Fissure Integrity and Volume Reduction in Emphysema: A Retrospective Study

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Key Words

Emphysema · Chronic obstructive pulmonary disease ·
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Abstract

Background: One-way endobronchial valves (EBVs) relieve symptoms of emphysema, particularly in patients without collateral ventilation between the target and adjacent lobes. Pretreatment knowledge of fissure integrity could serve as an aid in indicating EBV interventions. **Objective:** This study aimed to investigate the relationship between software-measured lung fissure integrity and clinically relevant lung volume reduction (≥ 350 ml) in emphysema patients treated with one-way EBVs using a lobar exclusion strategy. **Methods:** Of 108 patients treated between March 2008 and July 2014, 38 had both baseline and follow-up computed tomography (CT) scans acquired following a specific protocol for quantitative CT analysis and were included in the study (total of 39 treatments, two lungs treated in 1 patient). Outcome measures were fissure integrity measured on baseline CT scans, difference between pre- and postoperative lung vol-

ume (considering the lowest measured postoperative volume), and correlation between fissure integrity and volume change. **Results:** Fissure integrity $\geq 75\%$ correlated with volume reduction ≥ 350 ml (Spearman coefficient: -0.65 ; $p < 0.01$). The mean and median volume reductions were $1,223.96 \pm 907.5$ ml and 663 ml, respectively, for lungs with fissure integrity $\geq 75\%$ ($n = 31$). The accuracy of fissure integrity $\geq 75\%$ in predicting a volume reduction was 87.2%. The positive predictive value of fissure integrity $\geq 75\%$ to predict a volume reduction ≥ 350 ml was 83.9%, and it was 70% for fissure integrity 75–90% and 90.5% for fissure integrity $> 90\%$. **Conclusions:** A target lobe volume reduction using EBVs is possible with lung fissure integrity $\geq 75\%$. For patients with fissure integrity between 75 and 90%, a further evaluation of interlobar ventilation should be performed. A clinically relevant volume reduction following treatment with EBVs is likely with any level of fissure integrity $> 90\%$.

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This study was conducted at the Hospital de Clínicas de Porto Alegre (HCPA) and Hospital Moinhos de Vento (HMV).

Introduction

The estimated lifetime prevalence of emphysema, a chronic lung disease, was 20.2 per 1,000 people in the USA in 2011, with markedly increased observations in specific groups such as women and non-Hispanic blacks between 1999 and 2011 [1]. In its severe stage, emphysema is a crippling disease that impairs an individual's ability to perform the simple tasks of daily living.

There is well-documented evidence that lung volume reduction is beneficial for emphysema patients [2], a population still lacking treatment alternatives. Based on that evidence, and taking into account the high morbidity and mortality associated with lung volume reduction surgery, nonsurgical, minimally invasive alternatives have been proposed [2, 3]. Among these, the use of one-way endobronchial valves (EBVs) is the oldest and thus best-studied method among various bronchoscopic lung volume reduction (BLVR) techniques [4–11], even though a definitive prospective trial is still unavailable.

BLVR with EBVs is based on the mechanical occlusion of emphysematous portions of the lung. After implantation, trapped air passes through the duckbill valve, which then closes, preventing air from reentering the diseased portion of the lung and (as initially hypothesized) producing atelectasis. However, practice has shown that a clinically significant volume reduction is not always achieved, with atelectasis obtained in about 50% of cases [12–15]. Observations suggest that the lack of volume reduction is due to collateral ventilation [16, 17], a phenomenon with major implications for patient selection and EBV treatment outcome.

Collateral ventilation has been linked to interlobar fissure incompleteness [15–19]. The existence of intact, incomplete, or absent interlobar fissures [defined by visual inspection of computed tomography (CT) scans] [20] has been extensively described in the literature [21, 22]. Fairly recently, a randomized study of BLVR treatment of emphysema showed that radiographic evidence of fissure completeness was associated with a better response to treatment [5]. Nevertheless, the correlation between the degree of fissure (in)completeness and collateral flow across adjacent lobes remains to be elucidated [15, 20]. In addition, to date only a couple of studies have been specifically designed to evaluate the role of fissure integrity in lung volume reduction, with inconclusive or preliminary results [18, 23, 24].

The type of information provided by CT assessments of fissure integrity has been traditionally limited to classifications of fissures as intact, partial, or absent, but a

recent study has employed software analysis to measure the fissure area (expressed in cm^2) and identified a significant difference in the area of fissure defect between patients with and those without endoscopically measured collateral ventilation [15]. Our group has previously described the use of CT pulmonary imaging software optimized for bronchoscopically guided pulmonary procedures for the fast and accurate assessment of airway and parenchymal anatomy in patients with airway disease [25]. More recently, we have shown the value of computing a semi-automated fissure measurement for the purpose of improving the prediction of volume reduction in EBV treatment [23]. In the present study, we investigated the relationship between fissure integrity and clinically relevant lung volume reduction (≥ 350 ml) in a group of emphysema patients treated with EBVs.

Patients and Methods

Patients

This is a single-center, retrospective study of patients with advanced emphysema (GOLD stage III or IV). From a database of 108 patients, 38 individuals treated with EBVs (Zephyr®; Pulmonx, Redwood City, Calif., USA; <http://www.pulmonx.com/en/home2>) who had both baseline and follow-up CT scans acquired following a specific protocol for quantitative CT analysis using Apollo software (VIDA Diagnostics, Coralville, Iowa, USA) were eligible. These 38 patients were included in the study, for a total of 39 treatments (two lungs treated in 1 patient). The treatments were performed between March 2008 and July 2014. The study was approved by the Institutional Review Board of the Hospital de Clínicas de Porto Alegre (IRB No. 00000921; project approval No. 02-040). All patients signed an informed consent form at the time of the procedure, giving permission for future use of their data.

At our Emphysema Treatment Center, the following selection criteria are applied to all EBV candidates: dyspnea during usual tasks in the presence of optimal care, absence of other diseases that could cause dyspnea, residual volume $>150\%$, radiologic diagnosis of emphysema ($\geq 20\%$ of lung parenchyma with a density <-950 HU and 25% of target lobe parenchyma with a density <-950 HU), and not having smoked for ≥ 6 months prior to the EBV procedure. Exclusion criteria are chronic expectoration (suggestive of bronchial disease), comorbidities associated with <2 years of life expectancy, and not providing informed consent to BLVR.

Treatment Protocol

For the procedure, spirometry, gas transfer, and lung volumes as assessed by body plethysmography were measured using a Compact Lab System (Jaeger, Höchberg, Germany). For assessment of health-related quality of life, a validated Brazilian Portuguese version of the St. George's Respiratory Questionnaire (SGRQ) was used without modifications. The questionnaire was reproduced and used with written permission from the original investigators. The patients performed the 6-min walk test (6MWT) before and after BLVR, as described by the American Thoracic Society [26].

Table 1. Baseline data for the 38 patients with advanced emphysema

Patient ID	Age ^a , years	Sex	DLCO, ml/min/mm Hg [%]	RV, l [%]	SGRQ total score	6MWT, m	FEV ₁ , l [%]
23	75	F	–	–	65.3	–	–
25	69	M	–	–	69.9	3	0.58 [19.0]
29	59	M	6.49 [26.2]	7.60 [395.3]	69.4	100	0.58 [18.5]
31	83	M	10.24 [48.7]	5.98 [240.6]	70.2	230	1.08 [40.0]
32	53	M	2.20 [8.0]	9.35 [484.9]	86.8	215	0.68 [19.2]
34	70	F	6.40 [26.0]	5.27 [240.0]	–	–	0.69 [29.0]
38	71	M	7.08 [30.1]	4.04 [197.8]	56.9	310	0.56 [21.4]
40	73	F	10.62 [49.1]	4.8 [226.3]	59.4	215	0.71 [37.2]
42	79	M	10.86 [44.0]	3.82 [149.3]	46	–	1.15 [36.5]
45	70	M	–	–	29.4	–	–
49	77	F	6.38 [29.3]	4.96 [227.0]	–	50	0.78 [41.3]
54	64	M	12.59 [39.3]	5.70 [251.6]	42.4	380	1.12 [32.1]
58	71	M	–	–	74.1	–	–
59	81	F	–	5.08 [201.7]	72.7	85	0.51 [24.1]
60	66	M	9.48 [38.0]	6.47 [303.0]	57.1	330	0.93 [29.0]
62	69	M	–	–	86.8	–	0.41 [15.0]
68	65	M	5.33 [16.7]	8.76 [366.3]	76.5	230	0.64 [18.5]
70	77	M	–	–	47.5	237	0.73 [25.6]
76	68	M	–	–	64.3	343	1.05 [31.6]
77	58	M	8.72 [33.0]	3.55 [159.0]	57.8	493	1.05 [35.0]
78	55	F	–	–	–	–	–
79	62	M	–	–	51.4	–	–
81	65	M	1.27 [14.0]	6.75 [271.0]	67.5	252	1.03 [29.1]
82	80	M	4.18 [54.0]	3.45 [128.0]	40.4	444	1.51 [71.0]
83	70	M	4.75 [44.0]	5.82 [220.0]	21.5	312	1.69 [51.52]
88	76	M	10.62 [49.6]	5.26 [231.2]	55.4	270	0.79 [28.7]
89	55	M	–	10.1 [–]	80.4	65	0.49 [12.6]
96	65	F	–	–	75.1	–	–
97	79	F	6.92 [33.2]	5.89 [241.7]	66.6	205	0.90 [43.2]
98	70	M	–	–	83.8	–	–
99	76	M	–	–	–	–	–
100	51	F	–	–	54.4	–	0.36 [13.4]
101	63	M	1.99 [7.7]	4.86 [244.5]	93.6	182	0.72 [22.0]
102	65	M	11.05 [34.7]	5.38 [235.2]	61.5	435	0.85 [24.1]
105	65	F	6.60 [26.8]	4.36 [209.7]	47.8	375	1.17 [50.9]
106	56	M	4.01 [15.5]	5.62 [291.8]	91.3	162	0.65 [19.8]
107	76	M	7.20 [33.0]	6.16 [270.0]	48.3	285	0.90 [32.0]
108	69	M	11.51 [37.7]	4.57 [194.8]	67.7	333	1.63 [49.1]

Missing functional data reflect the inability to perform tests due to the severity of the disease. DLCO = Diffusion capacity of the lung for carbon monoxide; RV = residual volume. ^a Age at treatment.

To plan the treatment strategy, multidetector CT scans were analyzed using the FDA 510(k) cleared Apollo software (VIDA Diagnostics). Quantitative lung parameters, including lobar volumes, total emphysema scores, and heterogeneity gradient, were determined. As recommended by the Apollo software manufacturer, all scans were acquired using a thin-section low-dose protocol, with 1.0-mm collimation and 1.0-mm increments, a scanner-specific reconstruction algorithm (B30 for Siemens, FC01 for Toshiba, Standard for GE, and 'B' for Phillips), a 120-kVp tube

tension, an 80- to 100-mA tube current, and a 512 × 512 reconstruction matrix with no intravenous administration of iodinated contrast agent. A similar scan was acquired and analyzed for the target lobe volume at follow-up. A video showing the placement of a Zephyr[®] valve is available as supplementary material (online suppl. video 1; for all online suppl. material, see www.karger.com/doi/10.1159/000446288).

Endobronchial lobar occlusion was performed using Zephyr[®] valves placed in segmental or subsegmental bronchi. Pretreatment

analysis of airway morphology and virtual bronchoscopy using the Apollo software facilitated treatment planning, allowing the size and number of valves to be defined before the start of the procedure. This was helpful in decreasing the sedation time and the duration of the procedure, which are critical aspects given the severity of emphysema in these patients. All operations lasted up to 20 min. One patient underwent a staged treatment, with the valves being inserted on two separate occasions.

Fissure Integrity Analysis

Patient records were reviewed to identify patients treated with lobar exclusion and having at least one pre- and one posttreatment CT performed under protocol. The percentage of fissure integrity at baseline was determined using the Apollo software [23, 27, 28].

For left target lobes and for the right lower lobe, the corresponding oblique fissure integrity scores were used. For patients treated at the right upper lobe, the superior half of right oblique fissure plus horizontal fissure integrity score was assumed.

Statistical Analysis

Descriptive statistics are expressed as means $\pm$ SD or medians and ranges, as appropriate. Posttreatment outcome measures were compared with baseline values, and the statistical significance of changes from baseline was assessed either by paired *t* tests or by the nonparametric equivalent (Wilcoxon signed-rank test). The Spearman correlation coefficient was used to examine the association between fissure integrity and posttreatment lung volume change. A linear regression model with backward selection was developed to explore the relationship between volume reduction ≥ 350 ml and total lung emphysema score, heterogeneity gradient, and integrity score.

Results

The sample included 38 patients with advanced emphysema undergoing BLVR with Zephyr[®] valves and lobar exclusion between June 2008 and May 2014. Most patients were men (73.7%). The mean age at treatment was 67.9 ± 8.2 years. The median smoking history was 60 pack-years (range 20–140), and the mean baseline body mass index was 23.3 ± 3.3 . Table 1 shows the baseline patient data and functional parameters of disease severity. All the baseline and follow-up CT scans were performed at our center on the same scanner (Siemens) except for patients 23, 34, 45, 62, 78, 81, and 83. The CT images for these 7 patients were acquired with CT scanners (Siemens, Toshiba, GE, or Phillips) at other centers. Nevertheless, all images were acquired using the protocol described in the Patients and Methods section. The median interval between baseline and follow-up CT was 201 days (18–677).

The data on treatment strategy, fissure integrity, volume reduction, and heterogeneity gradient for 38 patients

and 39 lungs (1 patient treated bilaterally) are shown in table 2. Images of fissures analyzed in the present study are shown in figure 1.

A correlation (Spearman coefficient: -0.6 ; $p < 0.01$) was observed between fissure integrity $\geq 75\%$ and volume reduction ≥ 350 ml (fig. 2). The mean and median volume reductions were $1,223.96 \pm 907.5$ ml and 663 ml, respectively, for lungs with fissure integrity $\geq 75\%$ ($n = 31$). The accuracy of fissure integrity $\geq 75\%$ to predict a volume reduction was 87.2%. The positive predictive value of fissure integrity $\geq 75\%$ to predict a volume reduction ≥ 350 ml was 83.9%, versus 70% for fissure integrity 75–90% and 90.5% for fissure integrity $>90\%$. None of the 8 lobes with fissure integrity $<75\%$ (table 2) achieved a volume reduction ≥ 350 ml (negative predictive value of 100%).

Figure 3 shows scatter plots of relative changes in forced expiratory volume in the first second of expiration (FEV_1), 6MWT distance, and SGRQ total score with respect to target lobe volume reduction (22, 17, and 21 patients, respectively, for whom pre- and posttreatment results were available). Responders were defined as patients with an FEV_1 increase >100 ml for FEV_1 analysis [29], a minimal important difference of 26 ± 2 m in the 6MWT [30] for 6MWT analysis, or a 4-point decrease in global SGRQ score. Of the responders with a volume reduction ≥ 350 ml, 15, 12, and 15, respectively, had fissure integrity $\geq 75\%$. We also observed clinical responders with a target lobe volume reduction <350 ml.

To analyze the effects of total lung emphysema score, heterogeneity gradient, and integrity score on target lobe volume reduction, a multiple linear regression model with backward selection was used. The variables that remained in the final model were total lung emphysema score (coefficient: -25.928 ; $p = 0.034$) and fissure integrity (coefficient: -23.928 ; $p = 0.001$). The Shapiro-Wilk test was used to assess the normality of the residuals, which was not rejected ($p = 0.208$). The Durbin-Watson statistic for this model was 2.275, which indicates no serial autocorrelation in the residuals.

Discussion

In this study, we found that a clinically relevant lung volume reduction (≥ 350 ml) was achieved with treatment of emphysema patients using Zephyr[®] valves and a lobar occlusion strategy in the presence of partial fissure integrity ($\geq 75\%$). A consistent association was observed between fissure integrity as assessed by semi-automated

Table 2. Strategy, evaluation, and treatment results for the 38 patients and 39 lungs according to percent fissure integrity

Patient ID	Strategy	Fissure	Fissure integrity, %	Volume change ^a , ml	Target lobe volume change ^a , %	Heterogeneity gradient ^b , pp
23	RUL	HF + RUOF	26.0	110	8.85	45.7
58	RUL	HF + RUOF	29.7	35	1.96	19.2
101	RUL	HF + RUOF	35.9	-226	-8.55	63.4
42	RUL + RB6	HF + RUOF	48.0	-61	-7.66	16.0
60	RUL	HF + RUOF	65.3	150	6.84	31.0
29	RUL	HF + RUOF	69.9	9	0.35	37.7
45	RUL	HF + RUOF	73.5	-27	-1.42	36.0
81	LUL	LOF	73.8	189	11.4	32.2
34	LUL + LB6	LOF	77.2	-182	-16.60	28.0
59	RUL	HF + RUOF	78.5	-1,514	-51.29	21.0
88	RUL	HF + RUOF	79.0	-787	-49.24	30.7
82	LLL	LOF	80.0	-634	-43.69	22.0
105	RUL	HF + RUOF	81.0	-379	-28.49	37.6
49	RUL	HF + RUOF	82.4	-206	-18.79	30.0
98	RUL	HF + RUOF	83.2	-352	-22.47	50.4
106	RUL	HF + RUOF	83.8	-3,284	-100	35.9
83	RUL	HF + RUOF	85.0	-175	-9.04	40.0
31	LLL	LOF	86.0	-635	-34	25.7
107	RLL	ROF	90.5	-171	-10.7	17.8
99	LUL	LOF	92.9	-2,613	-100	29.7
79	LUL	LOF	93.2	-2,699	-97.2	19.7
76	RUL	HF + RUOF	93.6	-413	-15.1	70.0
62	LLL	LOF	93.9	-703	-62.9	30.8
32	LLL	LOF	94.4	-2,705	-93.4	44.1
96	LLL	LOF	94.6	-1,006	-50.1	27.3
38	RUL	HF + RUOF	94.7	-1,158	-100	21.0
100	LLL	LOF	95.0	-1,146	-50.8	47.5
25	LLL	LOF	95.1	-2,773	-54.7	87.0
89	RUL	HF + RUOF	95.8	-1,960	-36.6	41.5
78	LLL	LOF	97.0	-1,352	-78.5	40.0
68	RLL	ROF	97.1	-333	-15.7	9.5
54	LUL	LOF	98.0	-956	-97.4	18.3
102	RLL	ROF	98.2	-663	-25.6	25.7
70	RLL	ROF	98.3	-1,500	-99.9	27.0
108	LUL	LOF	98.6	-1,840	-100	13.4
77	LUL	LOF	98.9	-1,833	-100	19.0
29	LUL	LOF	99.0	-1,949	-100	39.8
97	RLL	ROF	99.8	-370	-34.1	5.8
40	RUL	HF + RUOF	99.9	-1,652	-100	56.5

Bold: volume reduction ≥ 350 ml. HF + RUOF = Superior half of right oblique fissure plus horizontal fissure integrity score; LLL = left lower lobe; LOF = left oblique fissure integrity score; LUL = left upper lobe; RLL = right lower lobe; ROF = right oblique fissure integrity score; RUL = right upper lobe. ^a Negative values indicate volume reduction. ^b Difference in lobe percent volumes with parenchymal density < -950 HU.

analysis of high-resolution CT scans using VIDA software and target lobe volume reduction ≥ 350 ml. The overall accuracy of a 75% fissure integrity cutoff point was 87.2% for a 350-ml reduction in target lobe volume.

We observed improvements in 6MWT distance and SGRQ total scores in some patients with a target lung volume reduction < 350 ml. Even though the low number of patients ($n = 17$) precludes a final conclusion, these find-

Fig. 1. a Left oblique fissure with 100% integrity. Right oblique fissure with 98.5% integrity and horizontal fissure plus upper segment of right oblique fissure with 74.6% integrity. The area in blue shows the presence of fissures; green shows the absence of fissures. **b** Left oblique fissure with 84.5% integrity. Horizontal fissure plus upper segment of right oblique fissure with 56.7% integrity. Colors refer to the online version only.

Fig. 2. Scatter plot of volume reduction and fissure integrity. Bold horizontal line: volume reduction = 350 ml.

ings might be explained by the high emphysema heterogeneity associated with relief of dynamic hyperinflation with valve treatment, as described by Hopkinson et al. [17]. Conversely, a target lobe volume reduction >350 ml (particularly in case of lobar atelectasis) may sometimes result in a shunt with a decrease in PaO₂ leading to a reduction of exercise capacity [31]. However, as with many aspects of emphysema, additional studies are urgently needed to elucidate these complex relationships. Another interesting observation was that of 5 patients with fissure integrity $\geq 75\%$ who did not achieve a target lung volume reduction ≥ 350 ml, 4 were treated in the right lung, and only one in the left lung. Lobar exclusion was achieved in all these patients. This might be associated with the presence of two fissures in the right lung, and should be further evaluated in future studies.

The present study has limitations that must be addressed. First of all, it is a retrospective study, and therefore the time point at which the lung volume reduction was measured was not strictly the same for all patients. Also, it is a single-center study, and because operator experience is crucial to interpreting fissure integrity with the Apollo software, despite the automated readings, interrater agreement should be evaluated across several centers. In fact, the need for an experienced operator is a limitation of the software itself. The automated detection and segmentation of lung fissures is a challenging task due in large part to the low contrast and variable shape of lobar fissures with disease (nearby tumors, atelectasis, emphysematous changes) and breathing. Also, because we treat many patients from other states, not all patients were able to return for follow-up after the same time interval.

It is also important to underscore the possibility of screening provided by this imaging method. Despite its simplicity and safety, BLVR with EBVs requires careful planning and follow-up, and should be performed only in centers of excellence. Because many candidates are severely ill, CT screening is useful in preventing unnecessary travel. In our emphysema center, 30–40% of patients are candidates for BLVR, and the possibility of CT-based

Fig. 3. **a** Scatter plots of changes in FEV₁ (n = 22 patients). **b** Changes in distance walked in the 6MWT (n = 17 patients). **c** Changes in SGRQ total score (n = 21 patients). Bold vertical line: volume reduction = 350 ml. Responders were defined as patients with an FEV₁ increase >100 ml for FEV₁ analysis [29], a minimal important difference of 26 ± 2 m in the 6MWT [30] for 6MWT analysis, or a 4-point decrease in global SGRQ score.

screening protects patients from strenuous physical effort, invasive measurement of collateral ventilation, or uncertain treatment results. Our current screening protocol recommends VIDA analysis of CT scans to determine parenchymal density and fissure integrity and additional measurement of collateral ventilation with the Chartis system [11, 19, 24] if fissure integrity is between 75 and 90%.

In conclusion, our results provide evidence that target lobe volume reduction is possible with lung fissure integrity $\geq 75\%$. Patients with fissure integrity $>90\%$ are likely to achieve a clinically relevant target lobe volume reduction with EBV treatment. Patients with fissure integrity between 75 and 90% should undergo further evaluation of interlobar ventilation, as previously noted [19, 24]. Pa-

tients with fissure integrity $<75\%$ are not likely to achieve any clinically relevant target lobe volume reduction with EBV.

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