113% pre-BMT values, p<0.02), day 210 (83 *vs* 108% pre-BMT, p<0.04), day 300 (92 *vs* 118% pre-BMT), and day 390 (86 *vs* 124% pre-BMT)

$p<0.002$); by days 30, 60, and 120 mean DLCO was also lower among leukaemic patients (84, 89 and 80% pre-BMT, respectively) compared to individuals with aplastic anaemia (93, 95 and 102% of pre-BMT, respectively), although without reaching statistical significance. There were no differences between patients grouped according to sex, age (under and over the age of 20), tobacco smoking or acute and chronic GVHD.

Despite these transient but mild to moderate lung function abnormalities, analysis of individual data revealed that Case 6 had severe irreversible chronic airflow obstruction with air trapping and pulmonary hyperinflation from day 75, consistent with obliterative bronchiolitis, the main characteristics of which have been reported elsewhere [11]. A second patient (Case 1) disclosed mild reductions in FEV_1 and in FEV_1/FVC ratio between days 210 and 300, still reversible after a standard bronchodilator therapeutic regimen. The third patient with obstructive defects (Case 30) had similar but milder and more transient (only at day 30) functional abnormalities than the latter subject. Five other individuals (Cases 2, 7, 10, 11 and 15) developed transient airway hyperreactivity mostly during the first trimester following BMT. While four out of the five patients with signs of bronchial hyperreactivity prior to BMT continued to have methacholine hyperresponsiveness, either transiently (Case 1) or permanently (Cases 17, 18 and 30), the remaining patient (Case 9) had normal methacholine responsiveness throughout the study. Finally, six patients showed either transient (Case 9) or permanent (Cases 2, 20, 26, 30 and 31) mild to moderate restrictive ventilatory changes, associated with airway hyperreactivity in three (Cases 2, 9 and 30). In brief, there were 14 individuals with ventilatory disturbances: eight with an obstructive ventilatory pattern alone, three others with restrictive abnormalities alone, and a mixed ventilatory pattern in the remaining three. In ten individuals there was either transient or permanent bronchial hyperreactivity.

Ten patients (Cases 1, 6, 10, 11, 17, 26–29, and 31) showed respiratory clinical complications at different stages of the follow-up. These were of mild to moderate severity, transient, lasting for one to three weeks and, occasionally, recurrent (Cases 10, 11 and 26). They were characterized by productive cough, sometimes with purulent phlegm, and mild to moderate shortness of breath, together with wheezing on auscultation. These episodes reversed within one to two weeks either spontaneously or after oral antibiotics, bronchodilators and/or high dose corticosteroids. In nine out of the fourteen individuals with lung function abnormalities (Cases 1, 6, 10, 11, 17, 18, 20, 26 and 30) ventilatory capacity disturbances coincided with clinical manifestations of respiratory disease. In seven (Cases 2, 6, 7, 10, 11, 15 and 26), ventilatory abnormalities were detected after the onset of either acute or chronic GVHD. However, no correlation was found between GVHD and the presence of an obstructive ventilatory pattern. Only one of the patients with restrictive ventilatory changes died of interstitial pneumonia (Case 20).

Discussion

Before bone marrow transplantation

Before the transplantation procedure, static and dynamic lung volumes, DLCO, and alveolar-arterial oxygen difference were within normal limits but, interestingly, there was an increased incidence of subclinical airway responsiveness to methacholine. The prevalence of airway hyperreactivity using a methacholine dose-response curve in 115 healthy nonsmoking persons living in our area is 9% [22]. This contrasts with the observed 5 out of 25 patients in the present study. Although airway hyperreactivity has not been studied so far in haematological patients who undergo BMT, a 14% incidence of airflow obstruction has previously been documented by routine forced spirometry in a population of BMT recipients (tobacco smoking was not specified) [23]. Presumably, the mechanism of bronchial hyperreactivity may be related to repeated subclinical bacterial and/or viral pulmonary infections in an otherwise immunocompromised host.

Our data confirm, as have other studies [24–28], that before marrow transplantation mean DLCO may range between mild to moderate reductions and normal values, even after adjustment for anaemia. Of further importance, however, was that the lower DLCO in patients with aplastic anaemia compared to those with leukaemia was mainly due to the lower haemoglobin concentration in the former individuals. Given that both types of haematological disease may be influenced by the same factors that may potentially damage the alveolar-capillary interphase, such as chemotherapy and pulmonary infections, and that $P(A\text{-}a)O_2$ was very close in each group, it appears reasonable to relate the lower values of DLCO in aplastic anaemia to the severity of the anaemia. The correction factor described by COTES *et al.* [14] of a Dm/Vc ratio of 0.7 (Dm: diffusing capacity of the alveolar-capillary membrane; Vc: volume of blood in the alveolar capillaries) is not necessarily valid for the patients in this study, and may be different for the two groups of patients. Consequently, the recommended adjustment of DLCO by one of the three accepted standardized formulae [14] may not be sufficient to properly correct the actual DLCO value when the haemoglobin concentration is extremely low and may explain some of the reduced gas transfer values found in previous studies [24–28]. This is consistent with the notion recently pointed out in a DLCO standardization conference [29] that all current methods of adjusting for Hb involve unproved assumptions, none having been uniformly accepted. An additional point is that there may still have been a tendency for DLCO to be lower in the smokers due to raised carboxyhaemoglobin, and this may have contributed to the lower DLCO in the patients with aplastic anaemia of whom 5 out of 8 were current and heavier smokers (8.4±0.8 pack-yrs) compared with only 5 out of 17 patients with leukaemia (3.8±1.0 pack-yrs).

Alternatively, the present data are in part at variance with those published by LINK *et al.* [25] where patients with leukaemia had less lung hyperinflation but more airflow obstruction than patients with aplastic anaemia.

Table 2. – Pre-transplantation lung function tests for all the participants grouped according to their haematological disorder (mean±SEM)

		All n=25	Leukaemia n=17	p	Aplastic anaemia n=8
Age	yrs	25±2	24±3		25±3
(range)		(8–44)	(9–44)		(8–40)
FVC	%	103±2	101±2		107±4
FEV_1	%	97±2	95±2	<0.03	103±3
FEV_1/FVC	%	80±2	80±2		82±2
$MEF_{50\%}$	%pred	88±4	85±5		95±7
$MEF_{75\%}$	%pred	66±4	64±5		72±7
Vtg	%pred	103±4	102±4		105±9
IC	%pred	101±3	101±4		103±3
VC	%pred	102±2	101±2		106±4
RV/TLC	%	26±1	26±1		27±3
sGaw	$l \cdot s^{-1} \cdot kPa^{-1}$	1.5±0.1	1.6±0.1		1.3±0.2
DLCO	%pred	81±3	85±3	<0.02	73±3
Kco	%pred	79±3	83±3		73±3
$P(A\text{-}a)O_2$	kPa	2.9±0.3	2.8±0.3		3.1±0.4
Hb	$mmol \cdot l^{-1}$	7.4±0.3	8.3±0.3	<0.0001	5.7±0.2

p values refer to differences between each haematological disease. FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; $MEF_{50\%}$, $MEF_{75\%}$: maximal expiratory flow when 50% and 75% of FVC remains to be exhaled, respectively; Vtg: thoracic gas volume; IC: inspiratory capacity; VC: vital capacity; TLC: total lung capacity; sGaw: specific airways conductance; DLCO: diffusing capacity for carbon monoxide; Kco: carbon monoxide transfer coefficient; $P(A\text{-}a)O_2$: alveolar-arterial oxygen tension difference; Hb: haemoglobin concentration.

Table 3. – Mean±SEM of pre-BMT lung function tests before and after transplantation (n=12)*

		Pre-BMT	Day 30	Day 120	Day 210	Day 300	Day 390
FVC	l	4.2±0.4	4.0±0.4	3.6±0.5 p<0.006	3.7±0.5 p<0.001	3.8±0.5	3.7±0.5
FEV_1	l	3.5±0.3	3.3±0.3	3.0±0.4	3.1±0.4	3.1±0.4	3.1±0.4
FEV_1/FVC	%	84±2.1	84±1.9	83±4.0	82±4.3	80±4.4	80±4.7
$MEF_{50\%}$	$l \cdot s^{-1}$	4.6±0.5	4.6±0.6	4.2±0.6	4.3±0.6	4.2±0.6	4.3±0.7
$MEF_{75\%}$	$l \cdot s^{-1}$	2.0±0.3	2.1±0.3	1.8±0.4	1.9±0.3	1.7±0.4	1.8±0.4
Vtg	l	2.5±0.3	2.5±0.3	2.5±0.2	2.7±0.3	2.9±0.3	2.8±0.3
IC	l	2.9±0.3	2.6±0.3	2.3±0.4 p<0.002	2.7±0.4	2.7±0.4	2.3±0.4 p<0.007
TLC	l	5.4±0.6	5.2±0.6	4.8±0.6 p<0.0001	5.3±0.7	5.6±0.6	4.9±0.6
VC	l	4.1±0.5	4.1±0.5	3.7±0.6 p<0.004	3.9±0.5	3.9±0.5 p<0.002	3.6±0.6
RV/TLC	%	25±2.0	23±1.8	27±3.5	26±3.0	32±3.6	30±5.0
sGaw	$l \cdot s^{-1} \cdot kPa^{-1}$	1.6±0.1	1.6±0.1	1.8±0.3	2.4±0.6	1.6±0.3	1.7±0.3
DLCO	$mmol \cdot min^{-1} \cdot kPa^{-1}$	8.0±0.7	6.9±0.6 p<0.001	7.4±0.8	7.9±0.8	8.7±0.8	8.4±1.0
Kco	$mmol \cdot min^{-1}$	1.8±0.1	1.6±0.1 p<0.005	1.6±0.1	1.6±0.1	1.8±0.1	1.8±0.1

*: n may differ for some variables; p values refer to differences between pre-BMT measurements and their respective days; BMT: bone marrow transplantation. For other abbreviations see legend to table 2.

lung volumes (not shown in the table) were close to day 30 values. The reductions in IC, TLC and VC at day 390 are probably related to the smaller number of patients (n=9) performing these lung function tests. By contrast, all the variables reflecting central and peripheral airflow limitation and/or air trapping remained essentially unchanged over the whole period of study. Alternatively, significant mild differences were observed in DLCO in leukaemic patients compared to those with aplastic anaemia at day 90 (86 *vs* 113% pre-BMT values, p<0.02), day 210 (83 *vs* 108% pre-BMT, p<0.04), day 300 (92 *vs* 118% pre-BMT), and day 390 (86 *vs* 124% pre-BMT)

p<0.002); by days 30, 60, and 120 mean DLCO was also lower among leukaemic patients (84, 89 and 80% pre-BMT, respectively) compared to individuals with aplastic anaemia (93, 95 and 102% of pre-BMT, respectively), although without reaching statistical significance. There were no differences between patients grouped according to sex, age (under and over the age of 20), tobacco smoking or acute and chronic GVHD.

Despite these transient but mild to moderate lung function abnormalities, analysis of individual data revealed that Case 6 had severe irreversible chronic airflow obstruction with air trapping and pulmonary hyperinflation from day 75, consistent with obliterative bronchiolitis, the main characteristics of which have been reported elsewhere [11]. A second patient (Case 1) disclosed mild reductions in FEV_1 and in FEV_1/FVC ratio between days 210 and 300, still reversible after a standard bronchodilator therapeutic regimen. The third patient with obstructive defects (Case 30) had similar but milder and more transient (only at day 30) functional abnormalities than the latter subject. Five other individuals (Cases 2, 7, 10, 11 and 15) developed transient airway hyperreactivity mostly during the first trimester following BMT. While four out of the five patients with signs of bronchial hyperreactivity prior to BMT continued to have methacholine hyperresponsiveness, either transiently (Case 1) or permanently (Cases 17, 18 and 30), the remaining patient (Case 9) had normal methacholine responsiveness throughout the study. Finally, six patients showed either transient (Case 9) or permanent (Cases 2, 20, 26, 30 and 31) mild to moderate restrictive ventilatory changes, associated with airway hyperreactivity in three (Cases 2, 9 and 30). In brief, there were 14 individuals with ventilatory disturbances: eight with an obstructive ventilatory pattern alone, three others with restrictive abnormalities alone, and a mixed ventilatory pattern in the remaining three. In ten individuals there was either transient or permanent bronchial hyperreactivity.

Ten patients (Cases 1, 6, 10, 11, 17, 26–29, and 31) showed respiratory clinical complications at different stages of the follow-up. These were of mild to moderate severity, transient, lasting for one to three weeks and, occasionally, recurrent (Cases 10, 11 and 26). They were characterized by productive cough, sometimes with purulent phlegm, and mild to moderate shortness of breath, together with wheezing on auscultation. These episodes reversed within one to two weeks either spontaneously or after oral antibiotics, bronchodilators and/or high dose corticosteroids. In nine out of the fourteen individuals with lung function abnormalities (Cases 1, 6, 10, 11, 17, 18, 20, 26 and 30) ventilatory capacity disturbances coincided with clinical manifestations of respiratory disease. In seven (Cases 2, 6, 7, 10, 11, 15 and 26), ventilatory abnormalities were detected after the onset of either acute or chronic GVHD. However, no correlation was found between GVHD and the presence of an obstructive ventilatory pattern. Only one of the patients with restrictive ventilatory changes died of interstitial pneumonia (Case 20).

Discussion

Before bone marrow transplantation

Before the transplantation procedure, static and dynamic lung volumes, DLCO, and alveolar-arterial oxygen difference were within normal limits but, interestingly, there was an increased incidence of subclinical airway responsiveness to methacholine. The prevalence of airway hyperreactivity using a methacholine dose-response curve in 115 healthy nonsmoking persons living in our area is 9% [22]. This contrasts with the observed 5 out of 25 patients in the present study. Although airway hyperreactivity has not been studied so far in haematological patients who undergo BMT, a 14% incidence of airflow obstruction has previously been documented by routine forced spirometry in a population of BMT recipients (tobacco smoking was not specified) [23]. Presumably, the mechanism of bronchial hyperreactivity may be related to repeated subclinical bacterial and/or viral pulmonary infections in an otherwise immunocompromised host.

Our data confirm, as have other studies [24–28], that before marrow transplantation mean DLCO may range between mild to moderate reductions and normal values, even after adjustment for anaemia. Of further importance, however, was that the lower DLCO in patients with aplastic anaemia compared to those with leukaemia was mainly due to the lower haemoglobin concentration in the former individuals. Given that both types of haematological disease may be influenced by the same factors that may potentially damage the alveolar-capillary interphase, such as chemotherapy and pulmonary infections, and that $P(A\text{-}a)O_2$ was very close in each group, it appears reasonable to relate the lower values of DLCO in aplastic anaemia to the severity of the anaemia. The correction factor described by COTES *et al.* [14] of a Dm/Vc ratio of 0.7 (Dm: diffusing capacity of the alveolar-capillary membrane; Vc: volume of blood in the alveolar capillaries) is not necessarily valid for the patients in this study, and may be different for the two groups of patients. Consequently, the recommended adjustment of DLCO by one of the three accepted standardized formulae [14] may not be sufficient to properly correct the actual DLCO value when the haemoglobin concentration is extremely low and may explain some of the reduced gas transfer values found in previous studies [24–28]. This is consistent with the notion recently pointed out in a DLCO standardization conference [29] that all current methods of adjusting for Hb involve unproved assumptions, none having been uniformly accepted. An additional point is that there may still have been a tendency for DLCO to be lower in the smokers due to raised carboxyhaemoglobin, and this may have contributed to the lower DLCO in the patients with aplastic anaemia of whom 5 out of 8 were current and heavier smokers (8.4±0.8 pack-yrs) compared with only 5 out of 17 patients with leukaemia (3.8±1.0 pack-yrs).

Alternatively, the present data are in part at variance with those published by LINK *et al.* [25] where patients with leukaemia had less lung hyperinflation but more airflow obstruction than patients with aplastic anaemia.

Although it is difficult to reconcile some of these contrasting results with our data, differences may be in part attributable to two interrelated factors. It is possible that their results reflect differences introduced by the selection of the patients. In our study, we included all the patients consecutively transplanted in our institution during eighteen months; in contrast, LINK *et al.* [25] paid especial attention to individuals in whom obstructive bronchiolitis was present. A second potential factor might be related to the use of the prediction equations for dynamic and static lung volumes and DLCO. While we compared most of our adult and childhood lung function results to our own predicted values [17–19], which met both the ATS [30] and ECCS [31] recommendations, Link *et al.* used reference values developed before these standardizations were implemented.

After marrow transplantation

Transient reductions in static lung volumes and DLCO were found early after performing BMT. These mild to moderate functional abnormalities have been previously reported [23, 24, 26–28] and related to different factors, namely high dose corticosteroids, chemotherapy, transplantation with T-cell depleted bone marrow, higher total body irradiation dose and the development of GVHD [28]. Alternatively, it has been recently documented that healthy individuals may show transient respiratory muscle weakness during several weeks following upper respiratory tract infections [32]. Most of these factors may not only injure the lung parenchyma but also lead to a debilitating clinical condition, including cachexia and malnutrition, with generalized muscle weakness with or without steroid myopathy. Also of interest was the finding that leukaemia patients had a lower DLCO than aplastic anaemia patients from day 90 to day 390, probably reflecting the harmful effects of a higher pre-BMT total body irradiation.

Analysis of individual data revealed a predominance of restrictive defects in six patients, although three individuals displayed clear-cut obstructive ventilatory abnormalities. In addition, the overall incidence of bronchial hyperreactivity doubled. Furthermore, most of these new ventilatory changes were accompanied by transient symptoms and/or signs of respiratory disease which reversed either spontaneously or after a standard therapeutic regimen. In the same way as it probably occurs before transplantation, the reversible nature of this increased airway responsiveness to methacholine after BMT may also be caused by repeated bacterial and/or viral infections of both the upper and lower respiratory tract. Interestingly, an overall incidence of 4.9% of adenovirus infection in bone marrow transplantation recipients has been reported [33]. More recently, both chronic GVHD and prolonged methotrexate treatment have been identified as important risk factors for development of airflow obstruction (as assessed by mild decrements in the FEV_1/FVC ratio) in 281 adult patients one year after BMT [7]. In our study, however, a relationship between airway obstruction and GVHD has not been proven. It is also of note that a marked bronchial hyperresponsiveness has been documented in 9 out of 10 cardio-pulmonary transplant recipients, whose mechanism remains obscure [34]. Conceivably, the presence of post-transplantation bronchial hyperreactivity in both bone marrow and cardiopulmonary recipients might suggest a similar mechanism specifically related to the transplantation *per se*, regardless of other associated potential pathogenic factors.

To summarize, patients who consecutively underwent allogeneic bone marrow transplantation showed before the procedure normal ventilatory capacity, DLCO in the lower normal range and an increased incidence of subclinical airway responsiveness to methacholine. In addition, patients with aplastic anaemia had a lower DLCO than those with leukaemia, a finding principally related to the severity of the anaemia. After transplantation, there were transient slight reductions in both static lung volumes and DLCO and the incidence of bronchial hyperreactivity doubled, patients with leukaemia had a lower DLCO than those with aplastic anaemia. Most of these functional changes were accompanied by mild to moderate clinical manifestations of respiratory disease.

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References

1. Gale RP, Kersey JH, Bortin MM, *et al.* – Bone-marrow transplantation for acute lymphoblastic leukaemia. *Lancet*, 1983, 2, 663–667.
2. Storb R, Thomas ED, Buckner CD, *et al.* – Marrow transplantation in thirty "untransfused" patients with severe aplastic anemia. *Ann Intern Med*, 1980, 92, 30–36.
3. Neiman PE, Reeves W, Ray G, *et al.* – A prospective analysis of interstitial pneumonia and opportunistic viral infection among recipients of allogeneic bone marrow grafts. *J Infect Dis*, 1977, 136, 754–767.
4. Shulman HM, Sullivan KM, Weiden PL, *et al.* – Chronic graft-*versus*-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. *Am J Med*, 1980, 69, 204–217.
5. Buckner CD, Meyers JD, Springmeyer SC, *et al.* – Pulmonary complications of marrow transplantation. Review of the Seattle Experience. *Exp Hematol*, 1984, 12 (Suppl. 15), 1–5.
6. Beschorner WE, Saral R, Hutchins GM, Tutschka PJ, Santos GW. – Lymphocytic bronchitis associated with graft-*versus*-host disease in recipients of bone-marrow transplants. *N Engl J Med*, 1978, 299, 1030–1036.
7. Clark JG, Schwartz DA, Flournoy N, *et al.* – Risk factors for airflow obstruction in recipients of bone marrow transplants. *Ann Int Med*, 1987, 107, 648–656.
8. Kurzrock R, Kanojia M, Vellekoop L, *et al.* – Obstructive lung disease after allogeneic bone marrow transplantation. *Transplantation*, 1984, 37, 156–160.
9. Ralph DD, Springmeyer SC, Sullivan KM, Hackman RC, Storb R, Thomas ED. – Rapidly progressive air flow obstruction in marrow transplant recipients. Possible association between obliterative bronchiolitis and chronic graft-*versus*-host disease. *Am Rev Respir Dis*, 1984, 126, 641–644.
10. Roca J, Grañena A, Rodríguez-Roisin R, Alvarez P,

Agustí-Vidal A, Rozman C. – Fatal airway disease in an adult with chronic graft-*versus*-host disease. *Thorax*, 1982, 37, 77–78.
11. Rodríguez-Roisin R, Roca J, Grañena A, Agustí-Vidal A, Rozman C. – Obliterative bronchiolitis. A distinct pathophysiological form of pulmonary involvement in bone marrow transplantation. *Exp Hematol*, 1984, 12 (Suppl. 15), 12–14.
12. Wyatt SE, Nunn P, Hows JM, *et al.* – Airways obstruction associated with graft-*versus*-host-disease after bone marrow transplantation. *Thorax*, 1984, 39, 887–894.
13. Chan CH, Hyland RH, Hutcheon MA, *et al.* – Small-airways disease in recipients of allogeneic bone marrow transplants. An analysis of 11 cases and a review of the literature. *Medicine (Baltimore)*, 1987, 66, 327–340.
14. Cotes JE, Dabbs JM, Elwood PC, Hall AM, McDonald A, Saunders MJ. – Iron-deficiency anaemia; its effect on transfer factor for the lung, diffusing capacity and ventilation and cardiac frequency during submaximal exercise. *Clin Sci*, 1972, 42, 325–335.
15. Dubois AB, Botelho SY, Comroe JH Jr. – A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory diseases. *J Clin Invest*, 1956, 35, 327–335.
16. Parker CD, Bilbo RE, Reed CE. – Methacholine aerosol as test for bronchial asthma. *Arch Intern Med*, 1965, 115, 452–458.
17. Roca J, Sanchis J, Agustí-Vidal A, *et al.* – Spirometric reference values for a mediterranean population. *Bull Eur Physiopathol Respir*, 1986, 22, 217–224.
18. Roca J, Segarra F, Rodríguez-Roisin R, Cobo E, Martinez J, Agustí-Vidal A. – Static lung volumes and single-breath diffusing capacity. Reference values from a latin population. *Am Rev Respir Dis*, 1985, 131, A352.
19. Casán P. – *In:* Valores espirométricos de referencia para niños y adolescentes. Tesis Doctoral, Universitat Autónoma de Barcelona, 1985.
20. Polgar G, Promadhat V. – *In:* Pulmonary function testing in children: techniques and standards. WB Saunders Co, Philadelphia, 1971, p. 303.
21. Kanner RE, Morris AH. – *In:* Clinical pulmonary function testing. A manual of uniform laboratory procedures for the Intermountain area. Intermountain Thoracic Society, Salt Lake City, 1975.
22. Sala HL. – *In:* Hiperreactividad bronquial en una pòblación de referencia. Tesis Doctoral, Universitat de Barcelona, 1982.
23. Springmeyer SC, Flournoy N, Sullivan KM, Storb R, Thomas ED. – Pulmonary function changes in long-term survivors of allogeneic marrow transplantation. *In*: Recent advances in bone marrow transplantation. R.P. Gale ed., Liss, New York, 1983, pp. 343–353.
24. Depledge MH, Barrett A, Powles RI. – Lung function after bone marrow grafting. *Int J Radiat Oncol Biol Phys*, 1983, 9, 145–151.
25. Link H, Reinhard V, Blaurock M, Ostendorf P. – Lung function changes after allogenic bone marrow transplantation. *Thorax*, 1986, 41, 508–512.
26. Sørensen PG, Ernst P, Panduro J, Møller J. – Reduced lung function in leukaemia patients undergoing bone marrow transplantation. *Scand J Hematol*, 1984, 32, 253–257.
27. Springmeyer SC, Silvestri RC, Flournoy N, *et al.* – Pulmonary function of marrow transplant patients. I. Effects of marrow infusion, acute graft-*versus*-host disease, and interstitial pneumonitis. *Exp Hematol*, 1984, 12, 805–810.
28. Sutedja TG, Apperley JF, Hughes JMB, *et al.* – Pulmonary function after bone marrow transplantation for chronic myeloid leukaemia. *Thorax*, 1988, 43, 163–169.
29. American Thoracic Society. – Single breath carbon monoxide diffusing capacity (transfer factor). Recommendations for a standard technique. *Am Rev Respir Dis*, 1987, 136, 1229–1307.
30. American Thoracic Society. – Snowbird workshop on standardization of spirometry. *Am Rev Respir Dis*, 1979, 119, 831–837.
31. Quanjer PH. – Standardized lung function testing. Report of a Working Party "Standardization of lung function tests". European Community for Coal and Steel. *Bull Eur Physiopathol Respir*, 1983, 19 (Suppl. 5), 7–10.
32. Mier-Jedrzejowicz A, Brophy C, Green M. – Respiratory muscle weakness during upper respiratory tract infections. *Am Rev Respir Dis*, 1988, 138, 5–7.
33. Shields AF, Hackman RC, Fife KH, Corey L, Meyers JD. – Adenovirus infections in patients undergoing bone-marrow transplantation. *N Engl J Med*, 1985, 213, 529–533.
34. Glanville AR, Burke CM, Theodore J, *et al.* – Bronchial hyper-responsiveness after cardiopulmonary transplantation. *Clin Sci*, 1987, 73, 299–303.

Fonction pulmonaire chez les receveurs de transplantation de moelle osseuse allogénique. R. Rodriguez-Roisin, J. Roca, A. Grañena, A.G.N. Agustí, P. Marín , C. Rozman.

RÉSUMÉ: Pour investiguer l'incidence des complications fonctionnelles pulmonaires faisant suite à une transplantation médullaire (BMT), nous avons conduit une étude prospective du suivi de 25 patients consécutifs. Les données ont été appréciées en série avant et tous les 30 jours pendant le premier trimestre, ensuite tous les 3 mois jusqu'à une année après la transplantation médullaire. Seize patients atteints de leucémie aiguë, huit d'anémie aplastique et un de leucémie chronique myéloïde, ont été incorporés dans l'étude. Avant BMT, tous les patients n'ont aucun symptôme respiratoire et ont des clichés thoraciques normaux, ainsi que des volumes pulmonaires statiques et dynamiques, une DLCO et une différence alvéolo-artérielle en oxygène, dans les limites de la normale. Toutefois, 5 patients ont une hyperréactivité des voies aériennes à la métacholine. Les patients atteints d'anémie aplastique ont une DLCO ajustée au taux d'hémoglobine significativement plus basse que ceux atteints de leucémie. Une analyse de régression multiple par étapes a montré que la différence dans la DLCO était en relation principalement avec la concentration d'hémoglobine dans chaque groupe 5.7±0.2 contre 8.3±0.2 mmol·l^{-1} ou 9.2±0.4 contre 13.3±0.5 gm·dl^{-1}, $p<0.0001$, respectivement). Cette concentration rend compte de 4% de la variabilité interindividuelle de la DLCO, le type de maladie hématologique n'entraînant pas de réduction accrue de la variance de la DLCO. Après BMT, l'on a noté des réductions transitoires significatives, légères à modérées, dans la DLCO et les volumes pulmonaires statiques. De plus, les patients atteints de leucémie avaient une DLCO significativement plus basse que ceux atteints d'anémie aplastique, du jour 90 au jour 360. L'examen des cas individuels montre le développement d'anomalies ventilatoires obstructives chez 8 patients (1 compatible avec une bronchiolite oblitérante), et celui d'anomalies restrictives chez 6 autres. Quatorze des vingt-cinq patients ont donc des troubles ventilatoires, dont dix avaient une hyperréactivité bronchique à la metacholine, transitoire ou permanente. Les modifications fonctionnelles pulmonaires post-BMT furent accompagnées transitoirement de signes légers à modérés de maladie respiratoire chez la plupart des patients.
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