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Volumetric and scintigraphic changes following endoscopic lung volume reduction

To the Editor:

Bronchoscopic treatment of emphysema represents an emerging therapeutic modality for advanced emphysematous lung destruction in chronic obstructive pulmonary disease (COPD). Within the proposed techniques for endoscopic lung volume reduction (ELVR), a significant amount of experience exists for the placement of endobronchial valves (EBV) (Zephyr® valves; Pulmonx, Inc., Redwood City, CA, USA) targeting atelectasis of the treated, emphysematous lobe [1, 2]. However, post-procedural clinical

improvement has also been documented in patients lacking lobar exclusion 3. While volumetric and density adaptations following ELVR have repeatedly been a focus [3, 4], the interaction of volume and perfusional/ventilatory changes remains unclear. In this observational study, we defined the extent of interdependency of ELVR-mediated volumetric and scintigraphic adaptations.

Among 36 patients receiving ELVR by EBV insertion at the Dept of Pneumology, University Hospital Bonn (Bonn, Germany) from November 2012 to February 2014, 24 patients were offered pre- and post-procedural imaging and qualified as eligible for inclusion in this study. As a pre-requisite for performance of ELVR, patients were required to meet the inclusion criteria of the Endobronchial Valve for Emphysema Palliation Trial (VENT) study [1]. Exclusion criteria for ELVR and consequently for study inclusion comprised continued nicotine consumption and frequent respiratory exacerbations ($\geqslant 2$ exacerbations per year). Flexible bronchoscopy was performed by an experienced bronchoscopist and executed under moderate sedation with propofol and midazolam, permitting spontaneous breathing. Absence of collateral ventilation as assessed by the Chartis® Pulmonary Assessment System (Pulmonx, Inc.) allowed for EBV placement [5]. The study had the approval of the local ethics committee.

The day prior to ELVR and 8 weeks afterwards, all patients underwent pulmonary function assessment, 6-min walk test (6MWT), COPD Assessment Test and N-terminal pro-brain natriuretic peptide (NT-proBNP) testing. In the same time interval, ventilation/perfusion scintigraphy was conducted and complemented by single-photon emission computed tomography (SPECT)/low-dose computed tomography imaging (scan parameters: 130 kVm 17 mAs, 5-mm slices). Scintigraphy and SPECT analyses were performed by experienced local nuclear physicians, blinded to the patient's clinical performance, by use of OsiriX® Medical Imaging Software (an open-source project; Pixmeo, Geneva, Switzerland).

Continuous variables were evaluated by use of paired t-test, categorical parameters by Pearson's Chi-squared test. A value of $p<0.05$ was considered statistically significant. The Spearman correlation test was applied for correlation analysis of volumetric, perfusional and ventilatory changes over time.

Pre-procedural clinical data of the 24 included patients are summarised in table 1. The study population comprised 58.3% males (14 out of 24) and exhibited a mean±SD age of 64.3 ± 8.8 years; all study participants were former smokers with a mean±SD of 39.8±14.3 pack-years. In a majority (37.5%) of the patients, the right upper lobe was targeted (left lower lobe 29.2%, right lower lobe 20.8%, left upper lobe 12.5%); the median number of EBV inserted per patient was four. Overall, the complication rate was low. Post-procedurally, exacerbations of COPD occurred in 12.5% of patients (n=3); two (8.3%) patients developed pneumothorax, both of whom were managed successfully by temporary chest tube implantation.

Post-procedural pulmonary function testing exhibited an increase in forced expiratory volume in 1 s by 15.3% of predicted (p=0.06) (table 1). Contrary to mean residual volume, the mean reduction in residual volume/total lung capacity ratio reached statistical significance (p=0.04). On average, target lobe volume decreased by 444.6 mL in absolute and 36.8% in relative terms (p=0.004) and correlated with target lobe perfusional changes (Spearman's rho 0.56; p=0.04), which in turn were linked to target lobe ventilatory adaptations (Spearman's rho 0.67; p=0.03). The ipsilateral and contralateral nontargeted lobes, as well as the contralateral concordant lobe, experienced volumetric increases that were significantly associated with one another. Clinical responsiveness to ELVR assessed by 6MWT and defined by a post-procedural improvement in 6MWT distance $\geqslant 25$ m [6] was exhibited by 17 (70.8%) patients. Irrespective of clinical responder status, changes in 6MWT distance correlated significantly with development of NT-proBNP levels (Spearman's rho -0.96; p<0.001). However, changes in both 6MWT and NT-proBNP were uninfluenced by the extent of volumetric and scintigraphic adaptations.

The mechanisms by which ELVR is supposed to alleviate dyspnoea in emphysematous COPD include reduction of overall hyperinflation with improvement in diaphragm mechanics and recovery of elastic retraction [7]. In the case of EBV insertion, lobar atelectasis is considered pre-requisite for treatment response. As clinical improvement also occurs in the absence of lobar exclusion [3], other mechanisms appear to have an impact on therapeutic outcome. Definition of volumetric, perfusional and ventilatory adaptations following unilateral EBV insertion and their interaction may clarify the underlying processes.

The observed mean reduction of target lobe volume accounting for 444.6 mL (95% CI 186.1–703.1 mL) is consistent with HERTH et al. [8], who defined a pre- to post-treatment volume reduction of $\geqslant 350$ mL as significant. Volume was redistributed to the ipsilateral, nontreated lung (relative volume gain 11.9%), followed by the contralateral, nonconcordant lung (relative volume gain 11.5%) and the contralateral, concordant lobe (relative volume gain 7.3%). Volume redistribution occurred in mutual interdependency; however, total lung volume remained unaltered. Simultaneously, target lobe volumetric decrease was significantly associated with perfusion reduction (relative perfusional reduction 41.5%), which in turn

TABLE 1 Pulmonary functional, volumetric, ventilatory, perfusional and clinical changes at 8-week follow-up[#]

	Baseline	Week 8	Absolute change (95% CI)	Relative change %	p-value
Pulmonary function					
FEV$_1$ L	0.91±0.24	1.03±0.33	0.12 (−0.11–0.25)	13.2	0.07
FEV$_1$ % predicted	32.99±6.39	38.02±12.41	5.03 (−0.14–10.20)	15.3	0.06
RV L	5.71±0.97	5.38±1.63	−0.34 (−0.99–0.32)	−6.0	0.30
RV % predicted	256.03±48.31	236.99±66.35	−19.04 (−49.81–11.73)	−7.4	0.21
RV/TLC ratio	74.83±6.32	70.87±10.11	−3.96 (−8.26–0.35)	−5.3	0.07
RV/TLC ratio % predicted	188.77±23.97	177.42±25.79	−11.35 (−22.45− −0.25)	−6.0	0.04
SPECT-guided volumetry mL					
Target lobe	1207.6±390.3	762.9±318.3	−444.6 (−703.1− −186.1)	−36.8	0.004
Ipsilateral, nontargeted lung	1229.9±279.6	1376.0±302.8	146.1 (4.6–287.5)	11.9	0.04
Total targeted lung	2437.6±451.9	2250.1±570.6	−187.4 (−375.1–0.2)	−7.7	0.05
Contralateral, concordant lobe	1120.7±251.9	1202.9±264.7	82.2 (−19.6–184.0)	7.3	0.10
Contralateral, nonconcordant lung	1437.9±451.5	1602.9±611.1	165.0 (−68.2–398.3)	11.5	0.14
Total nontargeted lung	2558.6±578.1	2694.8±586.3	136.1 (−91.6–363.9)	5.3	0.21
Scintigraphy-guided ventilation %					
Target lobe	8.38±3.98	5.25±3.31	−3.13 (−5.25− −1.00)	−37.4	0.007
Ipsilateral, nontargeted lung	37.83±7.52	40.26±8.44	2.43 (0.06–4.80)	6.4	0.04
Total targeted lung	46.31±7.18	45.60±7.72	−0.72 (−3.51–2.08)	−1.6	0.59
Contralateral, concordant lobe	14.00±5.22	13.32±5.69	−0.69 (−3.44–2.07)	−4.9	0.60
Contralateral, nonconcordant lung	39.69±4.22	41.24±6.97	1.56 (−1.68–4.79)	3.9	0.32
Total nontargeted lung	53.69±7.18	54.53±7.68	0.84 (−1.95–3.64)	1.6	0.53
Scintigraphy-guided perfusion %					
Target lobe	8.82±3.48	5.16±2.72	−3.66 (−5.06− −2.26)	−41.5	<0.001
Ipsilateral, nontargeted lung	35.67±7.51	36.47±8.20	0.80 (−1.30–2.89)	2.2	0.44
Total targeted lung	44.48±8.16	42.56±9.24	−1.92 (−4.85–1.00)	−4.3	0.19
Contralateral, concordant lobe	14.72±5.75	15.19±5.94	0.47 (−1.34–2.29)	3.2	0.59
Contralateral, nonconcordant lung	40.81±7.19	43.08±8.32	2.27 (0.45–4.09)	5.6	0.02
Total nontargeted lung	55.50±8.16	58.35±8.39	2.85 (0.44–5.26)	5.1	0.02
Patient outcomes					
6MWT m	298.6±120.4	365.9±119.9	67.4 (17.1–117.6)	22.6	0.01
NT-proBNP pg·mL^{-1}	175.6±126.4	153.6±139.4	−22.0 (−162.9–118.9)	−12.5	0.72
CAT points	24.8±7.3	22.6±6.2	−2.2 (−5.7–1.4)	−8.9	0.21

Data are presented as mean±SD, unless otherwise stated. FEV$_1$: forced expiratory volume in 1 s; RV: residual volume; TLC: total lung capacity; SPECT: single-photon emission computed tomography; 6MWT: 6-min walk test; NT-proBNP: N-terminal pro-brain natriuretic peptide; CAT: Chronic obstructive pulmonary disease Assessment Test. [#]: n=24.

correlated with ventilatory shifts. Both perfusion and ventilation were primarily redistributed to the contralateral nonconcordant and ipsilateral nontreated lobes. This gives evidence to show in which direction air and blood flow shifts post-ELVR and offers the possibility to optimise ELVR outcome by pre-procedural evaluation of its functional reserves.

Atelectasis occurred in 15 (62.5%) patients (including both aforementioned patients offering pneumothorax) and led to a mean target lobe volume reduction of 549.0 mL (95% CI 63.6–1034.5 mL; p=0.035), but was not significantly associated with clinical responsiveness, defined by improvement in 6MWT [6]. In turn, clinical responder status was accompanied by reduction of NT-proBNP levels. Although exercise limitation in emphysematous COPD has multiple contributory factors, the currently observed significant, post-procedural gain in exertional capacity has previously been shown to correlate with an improved left ventricular diastolic filling pattern, which in turn is associated with reduced dynamic hyperinflation [9]. Attenuation of progressive hyperinflation during exercise might partially restore cardiocirculatory function and consequently contribute to tapering NT-proBNP levels.

The finding that gain in 6MWT distance occurred irrespective of the extent of volumetric and scintigraphic shifts may be ascribed to the quality in terms of pulmonary capacity of the lobes to which ventilation and perfusion is directed, rather than to the mere quantity of shifted air and blood flows. This result is in line with CHUNG et al. [10], who performed serial scintigraphic assessment in six patients undergoing ELVR exclusively of the left upper lobe and determined a redistribution of ventilation and perfusion to the right lower region. In the current study, we additionally evaluated volumetric data and

found that redistribution was not solely directed to pulmonary regions but to concrete anatomic lobes. Moreover, we achieved a generalised redistribution pattern, irrespective of the treated lobe.

Consistent with COXSON et al. [3], we found total lung volume to remain unchanged but described interlobar volumetric shifts. Although COXSON et al. [3] only suggested perfusional and ventilatory changes underlying the physiological response to ELVR, we merged volumetric and scintigraphic data for the first time and identified significant mutual interdependency.

In summary, ELVR by EBV insertion is accompanied by volumetric and scintigraphic adaptations and favours exertional performance. Pre-procedural evaluation of contralateral lung emphysematous destruction and functional capability may be a valuable tool to predict ELVR efficacy.

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EBV treatment reduces target lobe volume, ventilation and perfusion with consistent redistributive pattern http://ow.ly/C95Ue

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