Original Article

The effect of primary graft dysfunction after lung transplantation on parenchymal remodeling detected by quantitative computed tomography

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Background: Regional analysis by computed tomography (CT) is an attractive technique to interpret lung patterns after transplantation (LTx). We evaluated the application of CT functional mask derived parameters to determine whether development of primary graft dysfunction (PGD) is associated with short and/or long-term postoperative evidences of pulmonary function alterations.

Methods: A total of 38 patients who underwent bilateral LTx were evaluated at 24, 48 and 72 hours after the end of surgery to establish PGD occurrence and grading. CT scans at 3 and 12 months after LTx were analyzed to measure specific gas volume (SV_g) changes normalized on expiratory SVgEXP of the whole lung ($\Delta SV_g/SV_{gEXP}$) and to obtain functional masks of density variation, namely maps of low ventilation (LV), consolidation (C), air trapping (AT) and healthy parenchyma (H).

Results: Our main result was the evidence of a marked decrease in $\Delta SV_g/SV_{gEXP}$ in all subjects, irrespectively on PGD, at each time point after LTx, indicating a high degree of ventilation defects versus healthy. High percentages of LV were found in all subjects while percentages of AT and C were negligible.

Conclusions: We demonstrate that quantification of ventilation defects by CT functional mask offers insights into the correlation between PGD and pulmonary function after LTx at short and mid-term.

Keywords: Lung transplantation; primary graft dysfunction (PGD); quantitative computed tomography (quantitative CT)

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Introduction

Primary graft dysfunction (PGD) is a syndrome related to allograft ischemia-reperfusion injury that occurs within the first 72 hours after lung transplantation. In the early days of lung transplantation, the incidence of PGD is difficult to assess accurately, with a reported range varying from 15% to 57%, partly as a result of differing definitions (1,2). The diagnosis is based on the presence of diffuse alveolar infiltrates on chest radiography without other identifiable causes and graduated on PaO_2 fraction of inspired oxygen (FiO_2) value (3,4). Notably, PGD is a risk factor for early and 1-year mortality; in addition, PGD is related to the development of bronchiolitis obliterans syndrome (5). Conversely, its role in association with functional

outcomes is less clear (3,6) and the evolution of tissue damaged from the ischemia-reperfusion injury has only sporadically been studied (7). In this scenario, functional analysis of multi-volumetric computed tomography (CT) represents an attractive tool that offers the possibility to study and understand the 'parenchymal outcome' after lung transplantation, opening the door to patient-tailored management (8).

The overall purpose of this pilot study was to determine whether development of PGD in the first 72 hours after lung transplantation influences parenchymal remodeling quantitatively assessed by CT at 3- and 12-month follow-up.

Methods

Study design

We designed a prospective, observational, single blind pilot study, based on dedicated institutional database. The study was performed in compliance with the principles of the declaration of Helsinki and received the approval of the local ethics committee (749_2016bis). All participants gave written informed consent before they were included in the study.

Patient population

We prospectively enrolled all patients who underwent bilateral lung transplantation at Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico of Milan between June 2013 and February 2017. Exclusion criteria were age <18 years and consent denied.

PGD diagnosis and grading

Patients were evaluated at 24, 48 and 72 hours after the end of surgery to establish PGD occurrence and grading. Two Authors (M Nosotti, A Palleschi) examined independently the chest X-ray. According to the standard ISHLT criteria, given the multi-factorial and likely additive nature of PGD risk factors, if parenchymal infiltrates were present, every other possibility was investigated and excluded (4). If any discrepancy occurred between the researchers, they proceeded to a collegial review of clinical and radiological parameters. PGD was graded on the basis of PaO_2/FiO_2 ratio and recorded on the database. Patients were classified in two groups according the worst PGD within the first 72 hours. Patients without evidence of PGD constituted the PGD0 Group; patients with grade 2 and/or 3 graft dysfunction within first 72 hours after lung transplantation composed the PGD Group.

Surveillance protocol

Besides fifteen-day medical examination, our standard surveillance protocol included pulmonary function tests (PFTs), multi-volumetric CT scans, and bronchoscopy with trans-bronchial biopsy at 3, 6 and 12 months. All data of interest were recorded in the dedicated database.

Specifically, PFT consists in a spirometry (Spirolab, Medical International Research, Italy) performed on the same day of the CT scan. This test included the measure of forced-expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC); the values were expressed also as percentage of predicted (FEV_1%, FVC %).

Patients underwent low dose, non-contrast CT scan with BrightSpeed™ Elite SD (GE Healthcare, CT, USA). CT images were acquired during breath holding at full end-inspiration (INSP) and full end-expiration (EXP) with the following parameters: tube voltage, 100 kVp, reference tube current, 245 mAs, pitch factor, 1.75, image matrix, 512×512, slice thickness 2.5 mm, with a smooth filter (B30). The DLP (Dose Length Product) was in the range between 110 and 328 mGy/cm, and the CTDIVol (Computed Tomography Dose Index Vol) was in the range between 1.8 and 4.9 mGy which is a low radiation dose compared to the doses used for routine chest scanning in many institutions (9).

Quantitative image analysis

For the aim of the study, we considered the surveillance CT scans at 3 and 12 months (±10 days) after transplantation. Image analysis was performed, in terms of specific gas volume (SV_g) for the entire lung. SV_g is defined as the difference between specific volume of tissue and gas and the specific volume of tissue, expressed in mL (gas)/g (tissue) (10-13). For the calculation of SV_g, voxels belonging to airways, blood vessels, and other structures of the lung were excluded and only those belonging to the parenchyma, i.e., with Hounsfield Unit values <–600 HU, were considered. Changes of SV_g ($\Delta SV_g = SV_{gINSP} - SV_{gEXP}$, expressed as $mL \cdot g^{-1}$, where SV_{gINSP} and SV_{gEXP} are specific gas volume at EXP and INSP, respectively) normalized on SV_{gEXP} were calculated as $\Delta SV_g/SV_{gEXP}$. Additional measures included CT total lung volumes (V_{EXP} and V_{INSP}) at each time point, as described elsewhere (9,10,12).

CT functional mask

In order to identify ventilation defects on a pixel-by-pixel basis, individual maps of CT density change between the two lung volumes ($\Delta HU = HU_{EXP} - HU_{INSP}$) were obtained on five different lung levels, from the aortic arch to the top of the diaphragm. Firstly, INSP and EXP images were semi-automatically segmented to separate lung parenchyma from the surrounding tissues. Successively, expiratory images were automatically deformed to the corresponding inspiratory images by using the Lucas-Kanade optical-flow algorithm (14,15) and then subtracted pixel-by-pixel, providing maps of ΔHU (10). Each pixel was then classified as belonging to four different possible functional settings: (I) low ventilated (green), (II) consolidation (blue), (III) air trapping (red) and (IV) healthy regions (black).

The change in density was calculated for each voxel of the ΔHU map and the classification was determined by imposing four thresholds: (I) the threshold for healthy regions (H, in black) was determined by considering a variation greater or equal to 100 (16); (II) pixels with values less than −950 HU on inspiration (HU_{INSP} <−950 HU) and less than −856 HU on expiration images (HU_{EXP} <−856) in conjunction with ΔHU <100 denoted air trapping (AT, in red) (8); (III) ΔHU <100, in conjunction with either HU_{EXP} >−856 or HU_{INSP} >−950 HU designated low ventilated regions (LV, in green) and (IV) ΔHU <100, in conjunction with HU_{EXP} and HU_{INSP} >−400 HU denoted the areas of abnormally high attenuation (C, in blue).

The percentages of LV, C, AT and H regions with respect to total area in the analyzed slices, denoted as %LV, %C, %AT and %H, respectively were calculated across the five ΔHU maps.

All algorithms for image processing and quantitative analysis were implemented by custom software developed in MATLAB (The MathWorksInc, Natick, MA).

Statistical analysis

Statistical analysis was performed using SigmaStat version 12.5 (Systat Software, San Jose, CA, USA). Bivariate analyses were conducted using Mann Whitney's U-test for continuous variables and chi-square or Fisher's exact tests for categorical variables. Paired *t*-test was used to assess differences between time points and groups. A one-tailed paired *t*-test was performed to analyze the extent of change in $\Delta SV_g/SVg_{EXP}$ and %LV between groups. Regression analyses were performed to correlate the relative change in V_{EXP}/V_{INSP} and $\Delta SV_g/SV_{gEXP}$ and %LV. A P<0.05 was considered statistically significant.

Results

The study population is shown in *Figure 1*. Namely, 38 subjects were included in this study; there were 13 males and 25 females, with a median age of 38 years. The characteristics of the patients are summarized in *Table 1*.

Functional outcomes

Three months after lung transplantation, PFTs showed that patients with or without PGD had statistically different reached values (FEV_1% 64±13 *vs.* 79±19, P=0.014; FVC% 65±11 *vs.* 77±16, P=0.032); conversely, comparable results were obtained at 12 months (FEV_1% 82±19 *vs.* 90±22; FVC% 81±15 *vs.* 91±21). The analysis of paired data revealed a significant growth in FEV_1% and FVC% (P<0.001) in both PGD group after 12 months.

Functional CT parameters

The distribution of $\Delta SV_g/SVg_{EXP}$ at study time-points is shown in *Figure 2*. At 3 months, $\Delta SV_g/SV_{gEXP}$ showed no significant differences among groups. At 12 months, $\Delta SV_g/SVg_{EXP}$ increased significantly in both groups, in PGD passing from 0.67±0.38 to 1.02±0.50 (P=0.028) and in PGD0 patients from 0.72±0.39 to 1.20±0.49 (P<0.001).

Results from functional mask analysis are reported in *Figure 3*. The distribution of %LV, %H %C, and %AT at 3 and 12 months post transplantation in PGD and PGD0 groups are showed.

The analysis for paired data revealed that there was a significant decrease in LV% in both PGD group after 12 months (P<0.05 and P<0.01, respectively) and a correspondent significant increase in H% (P<0.05 and P<0.01, respectively). %C and %AT were negligible in both transplanted groups at 3 and 12 months.

Figure 4 reports the values of paired data analysis for $\Delta SV_g/SV_{gEXP}$, %LV and %H at 3 and 12 months in PGD and PGD0 groups. A great variability was observed in both groups within the first year after lung transplantation, but there was a significant increase in $\Delta SV_g/SV_{gEXP}$ value at 12 months in both groups (*Figure 4A*,*B*). For the functional mask analysis, both groups demonstrated a significant decrease in the mean value of %LV (*Figure 4C*,*D*) and a consequent significant increase in %H (*Figure 4E*,*F*).

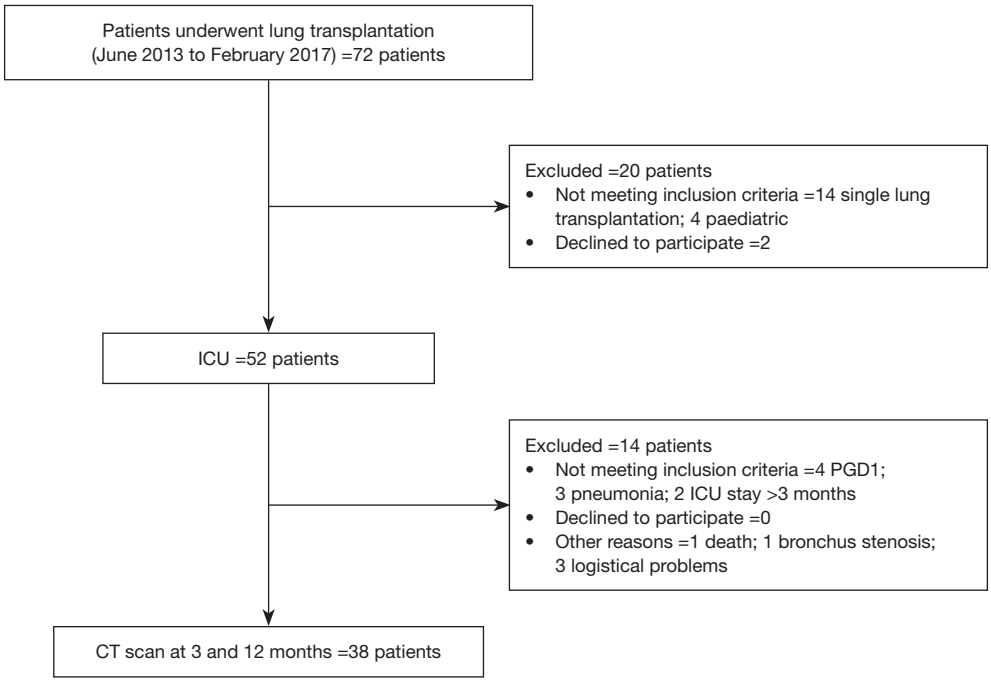

Figure 1 Description of the study cohort. PGD, primary graft dysfunction; ICU, intensive care unit.

Figure 5 shows CT functional masks at 3 and 12 months from two representative cases belonging to the two transplanted groups. In order to determine the relationship between CT parameters, $\Delta SV_g/SV_{gEXP}$ and %LV, and V_{EXP}/V_{INSP} correlations were performed in PGD and PGD0 patients (*Figure 6*). V_{EXP}/V_{INSP} from 3 to 12 months was inversely associated with $\Delta SV_g/SVg_{EXP}$ (r^2=0.71, P<0.0001) and with %LV (r^2=0.61, P<0.0001).

Discussion

Nowadays, lung transplantation is a consolidated approach for the treatment of end-stage respiratory diseases, but still burdened with high rates of complications. Despite technical progress has diminished the early postoperative mortality, the incidence of PGD remains significant; such syndrome is associated to poor early outcome as well as to impaired long-term survival (6,17,18). Why and how the early graft damage can affect the long-term outcome remains to be completely understood. The promising studies with CT scan were occasional and not conclusive (19). In the same manner, although considered a "gold standard", PFTs are subject to some degree of variability and patient compliance.

In our study, pulmonary function parameters were affected by the onset of PGD only at early time (3 months); at 12 months a decrease of the incidence of the effect of PGD was observed and no differences were found between the two transplanted groups. Furthermore, PFTs do not yield information about regional distribution of ventilation defects. Regional analysis with CT could be an attractive technique to interpret lung patterns after transplantation. In this study, we evaluate the application of CT functional mask derived parameters to determine whether development of severe PGD in the perioperative period is associated with short and/or long-term postoperative evidences of pulmonary function alterations. Quantitative CT regional analysis, proposed in the frame of this work, may provide a significant advance in the interpretation of ventilation abnormalities after lung transplant.

We enrolled patients who underwent lung transplantation in our center and we considered the subjects who completed the 1-year follow-up. To avoid the confounding effect of the native lung on pulmonary function we only selected bilateral recipients with the aim to evaluate the effect of PGD on the ventilation defects as well as their distribution in space and in time. We categorized our population into two groups based on the occurrence of PGD within the first 72 hours after surgery. PGD grade 1 was present in only one patient. We decided to exclude PGD grade 1 from

Table 1 Donor and recipient characteristics

Variables	PGD Group (n=13)	PGD0 Group (n=25)	P
Recipient			
Age (years), mean [SD]	38 [12]	42 [14]	0.956
Male sex, n [%]	5 [38]	10 [40]	n.s
Positive CMV status, n [%]	9 [69]	16 [64]	n.s
Weight (kg), mean [SD]	54 [11]	55 [8]	0.797
Height (m), mean [SD]	1.63 [0.1]	1.65 [0.1]	0.444
Disease, n [%]			
Cystic fibrosis	9 [69]	15 [60]	n.s
Pulmonary fibrosis	3 [23]	4 [16]	n.s
COPD	1 [8]	4 [16]	n.s
GVHD	–	2 [8]	
Donor			
Age (years), mean [SD]	47 [7]	47 [15]	0.221
Male sex, n [%]	7 [54]	13 [52]	n.s
History of smoking, n [%]	7 [54]	11 [44]	n.s
Positive CMV status, n [%]	11 [80]	15 [60]	n.s
Weight (kg), mean [SD]	70 [15]	74 [14]	0.279
Height (m), mean [SD]	1.70 [0.5]	1.70 [0.1]	0.546
OTO score, mean [SD]	4 [2]	3 [1]	0.683
Transplantation			
Cold ischemia time, minutes, median [IQR]	898 [698–978]	1,171 [837–1,416]	0.805
Warm ischemic time, minutes, median [IQR]	206 [160–188]	156 [138–175]	0.047
ECMO pre	3 [23]	3 [12]	n.s
ECMO intra	9 [69]	9 [36]	n.s
ECMO post	3 [23]	3 [12]	n.s

PGD Group, patients with grade 2 and/or 3 primary graft dysfunction; PGD0 Group, patients without diagnosis of PGD; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; GVHD, graft versus host disease; ECMO, extracorporeal membranous oxygenation; IQR, interquartile range; n.s, not significant.

the study for two main reasons: (I) grouping PGD1 with highest grade would had been misleading because, actually, the functional impairment is negligible; on the other hand, (II) grouping PGD1 with patients who did not experience pulmonary infiltrate was illogical. Only an adequate number of patients with PGD1 would allow a targeted analysis.

The major findings of our study are: (I) the significant reduction of the $\Delta SV_g/SV_{gEXP}$ in PGD and PGD0 patients compared to healthy (8); (II) the significant higher prevalence of low ventilation pattern in PGD and PGD0 groups at 3-month follow-up; (III) the negligible differences in $\Delta SV_g/SV_{gEXP}$ and %LV among transplanted groups at 3 months, and (IV) the significant higher correlation between the percentage of $\Delta SV_g/SV_{gEXP}$ and low ventilation and the V_{EXP}/V_{INSP} in both transplanted groups at 3 and 12-month follow-up.

We measured $\Delta SV_g/SV_{gEXP}$ of the whole lung in order to quantify in a single parameter the degree of lung

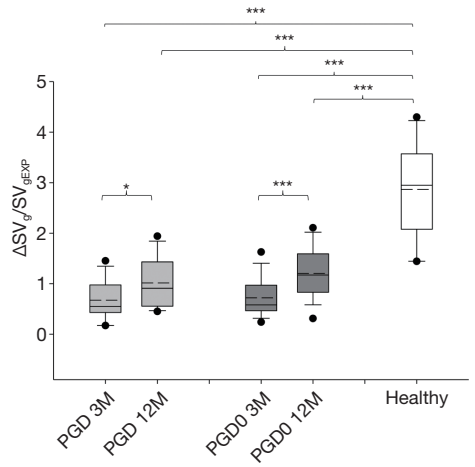

Figure 2 Box plots demonstrating distribution of $\Delta SV_g/SV_{gEXP}$ at 3 and 12 months post-transplant in patients with PGD, and PGD0. Healthy values derived from the results of our previous study (8). *, P<0.05; ***, P<0.001. PGD, primary graft dysfunction.

emptying (numerator) and expiratory lung hyperinflation/air trapping (denominator), providing a significant tool in the interpretation of ventilation abnormalities after lung transplantation. Our results demonstrate a marked decrease in $\Delta SV_g/SV_{gEXP}$ in all subjects, both at 3 and 12 months after lung transplantation, indicating a high degree of ventilation defects and/or expiratory lung hyperinflation affecting the normal distribution of lung ventilation even in patients with ideal post-transplantation course. In order to better identify the pattern of ventilation defects in the post-transplantation period, we introduced a novel CT-based methodology providing detailed information which could be the basis for future targeted interventions. Despite of PGD grading we found in all the subjects high percentages of low ventilation areas while air trapping or consolidation areas were negligible; once this clinical frame will be confirmed with larger studies, interventions such as non-invasive ventilation

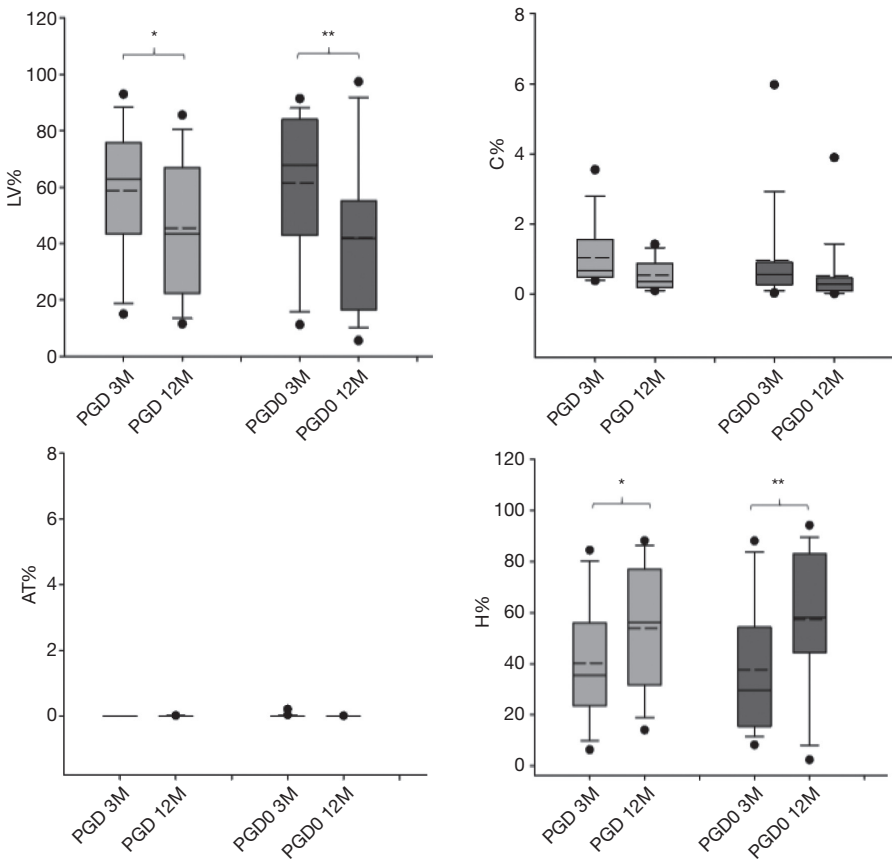

Figure 3 Box plots demonstrating distribution of percentages of lung volume denoted as %LV, %C, %AT and %H at 3 and 12 months post-transplant in patients with PGD and PGD0. PGD, primary graft dysfunction. *, P<0.05; **, P<0.01. PGD, primary graft dysfunction; LV, low ventilation; AT, air trapping; H, healthy parenchyma.

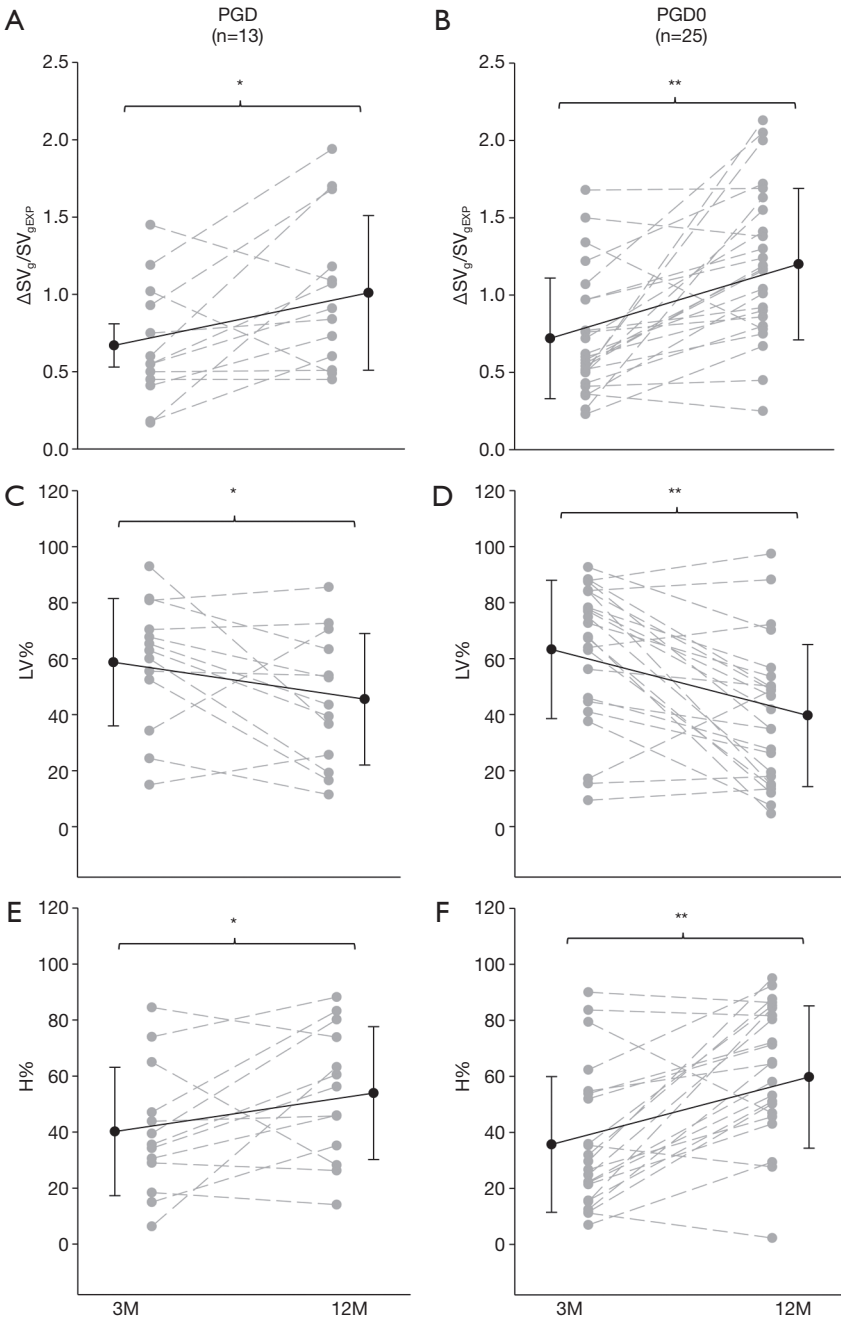

Figure 4 Line plots of $\Delta SV_g/SV_{gEXP}$ (A,B), %LV (C,D) and %H (E,F) obtained at 3 and 12 months post lung transplant in PGD (right panels) and PGD0 (left panels) group. *, P<0.05; **, P<0.01. PGD, primary graft dysfunction; LV, low ventilation; AT, air trapping; H, healthy parenchyma.

could be considered to counterbalance the persisting low ventilation pattern.

A further evidence that the decrease of $\Delta SV_g/SV_{gEXP}$ in transplanted patients is due more to ventilation defects rather than to air trapping and/or consolidation is provided by the results of *Figure 6*, showing that a significant, linear correlation between $\Delta SV_g/SV_{gEXP}$ and both the extent of low ventilation patterns and the decline of the ratio of lung

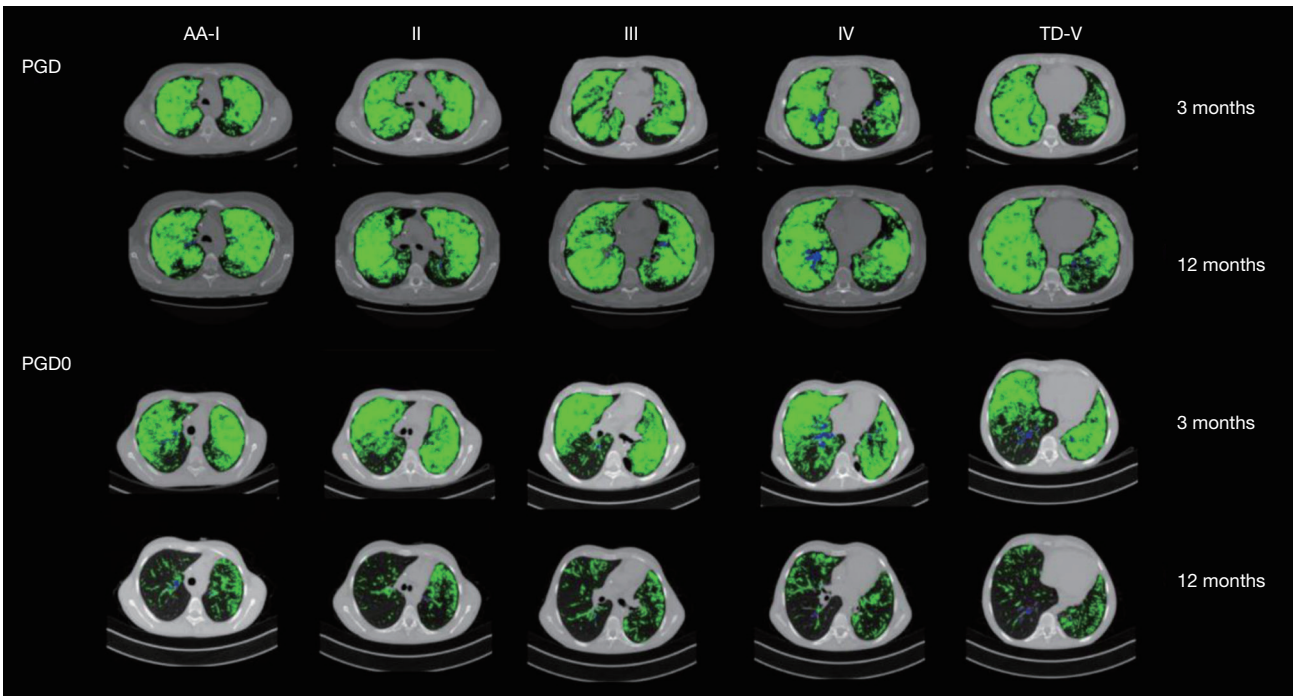

Figure 5 CT functional masks at 3 and 12 months from lung transplant of two representative PGD and PGD0 patients are shown at five equally-spaced lung levels from aortic arch (I-AA) to top diaphragm (VI-TD). Each pixel of the maps was classified as LV (green), C (blue), AT (red) and H (black). PGD, primary graft dysfunction; LV, low ventilation; AT, air trapping; H, healthy parenchyma.

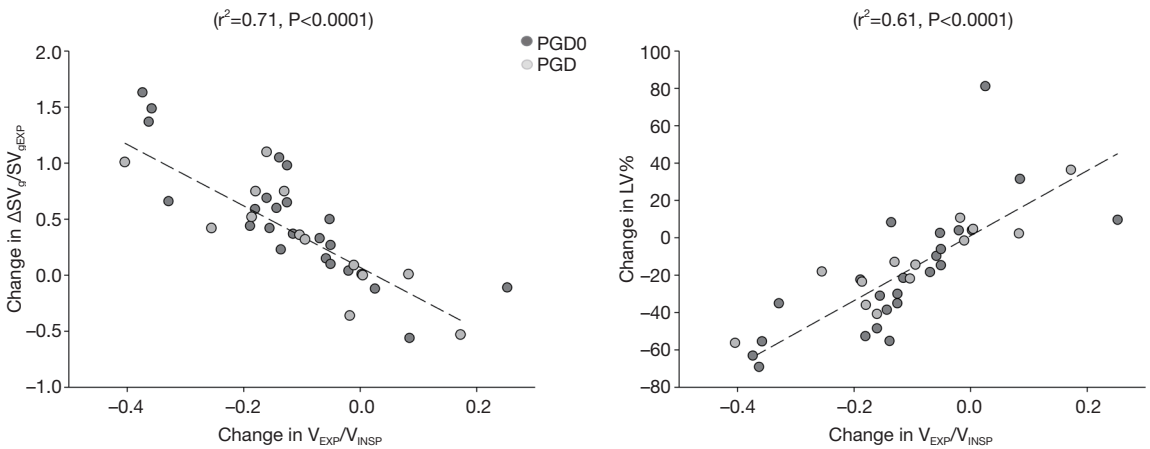

Figure 6 Correlation analysis are presented for the relative change in (A) $\Delta SV_g/SV_{gEXP}$ and (B) %LV to the relative change in V_{EXP}/V_{INSP} from 12 to 3 months in patients with PGD (gray circles) and PGD0 (dark gray circles). PGD, primary graft dysfunction; LV, low ventilation.

expiratory to inspiratory volumes (V_{EXP}/V_{INSP}) in the first year after lung transplantation.

Our results, therefore, suggest that when multi-volumetric CT scans are not available, in addition to spirometric indices, the measurement of static lung volumes might be useful to identify and differentiate particular physiological phenotypes and predict survival in patients with chronic lung allograft dysfunction as recently reported (20).

The negligible differences in $\Delta SV_g/SV_{gEXP}$ and %LV among transplanted groups at short and mid-term suggests

that a number of confounding factors could play a role in ventilation defects.

Our study has limitations that should be considered when interpreting the results. First, our study was a pilot prospective cohort study with a limited sample size. Furthermore, longer follow-up is necessary to study the chronic lung allograft dysfunction onset and identify the correlation with the PGD syndrome under the view of CT volume analysis.

Conclusions

In summary, we demonstrate that quantification of ventilation defects by CT functional mask can offer insight into the correlation between PGD and pulmonary function after lung transplantation at short and mid-term. Irrespective of whether or not the occurrence of PGD, our results suggest the importance of careful and integrated functional studies as a base to a tailored respiratory physiotherapy aimed at contrasting the persistence of low ventilation areas in the lung after transplantation. Further multi-centric studies using a larger sample size are essential to investigate the usefulness of this novel methodology in monitoring and quantifying the distribution of lung abnormalities in transplanted lungs.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the local ethics committee (749_2016bis) and written informed consent was obtained from all patients.

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