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Mechanisms for reduced pulmonary diffusing capacity in haematopoietic stem-cell transplantation recipients☆

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ABSTRACT

Lung diffusing capacity for CO (DL_{CO}) is compromised in haematopoietic stem-cell transplantation (HSCT) recipients. We derived alveolar–capillary membrane conductance ($D_{M,CO}$) and pulmonary capillary volume (V_C) from DL_{CO} and diffusing capacity for NO (DL_{NO}). Forty patients were studied before and 6 weeks after HSCT. Before HSCT, DL_{NO} and DL_{CO} were significantly lower than in 30 healthy controls. $D_{M,CO}$ was ~40% lower in patients than in controls ($p < 0.001$), whereas V_C did not differ significantly. After HSCT, DL_{NO} and $D_{M,CO}$ further decreased, the latter by ~22% from before HSCT ($p < 0.01$) while V_C did not change significantly. Lung density, serum CRP and reactive oxygen metabolites were significantly increased, with the latter being correlated ($R^2 = 0.71$, $p < 0.001$) with the decrement in DL_{NO}. We conclude that DL_{NO} and, to a lesser extent, DL_{CO} are compromised before HSCT mainly due to a $D_{M,CO}$ reduction. A further reduction of $D_{M,CO}$ without V_C loss occurs after HSCT, possibly related to development of oedema, or interstitial fibrosis, or both.

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1. Introduction

Haematopoietic stem-cell transplantation (HSCT) is an established therapeutic procedure for life-threatening haematological malignancies (Appelbaum, 2007), with non-relapse mortality ranging from 15% to 24% (Giebel et al., 2012). The procedure consists of a conditioning phase in which chemotherapy is given, with or without supralethal levels of radiation, followed by a salvage dose of bone marrow to regenerate haematopoietic stem-cell lineage (Thomas, 1995). Several studies have consistently shown that lung diffusing capacity for carbon monoxide (DL_{CO}) may be reduced either before (Afessa, 2005; Parimon et al., 2005) or after HSCT (Rodríguez-Roisin et al., 1989; Gore et al., 1996; Barisione et al., 2008), even in the absence of an evident restrictive abnormality. This change has been variably attributed to interstitial or vascular tissue involvement due to underlying disease (Parimon et al., 2005), myeloablative conditioning regimens (Gore et al., 1996), infections (Kotloff et al., 2004) and acute graft-*versus*-host disease (G*v*HD) (Ferrara et al., 2009). However, DL_{CO} is a global measure of CO uptake, which does not allow to identify the primary anatomical sites or mechanisms of dysfunction. It reflects passive diffusion of CO across the alveolar–capillary membrane *plus* intracapillary plasma ($D_{M,CO}$) and endothelial conductance (Roughton and Forster, 1957). The latter is determined by pulmonary capillary volume (V_C) and chemical combination of CO (θ_{CO}) with red cell haemoglobin (Hb), the concentration of which is often reduced in haematological malignancies (Appelbaum, 2007). Because the chemical combination of nitric oxide with blood (θ_{NO}) is much faster than θ_{CO} (Carlsen and Comroe, 1958), lung diffusing capacity for NO (DL_{NO}) represents a better index for alveolar–capillary membrane conductance (Guénard et al., 1987; Borland and Higenbottam, 1989; Meyer et al., 1990). Thus, the simultaneous measurement of DL_{NO} and DL_{CO} has been proposed as a method to separate the relative contributions of $D_{M,CO}$ and

☆ *Trial registry:* ClinicalTrials.gov; No.: NCT01735526 (DLNO/DLCO-HSCT); URL: http://www.clinicaltrials.gov/.

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V_C (Glénet et al., 2007; Hughes and van der Lee, 2013), provided adequate values are assumed for the θ_{NO}/θ_{CO} ratio.

In planning the present study, we reasoned that reduced DL_{CO} in HSCT recipients may be due to a $D_{M,CO}$ damage without capillary loss or to interstitial fibrosis with damage of both $D_{M,CO}$ and V_C. Alternatively, were the reduced DL_{CO} in the absence of lung restriction an expression of isolated vascular damage (Pellegrino et al., 2005), then V_C would be decreased with $D_{M,CO}$ damage due to reduction of capillary surface of the membrane. Moreover, changes in pulmonary diffusive capacity may differ in allogeneic and autologous HSCT because of different conditioning treatments or G*v*HD in the former (Panoskaltsis-Mortari et al., 2011).

To test these hypotheses, we simultaneously measured single-breath DL_{NO} and DL_{CO} in two groups of patients undergoing allogeneic or autologous HSCT and in a group of healthy controls. Results were compared with changes in standard pulmonary function tests, respiratory mechanics, serum concentrations of reactive oxygen metabolites (ROMs) (Carratelli et al., 2001) and C-reactive protein (CRP) (Pihusch et al., 2006) as well as with data obtained by quantitative computed tomography (CT) scan (Gattinoni et al., 2001).

2. Materials and methods

2.1. Study subjects and protocol

Between September 2012 and June 2013, fifty Caucasian patients affected by various haematological malignancies were consecutively considered for HSCT, either autologous, *i.e.*, with intravenous infusion of haematopoietic stem-cell taken from the patient itself, or allogeneic, *i.e.*, from an HLA-matched/mismatched related donor (Spangrude et al., 2004). Four of them died before HSCT due to relapse of haematological malignancy and 6 were not transplanted because of active withdrawal of donor's consent. Therefore, 40 patients undergoing allogeneic ($n = 28$) or autologous ($n = 12$) HSCT sourcing from bone marrow were studied (Table 1). The indications for HSCT were multiple myeloma ($n = 8$), Hodgkin's disease ($n = 8$), acute myeloid leukaemia ($n = 7$), acute lymphoblastic leukaemia ($n = 7$) or other conditions ($n = 10$). All of them were in stable clinical conditions at the time of study and none had a history of significant respiratory diseases or high-resolution CT findings of parenchymal lung disease. Thirty matched healthy subjects served as a control group for pre-HSCT lung function and to assess medium-term reproducibility of DL_{NO}–DL_{CO} measurements.

Patients undergoing allogeneic HSCT received conventional conditioning regimens with various combination of cyclophosphamide ($n = 23$), fludarabine ($n = 22$), thiothepa ($n = 11$), methotrexate ($n = 10$), busulfan ($n = 9$), and appropriate antibiotic prophylaxis. Eleven of them also received high-dose ($\geq$9.99 Gy) total body irradiation. To prevent G*v*HD, all patients were treated with cyclosporine A (6–10 mg kg^{-1} daily), 18 with mofetil mycophenolate, and 5 with antithymocyte globulin. Patients diagnosed with acute G*v*HD were treated with 6-α-methylprednisolone (2 mg kg^{-1} daily) for five consecutive days (Bacigalupo et al., 2006). Eight out of 12 patients undergoing autologous HSCT received melphalan as monotherapy, whereas the remaining 4 were conditioned with bischloroethylnitrosourea (BCNU), etoposide, cytarabine, and melphalan (BEAM scheme) at recommended doses (Caballero et al., 1997). All patients were studied 2 weeks before the start of conditioning treatment and, approximately, 6 weeks after HSCT.

The study protocol was approved by the institutional review board of IRCCS San Martino University Hospital (IRB no. 33/2012) and written informed consent was obtained from each subject before entering the study.

2.2. Spirometry, lung volumes and mechanics

Vital capacity (VC) and forced expiratory volume in one second (FEV_1) were measured by using a mass flow-meter (SensorMedics-Viasys, CareFusion; Höchberg, Germany) with numerical integration of the flow signal, according to the American Thoracic Society/European Respiratory Society recommendations (Miller et al., 2005). Functional residual capacity (FRC) was measured by whole-body plethysmography (V62J, SensorMedics-Viasys, CareFusion; Höchberg, Germany) during panting against a closed shutter at a frequency ranging from 0.5 to slightly <1.0 Hz. Residual volume (RV) was calculated by subtracting a linked expiratory reserve volume from FRC and total lung capacity (TLC) by adding the subsequent inspiratory VC (Wanger et al., 2005). Predicted values for spirometry and lung volumes were from Quanjer et al. (Quanjer et al., 1993).

The within-breath input impedance of the respiratory system (Z_{rs}) was measured at 5, 11, and 19 Hz by a forced oscillation technique (Barisione et al., 2012) (Resmon Pro, Restech s.r.l., Milan, Italy) while the subject was sitting and breathing quietly for 3 min, with his/her cheeks and mouth floor firmly supported by hands. The mean values of inspiratory resistance ($\bar{R}_{insp}$) and reactance ($\bar{X}_{insp}$) were calculated (Dellacà et al., 2009). Predicted values for $\bar{R}_{insp5}$ were from Pasker et al. (1994).

2.3. Pulmonary diffusion and arterial blood gases measurements

DL_{NO} and DL_{CO} were measured simultaneously during a single-breath manoeuvre (Guénard et al., 1987; Borland and Higenbottam, 1989) from the exponential disappearance rate of each gas with respect to He (Jones and Meade, 1961). A commercially available automated apparatus (MasterScreen PFT System, Jaeger-Viasys, CareFusion, Höchberg, Germany) was used with a gas mixture containing 0.28% CO, 9.0% He and 21% O_2, balanced with N_2 mixed with an NO/N_2 mixture (450 ppm NO in N_2; SOL S.p.A., Monza, Italy). The final concentrations of NO and O_2 in the plastic bag containing the gas mixture to be inhaled were 40 ppm and 19.1%, respectively. The apparatus was calibrated for gas fractions using automated procedures. The linearity of the electrochemical cell was factory checked. The subject was in a sitting position, wearing a nose-clip and breathing quietly through a mouthpiece with filter connected to a screen-type pneumotachograph. After several breaths of stable tidal volume, he/she was requested to make a full expiration to RV. Then, at the onset of the following deep inspiration to TLC, a valve was opened allowing the subject to inspire the gas mixture. A breath-hold of ~5 s was then requested, followed by a rapid expiration (Aguilaniu et al., 2008). The total breath-holding time was calculated from the beginning of inspiration (minus 30% of inspiratory time) to the middle of expiratory gas sampling (MacIntyre et al., 2005). The first 750 mL of expired gas were discarded and the following 750 mL were sampled from the bag to be analyzed for NO, CO and He. The values of DL_{NO} and DL_{CO} were accepted if two successive measurements of DL_{NO} and DL_{CO} were within 17.2 and 3.2 mL min^{-1} $mmHg^{-1}$, respectively. The mean value of two properly performed manoeuvres was retained for analysis (Zavorsky and Murias, 2006). Predicted values for DL_{NO} and DL_{CO} were from Aguilaniu et al. (2008).

$D_{M,CO}$ and V_C were calculated assuming either infinite or finite θ_{NO}. The coefficient linking DL_{NO} and $D_{M,CO}$ was set at 1.97 according to their diffusivity ratio (Wilhelm et al., 1977). Thus, $D_{M,CO}$ was equal to $DL_{NO}/1.97$ when θ_{NO} was assumed as infinite ($D_{M,CO\infty}$). When θ_{NO} was considered as finite, *i.e.*, 4.5 mL NO mL $blood^{-1}$ min^{-1} $mmHg^{-1}$ (Borland et al., 2010; Carlsen and Comroe, 1958), $D_{M,CO}$ values were calculated using the θ_{NO}/θ_{CO} ratio of 7.7 for normoxic conditions ($D_{M,CO7.7}$) (Martinot et al., 2013). Similarly,

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