Impact of pre-transplant diffusion lung capacity for nitric oxide (DLNO) and of DLNO/pre-transplant diffusion lung capacity for carbon monoxide (DLNO/DLCO) ratio on pulmonary outcomes in adults receiving allogeneic stem cell transplantation for hematological diseases

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Letter

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Incidence of pulmonary damages is high after allogeneic stem cell transplantation (allo-SCT) and accounting for one of the main causes of non-relapse mortality (NRM) and intensive care unit admission. Pre-transplant alteration of the lung function is considered as the most important parameter to take into account to predict pulmonary complications and outcomes.[1] As a consequence, pre-transplant pulmonary function testing (PFT) is required in all patients eligible for an allo-SCT. Diffusion lung capacity for carbon monoxide measured after a 10 second single breath-hold technique ($DLCO_{10s,}$ thereafter DLCO), which reflects the alveolar capillary interface, is considered as one of the key parameters to cancel the allograft. Indeed, reduction of the diffusion capacity has been shown to predict NRM, overall survival (OS) and early respiratory failure after allo-SCT.[1, 2] Thus, current guidelines suggest that patients with a pre-transplant DLCO < 60% of predicted normal value are not ideal candidates for allo-SCT. However, this recommendation is currently debated, especially since the predominant use of less toxic reduced-intensity conditioning (RIC) regimens.[3-5]

Other pulmonary parameters may help to discriminate patients at high-risk of severe lung complications. In 1987, Guénard et al, demonstrated that nitric oxide (NO), together with CO, can be used to measure the diffusion pathway from the alveoli to capillary plasma in the lung.[6] The lung diffusing capacity for NO (DLNO) is considered as a measure of membrane conductance which is less affected by any diffusive resistance associated with capillary erythrocytes, except the presence of free hemoglobin. In fact, DLNO reflects the distance between the alveoli and the capillaries mainly related to the alveolar-capillary membrane and the thickness of the alveolar blood barrier while DLCO rather reflects the capillary blood vessels function.[7] Also, DLNO/DLCO ratio represents a new index of gas exchange and an alternative way of investigating the alveolar membrane and the blood reacting with the gas. [8] Although explored in many lung diseases, [9-12] impact of DLNO and DLNO/DLCO ratio has not been yet established in the setting of allo-SCT. It is of particular interest as radiotherapy

and chemotherapy used to treat patients with hematological diseases affect mostly the alveolar-capillary membrane, which destruction is more appreciate by DLNO than DLCO measure. In our study, DLNO and DLNO/DLCO ratio seem more appropriate to predict pulmonary complications than DLCO after allo-SCT and therefore should be rather considered to define eligibility for transplant.

Between March 2012 and January 2014, 153 adults performed a pre-transplant PFT in our department. Fifty patients were excluded of the study because: 1) no DLNO measure was performed during the pre-transplant PFT (n=30); 2), an unevaluated pre-transplant diffusion lung capacity (n=10); 3) allograft was contra-indicated due to abnormal PFT (n=1), uncontrolled infection (n=4), psychiatric illness (n=1), relapse before transplant (n=3), or death during the conditioning regimen (n=1). Thus, overall, the full PFT data required for the study for each case was available in 103 patients. Characteristics of patients are summarized in Table 1. The study was approved by the Institutional Review Board of the French learned society for respiratory medicine -Société de Pneumologie de Langue Française (ref number CEPRO 2015-025) and patients gave their consents for anonymous use of their data.

All PFT were performed in routine at the CHU of Nantes in the same laboratory**.** Because of faster diffusion, DLNO is measured after a 5 (and not 10) second single breath-hold technique ($DLNO_{5s,}$ thereafter DLNO). DLCO can be measured simultaneously ($DLCO_{5s}$) for a double diffusion measure, allowing to calculate a $DLNO_{5s}/DLCO_{5s}$ ratio (thereafter DLNO/DLCO). Normal DLCO and DLNO percentage of predicted normal value PNV (>80%) were documented in 48 and 44 patients, respectively but median percentages for the all cohort were below the normal at transplant: DLCO: 78.9%, DLNO: 78.1%. Median DLNO/DLCO ratio was 5.3 (range: 2.7-8.6). Only 6 patients had a pejorative high-risk lung function score (LFS) (between 6 and 9).[13] Median DLCO was significantly decreased in older patients (>58 years, 75.4% of PNV vs 81.0%, p=0.05), patients with previous documented

respiratory events (72.3% vs 81.5%, p=0.001) or previous administration of drugs with cardiac or pulmonary toxicities (74.2% vs 80.6%, p=0.02). Median DLNO was also significantly decreased in patients with previous documented respiratory events (74.3% versus 80.9%, p=0.03) and patients with active or history of smoking (75.3% versus 81.8%, p=0.03). Finally, younger patients (≤58 years) had a significant lower median DLNO/DLCO ratio (5.2 vs 5.5, p=0.04).

Median follows up was 21.5 months (range: 3.8-34.7). Two years OS, disease free survival, relapse incidence and NRM were 65.4% (55.2-73.6), 52.5% (42.7-62.2), 31.8% (22.3-41.7) and 15.8% (9.4-23.5), respectively. Cumulative incidence (CI) of acute GVHD grade II-IV and grade III-V were 34% (25-43.2) and 19.4% (12.4-27.6) while CI of overall and extensive chronic GVHD were 25.5% (17.5-34.3) and 14.7% (8.6-22.3), respectively.

After transplant, any type of pulmonary event was collected retrospectively from clinical and radiologic data available in medical records. Thus, 77 respiratory events were documented in 53 patients: 27 bronchitis, 22 pneumonia, 14 invasive fungal infection, 4 bronchiolitis obliterans syndrome, 2 idiopathic pulmonary fibrosis, 2 pneumothorax, 1 tuberculosis, 1 sinusoidal obstruction syndrome, 1 mediastinal lymphoma, 1 acute pulmonary edema, 1 pulmonary embolus, and 1 case with multiple pulmonary nodules of undetermined significance. The median number of pulmonary events per patient after transplant was 1 (range: 0-7). Two year CI of severe pulmonary complication (SPC) (defined as any pulmonary complication responsible for hospitalization), acute respiratory distress syndrome (ARDS) and pulmonary related mortality (PRM) were 25.4% (17-34), 7.8% (4-14), and 4.9% (1.8-10.4), respectively. Overall, five patients died of a respiratory complication (1 invasive aspergillosis; 1 CMV pneumonia; 3 bacterial pneumonia in patients with severe acute or refractory chronic GVHD: *pseudomonas aeruginosa*: n=2, *pseudomonas aeruginosa* + *acinetobacter baumanii*: n=1).

In univariate analysis, when considering various cut-offs (>=80%, 60-80% and <60%), DLCO was not predictive of any outcomes considered for the analysis: ARDS, SPC, PRM and NRM (Table 2). Conversely, a DLNO value <60% was associated with significant higher incidences of SPC (>=80%: 20.5% vs 60-80%: 24% vs <60%: 59.3%, p=0.02) and ARDS (>=80%: 9.1% vs 60-80%: 2% vs <60%: 35.6%, p<0.005). When considering DLCO and DLNO as continuous variables, lower percentage were associated with higher risk of SPC for both parameters (p=0.048 and p=0.026, respectively). Also, lower DLNO/DLCO ratio (considered as a continuous variable) was associated with higher PRM (p=0.04). Previous history of pulmonary events was associated with higher risk of ARDS (no: 3.1% vs yes: 15.8%, p<0.01). Among factors related to patient, disease or transplant, only the type of disease impacted on pulmonary outcomes as lymphoid patients were associated with higher risk of ARDS (p=0.04), SPC (p=0.03) and PRM (p=0.02).

In multivariate analysis, there was a trend for a significant association between lower value of pre-transplant DLNO (<60%) and higher risk of ARDS (HR: 3.34, 95%CI: 0.99-11.2, p=0.05) and of SPC (HR: 2.5, 95%CI: 0.93-7.12, p=0.06).

At our knowledge, this is the first series reporting on the impact of pre-transplant DLNO percentage and DLNO/DLCO ratio after allo-SCT. In univariate analysis, lower value of DLNO (<60% of PNV) was associated with higher incidence of ARDS and SPC while lower DLNO/DLCO ratio was associated with an increased risk of PRM. Significance was not reached by multivariate analysis probably because of the relative small number of patients of our cohort.

Currently, lower pre-transplant DLCO percentage remains generally an excluding criteria when considering the eligibility of a patient for allo-SCT. Guidelines suggest that patients with pre-transplant DLCO <60% of PNV should not proceed with the transplant

because of an inacceptable increased risk of pulmonary complication and mortality. Here, we found no impact of lower pre-transplant DLCO value, confirming recent results observed in adults as well as in children.[3-5] In fact, DLCO is the most variable parameter in a PFT, particularly when a restrictive or obstructive ventilatory impairment is present, suggesting that lower value in a particular patient may be equivalent to a normal value in another. Thus, DLCO should not be retained anymore as unique criteria to decide or not to perform the graft in patient.

In the literature, DLNO/DLCO ratio has been observed between 4.3 and 5.3,[8] which is in accordance with the median value (4.9+-0.6) observed in a cohort of healthy subjects who performed PFT, including both DLNO and DLCO measures, in our department. If the median ratio was higher for haematological patients included in this study, it is difficult to define it as abnormal, as no normal values have been clearly reported currently. Higher median ratio may be the fact of older age of our cohort or higher concentration of free haemoglobin in this population, as it is highly reactive with NO.[14]

As a conclusion, DLNO and DLNO/DLCO ratio seem more appropriate to predict pulmonary complications than DLCO after allo-SCT and therefore should be rather considered to define eligibility for transplant. Howerer, the number of patients is low in our study and many variables may be involved explaining the results. Then multivariable analysis with a larger patient-group and clear exclusion criteria of transplant patients, who are considered not eligible because of preceding pulmonary problems, should be proposed in the future.

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Table 1: Characteristics of patients (N=103)

Variables	N= 103
Gender: male	68 (66%)
Median age at transplant: years (range)	58 (24-69.1)
Median weight at transplant: Kg (range)	72 (52-105)
Type of diseases:	
-Myeloid diseases: AML/MDS/MF/CML/AA	67 (65%): 47/10/7/2/1
-Lymphoid diseases: ALL/HD/DLBCL/FL/ATCL/PTCL/MCL/CLL/MM	36 (35%): 14/1/5/2/1/2/1/6/4
Status at transplant: CR (CR1/CR2)/PR/active non treated/refractory disease	56 (54.4%) (44/11)/23 (22.3%)/8 (7.8%)/16 (15.5%)
DRI: low/intermediate/high/very high/unavailable	13 (12.6%)/57 (55.3%)/29 (28.2%)/3 (2.9%)/1 (1%)
Type of donor: MRD/haplo-RD/MUD/MisMUD/UCB	35 (34%)/5 (4.9%)/43 (41.7%)/9 (8.7%)/11 (10.7%)
Type of stem cell source: BM/PBSC/UCB	10 (9.7%)/83 (80.6%)/10 (9.7%)

Conditioning regimen:*	
-RIC/MAC	85 (82.5%)/18 (17.5%)
-use of ATG: yes/no	85 (82.5%)/18 (17.5%)
-use of TBI>6gy: yes/no	5 (4.85%)/98 (95.15%)
Smoking history:	
-active smokers/former smokers/never smoked	17 (16.5%)/36 (35%)/50 (48.5%)
-median number of pack-years/smokers (range)	22 (2-45)
Previous administration of therapeutic with cardiac or pulmonary toxicities	
-previous graft: autograft/allograft	16 (15.5%)/5 (4.8%)
- bleomycin/methotrexate/anthracyclin/cyclophosphamide	2 (1.9%)/9 (8.7%)/82 (79.6%)/41 (39.8%),
-median number of drugs administered per patient (range)	1 (0-5)
- number of drugs administered per patient: <2 vs ≥2	63 (61.2%)/40 (38.8%)

Previous pulmonary events:	
-no/yes: (pulmonary embolism/bronchitis/bacterial pneumonia/IFI/ asthma/emphysema or COPD/pneumothorax/pleural effusion/ sarcoidosis/ Pulmonary involvement of the haemopathy)	65 (63.1%)/38 (36.9%) : (5/1/12/16/5/3/1/1/1/3)
HCT-CI: low risk (0)/intermediate risk (1-2)/high risk (≥3)	37 (35.9%)/37 (35.9%)/29 (28.2%)

AA : aplastic anemia, ALL: acute lymphoid leukemia, AML: acute myeloid leukemia, ATCL : angio-immunoblastic T-cell lymphoma, ATG: antithymocyte globulin, BM: bone marrow, COPD: chronic obstructive pulmonary disease, CLL : chronic lymphoid leukemia, CML: chronic myeloid leukemia, CR : complete remission, DLBCL : diffuse large B-cell lymphoma, DRI: Disease risk index,[15] FL : follicular lymphoma, IFI: invasive fungal infection, haplo-RD : haploidentical related donor, HD : hodgkin disease, HCT-CI: Hematopoietic Cell Transplantation-Comorbidity Index ,[2] MAC: myeloablative conditioning, MCL : mantle-cell lymphoma, MDS, myelodysplastic syndrome, MF: myelofibrosis, MM : multiple myeloma, MRD : matched related donor, MUD : matched unrelated donor, MisMUD: mismatched unrelated donor, PBSC: peripheral blood stem cell, PR : partial remission, PTCL : peripheral T-cell lymphoma, RIC: reduced intensity regimen, UCB: umbilical cord blood. *GVHD prophylaxis consisted of cyclosporine (CsA) alone or CsA + mycophenolate mofetyl after RIC allo-SCT using a sibling donor or an unrelated donor, respectively. Standard combination of CsA + short course of low dose methotrexate was used after MAC. Granulocyte-colony-stimulating factor was administered during aplasia only in patients receiving a cord blood transplant.

1 **Table 2** : Univariate analysis

	NRM		PRM		Severe pulmonary complication*		ARDS	
	%	p-value	%	p-value	%	p-value	%	p-value
DRI: low-risk + intermediate vs high-risk+very-high risk	14.4 (7.4-23.4) vs 9.4 (2.3-22.6)	0.25	5.8 (1,8-13.1) vs 3.1 (0.2-14.2)	0.56	25.9 (16.2-36.7) vs 25.0 (11.5-41.1)	0.55	10.1 (4.4-18.5) vs 3.1 (0.2-14.2)	0.16
Disease: lymphoid vs myeloid	19.8 (8.6-34.4) vs 9.0 (3.6-17.3)	0.04	11.4 (3.5-24.4) vs 1.5 (0.1-7.2)	0.02	39.7 (23.5-55.5) vs 17.9 (9.8-28.0)	0.03	14.2 (5.1-27.8) vs 4.5 (1.2-11.4)	0.04
HCT-CI: 0 vs ≥ 1	8.3 (2.1-20.2) vs 15.2 (7.7-24.9)	0.14	0.0 (0.0-0.0) vs 7.6 (2.8-15.6)	0.09	21.7 (10.0-36.3) vs 27.3 (17.1-38.4)	0.39	2.7 (0.2-12.3) vs 10.6 (4.6-19.5)	0.11

Previous pulmonary event: no vs yes	9.4 (3.8-18.1) vs 18.4 (8.0-32.4)	0.5	3.1 (0.6-9.8) vs 7,9 (2.0-19.4)	0,28	21.8 (12.6-32.6) vs 31.6 (17.5-46.7)	0.28	3.1 (0.06-0.09) vs 15.8 (6.3-29.2)	<0.01
Age: < vs ≥ median (58y)	15.6 (7.2-26.9) vs 9.8 (3.6-19.9)	0.57	3.9 (0.7-12.0) vs 5,9 (1.5-14.8)	0.65	26.8 (15.5-39.3) vs 24.0 (13.2-36.6)	0.94	7.6 (2.4-16.8) vs 8.0 (2.5-17.7)	0.76
Conditioning Regimen: RIC vs MAC	10.7 (5.2-18.4) vs 22.2 (6.6-43.6)	0.11	5.9 (2.2-12.5) vs 0.0 (0.0-0.0)	0.29	24.9 (16.2-34.6) vs 278 (9.6-49.6)	0.97	5.9 (2.2-12.5) vs 16.7 (3.9-37.2)	0.18
Use of ATG: yes vs no	9.5 (4.4-16.9) vs 27.8 (9.7-49.5)	0.12	3.6 (0.9-9.3) vs 11.1 (1.7-30.5)	0.18	23.7 (15.2-33.2) vs 33.3 (13.0-55.3)	0.52	5.9 (2.2-12.4) vs 16.7 (3.9-37.3)	0.18
LFS: 2 vs ≥ 3	12.7 (5.1-23.9) vs 12.7	0.79	4.3 (0.8-13.0) vs 5.5	0.76	19 (9.3-31.3) vs 30.9 (0.2-	0.06	6.4 (1.6-15.8) vs 9.1 (3.3-18.5)	0.40

	(5.5-23.0)		(1.4-13.8)		0.4)			
$DLCO_{10s}$ % of predicted normal value: > 80% vs 60-80% vs < 60%	12.7 (5.1-23.9) vs 12.8 (5.1-24.1) vs 12.5 (0.4-45.3)	0.95	4.3 (0.8-13.0) vs 4.3 (0.8- 13.0) vs 12.5 (0.4-45.3)	0.57	19.0 (9.3-31.3) vs 27.7 (15.7-41.0) vs 50.0 (12.2-79.6)	0.06	6.4 (1.6-15.8) vs 6.4 (1.6-15.9) vs 25.0 (3.0-57.9)	0.20
DLNO % of predicted normal value: > 80% vs 60-80% vs < 60%	18.2 (8.4-30.9) vs 8.0 (2.5-17.7) vs 11.1 (0.5-40.9)	0.26	9.1 (2.8-19.9) vs 0.0 (0.0-0.0) vs 11.1 (0.5-40.9)	0.07	20.5 (10.0-33.5) vs 24.0 (13.2-36.6) vs 59.3 (13.0-87.4)	0.02	9.1 (2.8-19.9) vs 2.0 (0.2-9.3) vs 35.6 (5.7-68.8)	<0.005
	HR	p-value	HR	p-value	HR	p-value	HR	p-value
$DLCO_{10s}$ % of	1.0 (1.0-1.1)	0.94	1.0 (0.9-1.0)	0.23	1.0 (0.9-1.0)	0.04	1.0 (0.9-1.0)	0.13

predicted normal value[$]								
DLNO % of predicted normal value[$]	1.0 (0.9-1.0)	0.35	1.0 (0.9-1.1)	0.45	2.0 (1.1-3.7)	0.02	1.0 (0.9-1.0)	0.17
DLNO/DLCO ratio[$]	0.9 (0.5-1.6)	0.7	1.6 (1.0-2.6)	0.04	0.9 (0.5-1.7)	0.78	1.6 (0.6-4.0)	0.34

*defined by complication requiring hospitalization, [$]: analysis considering continuous variables, ARDS: acute respiratory distress syndrome, ATG: antithymocyte globulin, DLCO: diffusion capacity for carbon monoxide (with correction for hemoglobin concentration), DLNO: diffusion capacity for nitric oxide, DRI: disease risk index,[15] LFS: lung function score,[13] MAC: myeloablative conditioning, NRM : cumulative incidence of non-relapse mortality, PRM : cumulative incidence of pulmonary related mortality, RIC: reduced intensity regimen, vs: versus