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Results Of Bronchoscopic Lung Volume Reduction with One-way Valve in Patients with Severe Emphysema in Vietnam

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Summary:

Background: Bronchoscopic lung volume reduction (BLVR) has been applied in COPD patients with heterogeneous emphysema. In this first clinical trial in Vietnam, we evaluated the safety and initial results of BLVR by one-way valve in COPD patients with severe emphysema.

Methods: We performed a prospective, nonrandomized, single center longitudinal study in 30 stable COPD patients with heterogeneous severe emphysema on CT-scanner, the average age of 65.17 years old, FEV1≤35 %pred., TLC ≥ 100 %pred., RV ≥ 150 %pred. and 6MWT < 450 meters. The Zephyr one-way bronchial valves (PulmonX, Redwood City, CA, USA) with the size of 5.5 mm and 4mm were placed in lobar or segmental bronchi via flexible bronchoscopy. 28 patients were placed only one valve, 1 patient with two and 1 patient with three valves. 23 valves with the size 5.5 mm diameters and 10 valves with the size 4.0mm used. All patients received optimal medical treatment at the time of procedure and during the study period. Outcomes will be assessed at 3 months after treatment include the changes of clinic, and lung function, the occurrence of complications.

Results: After 3 months, mean CAT scores decreased significantly compared with before procedure (17.73 ± 3.53 vs 20.10 ± 3.58) ($p<0.05$), with the median change of 2.73 points and the improvement more than 2 points in 76.67% of patients. 6 MWT increased at 3 months with mean 32.13 meters, 93.33% of the patients increased 6MWT, 46.67% of the patients increased 6MWT more than 26 meters. MRC decreased with the median change of 0.5 score. VC decreased by a mean 0.2 (L) (0.42 - 0.02), FEV1 increased by a mean 0.05 (L) (0.04 - 0.05) but not statistically significant ($p>0.05$); FVC increased by a mean 0.14 (L) (0.01 - 0.28), RV decreased by a mean 0.62 (L) (1.05 - 0.2), TLC decreased by a mean 0.52 (L) (0.77- 2.4) with statistically significant ($P<0.05$). The early complications were 13.33%, the later complications were 23.34% of the patients.

Conclusions: The unilateral bronchoscopic lung volume reduction with one-way valve (mainly one valve) in treatment of heterogeneous severe emphysema in stable COPD patients in Viet Nam have shown that this procedure is safe with encouraging initial results.

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Introduction

Chronic obstructive pulmonary disease (COPD) has been a major public health problem in Vietnam. The first national epidemiological study undertaken based on questionnaires and lung functional testing, estimated the prevalence of COPD in 2010 to be 4,2% in a sample population of subjects aged over 40 years (about 1.300.000 COPD patients): 7.1% of male and 1.9% of women[2]. Emphysema with the destruction of lung parenchyma is an important feature of COPD. It causes airflow obstruction, gas trapping and increased operating lung volumes, leading to the frequent progressive dyspnea, limitation of physical activities and decrease of life's quality. Lung volume reduction surgery for the treatment of emphysema were performed in the 1950s, and had ability to improve the clinical and functional status of selected patients affected by emphysema. However, the indications of this technique are limited and its mortality was about 5%[3,13,21,22,23]. Bronchoscopic lung volume reduction (BLVR) has been applied in COPD patients with heterogeneous emphysema, especially patients have a high surgical risk and a low probability of benefitting from the surgery. Treatments of BLVR include endobronchial stents, valves, endobronchial coils, sclerosing agents. Different technologies have been performed in clinic but the results are different[16]. One-way valves allow the air to exit the target areas during expiration by opening valve and close during inspiration. The placement of endobronchial valves using a fibreoptic bronchoscope, to allow air to leave but not enter emphysematous areas of the lung, causing them to collapse[15]. In Vietnam, 103 Military Hospital (General Hospital of Military Medical University) had performed the first national clinical trial of BLVR by one-way valve in COPD patients with severe emphysema sine 2012 (with the national code of trial: KC 10.20/11-15). In this article, we reported initial results and the safety with this procedure in COPD patients with severe emphysema at Viet Nam.

Method:

Study Design:

This is study a prospective, nonrandomized, single center longitudinal study to evaluate the short-term efficacy and safety of BLVR performed by placing one way endobronchial valves.

Thirty patients (all men, median age 65.17 years, range 50 to 70) entered this pilot study during a 3-month period, from Jan 2014 to Apr 2017. Selection criteria: stable COPD patients[7] with FEV1 ≤ 35% pred., TLC ≥ 100% pred., RV ≥150% pred., and heterogeneous emphysema on chest computed tomography (CT); 40≤ age ≤75 years. Exclusion criteria: homogeneous emphysema; currently smoking; $PaCO_2$≥50 mmHg; productive cough[15,24].

The protocol was approved by the ethical committee of the Military Medical University, authozied by Vietnam Ministry of Health. All patients knew of the BLVR procedure and understood it.

Patients were underwent clinical examination, pulmonary function tests performed with body plethysmography, carbon monoxide diffusion (DLCO) measurement and reversibility test, arterial blood gas analysis, chest X-ray, computed tomography scan, echocardiogram at times: before again 24 hours after the procedure, and after 1 and 3 months. Fiberoptic bronchoscopy was repeated after 1 and 3 months. The exercise tolerance was measured with the 6-minute walk test (6MWT), health-related quality of life measured with COPD assessment test (CAT) score. The

degree of dyspnea was measured by the Medical Research Council (MRC) dyspnea grading system. CT thorax was be reviewed by two radiologists independently to demonstrate heterogeneous emphysema with a defined target lobe.

The procedure of one way valve placement: The technique was performed in the bronchoscopy room. Patients were underwent flexible bronchoscopy under local anaesthesia by the technician with more than 5 years of experience in intervention bronchoscopy. The flexible bronchoscope is advanced into the target bronchus are chosen (the target bronchus selection was based on CT). Collateral ventilation was measured by Chartis system (PulmonX, USA). The Zephyr one-way bronchial valve (PulmonX, Redwood City, CA, USA) was used in the study, with the sizes of 4.0 and 5.5 mm. A flexible delivery catheter containing the valve is inserted through the operating channel of the bronchoscope to the targeted bronchus, pushed with a gentle rotation in the selected bronchial orifice, and the valve is delivered. All the patients were controlled the complication of pneumothorax by chest X-ray after the procedure. 28 patients were placed only one valve, 1 patient with two and 1 patient with three valves. 23 valves with the size 5.5 mm diameters and 10 valves with the size 4.0 mm diameters used.

All patients received optimal medical treatment based on Guilines of the Vietnam Ministry of Health at the time of procedure and during the study period.

Characteristics of patients are shown in the Table 1.

Table 1. Characteristics of studied patients before technique

Characteristics	**n = 30**
Age (years old)	65.17 ± 7.12
Male	30 (100%)
Smoking (pack-year)	30.42 ± 11.82
Duration of disease (years)	7.95 ± 3.63
BMI (kg/m²)	18.51 ± 2.50
CAT	20.10 ± 3.58
mMRC	2.47 ± 0.82
6MWT (m)	303.87 ± 61.75
VC (%pred.)	76.73 ± 20.63
VC (L)	2.47 ± 0.82
FVC (%pred.)	60.90 ± 16.33
FVC (L)	1.95 ± 0.43
FEV1 (%pred.)	35.13 ± 15.68
FEV1 (L)	0.88 ± 0.32
RV (%pred.)	242.00 ± 64.04
RV (L)	4.98 ± 1.22
TLC (%pred.)	134.53 ±19.50
TLC (L)	7.06 ± 1.16
Raw (cmH20/l/sec)	9.22 ± 4.46
PaO_2 (mmHg)	72.47 ± 7.78
$PaCO_2$ (mmHg)	43.1 ± 4.15

Outcome measures: Outcomes will be assessed at 3 months after treatment include the changes of CAT, MRC, 6MWT, and lung function (VC, FVC, FEV1, RV, TLC, Raw). The main safety analysis will be the occurrence of adverse events in the first 3 months: exacerbations, pneumothorax, hemoptysis, blocked valve because of mucus, granulation around the valve.

Statistical analysis: Data analysis was performed using a software program the SPSS 20.0; p values were calculated using a two-tailed, Student t test for matched pairs when normality assumptions were met. For nonparametric results, the Wilcoxon signed-rank test was used. A p value of less than 0.05 was considered to indicate statistical significance.

Result

The total valves were placed 33, with 28 patients (93.34%) placed only one, 1 patient (3.33%) with two and 1 patient (3.33%) with three valves. The valve with the size 5.5 mm diameters used was 69.7% (23 valves), 30.4% with valves of the size 4.0mm (10 valves). The valves were placed in the right lung was 87.88% of the patients (29 valves), in which the most was placed in the right lower lobe (44.24%), in the right upper lobe 40%, in the right middle lobe 3.64%. 4 valves (12.12%) were placed in the left lung. (Table 2)

After 3 months, mean CAT scores was 17.73 ± 3.53, decreased significantly compared with before

Table 2. Clinical changes after 3 months

	Before technique (n=30)	**After 3 months (n=30)**	**p**
CAT index:			
- $\bar{X}$ ± SD	20.10 ± 3.58	17.73 ± 3.53	0.001
- Δ ($\bar{X}$ ± SD) (max-min)	-2.37 ± 1.30 (-2.85 -1.88)		
- Decrease ≥ 2 points	23 (76.67)		
6 MWT**:**			
- $\bar{X}$ ± SD	303.87 ± 61.75	336.00 ± 64.29	0.001
- Δ ($\bar{X}$ ± SD) (max-min)	32.13 ± 27.38 (21.91 – 42.36)		
- Increase: n (%)	28 (93.33)		
- Increase ≥26 m: n (%)	14 (46.67)		
MRC:			
- $\bar{X}$± SD	2.47 ± 0.82	1.97 ± 1.03	0.001
- Δ ($\bar{X}$ ± SD) (max-min)	-0.50 ± 0.51 (-0.69 -0.31)		
- Decrease: n (%)	13 (43.33)		

procedure (17.73 ± 3.53 vs 20.10 ± 3.58) (p<0.05), with the median change of 2.73 points and the improvement more than 2 points in 76.67% of patients. The BLVR patients also had the significant improvement in 6 MWT and MRC. 6 MWT increased at 3 months with mean 32.13 meters, 93.33% of the patients increased 6MWT, 46.67% of the patients increased 6MWT more than 26 meters. MRC decreased with the median change of 0.5 score and 43.33% of the patients decreased MRC at 3 months. (Table 3)

The change of lung function was assessed at 3 months (Table 3). VC decreased by a mean 0.2 (L)

Table 3. Changes of lung function after 3 months

	Before procedure (n = 30)	**After 3 months (n = 30)**	**P**
VC:			
- $\bar{X}$ ± SD (%pred.)	76.73 ± 20.63	73.5 ± 21.87	0.07
- Δ ($\bar{X}$ ± SD)(max-min) (%pred.)	-3.23 ± 24,.12 (-12.24 - 5.77)		
- $\bar{X}$ ± SD (L)	2.47 ± 0.82	1.97 ± 1.03	0.469
- Δ ($\bar{X}$ ± SD) (max-min) (L)	-0.20 ± 0.58 (-0.42 – 0.02)		
- Increase: n(%)	16 (53.33)		
FVC:			
- $\bar{X}$ ± SD (%pred.)	60.90 ± 16.33	68.1 ± 24.34	0.051
- Δ ($\bar{X}$ ± SD) (max-min) (%pred.)	7.20 ± 19.41 (-0.05 – 14.45)		
- $\bar{X}$ ± SD (L)	1.95 ± 0.43	2.09 ± 0.43	0.037
- Δ ($\bar{X}$ ± SD) (max-min) (L)	0.14 ± 0.36 (0.01 – 0.28)		
- Increase: n (%)	22 (73.33)		
FEV1:			
- $\bar{X}$ ± SD (%pred.)	35.13 ± 15.68	36.20 ± 15.59	0.382
- Δ ($\bar{X}$± SD) (max-min) (%pred.)	1.07 ± 6.58 (-1.39 – 3.52)		
- $\bar{X}$ ± SD (L)	0.88 ± 0.32	0.88 ± 0.30	0.824

- Δ ($\bar{X}$ ± SD) (max-min) (L)	0.05 ± 0.13 (-0.04 – 0.05)		
- Increase: n (%)	14 (46.67)		
- Increase >10%: n (%)	4 (13.33)		
RV:			
- $\bar{X}$ ± SD (%)	242.00 ± 64.04	211.50 ± 62.02	0.007
- Δ ($\bar{X}$ ± SD) (max-min) (%pred.)	-30.5 ± 57.68 (-52.04 – -8.96)		
- $\bar{X}$ ± SD (L)	4.98 ± 1.22	4.36 ± 1.26	0.006
- Δ ($\bar{X}$± SD) (max-min) (L)	-0.62 ± 1.15 (-1.05 -0.2)		
- Decrease: n (%)	20 (66.67)		
TLC:			
- $\bar{X}$ ± SD (%)	134.53 ±19.50	130.00 ± 24.16	0.056
- Δ ($\bar{X}$ ± SD) (max-min) (%pred.)	-9.33 ± 25.68 (-18.92 – 0.26)		
- $\bar{X}$ ± SD (L)	7.06 ± 1.16	6.53 ± 1.28	0.024
- Δ ($\bar{X}$ ± SD) (max-min) (%)	-0.52 ± 1.2 (-0.97 – 0.07)		
- Decrease: n (%)	17 (56.67)		
Raw:			
- $\bar{X}$ ± SD (cmH_2O/l/sec)	9.22 ± 4.46	10.13 ± 4.61	0.219
- Δ ($\bar{X}$ ± SD) (max-min)	0.91 ± 0.73 (-0.77 – 2.4)		
- Decrease: n (%)	13 (43.33)		

(0.42 - 0.02), FEV1 increased by a mean 0.05 (L) (0.04 - 0.05) from baseline (before procedure) but not statistically significant (p>0.05); FVC increased by a mean 0.14 (L) (0.01 - 0.28) from baseline with statistically significant. The patients also had the significant decrease in RV and TLC at 3 months. RV decreased by a mean 0.62 (L) (1.05 - 0.2), TLC decreased by a mean 0.52 (L)(0.77- 2.4) from baseline. The change of Raw at 3 months was not statistically significant. (Table 4)

The median post-procedure stay was 5 days (range 2 to 11). No complicatiopns occurred during the procedure. The early complications were 13.33% of the patients at the first and third day post-procedure, in which 10.0 % of mild COPD exacerbations and 3.33% of pneumothorax. All patients were treated and recovered after 1 to 3 days. The later complications were the blocked valve because of mucus, granulation around the valve and hemoptysis, with the rate following by 10.0%, 6.67% and 6.67% of the patients. These were performed flexible bronchoscopy and cleaned mucus, the granulation. No valve was removed.

Discussion

Size and Location of Bronchial Valve:

In our study, most of patients (93.34%) were placed only one valve, with the valves were placed in the right lung was 87.88% of the patients (29 valves), in which the most was placed in the right lower lobe (44.24%), in the right upper lobe 40%, in the right middle lobe 3.64%. 4 valves (12.12%) were placed in the left lung. To compare with some previous trials, the amount of valves were placed more and the valves were placed more in the upper lobes[4,14,19]. 28 patients were placed only one valve. This limitation was due to the expenditure of this study. The national trial (managed by Vietnam Ministry of Science and Technology) sponsored only one valve per patient. Besides, this technique has been still not paid by Vietnam Health Insurance. There were 2 patients who were placed the second or third valve by self-financing. In the next time, we continue to to follow up and advise them place next valves when having enough condition. In our patients, the homogeneous emphysema on CT-scanner image was seen more in the lower lobes, with the portion of 66.66% (20 of 30 patients), therefore the amount of valves were placed in the lower lobes the highest. The study of Vietnam authors (2013), which was carried out in stable COPD patients, had the similar results, with homogeneous emphysema seen more in lower lobes[1].

Changes of Clinical Symptoms After Procedure:

At 3 months after procedure, the life's quality and physical ability of patients were improved, with the CAT index decreased significantly in comparison with baseline, in which the average change was 2.73 points and the improvement more than 2 points was seen in 76.67% of patients. The exercise capacity of patients was increased clearly, shown by significant improved

Table 4: Complications

Complications	*n*	%
Early:	4	13.33
Exacerbations of COPD	3	10.00
Pneumothorax	1	3.33
Later:	7	23.34
Hemoptysis	2	6.67
Blocked valve because of mucus	3	10.00
Granulation around the valve	2	6.67

6MWT after 3 months ($p<0.05$), with 93.33% of the patients increased 6MWT, 46.67% of the patients increased 6MWT more than 26 meters. Our data suggest that the improvement of exercise capacity exercise capacity was the most patients. The degree of dyspnea in patients had a improvement significantly, with the median change of 0.5 score and 43.33% of the patients decreased MRC at 3 months. The decrease of MRC was lower than the improvement of exercise capacity and quality of life. The results in our study have shown the patients with increased 6MWT is higher but 6MWT improvement ≥ 26 m is lower when comparing with the study of Davey C. et al. (2015)[4]. In some other trials, the degree of dyspnea, quality of life (SGRQ score, BODE index) and 6MWT had improved in BLVR patients, but in many different levels[9,12,15,17]. These different results may relate to some factors, including the amount of inserted valves, sizes of valves and time of outcome evaluation (3 or 6 months). This study was undertaken at a single center in selecting patients for lung volume reduction at only 3 months, therefore, it shows the initial early results, and we are now following up these patients to evaluate next results.

Changes of Pulmonary Function After Procedure:

At 3 months after procedure, the mean of FVC increased, while RV and TLC decreased significantly in comparison with baseline. The mean of FVC was 2.09 ± 0.43 (L) and improved statistically from baseline ($p<0.05$), with the average of increased FVC of 0.14 (L) and 73.33% of patients increased FVC. The patients had the significant decrease in RV and TLC at 3 months with RV decreased by a mean 0.62 (L) (1.05 - 0.2), TLC decreased by a mean 0.52 (L) (0.77- 2.4) from baseline ($P<0.05$). The portion of patients with increased FVC was the most, following by reduced RV and decreased TLC. The change of Raw at 3 months was not statistically significant. A similar trend was seen in the study of Hopkinson N.S et al. (2005), with RV reducing more than TLC, and increased FVC but insignificant improved VC[8]. The changes of pulmonary function in our study was lower than in some previous trials[5,10,14,18,20]. Lung volume reduction treatment is carried out in order to let the emphysema area collapse, leading the decrease of the compression on the normal lung, change of the pulmonary volumes and capacities and improvement of the clinical status of COPD patients. Some authors have shown that the most significant efficacies of bronchial valve in lung volume reduction were seen in the COPD patients with homogeneous emphysema and without collateral ventilation under the place of valve[4]. All of our patients were controlled the collateral ventilation by Chartis system. However, we could not determine the relation between the change of emphysema index on CT-scanner image and the levels of improvements of FVC, FEV1, RV, and TLC at 3 months after the procedure. The study of Hopkinson N.S et al. (2005) showed that the reduced of RV and TLC of patients happened even as there was no atelectasis on the chest X-ray. So, there is a difference between the changes of pulmonary volumes measured by plethysmography and CT-scanner image[8]. The different results of lung function change depended on the amount and sizes of the valves as well as the time of outcome evaluation.

Complications:

Following-up after the procedure, some complications were seen, including 3 patients (10.0%) having mild exacerbations of COPD on the first day after the technique with the cause related to infection. These patients recovered after 3 days of treatment. The appearance of infection mainly related to the change of mucosal cleansing after bronchoscopy[11]. One patient had pneumothorax at the 3rd day after valve placement and recovered after one day treated by chest drain. This patient had dyspnea and wheezing after bronchoscopy and was treated by bronchodilator drugs. So, pneumothorax could relate to the bronchospasm. The previous studies have shown that pneumothorax after valve placement related to the changes of pulmonary volumes more than the procedure[6,11]. Two patients (5.88%) had might hemoptysis after 1 week and recovered after 3 days of internal therapy. The common later adverse events included the blocked valve because of mucus after 1 month and granulation around the valve after 2 months, with the rate following by 10.0% and 6.67%. By flexible bronchoscopy, we cleaned mucus and cut the granulation to solve these problems with valves. No valve was removed. There was no death in our study. In some other previous studies, severe complication and death were reported while other

complications were similar our results, however, the portion of valve removal in these studies was more than in our[15,16]. In general, the technique of bronchial valve placement via flexible bronchoscopy is acceptable safe, with the mild complications.

Conclusion

The unilateral bronchoscopic lung volume reduction with one-way valve (mainly one valve) in treatment of heterogeneous severe emphysema in stable COPD patients in Viet Nam have shown that this procedure is safe with encouraging initial results (increased lightly exercise capacity exercise capacity and FVC, decreased lightly the degree of dyspnea, RV and TLC at 3 months).

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