ORIGINAL ARTICLE

Impact of unilateral diaphragm elevation on postoperative outcomes in bilateral lung transplantation – a retrospective single-center study

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SUMMARY

This study evaluated the impact of unilateral diaphragm elevation following bilateral lung transplantation on postoperative course. Patient data for all lung transplantations performed at our institution between 01/2010 and 12/2019 were reviewed. Presence of right or left diaphragm elevation was retrospectively evaluated using serial chest X-rays performed while patients were standing and breathing spontaneously. Right elevation was defined by a > 40 mm difference between right and left diaphragmatic height. Left elevation was present if the left diaphragm was at the same height or higher than the right diaphragm. In total, 1093/1213 (90%) lung transplant recipients were included. Of these, 255 (23%) patients exhibited radiologic evidence of diaphragm elevation (right, 55%; left 45%; permanent, 62%). Postoperative course did not differ between groups. Forced expiratory volume in 1 second, forced vital capacity and total lung capacity were lower at 1-year follow-up in patients with permanent than in patients with transient or absent diaphragmatic elevation ($P = 0.038$, $P < 0.001$, $P = 0.002$, respectively). Graft survival did not differ between these groups ($P = 0.597$). Radiologic evidence of diaphragm elevation was found in 23% of our lung transplant recipients. While lung function tests were worse in patients with permanent elevation, diaphragm elevation did not have any relevant impact on outcomes.

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Introduction

In lung transplantation, graft survival is impaired by primary graft dysfunction (PGD), infection, malignancy, and chronic rejection [1,2]. However, the impact of acquired diaphragm dysfunction on graft function and survival has not been thoroughly investigated [3–10].

Diaphragm dysfunction results in reduced or absent inspiratory movement, impairing lung expansion, leading to atelectasis, which in turn may predispose to lung infection [11–13]. Diagnosis of diaphragm dysfunction is based on chest X-rays, sonography, pulmonary function, and phrenic nerve stimulation tests [13–15]. Although two-projection chest X-rays do not give any information about diaphragm movement in comparison with sonography, they allow retrospective evaluation of diaphragm position in maximal inspiration, with the dysfunctional diaphragm showing a higher position than the normal, and may be considered a surrogate for diaphragm dysfunction [16].

After lung transplantation, diaphragm elevation may be secondary to an accidental injury of the phrenic nerve during surgery [10,11]. Moreover, patients requiring prolonged mechanical ventilation may also show ventilator-induced diaphragm weakness, leading to elevation [12,17,18].

Therefore, we designed this retrospective single-center study to evaluate the prevalence of unilateral diaphragm elevation after lung transplantation, and its impact on postoperative course, graft survival, and function.

Methods

Definition of diaphragmatic elevation

The presence of diaphragmatic elevation was retrospectively evaluated by two radiologists (JB. H. and LS. B.), using serial two-projection chest X-rays performed before hospital discharge, with patients standing upright and breathing spontaneously, without ventilatory support. All chest X-rays used for evaluating the presence of diaphragm elevation were performed at our institution in short inspiratory breath-hold, and simultaneously evaluated by both radiologists, in order to reduce inter-observer variability.

Pathologies, that could potentially mimic diaphragm elevation, such as pleura effusions, lung atelectasis, or hiatus hernia were excluded by carefully comparing the available chest X-rays. The patients did not routinely receive chest computed tomography (CT), as this would increase the patient radiation exposure. A right side subpulmonary effusion might theoretically be under diagnosed using chest X-rays. However, subpulmonary effusions are less frequent compared with "normal" pleural effusions. Significant amounts of pleural fluid (>250 ml) as well as "large" atelectasis can safely be detected on a chest X-Ray in frontal and lateral projections in inspiration. Smaller amounts of pleural fluid and distinct atelectasis do not cause a smooth diaphragm elevation according to our proposed way of assessment.

Radiologic definition of diaphragm elevation was applied as previously defined [16]. This definition is still actually used at our institution by our radiologists for every other patient and not only for lung-transplanted patients. Elevation of the right diaphragm was defined as > 40 mm difference between the right and left diaphragmatic heights. Elevation of the left diaphragm was considered present if the left diaphragm was at the same height or higher than the right (Fig. 1). Thus, chest X-rays permitted the identification of unilateral, but not of bilateral diaphragm elevation.

In addition, diaphragm displacement after transplantation was evaluated by calculating the difference between the pre- and post-transplant pulmonary apex-to-hemidiaphragm and apex-to-costophrenic recess distances.

Chest X-rays after hospital discharge were retrospectively checked to evaluate the persistence of diaphragm elevation. At follow-up, lung-transplanted patients usually received a chest X-ray at surveillance visits, that were planned every 3 months during the first year after transplantation, and every 6 months thereafter.

Patient selection

Clinical records of all patients undergoing isolated lung transplantation between January 2010 and December 2019 at our institution were reviewed.

Patients who underwent single-lung transplantation, or bilateral-lung transplantation requiring lobar or atypical lung resection, along with patients without ≥ 1 chest X-ray while spontaneously breathing were excluded (Fig. 2).

Patients with unilateral diaphragm elevation were further stratified according to the presence of transient or permanent elevation, as evaluated at the aforementioned serial radiologic controls performed during follow-up. Thus, included patients were classified into three groups for statistical analysis, a group including patients without diaphragm elevation, a second group including

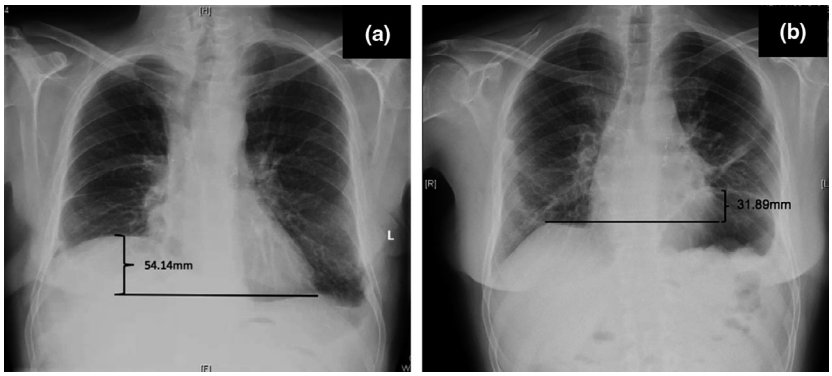

Figure 1 Figure shows the radiologic definition of diaphragmatic elevation. Elevation of the right diaphragm was defined by a > 40mm difference between the right and left diaphragmatic heights (a). Elevation of the left diaphragm was present if the left diaphragm was at the same height or higher than the right diaphragm (b).

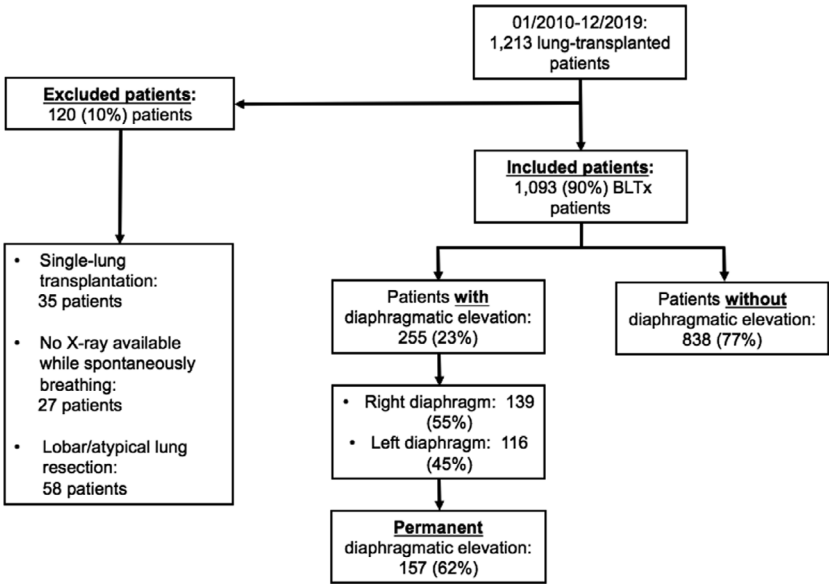

Figure 2 Figure presents a flowchart indicating the included and excluded patients.

patients with transient diaphragm elevation, and a third group including patients with permanent diaphragm elevation.

Follow-up concluded on February 1st, 2020, was 100% complete, and amounted to median 42 (20, 72) months. Patients requiring redo transplantation ($n = 41$) during the observation period were analyzed separately, with graft survival being truncated to the time of redo transplantation. In accordance with local German protocols, study approval by the institutional ethical review board was waived given its retrospective and noninterventional design. All patients had previously provided written informed consent regarding use of their personal clinical data for research purposes at the time of listing for lung transplantation.

Outcome definition

The primary endpoint was graft survival, defined as a composite endpoint of patient survival and freedom from redo transplantation.

Graft function was evaluated using bronchoscopic evidence for obstructive airway complications (OAC) and continual evaluation for the presence of chronic lung allograft dysfunction (CLAD). Routine lung function tests (forced expiratory volumes in 1 second, FEV_1; forced vital capacity, FVC; and the total lung capacity, TLC) were evaluated. The values recorded before transplantation, at discharge, at 1-year follow-up and at last available spirometric control were used for the analysis. All lung function tests were performed at our institution according to the previously reported guidelines [19,20].

Quality of life (QoL) was evaluated at each surveillance outpatient visit, using a Visual Analog Scale (VAS 0–10), where the value 0 corresponded to the worst quality of life and 10 to the best quality of life. Patients were in particular asked about the presence of symptoms such as dyspnea, their physical activity, and if they were able to work.

CLAD was defined as a confirmed and persistent decline in FEV_1 <81% of baseline, following exclusion of other causes [21]. CLAD onset was taken retrospectively as the date of first recorded $FEV_1 < 81\%$ baseline. Only patients with ≥ 2 spirometric measurements and surviving ≥ 90 days were included in the CLAD analysis.

OAC were diagnosed at bronchoscopy and considered requiring intervention when a standard 5.5 mm flexible bronchoscope no longer passed through a main or 1st generation segment bronchus. OAC lesions were defined as either proliferative (granulation tissue, polyps) or nonproliferative (stricture, malacia), as previously reported [22].

The 2005 definition of the International Society for Heart and Lung Transplantation (ISHLT) for PGD was used [23]. Patients with pulmonary artery hypertension (PAH) electively managed with veno-arterial ECMO in the early postoperative phase as institutional protocol, were graded according to arterial blood gases usually taken from the right radial artery, in cases where the arterial ECMO cannula was located in a femoral artery, as previously described [24].

Pneumonia was defined as the presence of a new infiltration on chest X-ray and positive sputum cultures or bronchoalveolar lavage cultures requiring antibiotic treatment.

Patient management

Management of lung-transplanted patients at our institution has been previously described [24–26], especially concerning the treatment of anti-HLA donor-specific antibodies [25] and the use of ECMO for cardiopulmonary support [24,26]. Patients did not receive any induction therapy. Post-transplant immunosuppressive therapy consisted of standard triple therapy: tacrolimus (initial through levels between 10 and 12 μg/ml); mycophenolate mofetil, that was later switched to everolimus in some patients; and prednisolone. On the intensive care unit (ICU), aggressive weaning from mechanical ventilation was applied whenever possible.

During index hospitalization, chest X-rays were performed on admission pretransplant, and daily on the ICU, and at least weekly after transfer to the normal ward. At discharge, all patients underwent a two-projection chest X-ray. At follow-up, chest X-rays were performed at each routine surveillance visit.

Data analysis

IBM SPSS 26.0 (IBM, NY, USA) was used for performing data analysis. The primary endpoint was graft survival, with secondary endpoints being freedom from CLAD, patient survival, development of OAC, lung infection episodes requiring hospitalization, and need for redo transplantation.

Categorical and continuous variables were summarized as percentages and median with interquartile range (IQR) and compared between the three groups, using the chi-square test and the non-parametric Kruskal–Wallis one-way ANOVA test, respectively.

Event-free survival from endpoints was calculated using the product-limit method of Kaplan–Meier and reported as percentage and standard deviation. Intergroup endpoints were compared using the log-rank test.

For the Cox multivariable analysis, graft survival was considered as time-to-event outcomes. The variables tested for estimating an association with the endpoint were those reported in Tables 1–3. Each variable was first tested for univariable association with the time-dependent endpoint. Then, the models for each outcome were constructed including risk factors with univariable P-values ≤ 0.15. Results were reported as hazard ratios (HR), with 95% confidence interval (CI) and corresponding P-value. The proportional hazards assumption was tested using the complementary log-log Kaplan–Meier plots and including the time-dependent coefficients into the regression models. The variables which did not satisfy this assumption were not included in the multivariable models.

P-values ≤ 0.05 were considered statistically significant.

Results

Patient groups

Between January 2010 and December 2019, 1213 patients underwent isolated lung transplantation at our institution.

One hundred and twenty (10%) patients were excluded from the study, due to undergoing single-lung transplantation ($n = 35$), bilateral-lung transplantation with lobar or atypical lung resection ($n = 58$), or were not weaned from the mechanical ventilation ($n = 27$)

Table 1. Preoperative recipient data.

Variable	No DE (n = 838)	DE (n = 255)	Transient DE (n = 98)	Permanent DE (n = 157)	P-value[§]
Female sex	409 (48.8)	103 (40.4)	39 (39.8)	64 (40.8)	0.061
Age (years)	51 (35–58)	54 (46–59)	53 (47–58)	55 (44–60)	<0.001
Weight (kg)	63.0 (52.0–75.8)	70.0 (60.0–80.0)	72.0 (60.0–81.2)	69.0 (59.0–80.0)	<0.001
Height (cm)	170.0 (164.0–177.0)	172.0 (165.0–180.0)	173.5 (163.7–181.2)	172.0 (165.0–178.0)	0.022
BSA (m^2)	1.74 (1.56–1.90)	1.81 (1.66–1.99)	1.85 (1.64–1.99)	1.80 (1.66–1.99)	<0.001
BMI (kg/m^2)	21.7 (18.7–25.1)	23.4 (20.8–26.3)	23.4 (21.0–26.3)	23.4 (20.5–26.4)	<0.001
Difference donor-recipient height (cm)	2 (−2.00–7.00)	2 (−2.00–7.00)	2 (−0.25–5.25)	2 (−3.00–6.00)	0.173
Previous thoracic operations	147 (17.5)	44 (17.2)	13 (13.3)	31 (19.7)	0.413
Pleurodesis	24 (2.9)	11 (4.3)	2 (2.0)	9 (5.7)	0.137
Lobar resection	16 (1.9)	3 (1.2)	0	3 (1.9)	0.386
Atypical resection	22 (2.6)	11 (4.3)	4 (4.1)	7 (4.5)	0.380
Coronary artery disease	62 (7.4)	24 (9.4)	9 (9.2)	15 (9.6)	0.576
CMV risk profile					
Low	174 (20.8)	54 (21.1)	24 (24.5)	30 (19.1)	0.584
Intermediate	391 (46.7)	113 (44.3)	34 (34.7)	79 (50.3)	0.041
High	272 (32.5)	88 (34.5)	40 (40.8)	48 (30.6)	0.200
Transplant indication					
COPD	243 (29.0)	91 (35.7)	36 (36.7)	55 (35.0)	0.122
Pulmonary fibrosis	234 (27.9)	87 (34.1)	33 (33.7))	54 (34.4)	0.163
Cystic fibrosis	188 (22.4)	34 (13.3)	13 (13.3)	21 (13.4)	0.007
Pulmonary arterial hypertension	52 (6.2)	16 (6.2)	4 (4.1)	12 (7.6)	0.519
Redo transplantation	55 (6.6)	13 (5.1)	4 (4.1)	9 (5.7)	0.606
Sarcoidosis	30 (3.6)	8 (3.1)	4 (4.1)	4 (2.5)	0.764
Other*	36 (4.3)	6 (2.3)	4 (4.1)	2 (1.3)	0.194
LAS score[†]	35.3 (32.8–41.2)	36.1 (32.8–41.5)	35.5 (32.7–42.3)	36.4 (32.9–40.5)	0.822
Pulmonary hypertension[‡]	336 (40.1)	118 (46.2)	44 (44.9)	74 (47.1)	0.202
Mechanical ventilation	20 (2.4)	4 (1.6)	1 (1.0)	3 (1.9)	0.660
Intensive care unit	73 (8.7)	17 (6.6)	4 (4.1)	13 (8.3)	0.288
ECMO as a bridge to transplantation	45 (5.4)	12 (4.7)	4 (4.1)	8 (5.1)	0.861
Anti-HLA antibodies	275 (32.8)	72 (28.2)	25 (25.5)	47 (29.9)	0.295
HLA class I	145 (17.3)	37 (14.5)	13 (13.3)	24 (15.3)	0.528
HLA class II	181 (21.6)	45 (17.6)	16 (16.3)	29 (18.5)	0.362
Pretransplant diaphragmatic elevation	16 (1.9)	20 (7.8)	1 (1.0)	19 (12.1)	<0.001

Values are expressed as median (1^{st}–3^{rd} quartiles) or N (%).

BMI: body mass index; BSA: body surface area; CMV: cytomegalovirus; COPD: chronic obstructive pulmonary disease; DE: diaphragmatic elevation; ECMO: extracorporeal membrane oxygenation; HLA: human leukocyte antigens; LAS: lung allocation score.

*For patients without DE: acute respiratory distress syndrome (n = 1); graft versus host disease of the lung (n = 15); bronchiectasis (n = 14); histiocytosis X and Wegener´s granulomatosis of the lung (n = 3); surfactant deficiency, n = 3). For patients with DE: histiocytosis X and Wegener´s granulomatosis of the lung (n = 1); bronchiectasis (n = 2); graft versus host disease of the lung (n = 3).

[†]Data available for 683 no DE patients, for 74 transient DE patients, and for 124 permanent DE patients.

[‡]Pulmonary hypertension was defined as a mean pulmonary artery pressure greater than 25 mmHg.

[§]P-value for comparison between patients without diaphragmatic elevation, patients with transient diaphragmatic elevation, and patients with permanent diaphragmatic elevation.

Table 2. Diaphragm displacement, and donor and intraoperative recipient data.

Variable	No DE (n = 838)	DE (n = 255)	Transient DE (n = 98)	Permanent DE (n = 157)	P-value[§]
Δ between pre- and post-tx apex-diaphragm distance (cm)					
Right	1.95 (−0.43–4.39)	1.92 (−0.69–5.33)	1.29 (−1.00–5.25)	2.19 (−0.55–5.40)	0.543
Left	1.66 (−0.65–4.13)	1.94 (−1.05–4.93)	1.58 (−0.98–4.91)	2.05 (−1.23–4.96)	0.429
Δ between pre- and post-tx apex-costophrenic recess distance (cm)					
Right	2.71 (−0.35–5.27)	2.97 (−0.39–6.57)	2.64 (−0.64–5.71)	3.57 (−0.19–7.14)	0.152
Left	2.53 (−0.37–4.84)	3.04 (−0.51–5.99)	2.49 (−0.24–6.12)	3.31 (−0.74–5.95)	0.412
Donor characteristics					
Female sex	431 (51.4)	122 (47.8)	43 (43.9)	79 (50.3)	0.366
Age (years)	48 (35–58)	49 (34–58)	50 (35–57)	46 (34–59)	0.964
Weight (kg)	75 (68–85)	78 (68–89)	80 (66–90)	75 (69–85)	0.546
Height (cm)	172 (165–180)	175 (167–180)	175 (170–182)	173 (165–180)	0.073
BSA (m^2)	1.90 (1.75–2.05)	1.93 (1.77–2.08)	1.95 (1.77–2.09)	1.91 (1.77–2.05)	0.304
BMI (kg/m^2)	24.9 (23.0–27.7)	25.4 (23.1–27.8)	25.4 (23.2–27.7)	25.5 (23.1–27.7)	0.822
Ventilation time (days)	4 (2–7)	4 (3–8)	4 (3–6)	5 (3–9)	0.071
pO_2 (100%, mmHg)	386 (317–450)	391 (325–454)	394 (327–456)	389 (324–453)	0.536
Smoking history	338 (40.4)	108 (42.3)	42 (42.9)	66 (42.0)	0.848
Lung contusion	88 (10.5)	20 (7.8)	7 (7.1)	13 (8.3)	0.441
Aspiration	52 (6.2)	20 (7.8)	10 (10.2)	10 (6.4)	0.318
Ex vivo lung perfusion	50 (6.0)	13 (5.1)	5 (5.1)	8 (5.1)	0.873
Intraoperative recipient characteristics					
Thoracotomy					
Sternum sparing	801 (95.6)	241 (94.5)	94 (95.9)	147 (93.6)	0.544
Clamshell	36 (4.3)	14 (5.4)	4 (4.1)	10 (6.4)	0.506
Cardiopulmonary support					
ECMO	195 (23.3)	59 (23.1)	40 (25.5)	19 (19.4)	0.534
Cardiopulmonary bypass	15 (1.8)	1 (0.4)	0	1 (0.6)	0.244
Cold ischemic time (min)					
First lung	398 (321–497)	402 (323–507)	415 (333–514)	396 (315–506)	0.511
Second lung	513 (431–607)	522 (435–621)	530 (443–635)	514 (431–603)	0.504
Blood products, intraoperative					
PRBCs (units)	2 (0–3)	2 (0–3)	2 (0–3)	2 (0–4)	0.807
PC (units)	0 (0–2)	0 (0–2)	0 (0–0)	0 (0–2)	0.161
FFP (units)	4 (2–5)		4 (2–5)	4 (3–6)	0.126
Postoperatively extended ECMO support	64 (7.6)	20 (7.8)	7 (7.1)	13 (8.3)	0.941

Values are expressed as median (1^{st}–3^{rd} quartiles) or N (%).

BSA: body surface area; BMI: body mass index; Δ: difference; DE: diaphragm elevation; ECMO: extracorporeal membrane oxygenation; FFP: fresh frozen plasma; PC: platelet concentrate; PRBCs: packed red blood cells; Tx: transplantation.

[§]P-value for comparison between patients without diaphragmatic elevation, patients with transient diaphragmatic elevation, and patients with permanent diaphragmatic elevation.

Table 3. Postoperative course after transplantation, before hospital discharge.

Variable	No DE (n = 838)	DE (n = 255)	Transient DE (n = 98)	Permanent DE (n = 157)	P-value[§]
PGD score grade 3					
24 h	41 (4.9)	13 (5.1)	3 (3.1)	10 (6.4)	0.491
48 h	37 (4.4)	11 (4.3)	4 (4.1)	7 (4.5)	0.987
72 h	28 (3.3)	10 (3.9)	3 (3.1)	7 (4.5)	0.761
Rethoracotomy for bleeding	50 (6.0)	25 (9.8)	7 (7.1)	18 (11.5)	0.044
Dialysis					
New	50 (6.0)	24 (9.4)	6 (6.1)	18 (11.5)	0.041
Permanent	18 (2.1)	13 (5.1)	4 (4.1)	9 (5.7))	0.034
Atrial fibrillation	89 (10.6)	38 (14.9)	11 (11.2)	27 (17.2)	0.061
Wound healing disorder	45 (5.4)	18 (7.1)	2 (2.0)	16 (10.2)	0.015
Cerebrovascular event	12 (1.4)	2 (0.8)	2 (2.0)	0	0.268
Postoperative pulsed-steroid therapy	231 (27.6)	75 (29.4)	26 (26.5)	49 (31.4)	0.582
Pneumonia	16 (1.9)	3 (1.2)	0	3 (1.9)	0.386
Blood products, overall					
PRBCs (units)	5 (3–10)	6 (3–10)	4 (2–8)	6 (4–11)	0.015
PC (units)	0 (0–2)	1 (0–2)	0 (0–2)	1 (0–2)	0.044
FFP (units)	4 (3–8)	5 (4–7)	4 (3–6)	6 (4–8)	0.049
Secondary ECMO	14 (1.7)	2 (0.8)	1 (1.0)	1 (0.6)	0.569
Anastomotic bronchial dehiscence	20 (2.4)	10 (3.9)	3 (3.1)	7 (4.5)	0.338
Early detectable DSA	194 (23.2)	59 (23.1)	18 (18.4)	41 (26.1)	0.361
Anti-HLA I	47 (5.6)	12 (4.7)	3 (3.1)	9 (5.7)	0.561
Anti-HLA II	163 (19.5)	51 (20)	16 (16.3)	35 (22.3)	0.496
Tracheostomy	68 (8.1)	25 (9.8)	5 (5.1)	20 (12.7)	0.073
Ventilation time (hours)	13 (9–26)	13 (9–26)	12 (9–22)	13 (9–34)	0.347
ICU stay (days)	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–5)	0.370
Hospital stay (days)	23 (21–28)	24 (21–31)	24 (22–29)	24 (21–35)	0.011
In-hospital mortality	22 (2.6)	6 (2.4)	2 (2.0)	4 (2.5)	0.942
Causes					
Infection	12 (54.5)	5 (83.3)	2 (100)	3 (75)	
Graft dysfunction	1 (4.5)	0	0	0	
Cardiac	0	0	0	0	
Bleeding	0	1 (16.7)	0	1 (25)	
Malignancy	1 (4.5)	0	0	0	
Cerebrovascular event	6 (27.3)	0	0	0	
Other	2 (9.1)	0	0	0	
Immunosuppressive therapy during hospitalization					
Cyclosporine	193 (23)	70 (27.4)	30 (30.6)	40 (25.5)	0.228
Tacrolimus	645 (77)	185 (72.6)	68 (69.4)	117 (74.5)	0.228

Values are expressed as median (1^{st}–3^{rd} quartiles) or N (%).

DSA: donor-specific antibodies; DE: diaphragm elevation; FFP: fresh frozen plasma; HLA: human leukocyte antigen; ICU: intensive care unit; PC: platelet concentrate; PGD: primary graft dysfunction; PRBCs: packed red blood cells.

[§]P-value for comparison between patients without diaphragmatic elevation, patients with transient diaphragmatic elevation, and patients with permanent diaphragmatic elevation.

during hospitalization (Fig. 2). Among these 27 patients, 18 (67%) patients died during the index admission.

Of the 1093 (90%) patients included in the analysis, 255 (23%) patients exhibited diaphragm elevation on chest X-ray, being identified at a median of 21 (19, 28) days after transplantation.

Patients with diaphragm elevation

Elevation of the right diaphragm was recorded in 139 (55%) patients, with 116 (45%) patients demonstrating elevation of the left diaphragm. In 98 (38%) patients, unilateral diaphragm elevation improved at a median of 43 (15, 156) days after transplantation (group with

Table 4. Cox's multivariable analysis for graft survival.

Variable Mortality or re-transplant (n = 283)	Univariable			Multivariable		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Categorical variables						
Coronary artery disease	1.526	1.051–2.217	0.026	1.586	1.090–2.308	0.016
Pediatric lung transplantation	0.465	0.239–0.903	0.024			
CMV risk profile, low	0.753	0.554–1.021	0.068			
Transplant indication						
Cystic fibrosis	0.726	0.532–0.991	0.044			
Sarcoidosis	0.416	0.155–1.117	0.082			
Other	1.548	0.920–2.604	0.100	1.838	1.090–3.098	0.022
ECMO as a bridge to transplantation	1.416	0.908–2.211	0.125			
Donor smoking history	1.286	1.018–1.625	0.035			
Intraoperative support, CPB	0.210	0.030–1.499	0.120			
Atrial fibrillation	1.690	1.238–2.306	0.001	1.384	1.002–1.912	0.049
Secondary ECMO	3.312	1.703–6.441	<0.001	3.188	1.622–6.266	0.001
Cyclosporine at discharge	1.831	1.439–2.330-	<0.001	1.748	1.365–2.237	<0.001
Tacrolimus at discharge	0.546	0.429–0.695-	<0.001			
Diaphragmatic elevation	1.139	0.869–1.493	0.345			
Permanent diaphragmatic elevation	1.075	0.766–1.507	0.676			
Continuous variables						
Recipient age (years)	1.010	1.002–1.019	0.019			
Recipient BMI (kg/m^2)	1.039	1.009–1.069	0.010			
Recipient BSA (m^2)	1.570	0.994–2.482	0.053			
Cold ischemic time, first lung (min.)	1.001	1.000–1.002	0.034			
Cold ischemic time, second lung (min.)	1.001	1.000–1.002	0.035			

BMI: body mass index; BSA: body surface area; CMV: cytomegalovirus; CPB: cardiopulmonary bypass; HR: hazard ration.

transient diaphragm elevation). In the remaining 157 (62%) patients, diaphragmatic elevation persisted at the last available chest X-ray, performed at a median of 30 (12, 63) months after transplantation (group with permanent diaphragm elevation).

Patient characteristics and postoperative course

Tables 1 and 2 show the pretransplant and intraoperative recipient and donor characteristics in the three patient groups. Before transplantation, 36 patients had shown diaphragm elevation, that was more common in patients who, after transplantation, presented with diaphragm elevation (7.8% vs. 1.9%, $P < 0.001$, Table 1). Among these 36 patients, 21 (58%) patients showed pulmonary fibrosis as indication to transplantation. One additional patient had previously undergone a resection of the right lower lobe, and two other patients showed destroyed lower lobes. Among the remaining 12 (33%) patients, a reason for diaphragm elevation was not apparently found. Evaluation of diaphragm displacement is reported in Table 2.

Donor characteristics and intraoperative recipient characteristics did not differ between groups (Table 2). Particularly, the difference between donor and recipient heights did not differ between groups ($P = 0.173$, Table 1).

The postoperative course did not differ between patients without diaphragmatic elevation and patients with transient diaphragmatic elevation, while patients with permanent diaphragm elevation showed a higher prevalence of rethoracotomy for bleeding ($P = 0.044$) and of new dialysis ($P = 0.041$), and more often required a tracheostomy ($P = 0.073$). Mechanical ventilation and ICU times did not differ between the three groups ($P = 0.347$, $P = 0.370$, respectively), but patients with permanent diaphragm elevation showed a longer hospital stay time ($P = 0.011$) (Table 3).

Graft and patient survival

Cox's multivariable analysis for graft survival, and graft and patient survival are reported in Tables 4 and 5. Graft survival did not differ between groups ($P = 0.597$). At the multivariable analysis, persistence of

unilateral diaphragm elevation at follow-up did not emerge as a risk factor for worse graft survival (HR = 1.075, 95% CI = 0.766–1.507, $P = 0.676$).

Similarly, overall patient survival and survival conditioned to hospital discharge did not differ between groups ($P = 0.274$ and $P = 0.190$, respectively, Table 5). Among the 32 patients who died of infection at follow-up, death was related to respiratory tract infection in 13 (54.2%) patients without diaphragm elevation, in 1 (100%) patients with temporary diaphragm elevation and in 3 (42.9%) patients with permanent diaphragm elevation ($P = 0.552$).

Secondary outcomes

Freedom from CLAD, redo transplantation, and OAC did not differ between groups ($P = 0.833$, $P = 0.292$, and $P = 0.426$, respectively, Tables 5 and 6). Similarly, freedom from respiratory tract infections did not differ between groups ($P = 0.311$), with 143 (17.1%) patients without diaphragm elevation, 17 (17.3%) patients with transient, and 21 (13.4%) patients with persistent elevation showing at least one episode of pneumonia at follow-up ($P = 0.509$). At discharge, 1-year follow-up and at last outpatient control, QoL did not differ between groups ($P = 0.496$, $P = 0.373$, and $P = 0.318$, respectively).

Lung function tests

Patients with permanent unilateral diaphragm elevation showed lower FEV_1, FVC, and TLC values (% predicted) than patients in the two other groups, at discharge and 1-year follow-up (Table 6). Lung function tests were similar in patients without elevation and in patients with transient unilateral elevation at each time point. However, an increase in the FEV_1 and FVC values between the discharge and 1-year time points was observed also in patients with permanent elevation (Table 6).

Table 5. Outcomes.

Variable	No DE ($n = 838$)	DE ($n = 255$)	Transient DE ($n = 98$)	Permanent DE ($n = 157$)	*P*-value[§]
Graft survival					
3 years	82 (80, 84)	80 (74, 86)	80 (72, 88)	90 (84, 96)	0.597
5 years	72 (68, 76)	70 (64, 76)	67 (55, 79)	72 (64, 80)	
8 years	64 (60, 68)	60 (52, 68)	60 (46, 74)	60 (48, 72)	
Patient survival, overall					
3 years	84 (80, 88)	82 (76, 88)	80 (72, 88)	83 (77, 89)	0.274
5 years	75 (71, 79)	72 (66, 78)	69 (59, 79)	75 (67, 83)	
8 years	69 (61, 77)	63 (55, 71)	61 (47, 75)	65 (53, 77)	
Patient survival conditioned to hospital discharge					
3 years	86 (84, 88)	84 (78, 90)	82 (74, 90)	85 (79, 91)	0.190
5 years	77 (73, 81)	74 (68, 80)	70 (60, 80)	77 (69, 85)	
8 years	71 (67, 75)	65 (57, 73)	62 (48, 76)	67 (55, 79)	
Causes of death after hospital discharge[§]					
CLAD	80 (9.8)	22 (8.8)	14 (14.6)	8 (5.2)	0.046
Infection	24 (2.9)	8 (3.2)	1 (1.0)	7 (4.6)	0.275
Malignancy	18 (2.2)	11 (4.4)	5 (5.2)	6 (3.9)	0.142
Cardiac	18 (2.2)	3 (1.2)	2 (2.1)	1 (0.7)	0.447
Other	19 (2.3)	13 (5.2)	5 (5.2)	8 (5.2)	0.064
Freedom from CLAD[‡]	($n = 804$)	($n = 244$)	($n = 95$)	($n = 149$)	
3 years	79 (75, 83)	79 (75, 83)	74 (64, 84)	77 (69, 85)	0.833
5 years	66 (62, 70)	66 (62, 70)	67 (55, 79)	70 (60, 80)	
8 years	54 (48, 60)	54 (48, 60)	53 (37, 69)	57 (43, 71)	

Values are expressed as mean % (95% confidence interval, CI) or N (%).

CLAD: chronic lung allograft dysfunction; DE: diaphragm elevation; ISHLT: international society for heart and lung transplantation.

[§]In-hospital deaths were not considered.

[‡]1048 (96%) patients showed at least 2 spirometric recordings for calculation of baseline and a survival of more than 90 days, and were considered for CLAD analysis.

[§]*P*-value for comparison between patients without diaphragmatic elevation, patients with transient diaphragmatic elevation, and patients with permanent diaphragmatic elevation.

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Table 6. Other outcomes and spirometry results.

Variable	No DE (n = 838)	DE (n = 255)	Transient DE (n = 98)	Permanent DE (n = 157)	P-value[§]
Freedom from redo transplantation					
3 years	97 (95, 99)	98 (96, 100)	100	95 (91, 99)	0.292
5 years	95 (93, 97)	97 (95, 99)	98 (96, 100)	95 (91, 99)	
8 years	93 (91, 95)	95 (91, 99)	98 (96, 100)	93 (87, 99)	
Freedom from respiratory tract infections					
1 year	83 (81, 85)	81 (75, 87)	76 (68, 84)	84 (78, 90)	0.311
5 years	66 (62, 70)	63 (55, 71)	66 (56, 76)	67 (57, 77)	
8 years	55 (49, 61)	55 (45, 65)	48 (32, 64)	59 (47, 71)	
Freedom from obstructive airway complications					
3 months	92 (90, 94)	92 (88, 96)	92 (86, 98)	92 (88, 96)	0.426
6 months	87 (85, 89)	86 (82, 90)	81 (73, 89)	88 (82, 94)	
1 year	87 (85, 89)	85 (81, 89)	81 (73, 89)	87 (81, 94)	
Quality of life (VAS 0–10)					
At discharge	7 (6–8)	7 (6–8)	7 (5–8)	7 (6–8)	0.496
At 1 year after transplantation	8 (7–9)	8 (7–9)	8 (6–9)	8 (7–9)	0.373
At last control*	8 (5–9)	8 (5–9)	7 (5–8)	8 (5–9)	0.318
FEV_1 (% predicted)					
Pretransplant	24 (18–40)	27 (18–44)	25 (17–43)	29 (18–44)	0.403
At discharge	68 (56 −82)	65 (55–78)	68 (59–81)	63 (52–77)	0.039
At 1 year after transplantation	88 (71–105)	85 (70–100)	88 (72–105)	81 (66–98)	0.038
At last control*	78 (54–96)	72 (52–94)	75 (49–98)	72 (53–91)	0.038
FVC (% predicted)					
Pretransplant	43 (34–56)	43 (34–56)	45 (33–60)	42 (35–55)	0.861
At discharge	72 (61–83)	69 (59–81)	71 (60–83)	69 (58–80)	0.034
At 1 year after transplantation	94 (84–101)	92 (77–98)	94 (87–99)	89 (72–97)	<0.001
At last control*	90 (74–99)	91 (73–98)	92 (71–100)	90 (73–97)	0.437
TLC (% predicted)					
Pretransplant	92 (57–117)	85 (52–122)	82 (55–123)	87 (49–122)	0.659
At discharge	85 (75–96)	82 (67–94)	84 (73–95)	81 (67–93)	0.020
At 1 year after transplantation	96 (87–103)	92 (83–99)	93 (89–99)	91 (79–98)	0.002
At last control*	94 (85–100)	93 (85–99)	93 (86–100)	93 (84–99)	0.594

Values are expressed as mean % (95% confidence interval, CI) or median (1^{st}–3^{rd} quartiles).

DE: diaphragm elevation; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; TLC: total lung capacity; VAS: Visual Analog Scale.

*last control was performed after a median of 40 (18–68) months.

[§]p-value for comparison between patients without diaphragmatic elevation, patients with transient diaphragmatic elevation, and patients with permanent diaphragmatic elevation.

Discussion

The study showed that, after lung transplantation, right or left diaphragm elevation occurred in 23% of the included patients, being permanent in more than half of them and occurring more frequently on the right side. Unilateral diaphragm elevation did not have any relevant impact on patient outcomes. While graft survival was similar between groups, patients with permanent elevation showed impaired lung function tests, which however did not translate in a higher incidence of CLAD. QoL did not differ between groups.

Evidence on the impact of diaphragmatic dysfunction after lung transplantation is scarce and limited to small case series [3–10]. More than 20 years ago, Dorffner et al showed that diaphragm dysfunction identified on ultrasound and confirmed by fluoroscopy was present in 12.1% of heart transplant recipients and 7.4% of lung transplant recipients and was associated with a significant higher incidence of pneumonia during hospitalization and a nonstatistically significant increased length of intubation compared with patients with normal diaphragm function [4]. More recently, LoMauro et al prospectively evaluated the diaphragmatic function in

30 lung-transplanted patients, using spirometry, test of diaphragmatic strength, opto-electronic plethysmography, electromyography obtained by phrenic nerve stimulation, and ultrasonography. They showed that, after lung transplantation, all patients showed a sub-clinical diaphragmatic dysfunction at discharge, that persisted for at least 3 to 6 months after surgery and then, slowly returned to normal function. Diaphragmatic dysfunction was mainly due to phrenic nerve neurapraxia [10].

In the present study, we were unable to perform such a thorough evaluation of diaphragm function [10]. While there is still not a gold standard for evaluating diaphragm function [12], chest X-ray is widely available, and allows some evaluation of diaphragm position. Detecting diaphragm elevation by chest X-ray suggests the presence of diaphragm dysfunction but does not prove it.

Dysfunction of diaphragm position may be primarily due to phrenic nerve injury, as suggested by the more frequent involvement of the right diaphragm in our study (Fig. 1). Predominant involvement of the right side may be explained anatomically. The right phrenic nerve runs more in proximity to the pulmonary artery and veins than the left phrenic nerve, and is therefore more susceptible to injury due to stretching and manipulation with forceps and electrical cauterization. Moreover, phrenic nerves may be injured in patients who had undergone thoracic surgery before transplantation, due to the presence of adhesions between the lungs and the pericardial pleura [11]. Particularly in redo transplantation, the right phrenic nerve runs directly above the previous pulmonary artery anastomosis and can be easily injured during instrumentation. The phrenic nerve can also be injured during isolation of the lower and upper pulmonary lobes, especially given its course near the diaphragm or its entry into the thorax cavity, where it cannot be easily identified. However, in the present study, patients who had previously undergone thoracic surgery, such as redo transplantation and pleurodesis, did not show an increased incidence of diaphragmatic elevation, probably due to the heightened attention of avoiding injury of the phrenic nerves in these cases. Finally, another mechanism of injury to the phrenic nerves, which was not used in our institution but has been described elsewhere [5,7,10], is the use of ice slush for topical cooling.

Prolonged mechanical ventilation may predispose to diaphragmatic weakness (ventilator-induced diaphragm dysfunction, VIDD), manifesting as diaphragmatic elevation on chest X-ray [12,17,18]. After transplantation, the diaphragm is usually slowly pushed to a lower position, as a consequence of the interaction between the transplanted lungs, thoracic cavity, and musculature. This is particularly true if patients are promptly weaned and allowed to breathe spontaneously using their intrinsic inspiratory muscle pump. Consequently, the longer the mechanical ventilation time, the higher the risk of diaphragm elevation. However, this hypothesis could not be confirmed by our study, since patients with and without diaphragmatic elevation showed similar ventilation times (Table 3). This may in part be due to a strategy of early weaning and patient mobilization after transplantation at our institution [24,26]. This strategy included early tracheostomy in patients where initial weaning from orotracheal mechanical ventilation had failed. Tracheostomy allows for more protective lung and diaphragm ventilation, thus minimizing the risk for VIDD and muscular atrophy [18,27,28]. Thus, we do not consider tracheostomy a complication anymore, but a valuable tool for accelerating weaning from mechanical ventilation.

A high BMI and obesity seemed to favor the presence of post-transplant diaphragm elevation (Table 1). In patients with obesity, the intraabdominal fat and the hepatomegaly due to the metabolic syndrome may push the diaphragm up. Moreover, these patients may require higher ventilatory pressures after transplantation, that may pose a higher strain on the diaphragm, thus, provoking diaphragm weakness and atrophy [27]. Contrarily, donor graft oversizing might explain the lower prevalence of diaphragm elevation in patients with cystic fibrosis (Table 1). In fact, the mismatch between donor and recipient heights was significantly greater in patients with cystic fibrosis (median 6cm, IQR: 1–10cm) than in patients transplanted for other reasons (median 1cm, IQR: −3–5cm) ($P < 0.001$).

The finding that more than half of patients with pretransplant diaphragm elevation showed pulmonary fibrosis as indication to transplantation is intriguing. In these patients, the diaphragms do not show an anomaly of movement, which is preserved, but of position. Patients with pulmonary fibrosis have usually small thoracic cavities, especially on the right side, where the presence of the liver pushes the corresponding diaphragm in a higher position than the left diaphragm.

In our study, post-transplant diaphragmatic elevation had no impact on the postoperative course and the outcomes at follow-up. The potential causal relationship between tracheostomy and permanent diaphragm elevation (Table 3) deserves more insight, because, in our retrospective study, the diagnosis of diaphragm elevation was usually established after the tracheostomy had

been performed, by checking the X-rays before hospital discharge. Diaphragm dysfunction might have played an important role in prolonging ventilatory weaning in some patients with diaphragm elevation, but this relationship should be better clarified by a prospective study. Moreover, patients with permanent diaphragmatic elevation showed worse lung function tests at discharge and at follow-up than patients in the other two groups. Lung function tests improved at follow-up in patients with permanent diaphragmatic elevation altogether, probably due to recruitment of accessory inspiratory musculature (Table 6). However, this finding did not translate in a higher incidence of respiratory tract infections, as reported by other authors [4], or CLAD (Tables 5 and 6).

Several surgical therapies have been proposed to treat diaphragm dysfunction, including phrenic nerve reconstruction [13,29], diaphragm plication [13,30–33], and diaphragm and phrenic nerve pacing [8,12,13,34,35]. Phrenic nerve reconstruction, for example using intercostal nerve to phrenic nerve grafting, has shown optimal recovery of diaphragm function. Diaphragm plication may be performed through an open or video-assisted thoracic or abdominal approach. Results showed a low prevalence of complications and a significant increase in lung function tests after surgery. In comparison with plication, permanent diaphragmatic pacing requires a functioning phrenic nerve and has been reserved to patients with high-level spinal cord injuries and central hypoventilation syndromes. Electrodes may be placed thorough a thoracoscopic or laparoscopic approach. However, the use of these techniques has not been reported in lung transplantation, except for the use of temporary diaphragm pacing [8].

At our institution, we did not use any of the previous interventions, since patients with diaphragm elevation were successfully weaned off the mechanical ventilation and showed similar quality of life as patients without elevation or with transient elevation did. Therefore, and in accordance with the available literature [13,35], we recommend that more conservative therapies such as rehabilitation and training should be first offered to patients with diaphragm elevation and that surgery should be reserved to patients with intractable symptoms and whose diaphragm elevation was refractory to more conservative treatment. Contrarily, diaphragm pacing using temporary electrodes may be offered to those patients who are expected to require a prolonged weaning from the mechanical ventilation, as a strategy for improving the ventilator-diaphragm coupling [8].

Accordingly, we focus on an aggressive weaning from the mechanical ventilation, thus avoiding the worsening of ventilator-induced diaphragm weakness [12,18], and on an intensive physiotherapy with early patient mobilization and ambulation, in order to preserve the accessory respiratory musculature. For this purpose, we have recently created an "high care" team, consisting of specialized nurses, respiratory therapists, and physicians at the ICU, that specifically addresses patients who require prolonged mechanical ventilation, as those with diaphragm elevation. Each patient who required tracheostomy for ventilatory weaning receives a weaning plan, where the timetable regulating the amount of assisted and spontaneous ventilation is fixed and daily adjourned to the patient needs.

Study limitations

The data were collected retrospectively and came from a single center. Our definition of diaphragm elevation was based on chest X-rays, and elevation may be considered only a surrogate of dysfunction. However, retrospective evaluation of diaphragm dysfunction is difficult, and only chest X-rays may allow it. While the sensitivity, specificity, positive, and negative predictive value of diaphragm elevation for the diagnosis of unilateral diaphragmatic dysfunction are 90%, 44%, 33%, and 93%, respectively [13], evaluation of serial chest X-rays allowed retrospective assessment of almost all patients in our cohort. However, the study had to exclude patients who were never weaned from the respirator ($n = 27$) as well as patients who underwent lung resection during transplantation ($n = 58$), and our definition of diaphragm elevation precluded the identification of bilateral diaphragmatic dysfunction.

Measurements of diaphragm displacement (Table 2) might have been biased by the lack of a reference scale in the pre and post-transplant chest X-rays. In this case, chest CT would allow more precise measurements and may be used for future prospective studies correlating diaphragm displacement with donor and recipient TLC.

Finally, the radiologic definition of diaphragmatic elevation [16] is still used by our radiologist in the everyday life. Therefore, the results of this study may not be extended to other centers, that use other radiologic definitions.

Conclusions

Unilateral diaphragm elevation was detected in 23% of patients who underwent lung transplantation but did have any relevant impact on the postoperative course.

While lung function tests were worse in patients with permanent elevation, long-term survival and freedom from CLAD did not differ between groups.

Authorship

All authors have contributed to preparing and drafting the manuscript and no person or persons other than the authors listed have contributed significantly to its preparation. In particular, research was designed by FI, JG, MMH, GW, and HD; research was conducted by FI, HD, JS, WS, TS, and DB; chest X-rays were checked by LSB and JBH; data analysis was performed by FI, DBöthig, and HD; writing of the manuscript was performed by FI, HD, MG, and JG; and critical revision of the manuscript was performed by MA, MG, NS, MMH, TW, AH, CK, GW, JG, and IT.

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Conflict of interest

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