Original Article
Uniportal thoracoscopic lung volume reduction surgery using enhanced recovery protocol for patients with diffuse emphysema: a midterm follow-up

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Abstract: Background: Lung volume reduction surgery (LVRS) is effective for selected patients with heterogeneous emphysema, however, reports about its effect on homogeneous cases is limited. The aim of this study is to investigate the efficacy of LVRS for patients with diffuse emphysema. Patients and methods: The data of 38 patients with bilateral diffuse emphysema who underwent uniportal thoracoscopic LVRS using enhanced recovery protocol was collected. The resected lung tissues were stained for pathological diagnosis. Their pulmonary function was evaluated by forced expiratory volume in 1 second (FEV_1), St George's Respiratory Questionnaire (SGRQ), modified Medical Research Council dyspnea scale (mMRC), and 6 minute walk distance (6-MWD). They were followed up online using smartphone after the operation. Results: All the patients survived after the operation. Five of them (5/38, 13.2%) with diffuse pulmonary fibrosis suffered from exacerbation of respiratory dysfunction during the perioperative period. The major surgery-related complications included 16 cases of air leakage (longer than 7 days) and 9 cases of nosocomial pneumonia. The other 33 (33/38, 86.8%) patients responded to bilateral LVRS, as indicated by the improved FEV_1, SGRQ, and 6-MWD at 3, 6, 12, 18, 24 and 30 months after the operation (P < 0.05, respectively). On the 54-month follow up, a total of 20 responders (20/33, 60.6%) had been re-hospitalized asking for medical therapy. Conclusion: The efficacy of minimally invasive LVRS using enhanced recovery protocol on diffuse emphysema could last for at least 30 months. High-quality studies are still needed.

Keywords: Uniportal, lung volume reduction surgery (LVRS), diffuse emphysema, enhanced recovery after surgery (ERAS)

Introduction

Chronic obstructive pulmonary emphysema (COPE) is a progressive disease with gradually advanced dyspnea because of airflow limitation and hyperinflation [1]. The therapeutic approaches for severe COPE include bronchodilators inhalation, long-term oxygen therapy, bronchial thermal vapor ablation, plication of the most emphysematous lung regions, lung volume reduction surgery (LVRS), and bronchoscopic LVR using coils or one-way valves. However, coils or valves are not suitable for patients with collateral ventilation, which could be evaluated by computed tomography (CT)-fissure analysis and Chartis measurement [2]. For patients with respiratory failure after LVRS or medical therapy, lung transplantation rema-ins an option [3], but lung transplantation is obviously limited by deficiency of donors [4]. Besides, the severity of lung fibrosis is the key predictor of 90-day mortality after surgery for lung cancer patients [5].

LVRS is aimed to improve ventilation mechanics and exercise tolerance for COPE patients. The National Emphysema Treatment Trial (NETT) has confirmed the efficacy of LVRS in the early 2000 s, which may be sustained for several years, although it does not confer a survival advantage over medical therapy [6]. It is reported that endothelial function and blood pressure are improved 3 months after LVRS [7]. Moreover, repeated LVRS could improve lung function of emphysema patients for at least 12 months [8]. Strictly selected homogeneous

emphysema patients could also benefit from LVRS for several years [9]. Based on these findings, uniport thoracoscopic LVRS using enhanced recovery protocol probably a choice for diffuse emphysema patients with collateral ventilation. Herein, a retrospective cohort study was performed on diffuse emphysema patients who underwent bilateral LVRS, with the aim to investigate the safety and mid-term efficacy of this procedure.

Patients and methods

From 2013 to 2015, LVRS was carried out on 38 male patients (mean age: 67 years). Their major complaint on admission was persistent respiratory distress. All these patients were severely incapacitated after maximal medical therapy. Physiological and anatomical assessment with regard to their suitability for LVRS were performed before surgery. It included spirometery, gas transfer, lung volumes, chest X-ray, echocardiography, and chest CT scan.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for patients before uniport thoracoscopic LVRS was settled in accordance with the previous report [10]. In detail, bilateral diffuse emphysema patients with Medical Research Council (MRC) dyspnea index of grade 3 or 4, forced expiratory volume in 1 second (FEV_1) < 40% of predicted, residual volume (RV) > 150%, total lung capacity (TLC) > 115%, and FEV_1/forced vital capacity (FVC) ratio < 50% were included. Patients with giant bullae with atelectasis or a history of repeated pneumothorax were also selected for surgery. Target areas for resection were identified as severe emphysema and ventilation/perfusion mismatch, using high-resolution CT scan and perfusion/ventilation scintigraphy. In contrast, patients with $PaCO_2$ > 7 kPa, FEV_1 < 20% of predicted and 6-minute walk distance (6-MWD) less than 100 meters were excluded [10]. Finally, the data of these 38 patients was retrospectively reviewed. This study was approved by Institutional Review Board of Xuzhou Central Hospital, and written informed consents were obtained from all the patients.

Surgery-oriented quantification of the emphysema was calculated in high-resolution computed tomography (HRCT) images as emphysema index [11]. Target areas for resection with

ventilation and perfusion mismatch were identified preoperatively by scintigraphy. Their exercise capacity on admission was measured by pulmonary function test, 6-MWD and St George's Respiratory Questionnaire (SGRQ). Each item was reviewed by two practitioners independently, with the aim to diminish bias in data collection. Most patients refused repeated blood test for personal reasons. As a result, data of arterial blood gas analysis was insufficient.

Enhanced recovery protocol

Fast-track protocol in thoracic surgery was performed individually according to the cardiopulmonary function of the patients. First, they received 6-8 weeks of outpatient pulmonary rehabilitation and physical intervention before the operation. Meanwhile, they received medical treatment intravenously using antibiotic, bronchodilator and expectorant. Second, 500 mL of maltodextrin solution was administered orally 6 h and 2 h before surgery as nutritional support, respectively. Third, patient-controlled analgesia was utilized to alleviate postoperative pain for 48 h. Oral feeding was started 6 h after the surgery. The pulmonary rehabilitation program was implemented according to the procedures as reported [12].

Uniportal thoracoscopic LVRS

The same surgeon performed bilateral LVRS on these patients. Surgery was performed under general anesthesia with double-lumen endotracheal intubation. A single surgical incision measuring 2.0-3.5 cm was made through the 4th-5th intercostal space along the mid-axillary line according to the target area for resection. The hyper-inflated pulmonary tissue was resected using endoscopic staplers (Endo-GIA), followed by biological glue for reinforcement of the margin. A total of 20% to 30% of the most diseased portion in both lungs was resected. Next, two 26-French tubes were placed in the apex and bottom of the pleural cavity separately, through this single incision.

Two-stage uniportal thoracoscopic LVRS was carried out on 11 cases with an interval of 3 months, while a single-stage bilateral LVRS (Bi-LVRS) was performed on the other 27 cases, respectively. The side that had worse ventilation/perfusion mismatch underwent LVRS first.

Table 1. Baseline profile of the patients before LVRS

Characteristics	Baseline (n=38)
Age, years	67.7±6.5
Body mass index, kg/m^2	24.4±2.0
Smoking history, pack-year	17.3±14.6
Non-smoker	8
≤ 20 pack-year	15
> 20 pack-year	15
SGRQ score	56.7±4.5
mMRC	2.5±0.6
6-MWD, meters	238.1±12.6
FEV$_1$, L	1.1±0.1
FEV$_1$, % predicted	36.4±3.0
History of pulmonary tuberculosis	4
Comorbidity	
Systemic hypertension	1
Coronary heart disease	2
Diabetes Mellitus	1
Obesity (BMI ≥ 28 according to Chinese Standard)	3
Silicosis	1
Pulmonary encephalopathy	1
α1 antitrypsin deficiency	1

Note: Data are presented as n (%), mean ± SD. Abbreviations: FEV$_1$, forced expiratory volume in 1 second; 6 MWD, 6-min walk distance; SGRQ, St George's Respiratory Questionnaire; mMRC, modified Medical Research Council dyspnea scale.

Subsequently, intensive care unit (ICU) stay, postoperative hospital stay and perioperative complications such as hemoptysis, exacerbation of dyspnea, pneumonia, and duration of air leak were recorded for safety evaluation.

Internet-based long-term follow-up

Surveys with regards to their perception of dyspnea (SGRQ and mMRC) and physical intervention were carried out by smartphone using WeChat, a free mobile chatting software, for 30-54 months. They also underwent spirometry, pulmonary function (FEV$_1$) and exercise testing (6-MWD) in local clinics. The physical interventions included Yoga, Tai Chi, and Baduanjin, while the psychological interventions were cognitive-behavior therapy (CBT) and symptom-triggered adjustment of oral medication. During this period, patients with decreased pulmonary function asking for additional therapy were re-hospitalized. The proportion of the responded patients during the follow-up was calculated using Kaplan-Meier analysis method.

Statistical analysis

Continuous variables were recorded as means ± standard deviation ($\bar{x} \pm s$), and then student's t test, ANOVA of repeated measurement data or non-parametric methods such as Mann-Whitney U test was applied for comparison of quantitative data. The statistical software SPSS, version 19.0 (IBM, Armonk, NY, USA) was utilized. $P < 0.05$ was considered statistically significant.

Results

The baseline characteristics of the 38 patients were shown in **Table 1**. Four patients had a history of pulmonary tuberculosis, and 1 patient had silicosis. Another case was diagnosed as α1 antitrypsin deficiency. Fifteen patients had a smoking history for more than 20 pack-years. The baseline FEV$_1$, SGRQ, mMRC and 6-MWD before the operation were (1.2±0.1) L, (56.8±4.5) scores, (2.5±0.6) scores, and (238.1±12.6) meters, respectively.

Perioperative events

The operations were conducted without conversion to thoracotomy. There was no 30-day mortality. The mean operation time, chest drainage time, ICU stay and postoperative hospital stay was (75.3±21.5) min, (9.4±3.5) d, (1.7±1.1) d, and (16.3±5.9) d, respectively. The perioperative adverse events included 5 cases of exacerbation of dyspnea, 16 cases of air leak longer than 7 days, 9 cases of pneumonia diagnosed by productive cough and chest X-ray, 1 case of atelectasis, and 7 cases of supraventricular arrhythmia.

The efficacy during the follow up

All these patients demonstrated re-expansion of the residual pulmonary tissue after LVRS. However, five (5/38, 13.2%) patients with pulmonary fibrosis, silicosis or α1 antitrypsin deficiency suffered from more severe dyspnea

Table 2. Pulmonary function parameters of the 33 responded patients before and after LVRS

Time	FEV_1 (L)	mMRC	SGRQ	6-MWD (m)
Before LVRS	1.1±0.1	2.1±0.7	56.5±4.6	235.4±12.8
After LVRS, months				
3	1.3±0.2*	1.6±0.5*	47.6±7.4*	277.6±25.3*
6	1.4±0.1*	1.5±0.6*	46.6±4.7*	294.4±21.2*
12	1.4±0.2*	1.6±0.6*	46.5±5.6*	303.6±28.7*
18	1.3±0.2*	1.7±0.7*	48.7±4.6*	304.4±27.2*
24	1.3±0.1*	1.7±0.6*	50.1±4.5*	268.1±20.1*
30	1.2±0.2*	1.8±0.7*	50.9±4.6*	255.3±20.5*

Note: The data was presented as mean ± standard deviation. *$P < 0.05$, compared with the data before surgery.
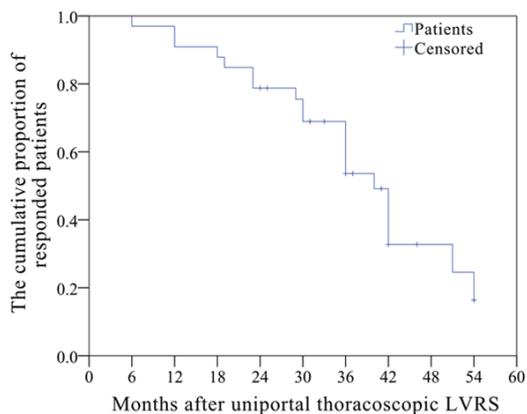
Figure 1. The cumulative proportion of responded patients after LVRS using Kaplan-Meier analysis method.

after surgery, who needed endotracheal intubation and prolonged ICU stay. These 5 cases were excluded for further study.

The other 33 cases (33/38, 86.8%) who responded to LVRS completed a 30-month follow-up online. There was a significant increase in FEV1, SGRQ, and 6-MWD at 3, 6, 12, 18, 24, 30 months respectively after surgery, as shown in **Table 2**. Specifically, they demonstrated significantly improved FEV1 [(1.1±0.1) L vs (1.3±0.2) L, P < 0.001], longer 6-MWD [(235.4±12.8) m vs (277.6±25.3) m, P < 0.001], and decreased SGRQ [(56.5±4.6) vs (47.6±7.4), P < 0.001] at 3 months, as compared with the baseline before LVRS. However, these benefits were gradually diminished as time went on.

Furthermore, on the 54-month follow up, a total of 20 patients (20/33, 60.6%) had been re-hospitalized, who required urgent medical treatment. The proportion of responders was evalu-

ated using Kaplan-Meier analysis method, as shown in **Figure 1**. The mean time of these 33 cases from LVRS to re-hospitalization was (37.9± 2.6) months (95% confidence interval: 32.8-43.1), while the median time from surgery to re-admission was (40.0±3.1) months (95% confidence interval: 33.8-46.1).

Discussion

In the era of precision medicine and fast track thoracic surgery, uniportal thoracoscopic LVRS could be considered for selected patients with severe diffuse emphysema, and it might provide a longer waiting period before lung transplantation. Concerns about the safety of bilateral LVRS have limited its application. A retrospective analysis indicates that 36% of the patients have improved FEV_1 after bilateral LVRS at the 5-year follow-up [13]. However, LVRS is underused probably because of the heterogeneity in response, moreover, sometimes it is difficult to predict who will benefit from LVRS. In our retrospective cohort study, 86.8% of patients with diffuse emphysema responded to LVRS for at least 30 months. Accordingly, there are several issues need to be elucidated.

The first issue is the identification of COPE patients who might benefit from LVRS. The distribution pattern and fissure integrity of the emphysema are essential. It is reported that cases with upper-lobe predominant, heterogeneous emphysema could gain favorable outcomes after LVRS [6]. The most common adverse events are air leak, pneumonia, and cardiovascular morbidity [14]. Incomplete lobar fissures or functional inter-lobar shunts should be confirmed before the surgery [15]. Lung perfusion scintigraphy and HRCT could be utilized to identify responders to LVRS [16]. Patients with FEV_1 less than 20% predicted, homogeneous emphysema, or carbon monoxide diffusion capacity (DLCO) less than 20% predicted have a mortality rate of 16%, therefore, they should be considered non-eligible for LVRS [17], although patients with shorter 6-MWD and more hyperinflation are likely to respond to LVRS [18]. Furthermore, pulmonary rehabilitation may improve the exercise capacity of emphysema individuals [19]. As shown in this

study, patients with diffuse pulmonary fibrosis because of tuberculosis or silicosis probably could not benefit from LVRS. The extent of fibrosis could be evaluated by objective quantitative CT and thin-section CT [20, 21].

Next, the procedures of LVRS for patients with bilateral diffuse COPE include unilateral, symptom-triggered sequential bilateral, and single-stage bilateral LVRS. The optimal choice is controversial. As indicated in this study, the FEV_1, 6MWD, and SGRQ scores were improved significantly after bilateral LVRS. In addition, the Kaplain-Meier analysis indicated that the efficacy could be sustained for nearly 40 months.

Although both unilateral and Bi-LVRS indicate similar efficacy in terms of cardiopulmonary circulation improvement [22], Bi-LVRS yields superior spirometry, functional capacity, oxygenation, and health-related quality of life as compared with the unilateral approach [23, 24], followed by better 2-year overall survival [25]. Similarly, a study indicates a significant improvement of BODE index (body mass index, airflow obstruction, dyspnea, and exercise capacity) and satisfactory survival from contralateral LVRS [26]. Therefore, Bi-LVRS should be considered for most patients [27]. However, unilateral LVRS is correlated with lower morbidity, earlier discharge and slower decline in physiological benefit comparing with Bi-LVRS [28]. Two-stage bilateral LVRS probably lead to a more prolonged overall benefit than single-stage bilateral LVRS [29]. Sequential LVRS has potential advantages comparing with single-stage procedure [11]. However, surgery on the contralateral side should be avoided if the patient shows decreased lung function after unilateral LVRS.

Moreover, LVRS-related morbidity contributes to the presence of bronchoscopic therapy using one-way endobronchial valve or coil. Patients with intact interlobar fissures show satisfactory efficacy after unilateral lobar occlusion by valves [30]. Coils induces regional reduction of parenchymal volume and recoil of the restoring lung tissue, which could improve the exercise capacity of severe emphysema patients [31]. Furthermore, uniportal thoracoscopic LVRS could offer reduced pain and faster recovery, as compared with multi-portal VATS [32].

Five patients with diffuse pulmonary fibrosis in this study does not indicate benefits from LVRS. Thus, alpha-1 antitrypsin deficiency, tuberculosis and silicosis might be considered as contraindications of LVRS. Alpha-1 proteinase inhibitor shows efficacy for emphysema patients with severe α1 antitrypsin deficiency in slowing disease progression [33]. Therefore, individualized indications of LVRS for patients with diffuse COPE need to be established.

Limitations of this retrospective cohort study

This retrospective analysis is limited by its small sample significantly. First, the selection of patients with severe diffuse emphysema for LVRS is difficult. This procedure is considered for selected patients in our hospital because several retrospective reports indicate the benefit of LVRS for diffuse cases [9, 10]. As indicated in this study, five patients suffered from exacerbation of dyspnea after the operation. In other words, patients may take the risk of pulmonary failure during the surgery. Second, a significant number of patients could not endure LVRS because of their poor cardiopulmonary functions on admission. Third, limitations of this study also include the small sample of patients with long-term follow-up, potential bias and under-reporting due to remote assessment online, lacking a control-group, and absence of arterial blood gas analysis.

In summary, the efficacy of bilateral uniportal thoracoscopic LVRS using enhanced recovery protocol in selected patients with diffuse emphysema is presented. The benefit could last for at least 30 months. However, patients with diffuse pulmonary fibrosis, silicosis or α1 antitrypsin deficiency are probably not suitable for LVRS. High-quality studies are warranted.

Disclosure of conflict of interest

None.

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