

Importance of bronchoscopic lung volume reduction coil therapy in potential candidates for lung transplantation

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Summary

Bronchoscopic lung volume reduction (BLVR) coil treatment is an alternative and promising treatment modality for selected severe emphysema patients. The main indication of this treatment modality is a forced expiration volume in one second (FEV₁) of 15-45% and a residual volume (RV) > 175%. The aim of this study was to investigate the efficacy of BLVR coil therapy in patients with end-stage emphysema who were potential candidates for lung transplantation and had FEV₁ values less than 25%. Twenty-one patients who underwent bilateral BLVR coil therapy between September 2013 and May 2015 were retrospectively reviewed. We compared the changes in clinical and laboratory parameters at the baseline and 12 months after the treatment. Twelve months after the bilateral BLVR coil treatment, we observed an average increase in FEV₁ (110 mL and 4.6%), a decrease in residual volume (660 mL and 33%), and an increase in 6-minute walk tests (67 m). The most common complications were chronic obstructive pulmonary disease exacerbation (47.6%) and pneumonia (23.8%). All patients tolerated the general anesthesia and procedure very well. BLVR coil therapy is safe and effective in patients with end-stage emphysema, who are potential candidates for lung transplantation within a short to medium period. The complication rates of this treatment were not different from those of the other coil treatments, and the improvements in the clinical parameters after the treatment resulted in gaining time for lung transplantation. Future research for evaluating the long-term efficacy of BLVR coil therapy in these patients is essential.

Keywords: Lung volume reduction, coil, emphysema, lung transplantation, low FEV₁

1. Introduction

Emphysema is one of the two manifestations of chronic obstructive pulmonary disease (COPD). Chronic inflammation and permanent parenchymal damage play an important role in the progress of this disease. The loss of elastic recoil of the lungs, hyperinflation, and air-trapping also disrupt the gas-exchange in the later course of the disease (1). This results in a gradual decrease in the exercise capacity and quality of life of patients and shortness of breath. Patients with end-stage emphysema

show an increase in residual volume (RV) and respiratory muscle dysfunction due to diaphragmatic and thoracic compression (2). This condition has no definitive treatment and medical treatment options are limited, which include beta-2-mimetic and anticholinergic inhaler treatments, smoking cessation, glucocorticoids, roflumilast, mucolytics, physical and pulmonary rehabilitation for increasing the exercise capacity, and long-term supplemental oxygen therapy (3).

In the last 10 years, surgical options for the treatment of this condition have been considered because the mechanical problems of the patients cannot be treated with medications. Removal of the damaged lung area by lung volume reduction surgery contributes to the improvement of the quality of life, exercise capacity, and respiratory function in patients (4). In addition, the National Emphysema Treatment Trial emphasized the importance of patient selection due

Released online in J-STAGE as advance publication August 28, 2018.

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to the high risk of postoperative pulmonary and non-pulmonary complications and mortality (5).

In recent years, bronchoscopic lung volume reduction (BLVR) has become an alternative and promising treatment modality for selected severe emphysema patients (6). The loss of elastic recoil and hyperinflation caused by the emphysema can be treated with BLVR using the coil, valve, or thermal vapor ablation method (7-9). The main indications of this treatment modality are a forced expiration volume in one second (FEV₁) of 15-45% and an RV of more than 175% in patients with emphysema diagnosed by computed tomography (CT). Therefore, all patients are in stages 3 and 4 according to the COPD Gold classification (10). However, if the patients have interlobar collateral ventilation, the best option is BLVR coil treatment. This treatment can be applied to both heterogeneous and homogenous emphysema.

The targeted lobe is implanted with an average of 10-14 coils using a bronchoscope. This is followed by a second session of implantation of coils in the other lung, which is performed within 4-8 weeks. The goal of this treatment is to reduce the air trapping and hyperinflation, and thus reduce the RV of the lungs. Studies have shown that this treatment is useful and safe in the short and medium term (6,7). Furthermore, improvements in quality of life, 6-minute walk test (6-MWT), and pulmonary function tests (PFT) were reported in recent studies (7,11,12). In addition, these treatments were also applied to patients who were potential candidates for lung transplantation, with very low FEV₁ values. According to the guidelines published by the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation in 2014, COPD patients with FEV₁ < 25% are candidates for lung transplantation, and those with FEV₁ < 15-20% are recommended to be included in the transplantation list (13).

The aim of this study was to investigate the efficacy of BLVR coil therapy in patients with end-stage emphysema who were potential candidates for lung transplantation and had FEV₁ values less than 25%.

2. Materials and Methods

2.1. Study design

Our study was a retrospective and observational study. Patients who were treated for BLVR coil treatment in the Department of Pneumology of the Şifa University Hospital, Bornova-Izmir, Turkey were included in the study. The inclusion and exclusion criteria were similar to those of some of the recent studies in the literature (6,7,11,12). Inclusion criteria were as follows: (i) bilateral emphysema diagnosed by CT; (ii) post-bronchodilator (salbutamol) FEV₁ of 15-45%; (iii) RV > 175%; (iv) arterial partial pressure of carbon

dioxide (PaCO₂) < 55 mmHg; (v) 6-MWT: 150-450 m; (vi) modified Medical Research Council scores ≥ 2; (vii) smoking cessation for > 8 weeks before treatment. Exclusion criteria were as follows: (i) post-bronchodilator (salbutamol) change in FEV₁ > 20% or diagnosis of asthma; (ii) COPD exacerbation (more than > 2 hospitalizations per year); (iii) bullous lesion on a single lung of more than one-third field or more than 4 cm; (iv) pulmonary artery pressure > 50 mmHg; (v) diagnosis of bronchiectasis or lung cancer; (vi) use of oral anticoagulant. The only difference in the inclusion criteria in our study with respect to the above-mentioned similar studies was the FEV₁ value of < 25%. In our study, the patients with FEV₁ between 25-45% were excluded. The flow of the study is presented in Figure 1. The study was conducted according to good clinical practice and the Declaration of Helsinki. Ethical committee approval was obtained from the local Ethics Committee in Izmir/Turkey

2.2. Data collection

Data from all patients who received BLVR coil treatment were selected from the electronic hospital data system and evaluated retrospectively, including the following: (1) epidemiological data (age, sex, smoking history, and use of long-term oxygen at home); (2) clinical data (such as symptoms, type of emphysema, and stage of COPD); (3) procedure data (target lobe, duration, number of coils, and complications); (4) laboratory data (arterial blood gas analyses, PFT parameters, and 6-MWT); (5) post-procedure data (admission to polyclinics, hospitalizations, and complications). The PFT parameters were evaluated with a Body Box 5500 Series pulmonary function testing system (Medisoft, Sorinnes, Belgium) according to ERS guidelines. The arterial blood gas samples were taken when patients were in a clinically stable condition and breathing room air. The baseline and 12-month follow-up data of the patients who underwent bilateral BLVR coil treatment between September 2013 and May 2015 were collected from the medical records.

2.3. BLVR coil procedure

Homogeneous or heterogeneous emphysema of all patients was diagnosed by CT, and the target lobe was selected under the guidance of ventilation/perfusion scintigraphy. All patients were in clinically stable conditions, under optimal medical and inhaler treatment, and were included in the necessary pulmonary rehabilitation program before the treatment. The patients also received recommendations for improving their nutritional status. All RePneu coils (PneumRx Inc., Mountain View, CA, USA) were implanted via a bronchoscopic approach with fluoroscopic guidance under general anesthesia. Each

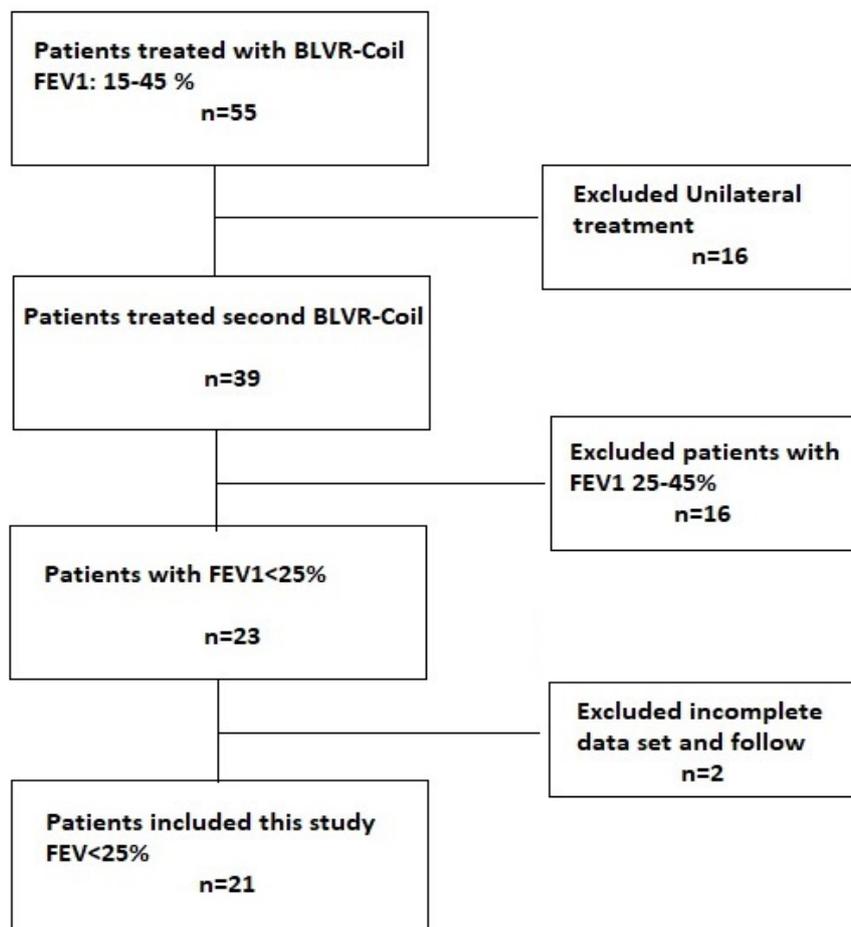


Figure 1. Case Selection Procedure. Twenty-one end-stage emphysema patients with a FEV₁ value of < 25% were included in the study.

patient received an average of 10 (range: 8-13) coils per lobe as standard treatment, and a second procedure for implantation of coils in the other lung was performed within 4 to 8 weeks.

2.4. Statistical analysis

The descriptive data are presented as the average \pm standard deviation or median (range). The categorized data are presented as absolute number with percentage. The changes between the baseline and 12-month data were analyzed using the paired *t*-test for normal distribution parameters and the Mann-Whitney *U* test for non-normal distribution parameters. The statistical significance threshold of *p* value was < 0.05 for the paired *t*-Test and < 0.01 for the Mann-Whitney *U* Test. All data were analyzed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA).

The minimum important difference (MID) was also reported to be 100 mL and 10% for FEV₁ (14), 400 mL for RV (15), 26 m for 6-MWT (16), and four points for St. George's Respiratory Questionnaire (17) in the previous studies.

3. Results

3.1. Demographic data at baseline

A total of 42 BLVR coil procedures were performed in 21 patients. The mean age of the 21 patients (3 women and 18 men) who participated in the study was 63.76 ± 8.2 years (range: 47-83 years). Of the total patients, 62% had homogenous emphysema and 38% had heterogenous emphysema. The body mass indexes of the patients were 25.25 ± 4.5 kg/m². The average level of cigarette consumption was 30.4 packs/year. Preoperatively, six patients (28.5%) had hypoxic respiratory failure and were on long-term oxygen therapy, and 11 patients (52.3%) had mild hypercapnic respiratory failure. At the baseline before treatment, the mean FEV₁ was 0.59 ± 0.10 L, which was equal to $20.5 \pm 3.3\%$ of the predicted value. The mean RV was 5.36 ± 0.60 L, which was equal to $238 \pm 34.2\%$ of the predicted value. The mean RV/total lung capacity ratio was $66.1 \pm 4.9\%$ of the predicted value. The mean arterial partial pressure of oxygen (PaO₂) was 58.0 ± 9.3 mmHg, and the mean PaCO₂ was 45.7 ± 6.3 mmHg. The mean distance walked during

the 6-MWT was 270 ± 64 m (Table 1). A total of 422 coils were used in 42 procedures (average of 10, range: 8-13), with a mean duration of 21.7 ± 8.1 min. The most common lobes for the implantation of coils were the left upper (35.7%) and the right upper (38.0%) lobes. The

coils were implanted to the two lower lobes of the lungs in 26.1% of the patients. After the procedure, the patients stayed in the hospital for an average of 1.5 ± 0.6 days (Table 2).

Table 1. Patient demographics at baseline

Number of Patients	21
Gender F/M	3/18
Age, years	63.76 ± 8.2
Body mass index, kg/m ²	25.25 ± 4.5
Type of Emphysema	
Homogeneous	13 (62%)
Heterogeneous	8 (38%)
ASA-Status	
Group II	1 (4.7%)
Group III	11 (53.3%)
Group IV	9 (42.8%)
Pulmonary Function	
FEV ₁ (l)	0.59 ± 0.1
FEV ₁ (%)	20.5 ± 3.3
FVC (l)	1.31 ± 0.3
RV	5.36 ± 0.6
RV (%)	238 ± 34
RV / TLC (%)	66.1 ± 4.9
6-min walk tests (m)	270 ± 64
Blood gase	
pH	7.37 ± 0.4
PaO ₂ , mmHg	58.0 ± 9.3
PaCO ₂ , mmHg	45.7 ± 6.3
O ₂ sat, %	88.3 ± 7.6
Respiratory Failure	
Hypoxic	6 (28.5%)
Hypercapnic (mild)	11(52.3%)

FEV₁, a forced expiration volume in 1 s; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood, LTOT, Long-term oxygen therapy; ASA, American Society of Anesthesiologists status.

Table 2. BLVR coil procedural results

Number of Procedures, <i>n</i>	42
Right upper lobe, <i>n</i>	15 (35.7%)
Right under lobe, <i>n</i>	6 (14.2%)
Left upper lobe, <i>n</i>	16 (38.0%)
Left under lobe, <i>n</i>	5 (11.9%)
Procedure time, min	21.7 ± 8.1
Number of Coils, <i>n</i>	422
Coils per procedure, <i>n</i>	10.0 (range 8-13)
Hospital stay, days	1.5 ± 0.6

3.2. Adverse events during the procedure

During the procedure, unexpected bronchial secretion was aspirated in 19.0% of the patients, and mild bleeding was observed in 9.5% patients. The mild bleeding was easily controlled by the application of saline and local adrenaline. Due to the lack of proper localization of the coils, some coils were successfully removed and repositioned in four (9.5%) patients. During this repositioning, the duration of the procedure was prolonged. Instability of vital parameters was observed in one patient, but the procedure was terminated successfully. During the procedure, pneumothorax or extrapulmonary complications were not observed. All patients tolerated the general anesthesia very well (Table 3).

3.3. Efficacy after 12 months

A significant improvements in the FEV₁ (an average increase of 110 mL, 4.6%), and RV (a average decrease of 0.66 L, 33.0%) were observed in all patients 12 months after bilateral BLVR coil procedure (Figure 2). Compared with the baseline, a significant improvement in the PaO₂ (an increase of 15.5 mmHg), arterial oxygen saturation (an increase of 5.6%), and 6-MWT results (an average increase of 67 m, 24.8%) were also observed 12 months after the BLVR coil treatment (Figure 3). However, no statistically significant improvements were observed in the arterial pH or PaCO₂ (Table 4).

Table 3. Adverse events during procedure

Aspiration of bronchial sekretion	8 (19.0%)
Mild haemorrhage	8 (19.0%)
Removal and Repositioning of Coils	4 (9.5%)
Prolonged procedure	2 (4.7%)
Instability of vital parameter	1 (2.3%)
Pneumothorax	0 (0%)

Events were scored for all 42 procedures in 21 patients.

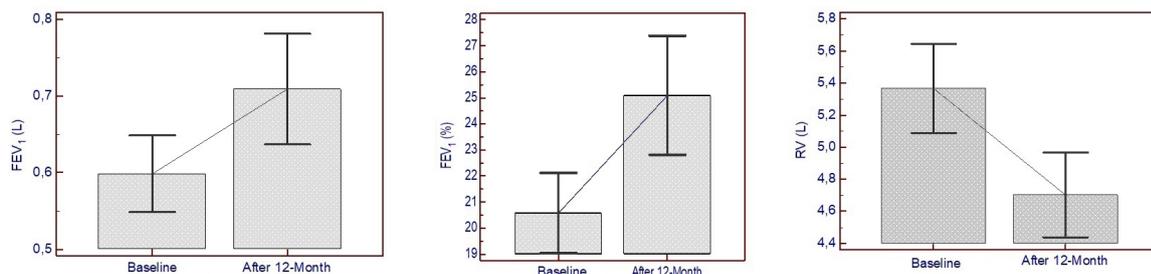


Figure 2. Comparison of baseline and 12-month pulmonary function parameters after bilateral lung volume reduction coil treatment. A significant improvements in the FEV₁ (an average increase of 110 mL, 4.6%), and RV (a average decrease of 0.66 L, 33.0%) were observed in all patients 12 months after bilateral BLVR coil procedure.

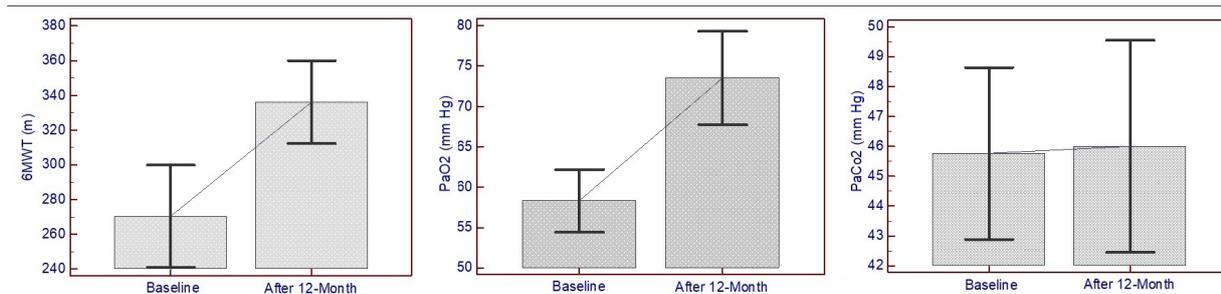


Figure 3. Comparison of baseline and 12-month 6-minute walk test (6MWT), and blood gas parameters after bilateral lung volume reduction coil treatment. A significant improvement in the PaO₂ (an increase of 15.5 mmHg), arterial oxygen saturation (an increase of 5.6%), and 6-MWT results (an average increase of 67 m, 24.8%) were also observed 12 months after the BLVR coil treatment.

Table 4. Comparison of pulmonary function parameters in 12-months follow-up

Test	Baseline	12 Months	Diff.	p-value
FEV ₁ , L	0.59 ± 0.10	0.70 ± 0.15	+ 0.11	0.001
FEV ₁ , %	20.5 ± 3.3	25.1 ± 5.0	+ 4.6	0.001
RV, L	5.36 ± 0.6	4.70 ± 0.5	- 0.66	0.001
RV, %	238 ± 34	205 ± 33.2	- 33	0.001
RV/TLC, %	66.1 ± 4.9	58.8 ± 5.0	- 7.3	0.001
6-MWT, m	270 ± 64	337 ± 49	+ 67	0.001
pH	7.37 ± 0.4	7.39 ± 0.5	+ 0.02	0.135
PO ₂ , mmHg	58.0 ± 9.3	73.5 ± 12.7	+ 15.5	0.001
PCO ₂ , mmHg	44.7 ± 6.3	46.0 ± 7.8	+ 1.3	0.896
O ₂ sat, %	88.3 ± 7.6	93.9 ± 2.4	+ 5.6	0.001

Data are presented as mean ± standard deviation. See Table 1 legend for expansion of other abbreviation.

3.4. Complications during the 12-month follow-Up

During the 12-month follow-up, mild side effects were observed in 33.3% of patients. These included cough (28.5%), mild hemoptysis (23.8%), pleuritic chest pain (9.5%), and hiccups (4.7%). Among the more serious complications, COPD exacerbations (47.6%) were the commonest. Pneumonia or procedure-related pneumonitis (23.8%) was the second most common complication. Among patients with these two major complications, 33.1% required hospitalization. None of the patients died or had pneumothorax or respiratory failure (Table 5).

4. Discussion

This retrospective study was performed on 21 patients with end-stage emphysema who were potential candidates for lung transplantation, with FEV₁ value of < 25%. Our study results indicate that BLVR coil treatment is effective and safe in this group of patients.

The main indication for BLVR coil treatment is an FEV₁ of 15-45% and RV > 175%, so all patients are at COPD Gold III and Gold IV levels. The studies conducted between in 2012-2018 show that the included patients have baseline mean FEV₁ between 0.58 and 0.91 L and between 22% and 33% predicted (Table 6) (7,11,12,18-26). Only one study was performed in

Table 5. Adverse events within 12-month follow-up

Mild events, n (%)	
Cough	6 (28.5%)
Pleuritic Pain	5 (23.8%)
Haemoptysis	2 (9.5%)
Hiccup	1 (4.7%)
Serious events, n (%)	
Exacerbation COPD	10 (47.6%)
Hospitalization, any reason	7 (33.1%)
Pneumonia, treated lung	5 (23.8%)
Pneumonia, other lung	1 (4.7%)
Pneumothorax	0 (0%)
Death	0 (0%)

Events were scored for all 42 procedures in 21 patients.

patients with FEV₁ < 20% (26). In a recent study, the 15-year survival rate of COPD Gold III patients was 5.3% and that of COPD Gold IV was 0% (27). It was also stated that in patients with an FEV₁ of less than 30%, the 2-year and 5-year survival rates were 65% and 30%, respectively (28). However, COPD patients have a lower priority for transplantation, and therefore, the time spent on the waiting list is usually very long (28). For this reason, it is necessary for these patients to gain time while waiting for transplantation. During this waiting period, besides controlling the symptoms, nutritional support, measures to increase the quality of life, and additional time-saving treatments are needed. Thus, the patient's FEV₁ value plays an important role

Table 6. Study's Baseline FEV1 in the Literature

Author	Year	n	Follow-up, M	FEV ₁ , L	FEV ₁ , % pred
Slebos <i>et al.</i> (7)	2012	16	6	0.72 ± 0.16	28.7 ± 7.1
RESET study (18)	2013	23	3	0.72	27.1
Klooster <i>et al.</i> (19)	2014	10	6	0.58	22.0
Deslee <i>et al.</i> (20)	2014	34	12	0.83 ± 0.25	30.1 ± 6.3
Hartman <i>et al.</i> (21)	2015	38	36	*	27.0
Zoumot <i>et al.</i> (22)	2015	45	12	0.76 ± 0.20	28.3 ± 8.0
Kloth <i>et al.</i> (23)	2016	30	6	0.91 ± 0.32	33.6 ± 9.0
RENEW (24)	2016	158	12	0.71 ± 0.20	25.7 ± 6.3
REVOLENS (11)	2017	50	12	0.75 ± 0.25	25.7 ± 7.5
Kontogianni (25)	2017	86	12	0.71 ± 0.21	27.0 ± 7.0
Gülksen <i>et al.</i> (12)	2017	40	6	0.68 ± 0.22	26.3 ± 9.1
Simon <i>et al.</i> (26)	2018	33	3	0.46 ± 0.12	15.0 ± 3.0
Our Study	2018	21	12	0.59 ± 0.10	20.5 ± 3.3

M, month; FEV₁, a forced expiration volume in 1 s; pred, predicted. * no data.

in determining the mortality and the BLVR treatment act as an intermediate treatment and increase the time patients have to prepare for transplantation. When the long-term efficacy of BLVR treatments is confirmed by future investigations, emphysema patients may not have any need for lung transplantation. In addition, the fewer number of donor lungs available can be used for transplantation in those with more serious diseases.

BLVR coil therapy has been increasingly used in recent years, and studies have shown improvement in 6-MWT, PFT parameters, and quality of life with this treatment (11,12,18-26). This treatment method is an alternative and effective treatment option for emphysema patients. The most recent and largest studies are the REVOLENS study and the RENEW study (11,24). In these studies, 50 patients and 158 patients were treated with BLVR coil therapy, respectively. In the REVOLENS study, the baseline mean FEV₁ value was 0.75 ± 0.25 L and 25.7 ± 7.5% predicted, and in the RENEW study, it was 0.71 ± 0.20 L and 25.7 ± 6.3% predicted. In both studies, improvements in PFT parameters, quality of life, and exercise capacity were reported (11,24). However, patients with FEV₁ of less than 25% and candidates for lung transplantation have not been studied separately. In the study involving only 33 patients by Simon *et al.* (26), a group of patients with a mean FEV₁ of 15 ± 3% was evaluated. A 100-mL increase in FEV₁, a 440-mL decrease in RV, and a 48-m increase in the 6-MWT were reported. The study concluded that BLVR coil therapy was safe in this patient group. In our study, patients with FEV₁ below 25% were investigated for 12 months. The results of our study were comparable with those of the above-mentioned studies, and it was also observed that the patients who are transplantation candidates responded well to this treatment. In addition, improvements in PaO₂ and arterial oxygen saturation values were also observed in our study. In our study, all important MID values increased significantly compared to the above-mentioned studies.

Patients with end-stage emphysema and COPD Gold IV are known to be at high risk for surgical treatments (5). Perioperative and postoperative risk increased due to low FEV₁ and diffusion capacities, restricted mobility, and increase in oxygen requirement. It has been reported that in short and medium-term studies, the BLVR coil treatments are safe with less complications. In the REVOLENS and RENEW studies, the frequencies of COPD exacerbation, pneumonia, and pneumothorax were 26%, 18%, and 2%, and 27.7%, 20%, and 9.7%, respectively (11,24). The mortality rate in the follow-up period was 8% and 6.5%, respectively (11,24). In one study, the mean complication rates of BLVR coil treatment were reported as 17-87% for COPD exacerbations, 5-46% for pneumonia, 6.0-11.6% for pneumothorax, and 0-8% for death (12). In our study, the complications during the procedure and during the follow-up time were found to be 33.3% and 61.9%, respectively. The most common complications during the procedure were mild hemoptysis (19.9%) and re-coiling (9.5%). No respiratory failure, pneumothorax, or death occurred during or after the procedure. During the 12-month follow-up period, exacerbations of COPD were found in 47.6% and pneumonia in 23.8%, and the findings were evaluated in accordance with those of similar studies in the literature. Thus, the end-stage emphysema patients who were candidates for transplantation were found to benefit from BLVR coil therapy with no serious complications, and it also provided time for these patients to prepare for lung transplantation.

The longest BLVR coil study was done by Hartman *et al.* (21). Patients with BLVR coil were followed-up for three years. The patients were classified as responders and non-responders. While BLVR coil treatment was found useful for a large group of patients one year later, it was reported that the mean of the general clinical parameters returned to baseline values at three years (21). This led to re-coiling, and a pilot study in a small patient group ($n = 8$) was conducted in

2017 by Hartmann *et al.*, in which patients got little or no benefit from re-treatment (29). However, there is a need for more extensive and larger studies to confirm these results. The results of both these studies show clearly that the patient for lung transplant gains an average time of three years with BLVR coil therapy. In our study, the FEV₁% predicted value increased from 20.1% to 25.1% at the end of first year. This result shows clearly that this group of patients has gained time for transplantation preparation.

There are several factors that limit the applicability of our study results such as, a relatively small group of patients, restricted data from only one center, and potential bias due to the nature and design of the retrospective study. Therefore, our findings cannot be generalized for all patients. However, our study results can add to the medical literature as only a few studies have been conducted on this topic. Our study showed that the BLVR coil treatment was safe and effective in this subgroup of patients with end-stage emphysema who were potential candidates for lung transplantation; this has also resulted in gaining time for lung transplantation. All other results of our study were similar to those of the few reported studies in the literature.

5. Conclusion

BLVR coil therapy is safe and effective in patients with end-stage emphysema, who are potential candidates for lung transplantation within a short to medium period. The complication rates of this treatment were not different from other coil treatments, and the improvements in clinical parameters after the treatment resulted in gaining time for lung transplantation. Future research for the evaluation of long-term efficacy of BLVR coil treatment in end-stage emphysema patients is essential.

Note: The author have stated explicitly that there are no conflicts of interest in connection with this article.

A.G. Study concept and design, data collection, analysis and interpretation of data, manuscript preparation, and drafting of the manuscript.

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(Received June 19, 2018; Revised August 15, 2018; Accepted August 17, 2018)