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Quantitative assessment of emphysematous parenchyma using multidetector-row computed tomography in patients scheduled for endobronchial treatment with one-way valves†

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Abstract

OBJECTIVES: To investigate the role of volume quantitative assessment using multidetector-row computed tomography to select patients scheduled for endobronchial one-way valves treatment.

METHODS: Twenty-five consecutive patients (15 with heterogeneous emphysema and 10 with giant emphysematous bulla) undergoing endobronchial valves treatment were enrolled. All patients were studied pre- and postoperatively with standard pulmonary functional tests and quantitative volume assessment of target lobe and entire lung. Emphysematous parenchyma was obtained applying density thresholds of −1.024/−950 Hounsfield units. Among different subtype of patients, we evaluated: (i) the differences between preoperative versus postoperative data; (ii) the correlation between functional and volumetric quantification changes and (iii) the critical threshold value of volumetric quantification of the target lobe in close association with clinical effects.

RESULTS: Among heterogeneous emphysematous and giant emphysematous bulla patients, a significant improvement of flow-expiratory volume in 1 s (from 36.9 ± 15.3 to 43.9 ± 10.4; $P = 0.01$; and from 35.8 ± 6.0 to 47.5 ± 7.9; $P < 0.0001$, respectively); and of forced vital capacity (from 41.9 ± 5.9 to 47.3 ± 9.3; $P = 0.0009$ and from 40.7 ± 5.9 to 48.8 ± 4.9; $P = 0.0002$, respectively); and a significant reduction of residual volume (from 185 ± 14 to 157 ± 14.7; $P = 0.005$; and from 196 ± 13.5 to 137 ± 21; $P < 0.0001$, respectively) and of total lung volume (from 166.7 ± 13 to 137 ± 18 ; $P = 0.0003$, and from 169 ± 15 to 134 ± 18; $P < 0.0001$, respectively) were seen after treatment. The volumetric measurements showed a reduction of volume of the treated lobe among heterogeneous emphysematous patients (from 1448 ± 204 to 1076 ± 364; $P = 0.0008$); and in those with giant emphysematous bulla (from 1668 ± 140 to 864 ± 199; $P < 0.0001$). The entire lung and target lobe volume changes were inversely correlated with change in forced expiratory volume in 1 s in patients with heterogeneous emphysematous ($r = -0.7$; $P = 0.0006$; and $r = -0.7$; $P = 0.0009$, respectively) and giant emphysematous bulla ($r = -0.8$; $P = 0.001$; and $r = -0.7$; $P = 0.009$, respectively). Among patients with heterogenous emphysematous and giant emphysematous bulla, the value of sensitivity and specificity were 66.6 and 83%, respectively (for a volumetric qunatification >1.5239), and of 60 and 100%, respectively (for a volumetric qunatification >1.762).

CONCLUSIONS: Our study showed that the volumetric quantification adds further informations to the routine evaluation for optimizing the selection of patients scheduled for endobronchial valve treatment.

Keywords: Emphysema • Endobronchial valves • Bulla • Computed tomography • Volumetric quantification

INTRODUCTION

Emphysema remains a worldwide leading cause of morbidity and mortality. Although some patients may benefit from pharmacological treatment and pulmonary rehabilitation, many remain significantly disabled, especially those with severe disease. Surgical procedures including bullectomy and/or lung volume reduction surgery (LVRS) have shown that in selected cases the removal of non-functioning lung areas may improve respiratory function. However, surgery in these already high-risk patients has a significant morbidity (20–30%) and a considerable operative mortality (7.9%) within 90 days of the procedures [1]. Thus, less invasive bronchoscopic techniques that are based on the presumed physiological effects of LVRS have been developed. Within the bronchoscopic options, the use of the removable one-way flow

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endobronchial valves (EBVs) to obtain the collapse of the most diseased target lobe is advantageous, being easy to employ and offering the possibility of temporal application.

Since BLVR benefits seem to be correlated with the lobar atelectasis obtained after valve placement, further preoperative investigations are mandatory to identify which patients may benefit from EBV treatment.

A number of radiological approaches have been developed to assess pulmonary emphysema. In particular, lung volume quantification using computed tomography (CT) have been shown to be useful in identifying emphysematous areas, and previous papers reported a good correlation between CT densitometry and functional outcome following LVRS [2, 3]. This method is underevaluated for evaluating clinical outcomes of patients undergoing EBV treatment. Thus, we aimed to assess if the quantitative CT analysis using an open source software was correlated with clinical outcome of different subgroups of patients affected by heterogeneous emphysema (HE) and giant emphysematous bulla (GEB) undergoing EBV treatment and could predict patients who will benefit from EBV procedure.

MATERIALS AND METHODS

Study design

It was a retrospective unicentre study enrolling all consecutive patients with HE and/or GEB treated with EBVs (Zephyr TM EBV; Pulmonx, Inc., Redwood, CA, USA) at Thoracic Surgery Unit of Second University of Naples in the last 5 years.

We selected for procedure (i) patients with GEB that occupied more than one-third of the hemithorax and developed in a lung destroyed by generalized emphysema; and (ii) patients with HE having marked hyperinflation and heterogeneous distribution of emphysema.

Inclusion criteria for EBV treatment were the standard acceptance criteria from Endobronchial Valve for Emphysema Palliation Trial (VENT study) [4] as following: (i) age of 40–75 years; (ii) forced expiratory volume in 1 s (FEV1) < 45% of predicted value; (iii) total lung volume (TLV) > 100% predicted; (iv) RV > 150% predicted; (v) measured at rest while breathing room air ($PaCO_2$) < 50 mmHg; (vi) partial pressure of oxygen in the blood (PaO_2) > 45 mmHg and (vii) 6-min walking test (6MWT) ≥140 metres.

Subjects were excluded if they (i) did not complete pulmonary functional tests (PFTs) and radiological exams before and after treatment; (ii) were listed for LVRS, bullectomy or lung transplantation; (iii) had any coexisting medical problem that would contraindicate a bronchoscopic procedure; (iv) were participating in a trial on an investigational drug or device, and (v) had complete absence of fissures on radiological study that did not allow to differentiate target from adjacent non-target lobe and preclude the success of EBVs treatment due to collateral ventilation. In fact, in the present study other instruments as Chartis system for measuring collateral ventilation was not available.

All patients underwent PFTs and radiological exams including CT densitometry using multidetector-row computed tomography (qMDCT) before and 2–3 months after treatment. The data were prospectively collected and then retrospectively analyzed. We evaluated (i) the differences between pre-operative versus postoperative data; (ii) the correlation between qMDCT and FEV1 changes and (iii) the critical threshold value of qMDCT of the treated lobe in close association with clinical effects. The study was approved by the Institutional Review Board of Second University of Naples and all patients gave informed consent to receive treatment with EBVs, and have their clinical information collected.

Study population

The analysis was performed on 25 consecutive patients (23 males and 2 females) who underwent EBV treatment between April 2007 and June 2013. All patients received PFTs and an initial high resolution CT of the chest to determine whether they met the selection criteria. Fifteen patients had HE with the highest percentage of emphysema and the greatest degree of heterogeneity in upper right lobe (6 cases) and upper left lobe (9 cases). 10 patients had GEB located in the right upper lobe ($n = 2$), in the left upper lobe ($n = 6$), in the lower right lobe ($n = 1$) and bilaterally in the right and left lobe ($n = 1$). All patients with GEB were unfit for surgical resection due to respiratory failure ($n = 6$) and/or cardiac disease ($n = 4$).

Pulmonary function tests

Pulmonary function tests were attended according to American Thoracic Society (ATS) guidelines [5]. Spirometry [FEV1; forced vital capacity (FVC), FEV1/FVC] lung volumes with plethysmography [TLV and residual volume (RV)]; diffusing capacity (DLCO); 6MWT; PaO_2 and $PaCO_2$ were measured.

All pulmonary function data are presented as a percentage of predicted values for the patient's age, gender and height. They were attended before operation and 2–3 months after the procedure. The interval between PFTs and radiological examinations was less than 1 week in all cases.

Computed tomography acquisition technique

All CT examinations were obtained from lung apices to bases using a spiral technique performed during a single breath-hold on a 4-slice MDCT scanner (Aquilion super 4, Toshiba Medical Systems, Otawara, Japan). Scanning parameters were: detector configuration 4 × 3 mm; rotation time 0,5 s; pitch 1.25:1; kVp 120; variable mAs (SURE-Exposure); rotation time 0.5 s; FOV 40–45 cm; matrix 512 × 512 pixels. Reconstruction parameters were: slice thickness/interval 3/1 mm; double reconstruction algorithm FC83 (bone) and FC10 (soft tissues). All examinations were transferred to an open source clinical software for segmentation, qualitative and quantitative analysis (Osirix v. 5.8.5, 32bit, Geneva, Switzerland). Qualitative and quantitative image evaluations, before and after EBV placement, were performed by two separate radiologists skilled in chest radiology, that were blinded each one for treatment and clinical outcome.

Qualitative image evaluation

The percentage of heterogeneity was defined as the difference in the quantitative emphysema score [proportion of pixels of less than −910 Hounsfield units (HU)] between the targeted lobe and the ipsilateral adjacent non-targeted lobe. Qualitative CT parameters considered were: (i) the integrity of the fissures before treatment; (ii) the grade of the atelectasis after treatment and (iii) the antero-postero thoracic diameter before and after treatment. Fissure integrity was defined as the completeness of the fissure on at least one axis (sagittal, axial or coronal views). Among patients with heterogeneous emphysema, the radiological response after EBV procedure was classified as 'positive CT response' in case of moderate atelectasis (volume loss was equivalent to one or more segments) or complete atelectasis (volume loss was equivalent to entire affected lobe) and as 'negative CT response' if no atelectasis, or mild atelectasis (volume loss equivalent to less than one segment) were found. Patients with GEB were defined after procedure as 'positive CT responders' in case of complete or partial atelectasis of bulla, or 'negative CT responders' if no atelectasis of bulla occurred.

Quantitative image evaluation

The total volume in mm^3 of the emphysematous lung tissue was calculated using a 3D region growing algorithm. The latter was based on an image processing technique known as 'thresholding'. This approach was able to create volumes that included only image voxels whose density values, in HU, fell within a certain interval. When this algorithm is used in a region growing segmentation software, its product is a 3D region of interest (ROI) that typically consists in a series of neighboring voxels whose density value is within a predefined interval. In our case the interval was specified using upper and lower thresholds, respectively in the range of −1.024/−950 HU [6]. Therefore, by selecting a point in a single axial image, recognized as included in an emphysematous region, a 3D ROI was generated, by propagating the first selection to the contiguous voxels along all existing planes; this process was automatically performed on all contiguous axial slices that were included in the volumetric CT scan (x, y, z, for each single lung). By this way each single 3D ROI was defined that corresponded to a volume that contained as many voxels as extracted by the above described algorithm. The trachea, main bronchi and intrapulmonary airways were manually deleted from obtained volumes by using the graphic tools of the software. According to this approach quantitative measures of volume and density of each segment were calculated in order to obtain the volume quantification (in mm^3) of (i) the treated lobe; (ii) the adjacent lobe(s) and (iii) the entire affected lung.

Device description

We used the last generation of Zephir EBV valves. This device incorporated a one-way silicone valve that allowed to drain air and secretions from the distal lung segment, while blocking entry of air. During the study, two sizes were available in Italy: EBV 4.0 designed for bronchial lumens with diameters of 4.0–7.00 mm, and EBV 5.5 designed for bronchial lumens with diameters of 5.5–8.5 mm.

Operative procedure

The technique was similar to that previously described. A flexible bronchoscopy was used for EBV implantation. The procedure was generally performed under deep conscious sedation while general anaesthesia with endotracheal intubation was used only in selected case. The valve was inserted through the working channel of the bronchoscope using a guided insertion device, which is used to size the airway for proper placement. EBVs were placed unilaterally in lobar, segmental or subsegmental bronchi on the basis of individual anatomy to completely isolate the targeted lobe. When the valve is delivered into the bronchus, the retainer expands to contact the walls of the lumen. Antibiotics were given intravenously before the procedure, for 24 h after the procedure and then orally for 7 days. If clinically indicated, a review bronchoscopy was attempted.

Statistical analysis

Data were expressed as means ± standard deviation (SD). Comparison of preoperative and postoperative results was evaluated using Fischer's exact test and/or paired t-test, as appropriate. Correlation between variables was assessed using Spearman's rank correlation coefficients. For diagnostic analysis of volumetric qMDCT, receiver operating characteristic (ROC) curve was used to assess the thresholds with the best sensitivity and specificity to predict patients with significant FEV1 improvement. A FEV1 value of >15% (dependent variable) was chosen as cut-off to define significant increase of respiratory function according to ATS [5]. A P-value of < 0.05 was considered significant. The MedCalc statistical software was used for the analysis.

RESULTS

The clinical outcome of the first 9 consecutive patients with GEB enrolled in the present study has been previously reported without volumetric qMDCT evaluation [7–9]. The present group of 25 patients evaluated with volumetric qMDCT evaluation was first reported. Briefly, the procedure was attended under deep conscious sedation in 20 cases and in general anaesthesia in 5 cases. A total of 87 valves were placed with a median of three valves (ranging from 2 to 6) per patient. The 5.5 EBV valve was used in 30% of cases, while 4.0 EBV was used in 70% of cases. In most cases (79%), the valves were placed in segmental bronchi and the remainder in the lobar and subsegmental bronchi. At the end of all procedures, the valves were well positioned and no intraoperative complications or deaths were registered. The median hospital stay was 3 days (ranging from 2 to 5 days). One patient had pneumothorax at the same site of treatment 11 days after the procedure. He was successfully treated with placement of Heimlich valve. Three patients experienced haemoptysis 3 days, 1 month and 6 months after the procedure, respectively. In 1 case (the patient who complained haemoptysis after 6 months), bronchoscopic review showed a granulation formation that required the extraction of valve. Cause of death included cardiac failure (1 patient 7 months after the procedure, and lung cancer (1 patient 17 months after the procedure).

Qualitative computed tomography analysis

The fissures resulted complete in 22 of 25 (88%) patients. Among patients with HE, complete atelectasis was present in 9 of 15 (60%) cases, moderate atelectasis in 2 of 15 (13%) cases and no atelectasis in the remaining 4 of 15 (27%) cases. Complete atelectasis of bulla with re-expansion of adjacent lung was observed in 7 of 10 (70%) patients, partial atelectasis in 2 of 10 (20%) patients, while in only 1 of 10 (10%) patients no atelectasis of bulla was found. All patients with positive CT response ($n = 20/25$; 80%) presented complete fissures. Among patients with negative CT response ($n = 5/25$; 20%), 2 of 5 (40%) patients, all with HE, had complete fissures and 3 of 5 (60%) patients, of which two with HE and one with GEB, presented no complete fissures. The patients with complete fissures presented a significant higher incidence of CT radiological response than those without fissures ($P = 0.004$). No significant reduction of thoracic diameter was seen before and after treatment in all patients (20.61 ± 2.8 vs 20.58 ± 3.5; $P = 0.07$); in subgroup with HE (21.48 ± 4.7 vs 21.46 ± 2.7; $P = 0.08$); and in subgroup with GEB (19.3 ± 2.7 vs 19.2 ± 4.7; $P = 0.08$).

Volumetric multidetector-row computed tomography

The results were summarized in Table 1. The volumetric qMDCT measurements showed that there was a significant reduction of volume of the treated lobe in all patients (from 1515 ± 231 to 1013 ± 342; $P < 0.0001$); among HE patients (from 1448 ± 204 to 1076 ± 364; $P = 0.0008$); in those with GEB due to collapse of bulla (from 1668 ± 140 to 864 ± 199; $P < 0.0001$); and in positive CT response patients (from 1526 ± 248 to 959 ± 361; $P < 0.0001$) after treatment. Similarly, a significant reduction of TLV was registered in all patients (from 1827 ± 278 to 1528 ± 210; $P < 0.0001$); in HE patients (from 1777 ± 74 to 1580 ± 63; $P < 0.0001$); in GEB patients (from 2075 ± 192 to 1295 ± 149; $P < 0.0001$); and in positive CT response patients (from 1687 ± 256 to 1513 ± 180; $P = 0.0001$) after treatment. Examples were reported in Figs 1 and 2. A significant increment of volume of adjacent lobe(s) were seen in all patients (from 359 ± 187 to 467 ± 343; $P = 0.02$); in patients with heterogeneous emphysema (from 385 ± 95 to 459 ± 77; $P = 0.04$): in patients with GEB (from 342 ± 122 to 518 ± 82; $P = 0.003$); and in positive CT response patients (from 358 ± 173 to 470 ± 373; $P = 0.01$) after treatment. Conversely, among negative CT response patients a mild volume reduction of treated lobe (from 1468 ± 153 to 1420 ± 141; $P = 0.6$) and TLV (from 1670 ± 339 to 1605 ± 325; $P = 0.3$) was seen but it was no significant. Examples of volumetric qMDCT analysis before and after treatment were reported in Supplementary Videos 1 and 2, respectively.

Pulmonary functional test

The results were summarized in Table 2. Among the whole study population, we observed a significant improvement of PFTs after treatment. FEV1 and FVC increased from 36.8 ± 7.1 to 44.6 ± 9.6 ($P = 0.0002$); and from 41.1 ± 8.6 to 48.3 ± 6.5 ($P = 0.0008$); respectively. RV and TLC decreased from 190 ± 18.1 to 147 ± 21 ($P < 0.0001$); and from 167 ± 9.4 to 136 ± 7.9 ($P = 0.0003$), respectively. A significant improvement before and after treatment was also found for DLCO (35 ± 4.9 vs 39 ± 4.9; $P = 0.01$); 6MWT (169 ± 10.4 vs 269 ± 8.1; $P = 0.0003$). Conversely no significant difference of FEV1/FVC, PaO_2 and $PaCO_2$ was seen before and after procedure. Similar results were observed if we considered the subgroups of patients separately. Among HE and GEB patients, a significant improvement of FEV1 (from 36.9 ± 15.3 to 43.9 ± 10.4; $P = 0.01$; and from 35.8 ± 6.0 to 47.5 ± 7.9; $P < 0.0001$, respectively); of FVC (from 41.9 ± 5.9 to 47.3 ± 9.3; $P = 0.0009$; and from 40.7 ± 5.9 to 48.8 ± 4.9; $P = 0.0002$, respectively); of DLCO (from 34.7 ± 8.3 to 38.6 ± 17; $P = 0.01$; and from 35.7 ± 6.9 to 39 ± 9.3 ;$P = 0.01$, respectively); and of 6MWT (from 169 ± 8.9 to 270 ± 9.4; $P = 0.0003$; and from 169.8 ± 8.9 to 268. ± 19; $P = 0.0003$, respectively); and a significant reduction of RV (from 185 ± 14 to 157 ± 14.7; $P = 0.005$; and from 196 ± 13.5 to 137 ± 21; $P < 0.0001$, respectively) and of TLV (from 166.7 ± 13 to 137 ± 18; $P = 0.0003$, and from 169 ± 15 to 134 ± 18; $P < 0.0001$, respectively) were seen after treatment. Conversely, in each subgroup no significant difference of FEV1/FVC, PaO_2 and $PaCO_2$ was seen after procedure. According to the radiological results, positive CT responders had a significant increase of FEV1 (36.4 ± 4.0 vs 45.2 ± 3.4; $P < 0.0001$); FVC (41.5 ± 4.6 vs 49.9 ± 6.5; $P = 0.0007$); DLCO (35 ± 9.8 vs 39 ± 15; $P = 0.01$); and 6MWT (169 ± 6.9 vs 269 ± 14; $P = 0.0003$); and a significant reduction of RV (190 ± 16.5 vs 141 ± 14.5; $P < 0.0001$); and of TLC (168 ± 11 vs 135 ± 11.5; $P = 0.0003$). No significant changes in spirometric values were seen in the five negative CT responder patients. However, 3 of 5 (2 with HE and 1 with GEB) of these patients declared an subjective improvement of their quality of life after treatment. We observed only a mild increment of FEV1 of 2%, 3% among HE patients, respectively, and of 2.3% in GEB patient but we were unable to quantify the changes in quality of life with other tests as dyspnea score and/or St. George's Respiratory Questionnaire (SGRQ).

Correlation between multidetector-row computed tomography and forced expiratory volume in 1 s changes

The results were summarized in Table 3. The lung and target lobe volume change was inversely correlated with change in FEV1

Table 1: Volume computed tomography quantification (cc)

Variables	Treatment	All Patients ($n = 25$)	HE ($n = 15$)	GEB ($n = 10$)	Positive CT Responders ($n = 20$)	Negative CT Responders ($n = 5$)
Treated Lobe	Pre	1515 ± 231	1448 ± 204	1668 ± 140	1526 ± 248	1468 ± 153
	Post	1013 ± 342	1076 ± 364	864 ± 199	959 ± 361	1420 ± 141
	P-value	< 0.0001	0.0008	<0.0001	<0.0001	0.6
Total lung	Pre	1827 ± 278	1777 ± 74	2075 ± 192	1835 ± 256	1765 ± 339
	Post	1528 ± 210	1580 ± 63	1295 ± 149	1513 ± 180	1653 ± 325
	P-value	<0.0001	<0.0001	<0.0001	0.0001	0.3
Adjacent lobe	Pre	359 ± 187	385 ± 95	342 ± 122	358 ± 173	360 ± 267
	Post	467 ± 343	459 ± 77	518 ± 82	470 ± 373	375 ± 365
	P-value	0.02	0.04	0.003	0.01	0.6

HE: heterogenous emphysema; GEB: giant emphysematous bulla; CT: computed tomography; data were expressed as means ± standard deviation. Statistical analysis: paired t-test.

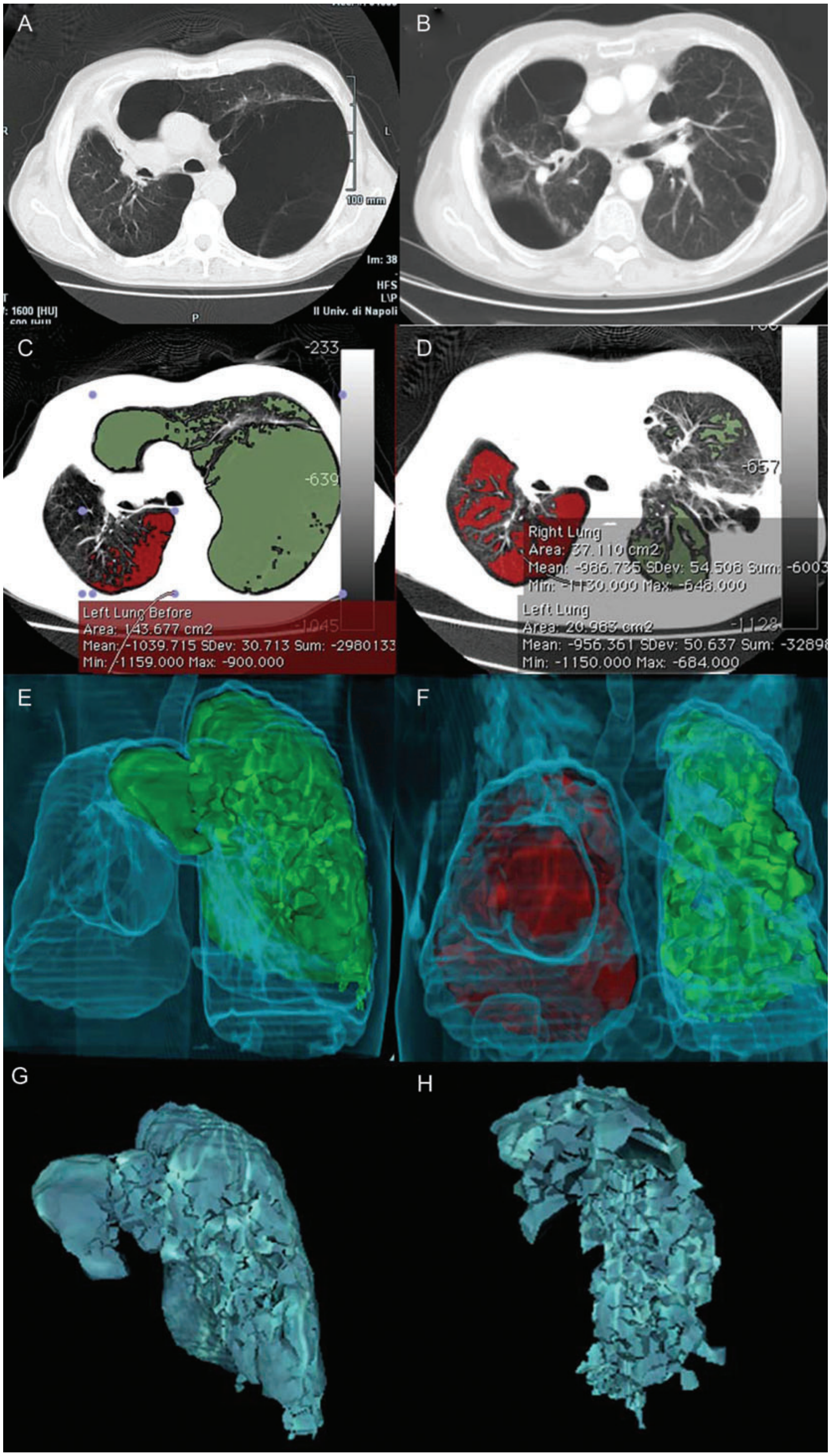

Figure 1: A 65-year old man presented a giant emphysematous bulla that occupied the entire left lobe (**A**). The axial computed tomography (CT) scans obtained at the same level after endobronchial valve treatment (**B**) showed the complete atelectasis of the bulla with subsequent re-expansion of adjacent parenchyma; the volumetric difference was appreciated on the same CT slices before (**C**) and after (**D**) treatment. Then, a 3D region growing algorithm was applied with subsequent superimposition of ROI masks (qMDCT) in the range of −1.024/−950 HU; virtual rendered (VR) images of volumes were obtained before (**E**) and after (**F**) treatment to easily represent the volume reduction, as calculated using a dedicated algorithm, to obtain a volumetric quantitative measurement. Finally, corresponding volumes obtained before (**G**) and after (**H**) treatment were shown after applying a 3D mesh to visualize previously segmented areas of each lung.

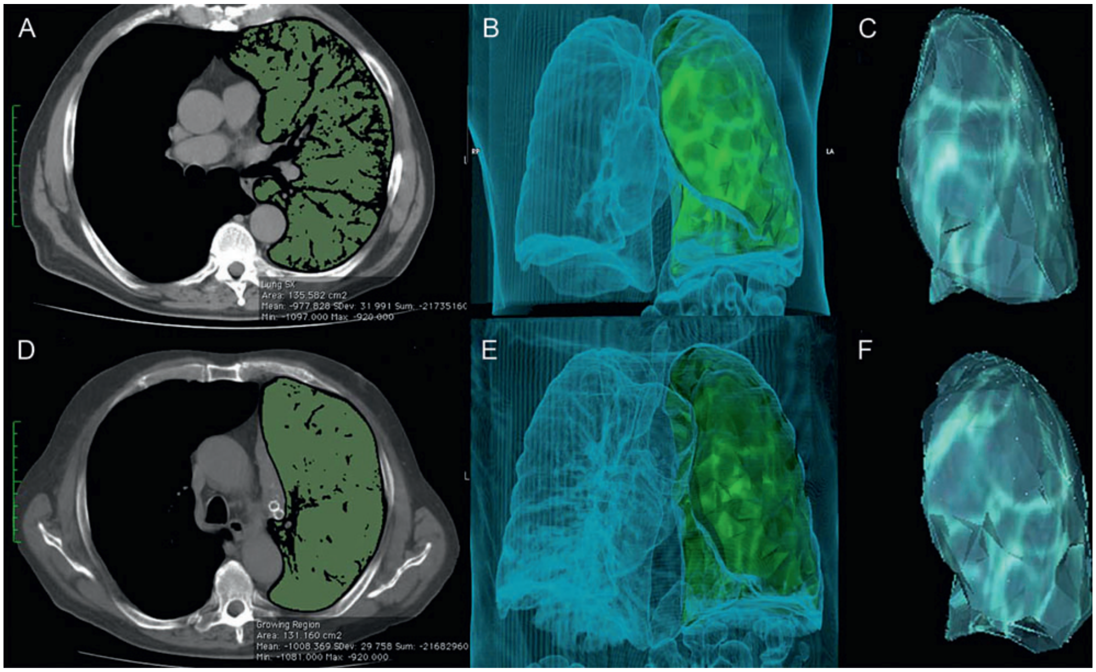

Figure 2: A 65-year old man presented a heterogeneous emphysema that affected mostly the left upper lobe. The entire segmentation process was shown starting from axial 2D CT scans obtained at the same level before (**A**) and after (**D**) treatment and subsequent superimposition of 2D ROI masks (qMDCT); the image segmentation process from 2D to 3D quantitative evaluation of emphysematous lung parenchyma was well represented before (**B**) and after (**E**) treatment using virtual rendered (VR) reconstructions; volumetric quantitative estimations in mm^3 are visualized after applying a 3D surface mesh on previously calculated volumes before (**C**) and after (**F**) treatment.

Table 2: Pulmonary functional test data

Variables	Treatment	All patients (*n* = 25)	Positive CT responders (*n* = 20)	Negative CT responders (*n* = 5)	HE (*n* = 15)	GEB (*n* = 10)
FEV1%	Pre	36.8 ± 7.1	36.4 ± 4.0	35 ± 8.3	36.9 ± 15.3	35.8 ± 6.0
	Post	44.6 ± 9.6	45.2 ± 3.4	37 ± 6.8	43.9 ± 10.4	47.5 ± 7.9
	P-value	0.0002	<0.0001	0.3	0.01	<0.0001
FVC%	Pre	41.1 ± 8.6	41.5 ± 4.6	40.9 ± 8.6	41.9 ± 5.9	40.7 ± 5.9
	Post	48.3 ± 6.5	49.9 ± 6.5	43.7 ± 12	47.3 ± 9.3	48.8 ± 4.9
	P-value	0.0008	0.0007	0.09	0.0009	0.0002
FEV1/FVC	Pre	88 ± 12.9	88 ± 7.4	86.8 ± 9.1	87.5 ± 10	88.7 ± 10.5
	Post	89.9 ± 11.2	89 ± 9.4	88 ± 5.9	88.5 ± 11.8	89 ± 8.3
	P-value	0.6	0.6	0.5	0.5	0.8
RV%	Pre	190 ± 18.1	190 ± 16.5	188 ± 13	185 ± 14	196 ± 13.5
	Post	147 ± 21	141 ± 14.5	181 ± 21	157 ± 14.7	137 ± 21
	P-value	<0.0001	<0.0001	0.3	0.005	<0.0001
TLV%	Pre	167 ± 9.4	168 ± 11	166 ± 13	166.7 ± 13	169 ± 15
	Post	136 ± 7.9	135 ± 11.5	160 ± 7.9	137 ± 18	134 ± 18
	P-value	0.0003	0.0003	0.09	0.0003	<0.0001
DLCO%	Pre	35 ± 4.9	35 ± 9.8	35 ± 8.9	34.7 ± 8.3	35.7 ± 6.9
	Post	39 ± 4.9	39 ± 15	35.9 ± 18	38.6 ± 17	39 ± 9.3
	P-value	0.01	0.01	0.8	0.01	0.01
6MWT m	Pre	169 ± 10.4	169 ± 6.9	168.7 ± 17	169 ± 8.9	169.8 ± 8.9
	Post	269 ± 8.1	269 ± 14	170 ± 7.7	270 ± 9.4	268. ± 19
	P-value	0.0003	0.0003	0.8	0.0003	0.0003
PaO_2	Pre	61 ± 5.5	61 ± 19	61 ± 9.7	61 ± 7.9	61 ± 21
	Post	63 ± 7.9	63 ± 20	62 ± 7.9	63 ± 12	63 ± 19
	P-value	0.08	0.07	0.1	0.08	0.08
$PaCO_2$	Pre	41 ± 7.1	41 ± 6.8	41 ± 17	40.8 ± 14	41.5 ± 14.7
	Post	40 ± 8.3	40 ± 3.4	40 ± 19	39.8 ± 8.3	40.5 ± 18.3
	P-value	0.09	0.09	0.09	0.09	0.09

FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLV: total lung volume; RV: residual volume; DLCO: diffusing capacity; 6MWT: 6 min walking test; CT: computed tomography; HE: heterogeneous emphysema; GEB: giant emphysematous bulla.
Data were expressed as means ± standard deviation. Statistical analysis: paired *t*-test.

Table 3: Correlation between qMDCT and FEV1 changes

Study population	Site	R	P-value	95% CI
All patients	Entire lung	−0.7	<0.0001	−0.879 to −0.490
	Treated Lobe	−0.8	<0.0001	−0.926 to −0.660
HE	Entire lung	−0.7	0.0006	−0.924 to −0.452
	Treated Lobe	−0.7	0.0009	−0.917 to −0.414
GEB	Entire lung	−0.8	0.001	−0.965 to −0.490
	Treated Lobe	−0.7	0.009	−0.942 to −0.271

HE: heterogenous emphysema; GEB: giant emphysematous bulla; r: Spearman's coefficient of rank correlation; *P*: significance level; 95% CI: 95% confidence interval.

among the whole study population (Fig. 3; A and B), in HE (Fig. 3; C and D); and in GEB patients (Fig. 3; E and F).

Receiver operating characteristic curve (ROC)

Among HE patients, the best value of sensitivity and specificity were 66.6% (95% confidence interval (CI): 9.4–99.2) and 83% (95% CI: 51.6–97.9) with a cut-off >1.523 (area under the ROC curve: 0.6; 95% CI: 0.333–0.844; Fig. 4A). Among GEB patients, the best value of sensitivity and specificity were 60% (95% CI: 14.7–94.7) and 100% (95% CI: 47.8–100) with a cut-off >1.762 (area under the ROC curve: 0.6; 95% CI: 0.262–0.878, Fig. 4B).

DISCUSSION

Bronchoscopic lung volume reduction (BLVR) using EBVs is a well-known procedure for the treatment of hyperinflantion due to advanced emphysema. The valves, allowing air to escape from a pulmonary lobe but not entering, may induce a reduction in lobar volume with improving lung function and exercise tolerance.

Despite several studies reported the clinical benefit of BLVR in the treatment of HE, the VENT study [10] recently showed modest improvements in lung function, exercise tolerance and quality of life compared with controls. However, subgroup analyses performed on both sets of data revealed that the degree of lung volume reduction and the associated clinical improvements were far more pronounced in the patients showing complete fissures on CT and where EBV placement had resulted in complete lobar occlusion. Thus, an accurate selection of patients is crucial to maximize the benefits of such treatment. Patients are usually reviewed on the basis of clinical, physiological and radio-anatomical assessments. However, standard PFTs do not provide regional information about the distribution of emphysema and standard CT scan may be unable to identify small volume changes in emphysematous parenchyma. Different authors have previously reported the correlations between changes in pulmonary function tests and volumetric quantitative CT parameters after EBVs treatment [11–13]. Herein, we evaluated the diagnostic value of quantitative CT analysis using a new software in patients with different diseases including HE and GEB. Considering the results from standard PFTs, visual and quantitative radiological studies, we aimed to identify which lobe should be treated to obtain the better clinical effects, not been reported before.

First, as expected we found that patients with complete fissure had a higher positive radiological response in terms of lobar atelectasis or collapse of bulla than patients with incomplete fissure. Koenigkam-Santos *et al*. [11] in a similar study evaluated the lung fissure completeness, post-treatment radiological response and quantitative CT analysis in 29 patients submitted to EBV implantation. They found that atelectasis was correlated with fissure completeness and a significant reduction of treated lobe volume was seen in patients with lobar atelectasis. However, the authors [11] did not correlate the radiological data with spirometric tests. The collateral ventilation is a well known mechanism that usually precludes the success of valve insertion. When the fissures are incomplete (3 of our cases), the occlusion of the target bronchus may be insufficient to obtain an adequate atelectasis of emphysematous lobe and/or collapse of bulla because air can still enter through interlobar channels from adjacent non-treated lung (collateral ventilation). Surprisingly, in 2 HE patients with complete fissures no atelectasis was obtained. A possible explanation may be the presence of millimetric gaps in the fissure, not visually identified on high resolution computed tomography, that allowed collateral ventilation [11]. To avoid such phenomena, the use of the Chartis Pulmonary Assessment System to measure collateral ventilation has recently been introduced [14].

Secondly, in agreement with previous experiences [11–13], the qMDCT measurements showed that there was a significant reduction of volume of the treated lobe in all patients and in the different subgroups of patients when considered separately. In patients with HE, the atelectasis of hyperinflated lobe allowed the re-expansion of untreated lobes with small increase of its volume. However, a significant reduction of the TLV was found because in the balance of lung capacity the small increase volume of the untreated lobe(s) had a modest impact in respect to the higher volume reduction of treated lobe. That was more evident in GEB patients where the collapse of bulla caused a higher reduction of dead space. As expected, in patients with positive CT response, a significant reduction of qMDCT volume of treated lobe was seen. Interestingly, also in the 5 patients where no evident atelectasis was seen on CT analysis, a qMDCT reduction of treated lobe was observed, however, it was small and non-significant. In theory, qMDCT evaluation was able to detect small changes in volume that could not be detected by standard CT analysis. Similarly, Koenigkam-Santos M *et al*. [11] reported that quantitative CT analysis could detect mild post-treatment volume changes not amenable to reliable visual detection on CT scans.

Conversely to D'Andrilli *et al*. [12], in our cases the reduction of TLV was not correlated with changes in diameter of chest cavity probably because the short time of the follow-up of our study did not permit a significant reduction of chest wall dimension.

Thirdly, the EBVs treatment resulted in significant clinical benefits. Among all patients, FEV1 improved to 7.8% (from 36.8 ± 7.1 to 44.6 ± 9.6) and FVC improved to 7.2% (from 48.3 ± 6.5 to 41.1 ± 8.6). Interestingly, if considering only GEB patients, we found a higher positive change in FEV1% (11.7%) in respect to that observed in HE patients (7%). The treatment was the same in both subgroups (the occlusion of the target lobe), but had different pathophysiological results as GEB and HE are different pathologies with different mechanism. For unknown reasons the pattern of emphysematous destruction varies considerably from patient to patient or even from one region of the lung to another. Proximal acinar (centrilobular) emphysema has often caused wider spread lung destruction and is thus most commonly associated with HE. Distal acinar (paraseptal) emphysema more severely involves the

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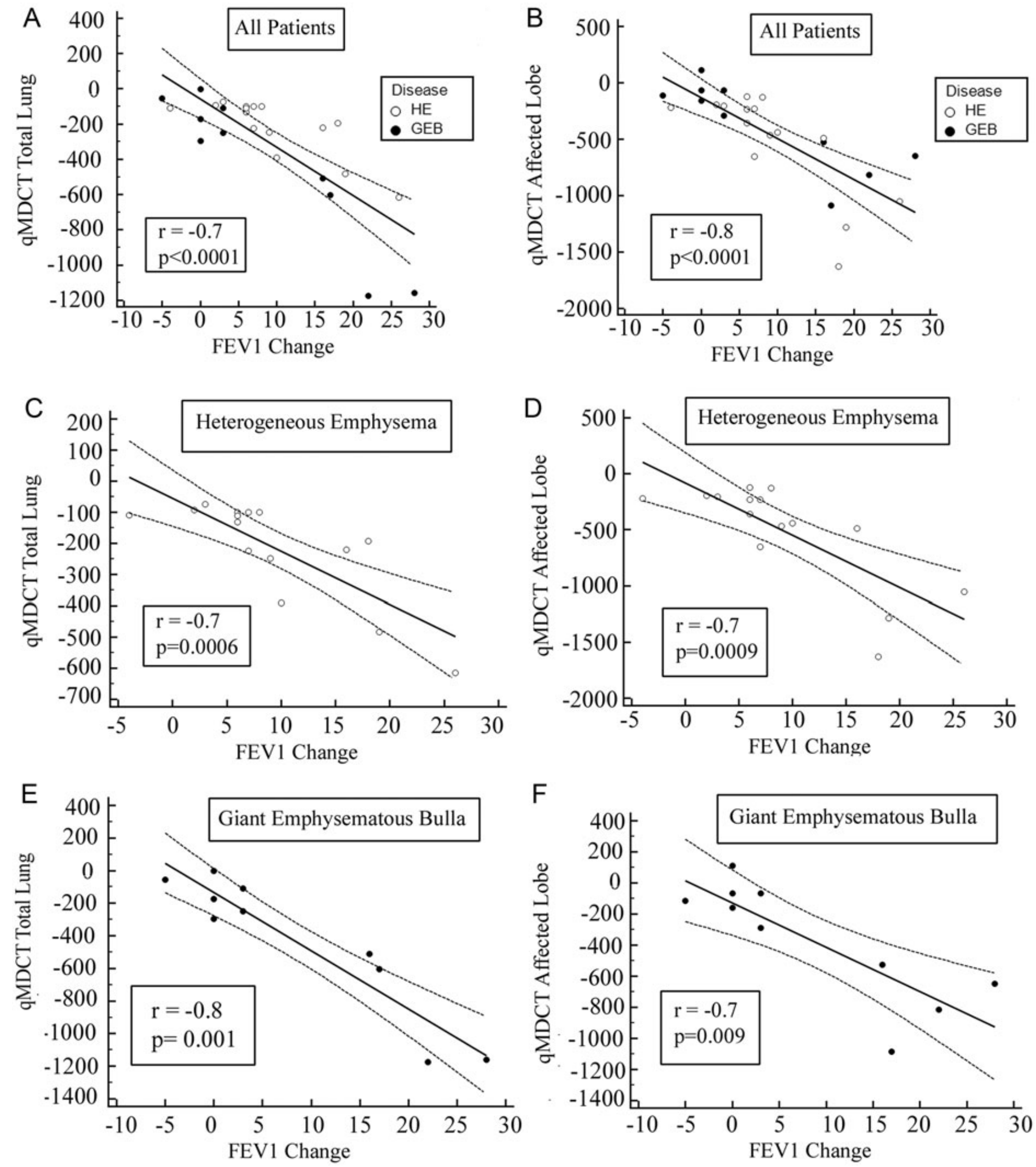

Figure 3: The lung and affected lobe volume change was inversely correlated with change in FEV1 among all patients (**A** and **B**), in patients with heterogeneous emphysema (**C** and **D**); and in those with giant emphysematous bulla (**E** and **F**). HE = heterogeneous emphysema; GEB: giant emphysematous bulla.

cortex, sparing the central portions of the lung. In addition, it is associated with the development of GEB, which can compromise lung function substantially while relatively much normal lung is still present [15]. In patients with HE, EBVs treatment mimicked the original concept of LVRS proposed by Brantigan *et al.* [16]. The atelectasis of more affected lobe obtained with EBVs reduced the lung hyperinflation. It normalized diaphragmatic and chest wall dimensions, improving ventilatory capacity by normalizing the operating length over which the respiratory muscles are required to function [17].

Differently, in patients with GEB the EBV procedure imitated the effect of bullectomy. GEB adversely affects respiratory physiology in several ways that may be different from mechanism of HE [18, 19]. GEB occupied a large volume of the chest cavity and compressed adjacent, more normal lung tissue. The compressed areas reduced aeration and elastic recoil. In addition, GEB could exert pressure on the diaphragm, leading to a flatter and less efficient shape. During exercise, bullae that communicate with the tracheobronchial tree increased in size due to dynamic hyperinflation and further impaired respiratory function. After collapse of bulla due to EBVs insertion, reinflation of compressed areas decreases the physiological dead space that was caused by compression of normal lung by the inflated bulla and improved matching of ventilation and perfusion. In addition, removing the space occupying effect of the bulla and reducing air trapping helped to restore the diaphragm to a more domed shape, which was more efficient.

Then, comparing qMDCT with changes in FEV1 and FVC, we found that they were inversely correlated in all patients and also when the two subgroups were considered separately. In other words, the greater the degree of reduction in qMDCT, the greater the improvement in pulmonary function. Similar data were reported by D'Andrilli *et al.* [12] who found in a study group of 9 patients undergoing EBVs treatment a significant correlation between the increase of FEV1 and the reduction in volume of treated lobe and total lung. Conversely, Coxson *et al.* [13] found in a case series of 57 patients undergoing BLVR that changes in lobar

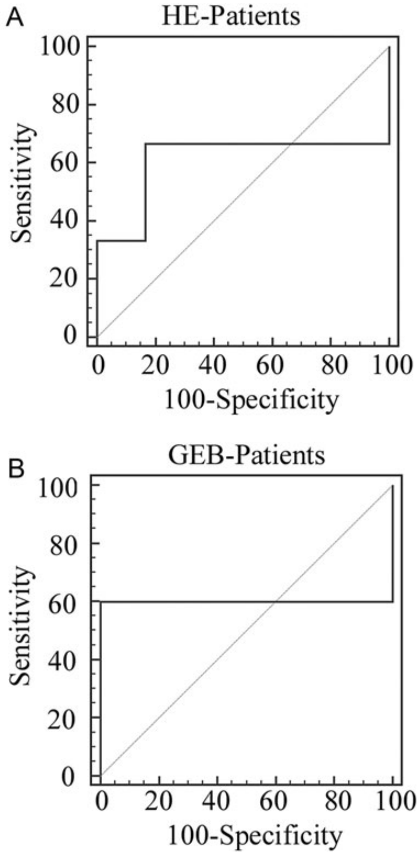

Figure 4: Among HE patients, the sensitivity and specificity were 66.6 and 83%, respectively, with a cut-off >1.523 [area under the ROC curve: 0.6; 95% confidence interval: 0.333–0.844; (**A**)]. Among GEB patients, the sensitivity and specificity were 60 and 100%, respectively with a cut-off >1.762. Area under the ROC curve: 0.6; 95% confidence interval: 0.262–0.878; (**B**).

volume were not correlated with the improvement in lung function parameters. The different results may be due to the different incidence of atelectasis and/or stage of disease. In our study in only 5 of 25 (20%) patients no atelectasis was found, probably as above reported, because we did not enroll patients without fissures detected on CT scan while Coxson *et al*. [13] found no atelectasis after procedure in 24 of 57 (42%) subjects. Yet, in Coxson's study most patients underwent bilateral procedure probably because they were in end-stage of emphysema in comparison to our population where unilateral procedure was applied in all patients except one.

Fourthly, we found that qMDCT evaluation may help to identify the target lobe to treat in order to exclude the regions of most damaged parenchyma from ventilation, and to allow the re-expansion of the remaining less damaged parenchyma. Our analysis showed that the target lobe having a qMDCT value >1523 and a qMDCT > 1.762 in HE and GEB patients, respectively, should be treated with high the probability of clinical success. As above reported, 3 of 5 patients reported a subjective improvement in their respiratory activity despite no evident spirometric and radiological changes were seen after procedure. Similarly, Wood *et al*. [20] found that some patients submitted to BLVRS procedure with clinical improvement did not exhibit atelectasis or TLV reduction. Yet, Coxson *et al*. [13] found a significant improvement in quality of life measured with SGRQ not correlated with changes in standard function parameters.

In our cases, 2 HE patients had a qMDCT value of 1526 cc and 1580 cc before treatment, respectively, while a GEB patient had a qMDCT value of 1.669. After treatment, in both HE patients a mild qMDCT reduction of treated lobe (2 and 3%, respectively) was seen. Also GEB patients had a mild qMDCT reduction of treated lobe (2.3%) without collapse of the bulla.

In theory, in HE patients the mild structural changes after procedure not seen on visual CT scan but detected by qMDCT analysis could help to redirect ventilation to better-perfused segments and improve ventilation-perfusion matching with clinical benefits. The lack of resolution of small airway obstruction may also explain the absence of spirometric changes [21]. The same mechanism may be advocated also for GEB patient because the compressed lung may not be 'normal' at all, but just relatively less diseased than the bulla. Thus, the EBVs procedure reduced the volume of treated lobe for its effect on hyperinflated emphysematous parenchyma also in the absence of bulla collapse. In the future volumetric qMDCT study could also be used in the follow-up of treated patient in order to predict when a controlateral treatment is indicated before an evident decline of spirometric tests is present.

Study limitations

The retrospective nature of the study, the small number of patient; the different pathologies (heterogeneous emphysema and/or GEB); the lack of tests to quantify the changes in quality of life, and the short term of the follow-up may affect our results since other similar studies with larger follow-up showed long-term benefits on some measure of lung volume and of quality of life; finally, as there was no enrollment requirement for patients to undergo pulmonary rehabilitation or optimization of medical treatment, the potential for variability in our sample was increased.

CONCLUSIONS

Our study showed that the values of qMDCT indexes of global and regional emphysema severity were correlated to outcome measures. Such method is of particular interest because it offers measurements of both morphological and functional information with the possibility to interrelate structure and function.

Conversely to PFTs that do not provide regional information about the distribution of emphysema, qMDCT offers the advantage of evaluating selectively the target lobe. Obviously, the radiological evidence of fissure in the target lobe is of paramount importance in patient selection especially if other instruments as Chartis to measure collateral ventilation are not available. qMDCT is an analytical evaluation method and not subject to the observer variability that may occur in visual CT analysis. Thus, it could add important independent information to the routine evaluation for optimizing the selection of patients scheduled for EBV therapy considering that such procedure is not cost saving. However, due to the small number and the heterogeneity of our study population, our conclusions should be tested in larger prospective trials.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

Conflict of interest: none declared.

REFERENCES

[1] Naunheim KS, Wood DE, Krasna MJ, DeCamp MM Jr, Ginsburg ME, McKenna RJ Jr *et al*. National Emphysema Treatment Trial Research Group. Predictors of operative mortality and cardiopulmonary morbidity in the National Emphysema Treatment Trial. J Thorac Cardiovasc Surg 2006;131:43–53.

[2] Carretta A, Ciriaco P, Melloni G, Ballarin A, Bandiera A, Sestini S *et al*. Correlation of computed tomography densitometry and pathological grading of emphysema with the variation of respiratory function after lobectomy for lung cancer. Interact CardioVasc Thorac Surg 2010;10: 914–7.

[3] Coxson HO, Whittall KP, Nakano Y, Rogers RM, Sciurba FC, Keenan RJ *et al*. Selection of patients for lung volume reduction surgery using a power law analysis of the computed tomographic scan. Thorax 2003;58: 510–4.

[4] Strange C, Herth FJ, Kovitz KL, McLennan G, Ernst A, Goldin J *et al*. Design of the Endobronchial Valve for Emphysema Palliation Trial (VENT): a non-surgical method of lung volume reduction. BMC Pulm Med 2007;7:10.

[5] American Thoracic Society Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152:S77–121.

[6] Madani A, Keyzer C, Gevenois PA. Quantitative computed tomography assessment of lung structure and function in pulmonary emphysema. Eur Respir J 2001;18:720–30.

[7] Santini M, Fiorelli A, Vicidomini G, Di Crescenzo VG, Messina G, Laperuta P. Endobronchial treatment of giant emphysematous bullae with one-way valves: a new approach for surgically unfit patients. Eur J Cardiothorac Surg 2011;40:1425–31.

[8] Santini M, Fiorelli A, Vicidomini G, Laperuta P, Di Crescenzo VG. Iatrogenic air leak successfully treated by bronchoscopic placement of unidirectional endobronchial valves. Ann Thorac Surg 2010;89: 2007–10.

[9] Santini M, Fiorello A, Di Crescenzo VG, Vicidomini G, Busiello L, Laperuta P. Use of unidirectional endobronchial valves for the treatment of giant emphysematous bulla. J Thorac Cardiovasc Surg 2010;139:224–6.

[10] Sciurba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH *et al*. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233–44.

[11] Koenigkam-Santos M, Paula WD, Gompelmann D, Kauczor HU, Heussel CP, Puderbach M. Endobronchial valves in severe emphysematous patients: CT evaluation of lung fissures completeness, treatment radiological response and quantitative emphysema analysis. Radiol Bras 2013;46:15–22.

[12] D'Andrilli A, Vismara L, Rolla M, Ibrahim M, Venuta F, Pochesci I *et al*. Computed tomography with volume rendering for the evaluation of parenchymal hyperinflation after bronchoscopic lung volume reduction. Eur J Cardiothorac Surg 2009;35:403–7.

[13] Coxson HO, Nasute Fauerbach PV, Storness-Bliss C, Müller NL, Cogswell S, Dillard DH *et al*. Computed tomography assessment of lung volume changes after bronchial valve treatment. Eur Respir J 2008;32:1443–50.

[14] Herth FJ, Eberhardt R, Gompelmann D, Ficker JH, Wagner M, Ek L *et al*. Radiological and clinical outcomes of using Chartis to plan endobronchial valve treatment. Eur Respir J 2013;41:302–8.

[15] Schipper PH, Meyers BF, Battafarano RJ, Guthrie TJ, Patterson GA, Cooper JD. Outcomes after resection of giant emphysematous bullae. Ann Thorac Surg 2004;78:976–82.

[16] Brantigan OC, Kress MB, Mueller EA. The surgical approach to pulmonary emphysema. Dis Chest 1961;39:485–501.

[17] Becker MD, Berkmen YM, Austin JH, Mun IK, Romney BM, Rozenshtein A *et al*. Lung volumes before and after lung volume reduction surgery: quantitative CT analysis. Am J Respir Crit Care Med 1998;157:1593–9.

[18] Snider GL. Reduction pneumoplasty for giant bullous emphysema. Implications for surgical treatment of nonbullous emphysema. Chest 1996;109:540–8.

[19] Kinnear WJ, Tattersfield AE. Emphysematous bullae. Br Med J 990;300: 208–9.

[20] Wood DE, McKenna RJ Jr, Yusen RD, Sterman DH, Ost DE, Springmeyer SC *et al*. A multicenter trial of an intrabronchial valve for treatment of severe emphysema. J Thorac Cardiovasc Surg 2007;133:65–73.

[21] Santini M, Fiorello A, Vicidomini G, Di Crescenzo VG, Laperuta P. Role of diffusing capacity in predicting complications after lung resection for cancer. Thorac Cardiovasc Surg 2007;55:391–4.