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CHEST

Emphysema lung lobe volume reduction: effects on the ipsilateral and contralateral lobes

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Abstract
Objectives To investigate volumetric and density changes in the ipsilateral and contralateral lobes following volume reduction of an emphysematous target lobe.
Methods The study included 289 subjects with heterogeneous emphysema, who underwent bronchoscopic volume reduction of the most diseased lobe with endobronchial valves and 132 untreated controls. Lobar volume and low-attenuation relative area (RA) changes post-procedure were measured from computed tomography images. Regression analysis (Spearman's rho) was performed to test the association between change in the target lobe volume and changes in volume and density variables in the other lobes.
Results The target lobe volume at full inspiration in the treatment group had a mean reduction of −0.45 L (SE=0.034, $P<0.0001$), and was associated with volume increases in the ipsilateral lobe (rho=−0.68, $P<0.0001$) and contralateral lung (rho=−0.16, $P=0.006$), and overall reductions in expiratory RA (rho=0.31, $P<0.0001$) and residual volume (RV)/total lung capacity (TLC) (rho=0.13, $P=0.03$).
Conclusions When the volume of an emphysematous target lobe is reduced, the volume is redistributed primarily to the ipsilateral lobe, with an overall reduction. Image-based changes in lobar volumes and densities indicate that target lobe volume reduction is associated with statistically significant overall reductions in air trapping, consistent with expansion of the healthier lung.
Key Points
- *Computed tomography allows assessment of the treatment of emphysema with endobronchial valves.*
- *Endobronchial valves can reduce the volume of an emphysematous lung lobe.*
- *Compensatory expansion is greater in ipsilateral lobes than in the contralateral lung.*
- *Reduced air trapping is measurable by RV/TLC and smaller low attenuation area.*

Keywords Chronic obstructive pulmonary disease · Computed tomography · Computer-assisted image processing · Lung · Lung volume reduction

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Introduction

Emphysema affects an estimated 1.8% of the population worldwide [1]. It involves the gradual, irreversible breakdown of lung tissue and loss of lung elastic recoil, leading to a reduction in expiratory airflow. As the disease progresses, heterogeneous air trapping, particularly within regions of the worst emphysema, causes total lung capacity (TLC) to

increase. The hyper-inflated segments of lung may then cause compression of adjacent, more viable lung tissue and impose other mechanical disadvantages to ventilation by affecting the diaphragm and other respiratory muscles. As a result of these abnormalities in lung mechanics, patients exhibit a progressive increase in dyspnoea, and reductions in exercise tolerance and quality of life.

Surgical treatments for emphysema include lung volume reduction surgery (LVRS), where the most diseased and hyperinflated lung tissue is resected. LVRS has been shown to benefit some patients with advanced emphysema [2–7], but studies have shown a wide range of individual outcomes [2, 5, 6, 8–13]. More recently, bronchoscopic lung volume reduction (BLVR) procedures have been investigated that aim to induce significant volume reduction in the most diseased lobe(s) [7, 14]. Resecting or collapsing the most compliant lung regions should lead to an overall increase in lung recoil, improved mechanical efficiency of the diaphragm and respiratory muscles, improved ventilation and perfusion matching, and reduced airflow obstruction [15–18].

Lung volumes and densities measured from thoracic imaging are now playing key roles in clinical trials of emphysema therapies [7, 19–21]. Quantitative assessment of the lungs using computed tomography (CT) imaging provides important complementary information to pulmonary function tests, including spirometry and lung volumes, because CT allows assessment of both whole and lobar lung volumes [22, 23], vascular density, mediastinal shift and changes in heart size. In some studies the change in ipsilateral lung volume post-treatment has been used as a primary outcome variable [20].

Other studies have investigated overall changes in lung function from BLVR [15] and treatment efficacy. The purpose of this work is to investigate the lobar radiographic changes following volume reduction of the single worst lobe of emphysema in a cohort of severely affected heterogeneous emphysema patients. The effect of differing amounts of bronchoscopic target lobe volume reduction on the ipsilateral and contralateral lobes are studied. Volume redistribution to the adjacent lobe at TLC has been reported previously [21], and in this article we provide expanded analyses including the contralateral lobes as well as at redistribution at residual volume (RV). A key question in BLVR is whether healthier lung expands after target lobe reduction; in fact this is an underlying assumption of the treatment that warrants investigation. In this article we report on lobar changes in air trapping (RV/TLC) and density as measured by low attenuation relative area (RA) to provide insight into the status of the expanded lung and the mechanics that bring about overall changes in lung function.

Materials and methods

Data collection

Patients in the prospective, randomised multicenter VENT study [19, 21] received CT at baseline screening and at 6± 1 months to assess the impact of the Zephyr® endobronchial valve (Pulmonx, Inc., Redwood City, CA, USA) in advanced heterogeneous emphysema. This study is a retrospective analysis of the CT from 289 treated subjects and 132 untreated controls with the following inclusion criteria: (1) interlobar emphysema heterogeneity, and (2) interpretable inspiratory and expiratory CT images available before treatment and nominally 6 months post-procedure. Full inclusion and exclusion criteria for study inclusion are published elsewhere [19]. Image data were collected during the period January 2003 to December 2006. All patients gave written informed consent for study participation; this study received UCLA IRB approval for retrospective CT review. The treatment involved placing one-way valves in the segmental airways of the most diseased lobe to cause lobar occlusion and prevent air from entering these portions of the lung while still allowing air to exit. Disease heterogeneity and targeting of the most diseased lobe were determined quantitatively by RA on CT [19].

Inspiratory and expiratory CT imaging of the lung was performed pre- and 6±0.5 months post-treatment (screening to 6-month post-treatment interval of approximately 9 months: median 8 months 27 days with an interquartile range of 1 month 24 days), with 5- to 10-mm slice thickness and 140–300 mAs. Each study centre submitted the first CT for quality control review to the CT core laboratory before further image acquisition to ensure that all images, regardless of study site location, were taken under repeatable and consistent conditions. Thick-section CT images were used because the RA measure was originally developed and validated for emphysema assessment with this slice thickness [24, 25]. During image acquisition careful attention was paid to breathing instructions, and reproducibility of breath hold and lung volume measurements were confirmed in previous research [26].

Quantitative image analysis

Quantitative image analysis (QIA) was performed on pre- and post-treatment images. Lobar volume, RA and RV/TLC ratio were computed for the target lobe, ipsilateral lobe(s), contralateral lung and whole lung.

Initial volumetric lung segmentation was performed using an automated 3D technique. This technique uses a parametric model of thoracic anatomy to guide automated segmentation based on attenuation thresholding [<−500 Hounsfield units (HU) for the lungs], region-growing and mathematical

morphology. The automated segmentation method has been described in detail in previous publications [27, 28]. The results were manually edited as necessary, for example, to remove large central airways from the segmentation. Lobar segmentation was performed using a semi-automated technique where fissures were drawn manually and used to divide the lungs into lobes. Lobar segmentation results are shown in Fig. 1. Lung volumes measured with this technique have been shown previously to correlate well with pulmonary function tests (PFTs) and be highly reproducible [26]. For the purposes of analysis, the right middle lobe (RML) was grouped with either the right upper lobe or the right lower lobe to calculate untreated ipsilateral lobe measurements as the RML was never targeted for therapy.

Lobar volumes were then computed as the sum of the volumes of voxels included in the segmentation. For a given CT the voxel volume was computed as the product of the (in-plane) pixel size and reconstruction interval spacing between slices. For each lobe, RA was computed as the percentage of voxels<−910 HU divided by the total number of voxels. Based on previous studies, RA is computed on inspiratory (RA_I) and expiratory (RA_E) images [29, 30]. The extent of emphysema is quantified by RA_I, while pulmonary airflow obstruction and gas trapping are assessed using the correlate RA_E [30].

Computed tomography volumes were also used to compute RV/TLC for each lobe as a measure of air trapping. Air trapping, as determined by the RV/TLC ratio, is strongly correlated with the degree of airways obstruction (FEV_1 % predicted) [31]. Thus, RV/TLC from imaging can provide an indirect indication of lobar lung function rather than a global estimate as from PFTs.

Statistical analysis

Baseline and post-treatment changes in QIA variables were evaluated in all subjects. Lobar volume changes were reported in litres. The RA and RV/TLC ratio were expressed as percentages, and the percentage point differences were computed between baseline and follow-up. Regression analysis (Spearman's rho) was performed in the treatment and control groups to test the association between change in the target lobe volume and changes in QIA variables in the other lobes. Although subjects in the control group were not treated, a target lobe was computed for these subjects using the same algorithm as for the treatment group [19].

As most cases showed only small changes in target lobe volume, overall descriptive statistics do not reflect the magnitude of changes that occur when there are large reductions in the target lobe volume. Therefore descriptive statistics were computed separately for the following subject groups based on the post-treatment reduction in target lobe volume: control (n=132), none (<15% target volume decrease, n=150), moderate (15–50% target volume decrease, n=87) and large (> 50% target volume decrease, n=52). These data are presented as bar graphs (mean and standard error) for key variables. The purpose of these graphs is to provide insight into the magnitude of changes, so statistical tests as to whether they are different from zero are presented rather than group comparisons. Responder group analysis would require pulmonary function test data and is outside the scope of this paper. However, control group data are included to assess whether changes observed in the treatment group are actually due to target lobe volume reduction or merely to differences in levels of inspiration as could occur in the controls.

Results

The baseline PFT and CT characteristics of the groups are shown in Table 1. The P values indicate that the treatment and control groups were well matched. In the treatment group the target lobe volume at TLC had a mean reduction of −0.45 l (SE=0.034, P<0.0001), and in the control group the target lobe volume change was −0.005 l (SE=0.012, P=0.70). Figure 2 shows plots of ipsilateral lobe volume changes at TLC versus target lobe volume change for control and treatment groups, along with the Spearman correlation. The significance of these associations is given in terms of P value. Figures 3 and 4 show similar plots for the contralateral lung and whole lung respectively.

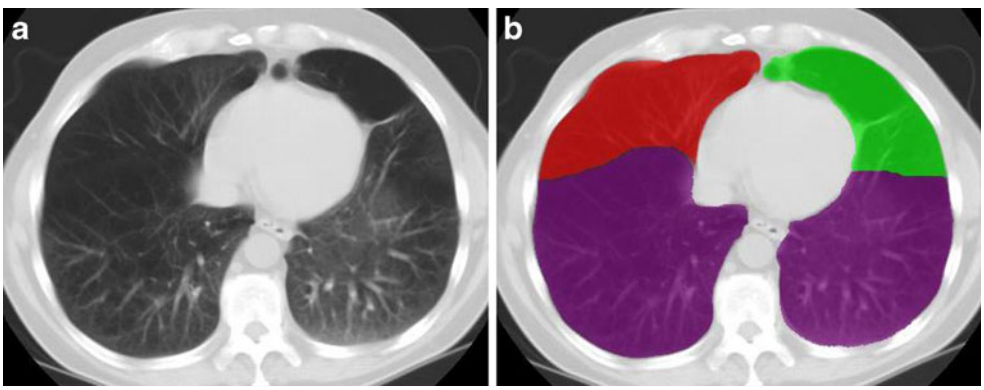

Fig. 1 Semi-automated lobar segmentation for a thick CT. **a** Original CT image. **b** Segmentation of the left upper, left lower, right middle and right lower lobes (right upper lobe is present on superior slices only)

Table 1 Baseline patient characteristics for treatment and control groups

Characteristics	Patient group		*P* value across group
	Control (*n*=132) mean (SD)	Treatment (*n*=289) mean (SD)	
PFT TLC[a], l	7.69 (1.49)	7.68 (1.46)	0.90
PFT RV[a], l	4.92 (1.21)	4.86 (1.21)	0.76
PFT RV/TLC[a], %	63.93 (8.53)	63.15 (9.12)	0.57
CT TLC, l	6.92 (1.36)	7.09 (1.39)	0.23
CT RV[b], l	5.18 (1.26)	5.29 (1.21)	0.42
CT RV/TLC[b], %	74.54 (8.86)	74.76 (9.90)	0.83
CT RA_I, %	56.36 (10.07)	57.27 (10.20)	0.39
CT RA_E[b], %	39.80 (12.92)	41.09 (13.53)	0.37

PFT pulmonary function test, *TLC* total lung capacity, *RV* residual volume, RA_I relative area inspiratory, RA_E relative area expiratory

[a] Baseline PFTs were not available for all subjects: *n*=130 in the control group, *n*=282 in the treated group

[b] Baseline RV images were not available for all subjects: *n*=129 in control, *n*=281 in treatment group

Figure 5 includes plots of the RV changes in the target lobe, ipsilateral lobe, contralateral lung and whole lung versus target lobe volume change at TLC. Figures 6, 7 and 8 are similar figures for RA_I, RA_E and RV/TLC respectively, all of which showed significant whole-lung associations with reduction in target lobe volume. The control group is not included in Figs. 5–8, as Figs. 2–4 show that subjects in the control group have uniformly small changes in the target lobe and behave similarly to subjects in the treatment group with low target lobe change.

Figures 9, 10 and 11 show bar graphs of lobar changes in RV, RA_E and RV/TLC respectively for the treatment subgroups. For subjects with>50% reduction in target lobe volume (*n*=49 with both TLC and RV images available), the target lobe had a mean RV reduction of −1.09 l (SE=0.058, *P*<0.0001), the ipsilateral lobe RV increased by 0.481 l (SE=0.047, *P*<0.0001), the contralateral lobe RV change of 0.06 l was not significant (SE=0.040, *P*=0.16), and the whole lung RV was reduced by −0.555 l (SE=0.087, *P*<0.0001). In this subgroup there was an RA_E reduction of 4.8 percentage points (SE=1.2) and an RV/TLC reduction of 4.5 percentage points (SE=1.3). In the control group there was no significant change in any quantitative variable in any lobe (*P*>0.2). Figure 12 shows 3D rendering of lobar bronchovascular anatomy pre- and post-treatment with large target lobe volume reduction.

Discussion

Bronchoscopic lung volume reduction using lobar targeting of endobronchial valves has generated a new platform for evaluating emphysema lung physiology through changes on

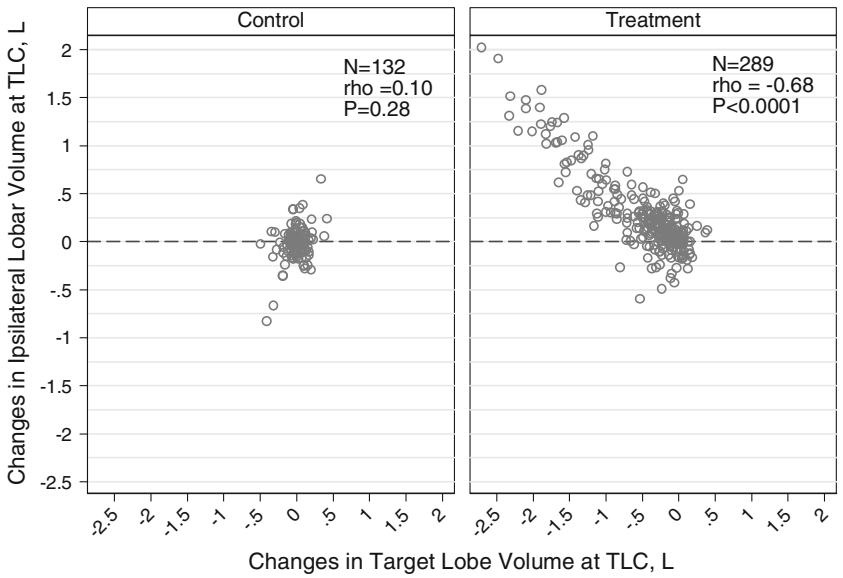

Fig. 2 Ipsilateral lobe volume changes at total lung capacity (*TLC*) versus target lobe volume change for control and treatment groups

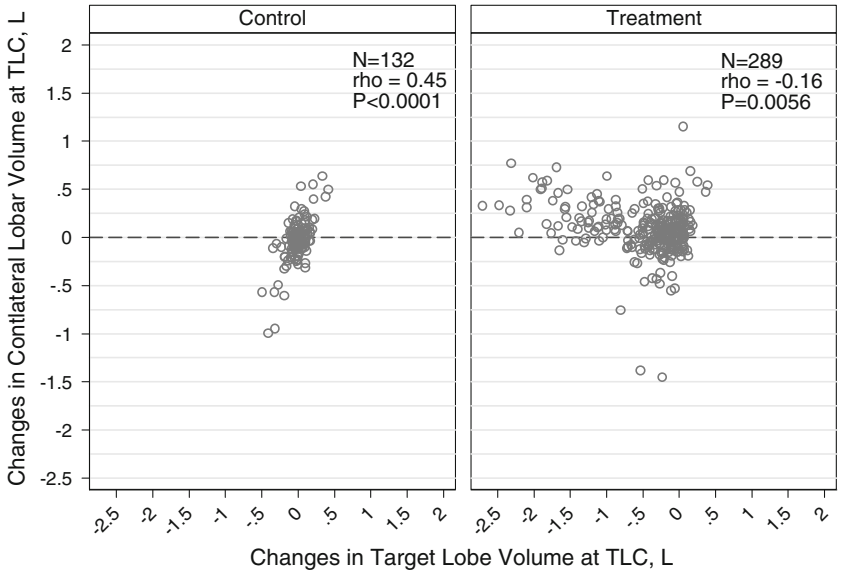

Fig. 3 Contralateral lobe volume changes at TLC versus target lobe volume change for control and treatment groups

CT imaging. Because of collateral ventilation across lobar fissures and incomplete lobar isolation, many targeted lobes in this study did not achieve full volume loss [21]. The current analysis uses these observations to assess the impact of differing degrees of lobar volume reduction on ipsilateral, contralateral, and total thoracic volume and density changes. Assessment of overall treatment efficacy in the patient population is outside the scope of this article. Correlation of imaging findings with clinical outcome measures has been previously reported for BLVR procedures [20, 21].

Both regression analyses and descriptive subgroup analyses were reported to provide a clear and informative view of the data. In the subgroup analysis the 15% target lobe volume reduction threshold was chosen, as the control group 95% confidence interval was ±15%. The 50% threshold was chosen to reflect a large target lobe volume reduction. Control patients did not appreciably change spirometric or CT variables over the study interval.

Ipsilateral lobe volume changes at TLC showed a significant negative association with target lobe volume change in the treatment group (Fig. 2), i.e. ipsilateral volume increased with a reduction in target lobe volume. This reflects redistribution of lung volume from the target to the ipsilateral lobe consistent with Sciurba et al. [21] and Coxson et al. [20]. We presented new data for contralateral lung volume changes that showed a significant negative association with target lobe volume change in the treatment group (Fig. 3), i.e. contralateral volume also increased with a reduction in target lobe volume. This is consistent with redistribution of lung volume from the target to the contralateral lung. The slope is less than for the ipsilateral lobe, indicating that most of the volume is redistributed to the ipsilateral lobe with a

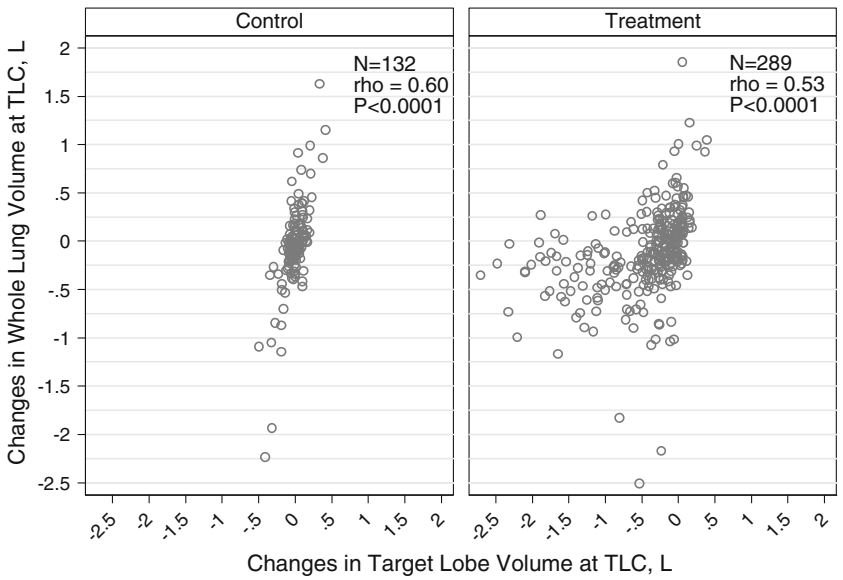

Fig. 4 Whole lung volume changes at TLC versus target lobe volume change for control and treatment groups

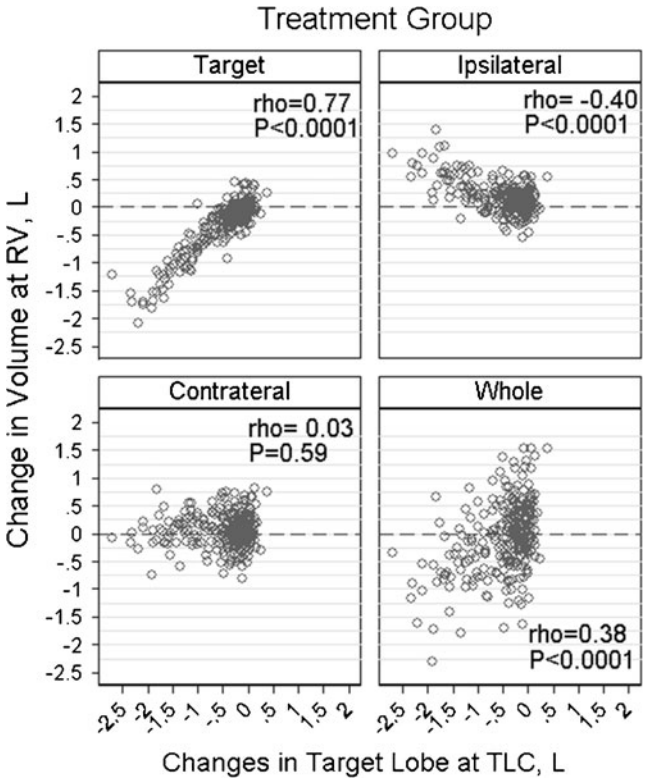

Fig. 5 Lobar residual volume (*RV*) changes versus target lobe volume change post-treatment

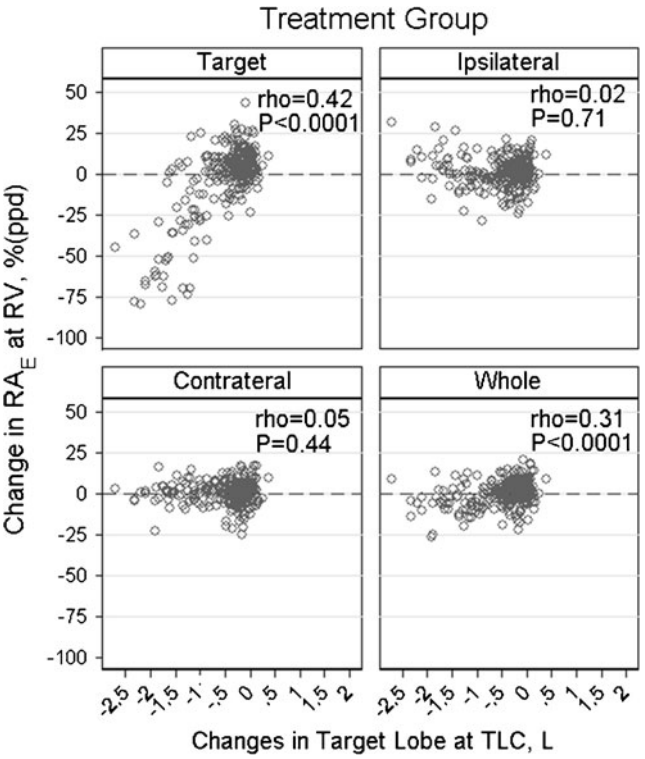

Fig. 7 Lobar relative area expiratory (RA_E) changes versus target lobe volume change post-treatment

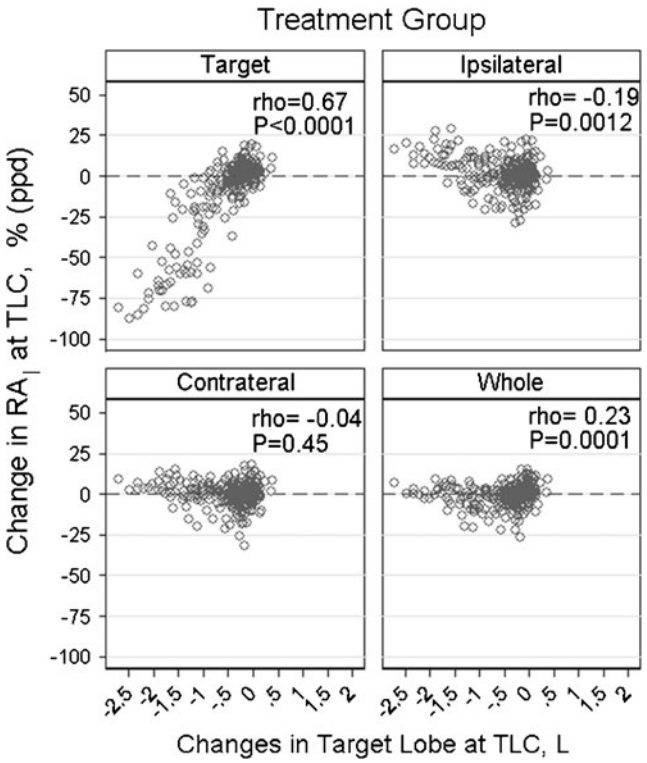

Fig. 6 Lobar relative area inspiratory (RA_I) changes versus target lobe volume change post-treatment. *ppd* percentage point difference

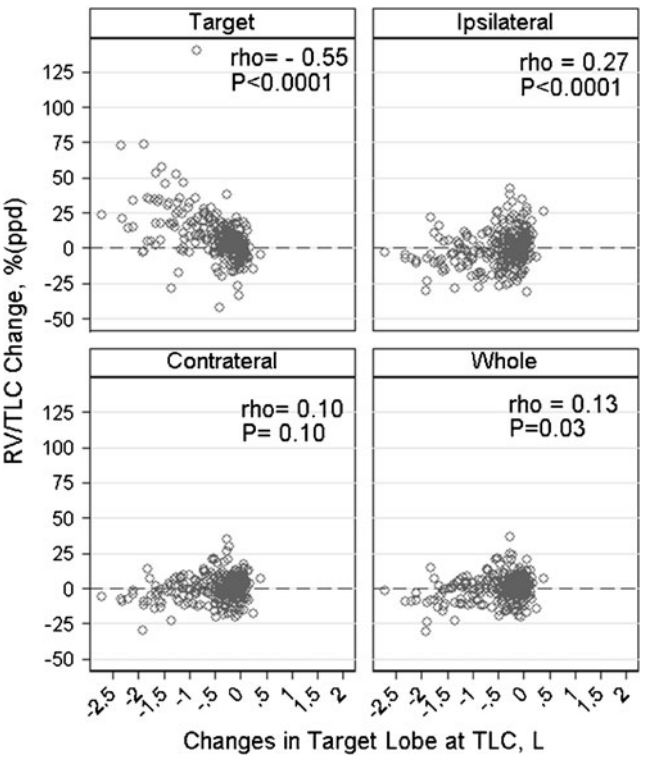

Fig. 8 Lobar volume ratio changes versus target lobe volume change post-treatment

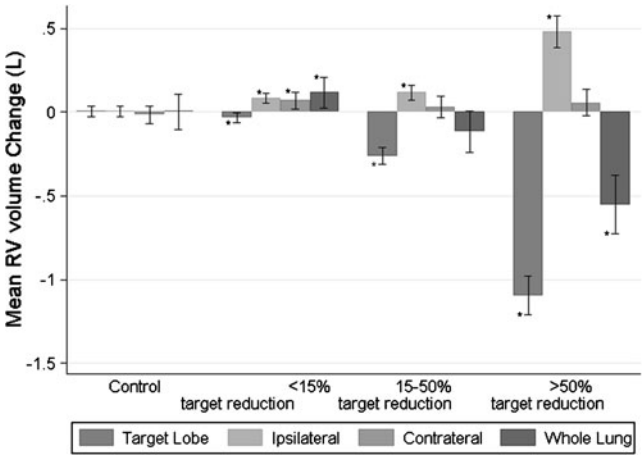

Fig. 9 Lobar RV changes (mean and standard error) post-treatment for the control group and the treatment subgroups based on target lobe percentage volume reduction. Numbers of subjects with RV imaging data available: control (n=126), <15% target volume decrease (n=140), 15–50% target volume decrease (n=85), >50% target volume decrease (n=49)

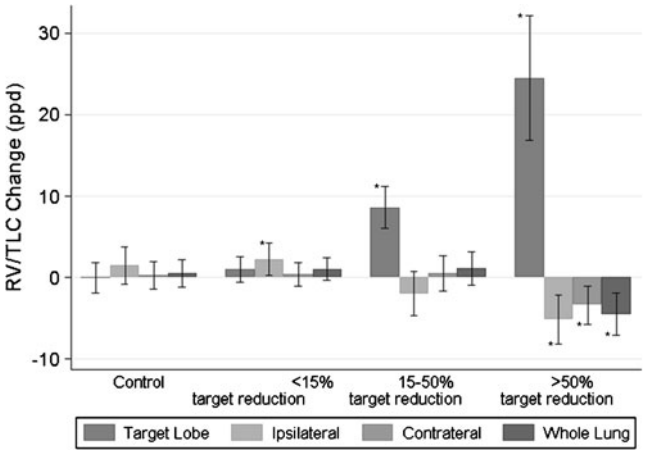

Fig. 11 Lobar RV/TLC changes (percentage point difference) post-treatment for the control group and the treatment subgroups based on target lobe percentage volume reduction. Numbers of subjects with both TLC and RV imaging data available: control (n=126), <15% target volume decrease (n=140), 15–50% target volume decrease (n=85), >50% target volume decrease (n=49)

small portion to the contralateral lung. However, this result explains why the net reduction in TLC (whole lung), while higher in the large target lobe reduction group, is modest and appears to plateau. In the control group there were no large target lobe volume reductions and no significant association with volume change in the ipsilateral lobe (Fig. 2). However, there was a significant positive association with volume change in the contralateral lung (Fig. 3). This positive association reflects small changes in volume due to differences in the inspiration level between the two time points that affect both target and contralateral lobes consistently, and is contrary to the negative association found in the treatment group.

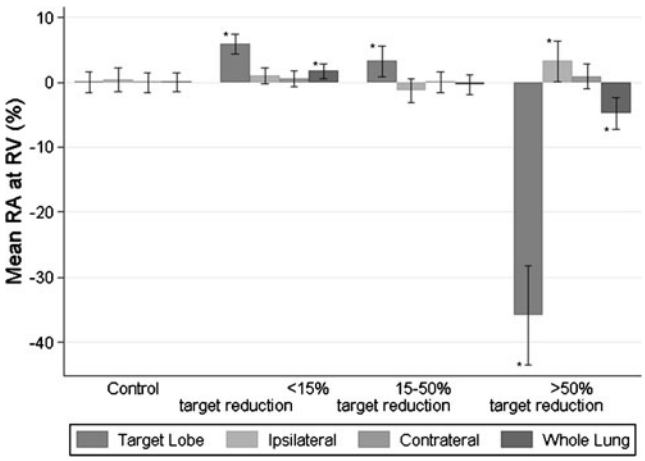

Fig. 10 Lobar RA_E changes (mean and standard error) post-treatment for the control group and the treatment subgroups based on target lobe percentage volume reduction. Numbers of subjects with RV imaging data available: control (n=126), <15% target volume decrease (n=140), 15–50% target volume decrease (n=85), >50% target volume decrease (n=49)

This article also presents new data on measures of air trapping at RV (Fig. 5). The volume redistribution is similar to TLC, except that there is no significant redistribution to the contralateral lobe. Therefore, with lobar volume reduction thresholds of greater than 15%, the RV of the entire lung falls, as shown in Fig. 9. However, RV/TLC, an important correlate of dyspnoea and gas exchange in COPD, does not appreciably decline until target lobe volume reduction is >50%. The lack of target lobe emptying is likely multifactorial as there is trapped gas behind the added resistance of the endobronchial valves. Additionally, the target lobes that fail to achieve volume loss after valve placement likely have excess collateral ventilation. These collateral channels may have more expiratory airflow resistance than native airways.

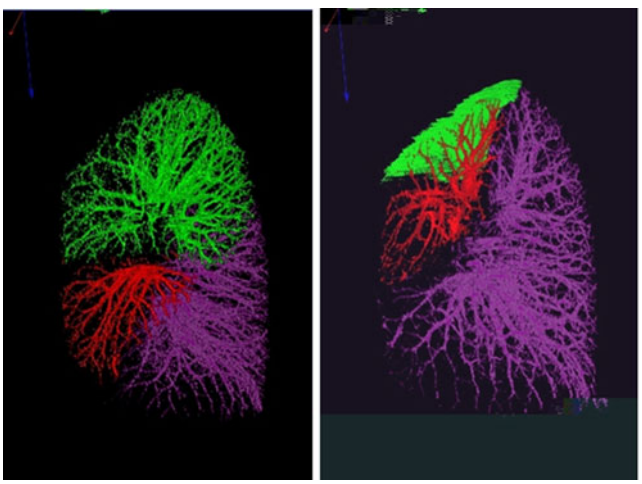

Fig. 12 Segmented lobes of the right lung from a thin-section CT examination acquired at total lung capacity: **a** pre-treatment imaging; **b** following right upper lobe volume reduction

As a result, the RV/TLC of these targeted lobes will remain high. Conversely, at high target lobe volume reductions, there were RV/TLC improvements (reductions) in the ipsilateral and contralateral lobes and whole lung, reflecting an overall improvement in respiratory mechanics.

Previous studies based on lung function testing volumes have found that RV and RV/TLC are more sensitive than TLC to the degree of airway obstruction. In one recent study, transition from mild obstruction (90% of predicted FEV_1) to moderate obstruction (50% of predicted FEV_1) was associated with an increase in mean RV from 100 to 140% of that predicted, while the TLC showed less change [31]. In the current study we also found a larger overall reduction in RV than TLC. Previous studies with BLVR have also found overall reductions in TLC and RV (measured by lung function testing), with RV having a greater reduction [15]. The findings of this study are consistent with those reported in Sciurba et al. [21], who found that target lobe volume change was inversely correlated with changes in FEV_1. This study suggests that expansion of healthier lung and reduction in air trapping contribute to these improvements in FEV_1.

Lung hyperinflation has been shown to correlate with the high cost of breathing in patients with COPD [32]. Hyperinflation is associated with distortions of chest wall motion, impairment of inspiratory muscle function, gas exchange and exercise performance, increased work involved in breathing and greater severity of breathlessness [33, 34]. The lessening of hyperinflation and associated improvements in chest wall mechanics and elastic properties of the lung may be partly responsible for symptomatic improvements [15, 35]. A reduction in end-expiratory volume in these hyperinflated individuals lessens the need to overcome the elastic recoil of the chest wall during inspiration and results in reduced work involved in breathing.

One additional goal of treatment is to redistribute airflow to more functional areas of the lung. For this reason, the target lobe for treatment was selected as the one with the most emphysema. Subjects with heterogeneous disease may also have compression of the adjacent normal lung if the air trapping in the emphysematous portions of the lung is sufficient. The current analysis of lobar density does not fully answer mechanistic questions on air and blood-flow redistribution following lobar collapse, but is informative. If compressed lung tissue is decompressed after treatment, functional airways, alveoli and capillaries may be recruited. If, on the other hand, diseased lung is uncompressed to occupy a larger volume, the overall lung density could actually be reduced. An important finding of this study is that the RA_E of the expanded ipsilateral lobe was only slightly increased despite now occupying a much larger volume, indicating that the healthier tissue is indeed being uncompressed. Thus a reduction in the target (highest RA_E) lobe is not offset by the ipsilateral lobe and results in an overall reduction in RA_E (Fig. 10). This is consistent with volume redistribution to better ventilated lobes and less overall air trapping [30]. It may also reflect enhanced blood flow as vasculature is a component of lung density.

Other CT and spirometric biomarkers may emerge as correlates of lung volume reduction treatment success. Future work should involve development of predictive models to determine which patients will achieve target lobe volume reduction and functional improvements. Previous model-based analyses by Fessler et al. for LVRS suggest that RV/TLC may be another significant predictive variable of spirometric improvement after surgery [13]. Other predictive variables may include the presence and degree of collateral ventilation, and number and location of valves placed [14, 15, 36]. Future work could also involve radiographic measurement of diaphragmatic curvature, which has been used to assess hyperinflation and found to correlate with the high cost of breathing in patients with COPD [32].

The VENT study protocol required use of thick-section CT imaging and RA at a threshold of −910 HU, because at the time this was the most widely used CT emphysema assessment technique based on the original validation of Muller et al. [24]. Manual fissure delineation was used as automated algorithms are only reliable on thin-section images. However, thin-section CT images were reviewed during this process to guide manual placement of fissure contours. The resulting whole lung volume measurements on thick-section VENT data have been shown to correlate with pulmonary function test results and lobar volumes to be highly reproducible [26]. Current studies typically use thin-section imaging to facilitate lobar segmentation and RA at a threshold of −950 HU for emphysema assessment [29, 30].

When the volume of an emphysematous target lobe is reduced during treatment, the volume is redistributed primarily to the ipsilateral lobe, with overall inspiratory and expiratory volume reductions. It has been shown that despite the non-target lobes occupying a larger volume post-treatment, the overall inspiratory area of low attenuation is reduced, consistent with expansion of healthier lung. Target lobe volume reduction is associated with statistically significant overall improvements in the expiratory low attenuation area and RV/TLC, indicating a reduction in air trapping and an improvement in lung mechanics.

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References

1. Halbert RJ, Natoli JL, Gano A, Badmagarav E, Buist AS, Mannino DM (2006) Global burden of COPD: systematic review and meta-analysis. Eur Respir J 28:523–532
2. Sciurba FC, Rogers RM, Keenan RJ et al (1996) Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. N Engl J Med 334:1095–1099

3. Martinez FJ, de Oca MM, Whyte RI, Stetz J, Gay SE, Celli BR (1997) Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. Am J Respir Crit Care Med 155:1984–1990
4. Sabanathan A, Sabanathan S, Shah R, Richardson J (1998) Lung volume reduction surgery for emphysema. A review. J Cardiovasc Surg 39:237–243
5. Geddes D, Davies M, Koyama H et al (2000) Effect of lung-column-reduction surgery in patients with severe emphysema. N Engl J Med 343:239–245
6. Gelb AF, McKenna RJ Jr, Brenner M, Schein MJ, Zamel N, Fischel R (1999) Lung function 4 years after lung volume reduction surgery for emphysema. Chest 116:1608–1615
7. Fishman A, Martinez F, Naunheim K et al (2003) A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 348:2059–2073
8. Brenner M, McKenna R, Gelb A et al (1997) Objective predictors of response for staple versus laser emphysematous lung reduction. Am J Respir Crit Care Med 155:1295–1301
9. Cooper JD, Patterson GA, Sundaresan RS, Trulock EP, Yusen R (1996) Reduction procedures in patients with severe emphysema. J Thorac Cardiovasc Surg 112:1319–1330
10. Ingenito EP, Evans RB, Loring SH et al (1998) Relation between preoperative inspiratory lung resistance and the outcome of lung-volume reduction surgery for emphysema. N Engl J Med 338:1181–1185
11. McKenna R, Brenner M, Fischel RJ et al (1997) Patient selection criteria for lung volume reduction surgery. J Thorac Cardiovasc Surg 114:957–967
12. Thurnheer R, Engel H, Weder W et al (1999) Role of lung perfusion scintigraphy in relation to chest computed tomography and pulmonary function in the evaluation of candidates for lung volume reduction surgery. Am J Respir Crit Care Med 159:301–310
13. Fessler HE, Scharf SM, Permutt S (2002) Improvement in spirometry following lung volume reduction surgery. Application of Physiologic Model. Am J Respir Crit Care Med 165:34–40
14. Fessler HE, Scharf SM, Ingenito EP, McKenna RJ Jr, Sharafkhaneh A (2008) Physiologic basis for improved pulmonary function after lung volume reduction. Proc Am Thorac Soc 5:416–420
15. Hopkinson NS, Toma TP, Hansell DM et al (2005) Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. Am J Crit Care Med 171:453–460
16. Hoppin F (1997) Theoretical basis for improvement following reduction pneumoplasty in emphysema. Am J Respir Crit Care Med 155:520–525
17. Weinmann CG, Hyatt R (1996) Evaluation and research in lung volume reduction surgery. Am J Respir Crit Care Med 154:1913–1918
18. Rogers RM, Sciurba FC, Keenan RJ (1996) Lung reduction surgery in chronic obstructive lung disease. Med Clin N Am 80:623–644
19. Strange C, Herth FJ, Kovitz KL, the VENT Study Group et al (2007) Design of the endobronchial valve for emphysema palliation trial (VENT): a non-surgical method of lung volume reduction. BMC Pulm Med 7:10
20. Coxson HO, Nasute Fauerbach PV, Storness-Bliss C et al (2008) Computed tomography assessment of lung volume changes after bronchial valve treatment. Eur Respir J 32:1443–1450
21. Sciurba FC, Ernst A, Herth FJ, for the VENT Study Group et al (2010) A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 363:1233–1244
22. Brown MS, McNitt-Gray MF, Goldin JG et al (1999) Automated measurement of single and total lung volume from CT. J Comput Assist Tomogr 23:632–640
23. Zhang L, Hoffman EA, Reinhardt JM (2003) Atlas-driven lung lobe segmentation in volumetric x-ray CT images. Proc SPIE 5032:309–319
24. Muller NL, Staples CA, Miller RR, Abboud RT (1988) Density mask: an objective method to quantitative emphysema using computed tomography. Chest 94:782–787
25. Coxson HO, Rogers RM, Whittall KP (1995) The measurement of lung expansion with computed tomography and comparison with quantitative histology. J Appl Physiol 79:1525–1530
26. Brown MS, Kim HJ, Abtin F et al (2010) Reproducibility of lung and lobar volume measurements using computed tomography. Acad Radiol 17:316–322
27. Brown MS, McNitt-Gray MF, Mankovich NJ et al (1997) Method for segmenting chest CT image data using an anatomical model: preliminary results. IEEE Trans Med Imaging 16:828–839
28. Brown MS, Goldin JG, McNitt-Gray MF et al (2000) Knowledge-based segmentation of thoracic CT images for assessment of split lung function. Med Phys 27:592–598
29. Gevenois PA, De Vuyst P, Sy M et al (1996) Pulmonary emphysema: quantitative CT during expiration. Radiology 199:825–829
30. Dowson LJ, Guest PJ, Hill SL, Holder RL, Stockley RA (2001) High-resolution computed tomography scanning in antitrypsin deficiency: relationship to lung function and health status. Eur Respir J 17:1097–1104
31. Dykstra BJ, Scanlon PD, Kester MM, Beck KC, Enright PL (1999) Lung volumes in 4,744 patients with obstructive lung disease. Chest 115:68–74
32. Pitcher WD, Cunningham HS (1993) Oxygen cost of increasing tidal volume and diaphragm flattening in obstructive pulmonary disease. J Appl Physiol 74:2750–2756
33. Matsuoka S, Kurihara Y, Yagihashi K, Hoshino M, Watanabe N, Nakajima Y (2008) Quantitative assessment of air trapping in chronic obstructive pulmonary disease using inspiratory and expiratory volumetric MDCT. AJR Am J Roentgenol 190:762–769
34. Ferguson GT (2006) Why does the lung hyperinflate? Proc Am Thorac Soc 3:176–179
35. Woolcock AJ, Read J (1966) Lung volumes in exacerbations of asthma. Am J Med 41:259–273
36. Brenner M, Hanna NM, Mina-Araghi R, Gelb AF, McKenna RJ Jr, Colt H (2004) Innovative approaches to lung volume reduction for emphysema. Chest 126:238–248