

Original Article

Complications related to endoscopic lung volume reduction for emphysema with endobronchial valves: results of a multicenter study

Alfonso Fiorelli^{1#}, Antonio D'Andrilli^{2#}, Michela Bezzi³, Mohsen Ibrahim², Marco Anile⁴, Daniele Diso⁴, Giacomo Cusumano⁵, Alberto Terminella⁵, Valentina Luzzi³, Margherita Innocenti³, Mauro Novali⁶, Emanuele Carelli¹, Chiara Freda¹, Giovanni Natale¹, Valentina Peritore², Camilla Poggi⁴, Giuseppe Failla⁷, Marco Basile⁷, Emilia Mazzucca⁷, Serena Conforti⁸, Nicola Serra⁹, Massimo Torre⁸, Federico Venuta⁴, Erino Angelo Rendina², Mario Santini¹, Claudio Andreotti²

¹Thoracic Surgery Unit, Università della Campania "Luigi Vanvitelli", Naples, Italy; ²Thoracic Surgery Unit, Università La Sapienza, Sant'Andrea Hospital, Rome, Italy; ³Interventional Pneumology Unit, Policlinico Firenze, Florence, Italy; ⁴Thoracic Surgery Unit, Università La Sapienza, Policlinico Hospital, Rome, Italy; ⁵Thoracic Surgery Unit, Policlinico Vittorio Emanuele Hospital, Catania, Italy; ⁶Interventional Pneumology Unit, Spedili Civili Brescia, Brescia, Italy; ⁷Interventional Pneumology Unit, Ospedale Civico Palermo, Palermo, Italy; ⁸Thoracic Surgery Unit, Ospedale Niguarda, Milan, Italy; ⁹Department of Pediatrics, University Federico II of Naples, Naples, Italy

Contributions: (I) Conception and design: A Fiorelli, A D'Andrilli, C Andreotti, M Bezzi; (II) Administrative support: N Serra; (III) Provision of study materials or patients: M Ibrahim, M Anile, D Diso, G Cusumano, A Terminella, M Novali, C Poggi, G Failla, S Conforti, M Torre, F Venuta, EA Rendina, M Santini; (IV) Collection and assembly of data: V Luzzi, M Innocenti, E Carelli, C Freda, G Natale, V Peritore, M Basile, E Mazzucca; (V) Data analysis and interpretation: N Serra; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Alfonso Fiorelli, MD, PhD. Thoracic Surgery Unit, Università degli Studi della Campania "Luigi Vanvitelli", Piazza Miraglia 2, I-80138 Naples, Italy. Email: alfonso.fiorelli@unicampania.it.

Background: Despite bronchoscopic lung volume reduction (BLVR) with valves is a minimally invasive treatment for emphysema, it can associate with some complications. We aimed at evaluating the rate and type of complications related to valve treatment and their impact on clinical outcomes.

Methods: It is a retrospective multicenter study including all consecutive patients with severe heterogeneous emphysema undergoing BLVR with endobronchial valve treatment and developed any complications related to this procedure. The type of complication, the time of onset, the treatment required and the out-come were evaluated. Response to treatment was assessed according to the minimal clinically important difference (MCID) as follows: an improvement of $\geq 15\%$ in forced expiratory volume in one second (FEV_1); of -8% in residual volume (RV); of ≥ 26 m in 6-minute walking distance (6MWD); and of ≥ 4 points on the St. George's Respiratory Questionnaire (SGRQ). Target lobe volume reduction (TLVR) ≥ 350 mL was considered significant.

Results: One hundred and seven out of 423 (25.3%) treated patients had complications related to valve treatment including pneumothorax (17.3%); pneumonia (1.7%), chronic obstructive pulmonary disease (COPD) exacerbation (0.9%), respiratory failure (1.4%), valve migration (2.1%), and hemoptysis (1.9%). In all cases complications resolved with appropriate treatment including removal of valves in 21/107 cases (19.6%). Patients with TLVR ≥ 350 mL ($n=64$) *vs.* those < 350 mL ($n=43$) had a statistically significant higher improvement in FEV_1 ($19.0\% \pm 3.9\%$ *vs.* $3.0\% \pm 0.9\%$; $P=0.0003$); in RV ($-10.0\% \pm 4.8\%$ *vs.* $-4.0\% \pm 2.9\%$; $P=0.002$); in 6MWD (33.0 ± 19.0 *vs.* 12.0 ± 6.3 metres; $P=0.001$); and in SGRQ (-15.0 ± 2.9 *vs.* -8.0 ± 3.5 points; $P=0.01$). Only patients with TLVR ≥ 350 mL met or exceeded the MCID cut-off criteria for FEV_1 ($19.0\% \pm 3.9\%$), RV ($-10.0\% \pm 4.8\%$), 6MWD (33.0 ± 19.0 metres), and SGRQ (-15.0 ± 2.9 points). Five patients (1.2%) died during follow-up for causes not related to valves treatment neither to any of the complications described.

Conclusions: Valve treatment is a safe and reversible procedure. The presence of complications seems not to have a significant impact on clinical outcome in patients with lobar atelectasis. Due to poor clinical conditions and possible complications, BLVR should be performed in high volume centers with a multidisciplinary approach.

Keywords: Zephyr endo-bronchial valves; bronchoscopic lung volume reduction (BLVR); emphysema

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Introduction

Emphysema is a leading cause of morbidity and mortality. Lung transplantation is the only curative treatment but the strict eligibility criteria and an inadequate supply of donor organs make it available only in a limited number of patients. Lung volume reduction surgery (LVRS) has been proposed as a viable option for patients with heterogeneous emphysema. Despite the positive clinical results, LVRS is associated with significant morbidity (20–30%) and high 90 days operative mortality (7.9%) (1). Thus, over the years alternative minimally invasive techniques have been explored as the implantation of non-blocking (i.e., coil, sealant, vapor) or blocking devices [endobronchial valves (EBV)] to obtain bronchoscopic lung volume reduction (BLVR). Among these, EBV are the best studied to date. EBVs are designed to achieve BLVR by inducing lobar atelectasis. Exclusion of the most destroyed emphysematous lobe with EBV allows air to exit during expiration, but stops it from entering during inspiration, thus resulting in atelectasis of the target lobe and reducing hyperinflation. Heterogeneous emphysema and the absence of interlobar collateral ventilation (CV-negative patients) are the main predictive factors for the success of the procedure. EBV treatment is a well-tolerated procedure that provides clinically significant results in selected cases, but it can be associated with different complications that are challenge to treat due to poor clinical conditions of patients (2-8). Most of the papers published focused on the clinical results of EBV treatment while the incidence and management of complications related to EBV treatment remain less explored issue. The aim of the present paper is to evaluate the rate and type of complications related to EBV treatment and their impact on clinical outcomes.

Methods

Study design

This is a retrospective multicenter study including 8 Italian centers with long experience in EBV treatment. All consecutive patients with heterogeneous emphysema undergoing BLVR with Zephyr EBVs from January 2012 to May 2017 and developing any type of complication related to the procedure were considered. Patients with lack of data regarding the type of complications and their treatment, and/or with incomplete follow-up were excluded. The goals of the paper were (I) to evaluate the incidence and the management of complications related to the procedure and (II) whether these complications could affect clinical outcome. Being it a retrospective study, the management of complications and the timing of follow-up were not standardized but decided by each participating center according to personal experience and guidelines. The study design was approved by the Ethic Local Committee of the two Coordinating Centers (University of Campania “Luigi Vanvitelli” and Sapienza University-Rome Sant’ Andrea Hospital). Patients signed a written informed consent for the EBV treatment and they were aware that their data could be anonymously analyzed for scientific purposes only. As the data in this current analysis were retrospectively analyzed, no further patients consent was required.

Study population

Patients were scheduled for EBV treatment according to the published best practice criteria (9-17). All patients had a diagnosis of severe emphysema (GOLD stage III or IV) and a residual volume (RV) \geq 150% predicted. Emphysema

distribution was assessed by high resolution computed tomography (HRCT) scan with volume rendering and lung perfusion scan; only lobes showing a clear density reduction without perfusion were treated (9,10). According to standard clinical practice (11-13), only patients considered as CV-negative for completeness of fissure $\geq 90\%$ on HRCT-analysis and/or for the absence of CV at Chartis assessment were treated. Pulmonary function tests (PFTs) included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), total lung capacity (TLC), RV, diffusing capacity (DLCO), 6-minute walking test (6MWT), PaO_2 and $PaCO_2$ (measured at rest while breathing room air). All pulmonary function data were presented as a percentage of predicted values for the patient's age, gender and height. Quality of life was measured by the St. George's Respiratory Questionnaire (SGRQ), ranging from 0 to 100, with a higher score indicating a worse quality of life. After treatment, all patients underwent standard clinical and radiological follow-up performed 3, 6, 12 months after the valves implantation, and then yearly.

Procedure of valve implant

The type of anesthesia used during the procedure varied across the centers, depending on patient condition and physician preference. Generally, the procedure was performed with IV sedation, spontaneous breathing, and flexible bronchoscopy. Alternatively, general anesthesia with either a laryngeal mask or endotracheal tube or rigid bronchoscopic to provide positive airway pressure or intermittent negative pressure ventilation was used. Three different size of valves were used: EBV 4.0 or EBV 4.0 LP (shorter), and EBV 5.5 for bronchial lumens with diameters of 4.0–7.0 mm and of 5.5–8.5 mm, respectively. After estimating the size of the target bronchus with a dedicated catheter, the valves were delivered through the same catheter to obtain the complete occlusion of the target lobe. All patients were hospitalized for a minimum of 48–72 hours after the procedure. A chest X-ray was performed few hours later or the day after the procedure according to the center's experience, to assess the lobar volume reduction and to determine EBV location and to evaluate the presence of pneumothorax or other complications. In presence of any complications, additional diagnostic exams and treatment were carried out.

Morbidity and mortality

The type of complications, the time of onset from EBV

implant (hour or days), the treatment and clinical and functional out-come were analyzed. In agreement with previous studies, the clinical response to treatment was assessed using the principle of minimal clinically important differences (MCID) that was defined according to the following specific responders criteria: an improvement of $\geq 15\%$ in FEV_1 ; an improvement of -8% in RV; an improvement of ≥ 26 m in 6MWT; an improvement of ≥ 4 points on the SGRQ. A target lobe volume reduction (TLVR) ≥ 350 mL defined the significant cut-off criterion for lung volume reduction.

Statistical analysis

Data were expressed as means \pm standard deviation (SD) for continuous variables and absolute number and percentage for categorical variables. The delta for each variable was calculated by the variation between the value of the last follow-up and the baseline value. The difference between the different groups were calculated using Student's *t*-test for quantitative variables and Chi-square test for categorical variable. A P value < 0.05 was considered statistical significant. MedCalc statistical software (version 12.3, Broekstraat 52; 9030 Mariakerke; Belgium) was used for the analysis.

Results

In the study period 423 patients underwent EBV treatment for severe emphysema. Of these, 107 (25.3%) patients developed EBV-related complications and were included in the study. The characteristics of the study population are summarized in *Table 1*. Mean age was 63.2 ± 11.0 years old and most of patients were male (77.6%). Thirty-five patients (32.7%) presented pre-procedural co-morbidities. Before treatment, the mean value of $FEV_1\%$ and of RV% were 43.0 ± 4.9 and 237 ± 19 , respectively. The left upper lobe (LUL) was the most treated lobe (43.9%). The mean number of valves per patient were 2.9 ± 0.7 and most of the procedures were performed with conscious sedation (63.6%).

Complications related to valves

The type of complications, treatment and outcome are summarized in *Table 2*. During the study period 5 out of 423 (1.2%) treated patients died 27.0 ± 3.9 months from treatment. In all cases the cause of death was not related

Table 1 Characteristics of study population (n=107)

| Variable | Value |
|--|---------------------|
| Age, mean \pm SD (years) | 63.2 \pm 11.0 |
| Sex (male/female), n (%) | 83 (77.6)/24 (22.4) |
| Pre-procedural comorbidities, n (%) | 35 (32.7) |
| Cardio-vascular | 15 (14.0) |
| Cerebral | 5 (4.7) |
| Diabetes | 7 (6.5) |
| Gastric | 3 (2.8) |
| Infective | 2 (1.9) |
| Cancer | 3 (2.8) |
| O ₂ saturation (%), mean \pm SD | 93.0 \pm 3.5 |
| pO ₂ (%), mean \pm SD | 75.0 \pm 9.2 |
| pCO ₂ (%), mean \pm SD | 39.0 \pm 5.5 |
| FEV ₁ %, mean \pm SD | 43.0 \pm 4.9 |
| FVC%, mean \pm SD | 37.0 \pm 3.7 |
| RV%, mean \pm SD | 237 \pm 19 |
| TLC%, mean \pm SD | 135 \pm 23 |
| 6MWT, mean \pm SD (metres) | 199 \pm 31 |
| DLCO%, mean \pm SD | 57.0 \pm 8.9 |
| SGRQ, mean \pm SD (points) | 60.0 \pm 3.1 |
| Target lobe, n (%) | |
| RUL | 31 (29.0) |
| RLL | 19 (17.8) |
| LUL | 47 (43.9) |
| LLL | 10 (9.3) |
| Valve per patient, mean \pm SD | 2.9 \pm 0.7 |
| Type of procedure, n (%) | |
| Conscious sedation | 68 (63.6) |
| General anaesthesia | 39 (36.4) |

SGRQ, St. George's Respiratory Questionnaire; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; 6MWT, 6-minute walking test; DLCO, diffusing capacity of the lung for carbon monoxide; RUL, right upper lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe.

to valves treatment. Two patients died for lung and brain cancer, respectively, one for stroke, one for myocardial ischemic attack, and one for drug-induced anaphylaxis.

Pneumothorax

Pneumothorax was the most common complication, observed in 73 out of 423 (17.3%) treated patients. Among these, 54/73 (74.0%) patients had a TLVR >350 mL. In 86.3% (63/73 patients) of cases pneumothorax occurred during hospitalization (22.0 \pm 9.3 hours after valve implant) and in 13.7% (10/73 patients) pneumothorax occurred after a mean time of 5.3 \pm 2.8 months. The treatment included clinical observation in 23 (31.5%) cases (*Figure 1*); chest drainage in 38 (52.1%) cases for the presence of massive pneumothorax (*Figure 2*), and chest drainage with valve(s) removal in 12 (16.5%) cases for persistent air leaks (more than 5 days) (*Figure 3*). In all cases the pneumothorax successfully resolved after a mean time of 4.0 \pm 1.9 days. Eight of 12 (66.7%) patients, in whom the valves were removed, underwent re-implantation of the valves and TLVR >350 mL was obtained in seven of these (87%).

Respiratory failure

Respiratory failure was observed in 6 (1.4%) patients. Of these four patients presented a TLVR >350 mL. In 4 (66.7%) cases, respiratory failure developed during hospitalization (mean time 9.3 \pm 5.4 hours) and in the remaining 2 (33.3%) cases 4.2 \pm 1.7 months later. The treatment required invasive ventilation more than 24 hours in 3 (50.0%) cases, medical therapy in 2 (33.3%) cases and medical therapy with valve removal in 1 (16.7%) case. In all cases, respiratory failure resolved.

Pneumonia

Pneumonia was observed in 7 (1.7%) patients 7.5 \pm 2.3 months after the treatment. Six (85.7%) patients presented a TLVR >350 mL. Pneumonia resolved with medical therapy in 5 (71.4%) cases. In 2 (28.6%) patients the valves were removed and in only one they were re-implanted obtaining a TLVR >350 mL.

COPD exacerbation

COPD exacerbation was observed in 4 (0.9%) patients. Only one patient presented a TLVR >350 mL. In one case COPD exacerbation occurred during hospitalization and its treatment required the removal of the valve. In the other three cases it occurred 2.9 \pm 0.7 months after treatment and resolved with medical therapy alone.

Migration and/or expectoration

Migration and/or expectoration were observed in 9 (2.1%) of patients (*Figure 4*). In 3 (33.3%) patients it occurred during hospitalization (mean time: 32 \pm 11 hours from implant)

Table 2 Type of complications, treatment and outcome. The rate of complications (n=107) is calculated on the patients treated during the study period (n=423)

| Type of complication | N (%) | TLVR >500 during complication, N (%) | Time of presentation from valves implant | Treatment | Outcome | Valves re-implanted, N (%) | TLVR >350 mL after resolution of complication, N (%) |
|---------------------------|--|--------------------------------------|--|---|------------|----------------------------|--|
| Pneumothorax | 73 (17.3); during hospitalization, 63/73 (86.3); after hospitalization, 10/73 (13.7) | 50 (38.4%) | 22.0±9.3 hours; 5.3±2.8 months | Observation (n=23); chest drainage (n=38); chest drainage and valve removal (n=12) | Resolution | 8/12 (66.7) | 49 (67.1) |
| Respiratory failure | 6 (1.4); during hospitalization, 4/6 (66.7); after hospitalization, 2/6 (33.3) | 4 (66.6%) | 9.3±5.4 hours; 4.2±1.7 months | Mechanical ventilation (n=3); medical therapy and valve removal (n=1) | Resolution | No | 3 (50.0) |
| Pneumonia | 7 (1.7) | 6 (85.7) | 7.5±2.3 months | Medical therapy (n=5); medical therapy and valve removal (n=2) | Resolution | 1/2 (50.0) | 5 (71.4) |
| COPD exacerbation | 4 (0.9); during hospitalization, 1/4 (25.0); after hospitalization, 3/4 (75.0) | 1 (25.0) | 58 hours; 2.9±0.7 months | Medical therapy (n=3); medical therapy and valves removal (n=1) | Resolution | 0 | 0 |
| Dislocation/expectoration | 9 (2.1); during hospitalization, 3/9 (33.3); after hospitalization, 6/9 (66.7) | 0 | 32±11 hours; 3.7±2.1 months | - | - | 8 (88.9) | 6 (66.7) |
| Hemoptysis | 8 (1.9); granuloma, 5/8 (62.5); micetoma, 1/8 (37.5) | 5 (62.5) | 10.0±6.9 months | Medical therapy (n=2); embolization (n=1); valve removal (n=3); valve removal and laser therapy (n=2) | Resolution | 1/5 (20.0) | 1 (12.5) |

TLVR, target lobe volume reduction; COPD, chronic obstructive pulmonary disease.

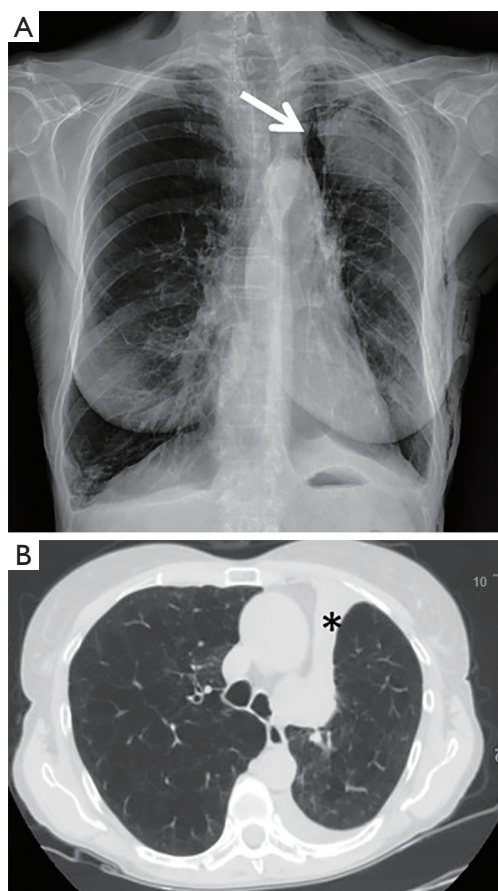


Figure 1 Small, asymptomatic pneumothorax (white arrow) (A) spontaneously resolved with clinical observation (B). Lobar atelectasis (*) of left upper lobe was preserved after resolution of pneumothorax.

and in 6 (66.7%) of patients 3.7 ± 2.1 months from implant. No patient had a significant TLVR. In all cases the valves were re-implanted after a mean time of 3.5 ± 1.3 months obtaining a TLVR >350 mL in six patients. An example of valve migration is reported in *Figure 4*.

Hemoptysis

Hemoptysis was observed in 8 (1.9%) patients 10.0 ± 6.9 months after valve implant. In one case hemoptysis was massive due the presence of a micetoma and required embolization. In five cases it was mild and due to granuloma formation (*Figure 5*). In all cases the valves were removed and in 2 of these the granulomas were resected with laser. In the remaining two patients, hemoptysis resolved with medical therapy. Only 1 (20.0%) patient underwent re-implantation of valve obtaining a TLVR >350 mL. An example of hemoptysis due

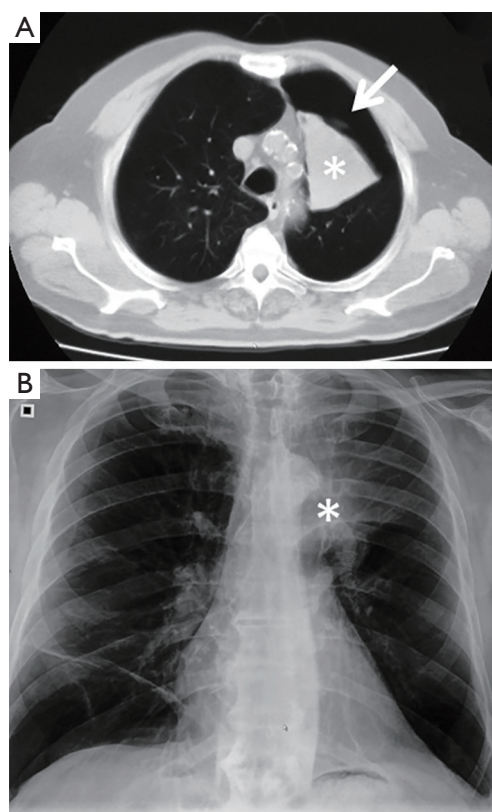


Figure 2 Massive, symptomatic, pneumothorax (white arrow) (A) resolved with insertion of chest drainage (B). Lobar atelectasis (*) of left upper lobe was preserved after resolution of pneumothorax.

to granuloma is reported in *Figure 5*.

Clinical outcome

Data are summarized in *Table 3*. The rate of patients with TLVR >350 mL did not change after the treatment of complications (61.6% vs. 59.8%, $P=0.9$) confirming that whatever complication did not affect the lobar atelectasis rate.

Patients with TLVR >350 mL ($n=64$) compared to those with TLVR <350 mL ($n=43$) had a significant improvement in delta FEV₁ ($19.0 \pm 3.9\%$ vs. $3.0 \pm 0.9\%$; $P=0.0003$); in delta RV ($-10.0 \pm 4.8\%$ vs. $-4.0 \pm 2.9\%$; $P=0.002$); in delta 6MWT (33.0 ± 19.0 vs. 12.0 ± 6.3 metres; $P=0.001$); and in delta SGQR (-15.0 ± 2.9 vs. -8.0 ± 3.5 points; $P=0.01$). Only patients having TLVR ≥ 350 mL met or exceeded the MCID cut-off criteria for FEV₁ ($19.0 \pm 3.9\%$), RV ($-10.0 \pm 4.8\%$), 6MWT (33.0 ± 19.0 metres), and SGQR (-15 ± 2.9 points) while in patients with TLVR <350 we observed only the MCID for SGQR (-8.0 ± 3.5 points).

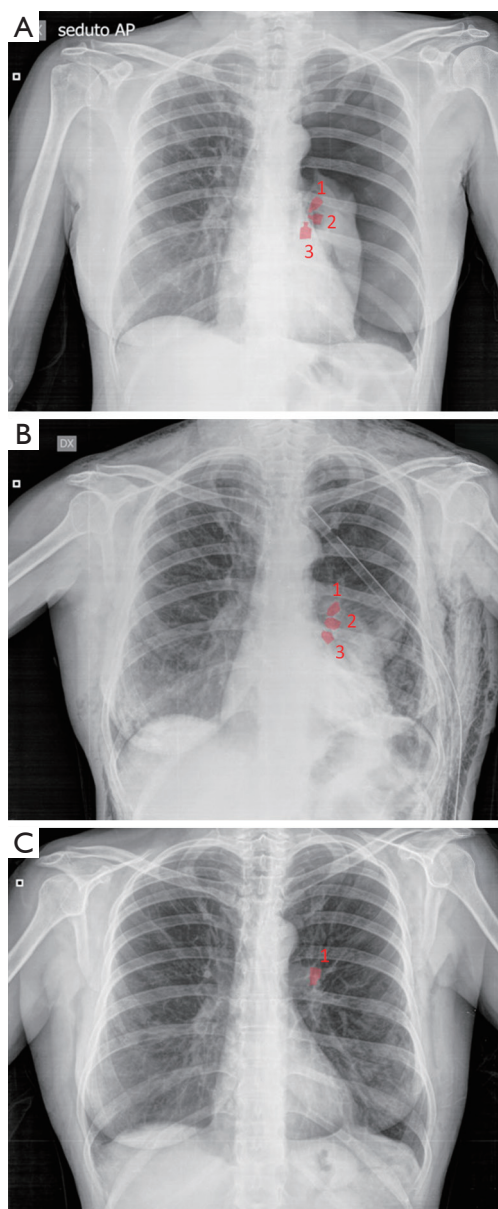


Figure 3 Massive, symptomatic pneumothorax following insertion of three valves in the left upper lobe (A). Pneumothorax resolved with chest drainage (B) but the persistent air-leaks required the removal of the 2th and the 3th valves (C).

Discussion

EBV treatment in patients with heterogeneous emphysema and with proven absence of CV provided significant clinical benefits (2-8). The lobar atelectasis obtained with EBV implant mimics the same physiologic effects of LVRS in terms of reduction of RV and improves respiratory mechanics a larger application and shorter length of

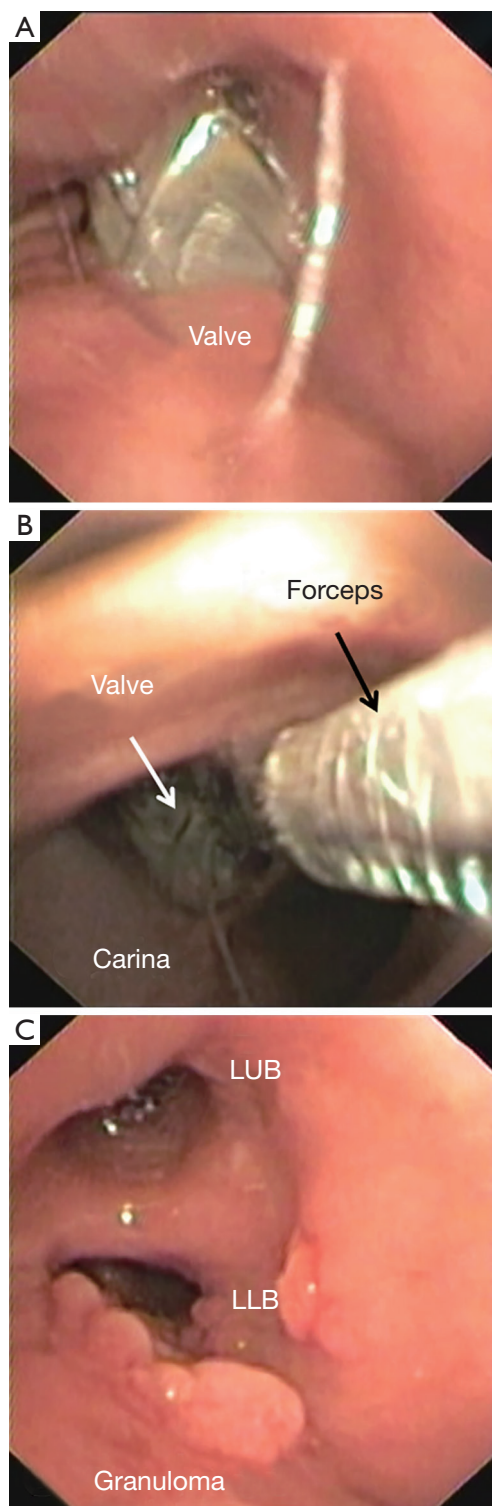


Figure 4 A large valve dislocated and obstructed the main left bronchus (A). It was extracted using rigid bronchoscopy (B) restoring the air way patency (C). It was well evident the formation of granulomas due to the injury of air-way mucosa by valve. LUB, left upper bronchus; LLB, left lower bronchus.

hospital stay, and reduced morbidity and mortality. EBV treatment is *per se* a safe and well tolerated procedure. A recent metanalysis by Liu *et al.* (14) showed that EBV

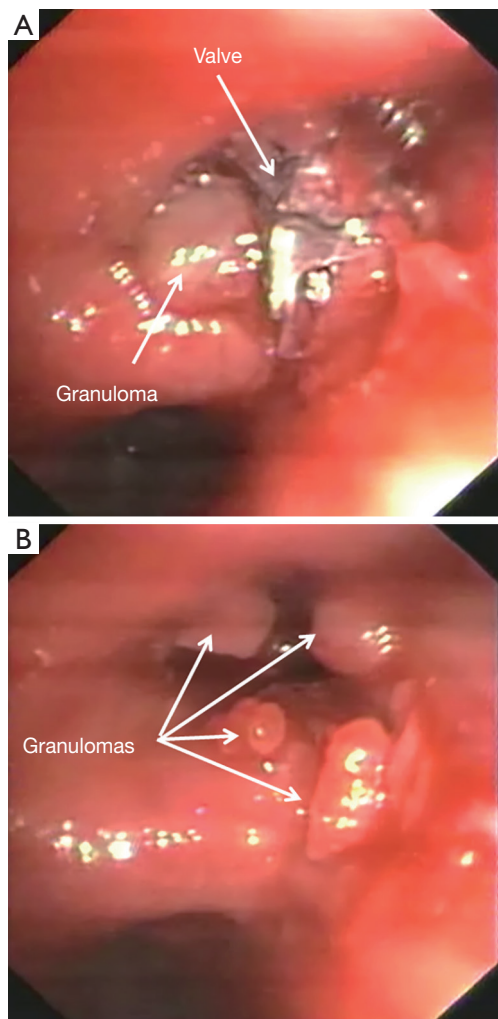


Figure 5 Hemoptysis due to the granuloma formation (A) resolved with valve removal (B).

treatment in comparison with standard medication and sham EBV did not increase the overall rate of mortality and morbidity except for mild hemoptysis which was more common in the EBV groups than in control groups ($P=0.03$). However, EBV treatment as well as most thoracic procedures can be accompanied by severe and less severe complications as reported in randomized clinical trials (RCTs) (2-7). Despite all, this issue is not largely evaluated in the literature. All published papers (15-17) focused on the incidence, treatment and clinical outcome of pneumothorax which is the most frequent EBV complication but there are other potential complications related to EBV treatment that remain under evaluated. To overcome these limits, we conducted this retrospective multicenter study with the aim of evaluating all complications due to EBV treatment and their impact on clinical outcome, an issue which has not been reported before.

As expected, pneumothorax was the most frequent complications (17.3% of patients). Early trials as the US VENT (2) and its European cohort (3) reported a lower rate of pneumothorax (4% and 8%, respectively) than the more recent (3,4,6) where it ranged between 17% and 23%. The reason for this different pneumothorax is the better selection of patient with only CV-negative being treated. In the VENT study (2) 67% of patients in the treatment group presented incomplete fissure at CT scan (CV-positive patients) while more recent trials as STELVIO (3), LIVE (4), and TRANSFORM (6) enrolled only patients defined as CV-negative (complete fissure at visual CT scan and/or CV-negative at Chartist). Since pneumothorax seems to be an indicator of successful valve therapy, there is the tendency among physicians to consider it as a “good complication” (if it is ethically right to consider a complication as “good”). In line with this evidence, in our series the incidence of pneumothorax was higher in responders (having a TLVR more than 350 mL) compared to non-responders. Despite all, 10/73 (13.7%)

Table 3 Clinical changes according to the minimal clinically important difference (MCID) cut-off criteria

| Variables | MCID cut-off criteria | TLVR ≥ 350 mL (n=64) | TLVR < 350 mL (n=43) | P value |
|--------------------------|-----------------------|---------------------------|------------------------|---------|
| Delta FEV ₁ % | ≥ 15 | 19.0 \pm 3.9 | 3.0 \pm 0.9 | 0.0003 |
| Delta RV% | -8 | -10.0 \pm 4.8 | -4.0 \pm 2.9 | 0.002 |
| Delta 6MWT (metres) | ≥ 26 | 33.0 \pm 19.0 | 12.0 \pm 6.3 | 0.001 |
| Delta SGQR (points) | ≥ 4 | -15.0 \pm 2.9 | -8.0 \pm 3.5 | 0.01 |

TLVR, target lobe volume reduction; SGRQ, St. George's Respiratory Questionnaire; FEV₁, forced expiratory volume in one second; RV, residual volume; 6MWT, 6-minute walking test; RV, residual volume.

Table 4 Review of the complications related to valve-treatment reported in the randomized control trials (RCTs)

| Variables | US VENT (n=214), n (%) | EU VENT (n=111), n (%) | STELVIO (n=34), n (%) | LIVE (n=343), n (%) | BeLieVeR-HiFi (n=25), n (%) | TRANSFORM (n=65), n (%) | Present study (n=423), n (%) |
|---------------------------|---------------------------|---------------------------|--------------------------|------------------------|--------------------------------|----------------------------|---------------------------------|
| Death | 6 (2.8) | 6 (5.4) | 1 (2.9) | 0 | 2 (8.0) | 1 (1.5) | 5 (1.2) |
| Pneumothorax | 9 (4.2) | 9 (8.1) | 6 (17.6) | 35 (10.2) | 2 (8.0) | 15 (23.1) | 73 (17.3) |
| COPD exacerbation | 22 (10.3) | 42 (37.8) | 4 (11.8) | 5 (1.5) | 5 (20.0) | 6 (9.2) | 4 (0.9) |
| Pneumonia | 17 (7.9) | 20 (18.0) | 3 (8.8) | 4 (1.2) | 2 (8.0) | 6 (9.2) | 7 (1.7) |
| Valve dislocation | 10 (4.7) | 10 (9.0) | 2 (5.9) | 3 (0.9) | 5 (20.0) | – | 9 (2.1) |
| Granulation | 9 (4.2) | 5 (4.5) | 1 (2.9) | – | – | – | 5 (1.2) |
| Respiratory failure | 3 (1.4) | 10 (9.0) | – | 1 (0.3) | – | 8 (12.3) | 6 (1.4) |
| Hemoptysis | 13 (6.1) | 14 (12.6) | – | 1 (0.3) | – | 1 (1.5) | 8 (1.9) |
| Cardiovascular disease | 6 (2.8) | 4 (3.6) | – | – | – | – | – |
| Lobar torsion | 1 (0.5) | 1 (0.9) | 2 (5.8) | – | – | – | – |
| Other | – | – | 4 (11.8) | 17 (5.0) | – | 13 (20.0) | – |

COPD, chronic obstructive pulmonary disease.

patients without significant lobar collapse experienced pneumothorax. This phenomenon is also reported in the European cohort of the VENT study (3) and in the study of Gompelmann *et al.* (15) where 7/25 (28%) and 42/70 (60%) patients, respectively, developed pneumothorax despite no lobar collapse. In agreement with previous RCTs (3,4) and Gompelmann's study (15), pneumothorax (86%) occurred within the first 72 hours confirming need to prolong hospitalization for a minimum of 72 hours. In 3 (4.1%) of our patients, pneumothorax occurred during the procedure. Thus, a sudden and an unexpected respiratory failure during or immediately after valve implantation should make you suspect a pneumothorax and physicians should be ready for an emergency treatment (i.e., chest drainage). In theory, the rapid re-expansion of the ipsilateral untreated lung due to sudden atelectasis favors the rupture of parenchyma with consequent pneumothorax. On the other hand, 10/73 (13.7%) of our patients developed pneumothorax several months after treatment making difficult to define whether this event is due or not to the valve treatment.

Due to the retrospective nature of the study, each participant centers managed pneumothorax according to their experience, but in all cases the treatment was in line with standard recommendations (16,17). A “watch and wait strategy” was applied in 31.5% of cases for asymptomatic

pneumothorax. Chest tube drainage insertion was required in 68.5% of cases for symptomatic pneumothorax. This datum is in line with the STELVIO study (3) and Gompelmann's study (15) where 80% of patients with pneumothorax underwent chest insertion. In 16.4% of cases, persistent air-leaks (more than 5 days) required removal of the valve. The STELVIO study (3) and Gompelman's study (15) reported a rate of valve removal of 50% and 44%, respectively, for the management of pneumothorax and persistent air-leaks. In all cases the persistent air leaks resolved with no need for surgery.

Other complications seen in our series were pneumonia (1.7%), COPD exacerbation (0.9%), respiratory failure (1.4%), valve migration or expectoration (2.1%) and hemoptysis (1.9%) caused by micetoma or granulation. Their rates were similar to RCTs studies summarized in *Table 4* and resolved with appropriate medical treatment and in selected cases with valve removal (nine cases). Only COPD exacerbation presented a lower rate in our than in other series. In theory, COPD exacerbation is a phenomenon that occur in all COPD patients. Thus, in our study it could be under evaluated due to the difficult to define whether it was related or not to valve treatment considering the retrospective nature of the study and the lack of a control group.

EBV treatment is a reversible procedure and complete resolution of complications without further side effects was observed in all patients where the valves were removed (21 patients). However, we found that again the presence of lobar atelectasis after the resolution of the complication was the only predictive factor for significant clinical improvement. This is line with the VENT study and Gompelmann's analysis. In the VENT study (2), patients who experienced pneumothorax had similar clinical benefits in terms of FEV₁ and 6MWD compared to the subgroup of patients with complete fissure and without any complication. In Gompelmann's series (15), 3 months after pneumothorax, valve therapy was associated with significant improvement in all lung function parameters except VC in patients with lobar atelectasis. Thus, patients, in whom the valves are removed for the management of complication, should be reviewed for re-implanting valves in order to obtain lobar collapse. Furthermore, we observed in 23/73 (31.5%) patients with pneumothorax the reexpansion of the target lobe despite the valves were not removed. In theory, the abnormal movement of the lung during the pneumothorax could favor a small dislocation of the valves, resulting in a lack of significant TLVR. Thus, in these patients a CT scan followed by bronchoscopy check is indicated in order to diagnose any valve dislocation.

Our study confirmed that delayed complications can occur also several months after valve implant, underlying the necessity of a prolonged follow-up. Because the patients will often back under the care of their primary physicians, it is mandatory to inform the patient and his family regarding the most common clinical signs of the complications. A sudden and unexpected chest pain associated with respiratory failure could be related to pneumothorax, a loss of clinical benefit or increased coughing could be associated with valve migration (18,19), hemoptysis with granuloma formation, while persistent infection with pneumonia. In this way, the patient and his/her family are able to understand when to alert their threatening physicians and/or refer to a local hospital for an emergency treatment. EBV treatment is not largely performed and in the most hospital there is a lack of knowledge about the role, the function, and the complications of valves. Thus, establishing a link with minor hospitals should be encouraged in order to allow the early transfer of the patient to the threatening expert centers after stabilization of his/her clinical condition. BLVR has been developed for people considered to be too disabled to withstand LVRS, thus the treatment of any complication could be a challenge due to poor clinical

condition of the patient. There are cases of death (20) reported in patients who had pneumothorax after discharge from the hospital. In the BeLieVeR-HIFi (6) study two patients died and one occurred as a complication of valve removal. Thus, BLVR should be performed in expert centers by a multi-disciplinary approach including thoracic surgeons, anesthesiologists and pulmonologists.

The retrospective and multicentric nature of the study, the different experience among participating centers, and the non-standardized protocol for the treatment of complications are all factors that should be considered before drawing definitive conclusions from our results.

Conclusions

Despite safe and well tolerated, EBV treatment could be associated with early and delayed complications. However, it is a reversible procedure and complete resolution of complications is obtained with or without valve removal. Complications did not have significant impact on clinical outcome in patients with lobar atelectasis. However, it is crucial to remember that some of these complications could be potentially life-threatening if not promptly treated.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study design was approved by the Ethic Local Committee of the two Coordinating Centers (University of Campania "Luigi Vanvitelli" and Sapienza University-Rome Sant' Andrea Hospital). Patients signed a written informed consent for the EBV treatment and they were aware that their data could be anonymously analyzed for scientific purposes only.

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