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Review

Endoscopic Lung Volume Reduction with Autologous Blood: What is the Evidence?

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Abstract

Biological lung volume reduction (BioLVR) is a novel and low-cost endobronchial treatment method aimed at reducing the volume of the target lung lobe using biological agents, including fibrin-based hydrogel, fibrinogen, and autologous blood (AB) with thrombin. BioLVR induces local inflammation, resulting in acute airway obstruction, resorption atelectasis, fibrosis, and finally tissue remodeling by contraction of the target lobe and reduction in the lung volume, similar to the application of hot water vapor and foam. In addition, patients with severe impairment in lung function and quality of life may refuses to undergo surgery, resulting in limited treatment options. In such complex clinical scenarios, BioLVR with AB appears to be a good therapeutic option. These treatment modalities resulted in favorable outcomes in patients with heterogeneous and bullous emphysema, pulmonary lymphangioleiomyomatosis, and giant bullous lesions. AB applications result in functional improvement, improvement in the quality of life, decrease in dyspnea scores, and reduction in the size of bullae. Based on the available evidence, application of AB for lung volume reduction is minimally invasive and well tolerated by patients. There was no incidence of pneumothorax or mortality. This review aimed to investigate the benefits, complications, and future perspectives of AB application as BioLVR in the treatment of hyperinflated lung diseases.

KEYWORDS: Autologous blood, bronchoscopic, endoscopic, lung volume reduction

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INTRODUCTION

Bronchoscopic or endoscopic lung volume reduction (ELVR) therapies have become an important option in the treatment of patients with severe emphysema in recent years. Numerous studies with silicone, stainless steel, and nitinol-containing implants, including valve, coil, and airway bypass stents have shown to improve pulmonary function, quality of life, and exercise capacity [1]. Furthermore, a new implant called the "reverser" is currently being developed and tested in animals [2]. These therapeutic modalities generally aim to reduce hyperinflation, total lung capacity (TLC), and residual volume (RV) through variable mechanisms of action [3]. Besides prosthetic implants, volume reduction can also be achieved by the application of hot water vapor and a foam-like liquid. This causes local inflammation with parenchymal fibrosis and atelectasis in the targeted lung lobe, leading to volume reduction [1, 3].

Biological lung volume reduction (BioLVR) is a novel and low-cost endobronchial treatment method aimed at reducing the volume of the target lung lobe using biological agents, including fibrin-based hydrogel, fibrinogen, and autologous blood (AB) with thrombin [4-11]. BioLVR induces local inflammation, resulting in acute airway obstruction, resorption atelectasis, fibrosis, and finally, tissue remodeling by contraction of the target lobe and reduction in lung volume, similar to the application of hot water vapor and foam [4, 5]. The onset of reduction in lung volume usually occurs after 6 to 8 weeks of treatment [4].

There are limitations to the most commonly used techniques of ELVR (valve, coil, airway stent, and thermal vapor). These include ineffectiveness of the valve in patients with collateral ventilation. In addition, coil treatments are contraindicated in patients with paraseptal emphysema and in those with bullous lesions greater than 3 cm or more than one-third of the hemithorax [1, 12]. Surgical volume reduction, bullectomy, or lobectomy may be performed if there are contraindications to ELVR. However, such patients generally have severe chronic obstructive pulmonary disease (COPD), other comorbid diseases, and poor general health. Furthermore, some patients may refuse to undergo anesthesia and surgery. Alternative treatment modalities are required in such situations. There are several successful reports of endobronchial application of AB in patients with large bullous lesions and lymphangioleiomyomatosis (LAM) under difficult clinical conditions [5, 9]. Furthermore, AB application was successful in a small case series of patients with severe COPD and emphysema (FEV1

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18%–22%). AB application was less invasive and safer compared with surgery in these patients [5]. This review aimed to investigate the benefits, complications, and future perspectives of AB application as BioLVR in the treatment of hyperinflated lung diseases.

MATERIAL AND METHODS

Articles and case reports on AB published between 2008 and 2018 were retrieved by searching 4 international databases (PubMed, Cochrane, CINAHL, and EMBASE). Search terms such as "autologous blood, endoscopic, lung volume reduction, and emphysema" were determined for the search. A total of 3 case reports, 4 case series, and 4 small-scale studies (n=12–30) were retrieved. According to the search results, AB applications are used to treat patients with giant bullae, pulmonary LAM, heterogeneous and homogenous emphysema with bullous lesion.

Background of Biological Lung Volume Reduction

Biological ELVR was first performed by Ingenito in 2001 in a sheep model with papain-induced emphysema using a novel fibrin-based glue system utilizing tissue engineering [13]. In this pilot study, post-procedural complications were found to be less compared with lung volume reduction surgery. A success rate of 55% was reported with collapse of the lung and focal scarring. This novel and largely irreversible endoscopic procedure transforms targeted emphysematous areas into a contracted area by the application of biologically active reagents (10 mL solution containing 0.1% chondroitin sulfate, 0.1% polylysine-fibrin glue, and 1,000 U thrombin) [13, 14].

In a small, preliminary phase-1 study with fibrinogen and thrombin (hydrogel), there was a 7.2% increase in FVC, 7.2% reduction in RV, 6.6% reduction in RV/TLC, and a mean increase of 14.5% in the 6-minute walk distance (6MWD) in patients with upper lobe-dominant heterogeneous emphysema [4]. In a phase 2 study, it was reported that administration of 20 mL per site at 8 subsegmental areas could be a safe and effective treatment in patients with advanced homogeneous emphysema [10]. After the treatment, a self-limiting flu-like illness with mild-to-moderate inflammatory reaction was observed in all patients; the illness resolved within 24-48 hours using a general supportive medical treatment.

MAIN POINTS

- Endoscopic lung volume reduction (ELVR) therapies have become an important option in the treatment of patients with severe emphysema.
- There are limitations to the most commonly used techniques of ELVR (valve, coil, airway stent, and thermal vapor).
- In cases where ELVR treatments cannot be applied, autologous blood can be used as an alternative treatment method.
- There are several successful reports, particularly regarding the treatment of large bullous lesions and lymphangioleiomyomatosis.
- The Autologous blood treatment procedure needs to be standardized.

Following these reports, the application of biologically reactive agents has been shown to be beneficial and safe in both heterogeneous and homogenous emphysema [10].

A polymer foam-like liquid (AeriSeal, Aeris Therapeutics, Inc., Woburn, MA, USA) was later developed and investigated in 2011 in a small group of 14 patients [15]. Using this agent, an improvement in FEV1 by 15.9%, RV/TLC ratio by 7.4%, an increase in the 6MWD by 28.7 m, and an improvement in the quality of life (change in the St. George's Respiratory Questionnaire [SGRQ] of –9.9 points) have been reported [15]. Although the initial therapeutic effects appear promising, complications have also been reported owing to the inflammatory process. Following these observations, the BioLVR study (ASPIRE) using sclerosants and profibrotic hydrogel was terminated in November 2013 because of non-regulatory and non-medical reasons [16]. The use of hydrogel is currently not approved in our routine clinical practice.

Current Evidence and Efficacy of Autologous Blood Application

AB applications lead to changes in radiological, functional, and clinical parameters in patients. All available data on AB application are summarized in Table 1. Interestingly, a trial (NCT03010449) with the combined administration of AB and intrabronchial valve therapy is still currently recruiting patients and is expected to be completed in 2020.

Radiological Outcome

The first set of ELVR reports with AB application was usually among patients with giant bullous lesions [7, 17, 18]. In 2008, Kanoh et al. [7] reported the first use of AB with a fibrinogen solution into a 12-cm giant bullous lesion under fluoroscopic guidance with the result that the lesion diameter revealed contraction from 12 cm to 3 cm (Figure 1). Zoumot et al. [17] carried out intrabullous administration of AB and reported prominent shrinkage of giant bullae in radiological images. In a more extensive study (n=20) with a limited 2-week follow-up, reduction in the size of bullae on chest radiography (5.20 cm to 4.5 cm), and high-resolution computed tomography (12.7 cm to 7.6 cm) have been reported [19]. In the most recent study, although improvement in some of the parameters of lung function was not statistically significant; on radiological imaging, the average volume of all bullae had decreased significantly (from 461.6 mL to 290.0 mL, p=0.034) [20]. However, in a study involving 30 patients in 2017, only a small reduction in bullae densities (from 10.9 cm to 9.1 cm) was observed [21].

Functional Outcome: AB applications cause a significant improvement in pulmonary function parameters. Kanoh et al. [7] reported the first use of AB with a fibrinogen into a giant bullous lesion. Following treatment, FEV1 increased from 1.94 (69% of predicted value) to 2.18 L (78% of predicted value), TLC decreased from 6.59 to 5.76 L, and RV decreased from 2.85 to 2.09 L [7]. In another study, Kanoh et al. [9] applied this treatment modality bilaterally to a patient with pulmonary LAM. At the end of 6 months, FEV1 increased by 150 mL; and there was a decrease in TLC by 240 mL and in RV by 530 mL.

After these initial successful case reports, in a pilot study, Zoumot et al. [17] carried out intrabullous administration of

Table 1. Overview of principal ELVR-autologous blood studies and case reports

Author	Year	n	Follow-up (M)	Type	ΔFEV1 (L)	ΔTLC (L)	ΔRV (L)	6MWD (m)	SGRQ (p)
Kanoh S.[7]	2008	1	After	G. bullae	+0.24	-0.83	-0.77	-	-
Kobayashi[8]	2009	4	After	E, LAM	+0.25	-0.38	-	-	-
Kanoh S.[9]	2009	1	6	LAM	+0.15	-0.24	-0.53	+65	-
Zoumot[17]	2013	5	3	G. bullae	+17.3%	-	-0.73	+88	-11.1
McNulty[18]	2014	6	3	G. bullae	+0.23	-	-0.82	+100	-10.9
Mizumori[5]	2015	3	18	Homo. E.	+0.34	-	-	+43*	-
Bakeer[6]	2016	7£ 8¥	3 3	Hetero. E.	+ 8%£ +17%¥	-	-	+16£ +96¥	-28.1£ -34.3¥
Kemp[22]	2016	1	36	G. bullae	+0.36	-	-0.56	-	-
Atta ME.[19]	2017	20	1/2	Bullous E	+6.7%	-	-	-	-
Mohamed[20]	2017	12	3	Bullous E	+0.13	-0.62	-0.23	-	-
Radwan[21]	2017	30	1	Bullous E. Hetero. E.	+17.7%	-	-8%	+67.5	-

M: month; Δ: change; LAM: lymphangioleiomyomatosis; E: emphysema; G: giant; Homo: homogeneous; Hetero: heterogeneous; FEV1: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; 6MWD: 6-minute walk distance; SGRQ: St George's respiratory questionnaire; *: 3MWD; £: autologous blood application; ¥: fibrin glue application

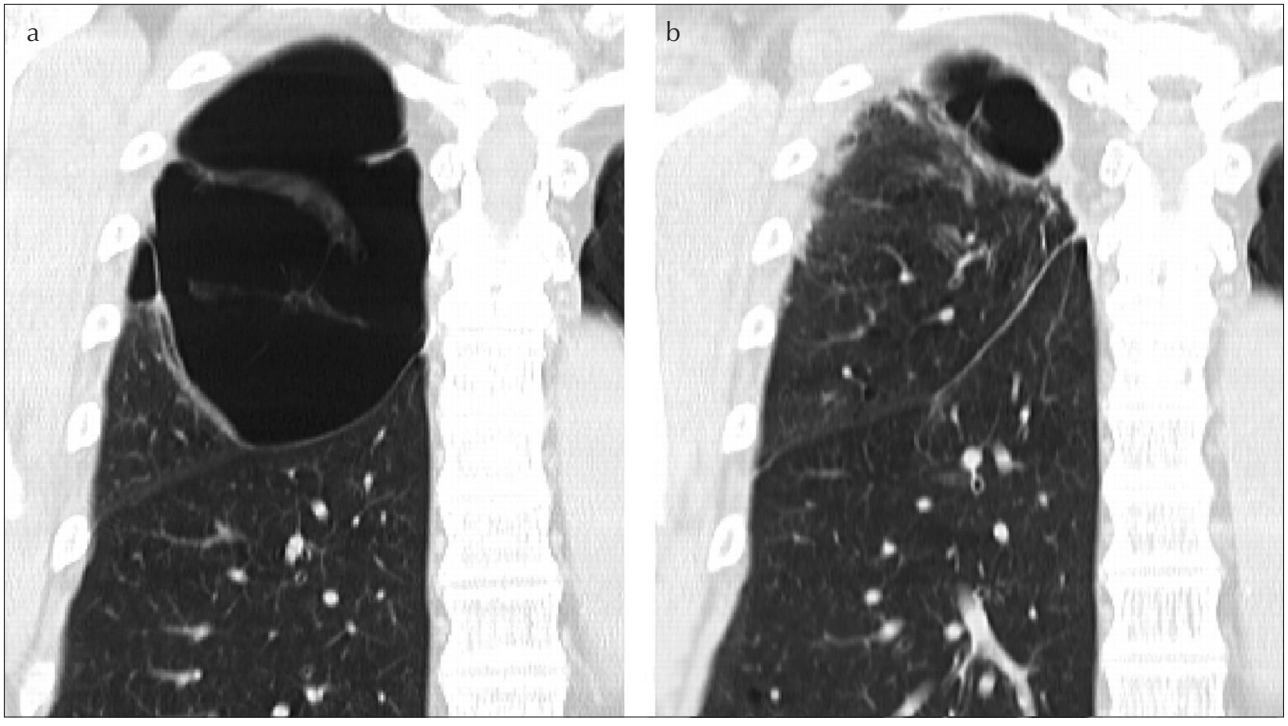

Figure 1. a, b. Coronal computed tomography image, before (a) and after (b) treatment with autologous blood instillation. After treatment, the diameter of the giant bulla decreased from 12 cm to 3 cm
*Quoted from ref. 7 with permission

AB using moderate sedation in 5 patients with giant bullous lesions who carried a high operative risk. After 3 months, there was an improvement in the pulmonary function tests (RV -0.73 L and FEV1 +17.3%), suggesting that this minimally invasive and inexpensive treatment modality could be an alternative to surgery. In another report with the same technique, intrabullous AB instillation was performed in 6 patients with severe COPD and with hyperinflation and giant bullous lesions who refused to undergo surgery [18]. Three months after the procedure, FEV1 increased by 230 mL, the forced vital capacity increased by 470 mL, and RV decreased by 830 mL.

Bakeer et al. [6] compared the 12-week efficacy and safety using AB (n=7) and fibrin glue (n=8) in patients with heterogeneous emphysema. A statistically significant decrease in the RV/TLC ratio was reported in both groups at 12 weeks compared with baseline values. The RV/TLC ratio decreased from 154% to 125% with AB and from 138% to 87% with fibrin glue application. Pulmonary function and hyperinflation parameters, exercise capacity, and quality of life scores

improved significantly in both groups and were more prominent with fibrin glue application. In a more extensive study (n=20), improvement in FEV1 (25.7% to 32.7%) was reported 2 weeks after administration [19].

In the most recent study, patients were divided into 2 groups—those with a bullae volume >515 mL (group 1) and those with a bullae volume <515 mL (group 2) [20]. Lung function was compared with baseline values after 3 months of intrabullous AB administration. After 1 week of treatment, improved lung function was observed only in 2 patients (FEV1 improved by 216-239 mL, and the RV reduced by 310–360 mL). However, after 3 months, there was an improvement in the mean FEV1 (from 1.52 L to 1.65 L, p=0.103), a decrease in RV (from 5.19 to 4.96 L, p=0.301), and TLC (from 8.48 to 7.86 L, p=0.004) [20].

In a study that included 30 patients (n=13 with heterogeneous emphysema and n=17 with bullous emphysema) in 2017, Radwan et al. [21] compared baseline values with those after 1 month of treatment. An improvement in FEV1 (from 32.9% to 50.6%) and a decrease in RV (from 156% to 144%) was reported. This study suggests that AB administration resulted in improvement in both groups of patients; however, the evaluation was limited to 1 month after treatment.

Data on the long-term effects of AB administration have been reported in only 1 patient over a 36-month period (between 2013 and 2016) [22]. Intrabullous AB was applied to a patient with COPD and a giant bullous lesion. At the end of 3 years, an increase in FEV1 (from 1.50 L to 1.86 L), a decrease in RV (from 4.27 L to 3.71 L), and a reduction in the RV/TLC ratio (from 56.2% to 47.7%) were reported and persisted over the period of observation.

Clinical Outcome: AB applications may also lead to improvements in the quality of life, dyspnea scores, and blood gas values. Kobayashi et al. [8] applied this method in 4 patients (1 with an emphysematous bulla, 1 with LAM, and 2 with advanced emphysema). The procedure was well tolerated by all patients and no major complications were observed. Also, Besides, an increase in exercise capacity was observed in 2 patients, and an improvement in the blood gas values was noted in 3 patients. Kanoh et al. [9] applied this treatment modality bilaterally to a patient with pulmonary LAM. At the end of 6 months, an improvement in pulmonary function parameters was observed as well as an increase in 6MWD by 65 m.

Zoumot et al. [17] applied intrabullous AB to 5 patients with giant bullous. As a result, reduction in SGRQ score (–11.1 point) and increase in 6MWT (+88 m) was reported. Similarly, McNulty et al. [18] reported a decrease in SGRQ score (–10.9 points) and an increase in 6MWT (+100 m)

In 2015, Mizumori et al. [5] performed the first application of AB to patients with severe COPD and emphysema. Although the lung function returned to baseline levels in some patients after 6 to 12 months, an improvement in exercise capacity was reported to last longer and a positive change was noted after a total of 5 procedures. Besides, there was a sustained improvement in partial pressure of carbon dioxide values in 2 patients with hypercapnic respiratory failure for 12-18 months. Although the effect of ELVR treatment on blood gas parameters is not clearly known, it has been recently reported that coil treatments have similar beneficial effects [23]. In a study involving 30 patients, an increase in 6MWT (from 275 m to 343 m) and an increase in the partial pressure of oxygen values (from 66.0 mmHg to 70.9 mmHg) after 1 month of AB administration was observed [21].

Current Methodology of Autologous Blood Application

Even though there are minor differences in methodology, the procedure is generally performed under light to moderate sedation with topical anesthesia. Application may be intrabullous in patients with giant bullous lesions or endobronchial to the targeted emphysematous lobe. According to previous reports, a combination of AB with different drugs, including thrombin, tranexamic acid, and fibrinogen was applied to the affected segments. Kanoh et al. [7, 9] applied a combination of 5-10 mL of AB with thrombin; Bakeer et al. [6] combined 30 mL AB with 3 mL tranexamic acid; Atta et al. [19] used a combination of 10 mL AB with 5 mL of tranexamic acid; and Radwan et al. [21] used 10 mL of AB, 5 mL of tranexamic acid, and 10 mL of prepared gel foam (Cutanplast® pieces and 10 mL of normal saline). Zoumot et al. [17] and McNulty et al. [18] applied 240 mL of AB in 60 mL aliquots to the giant bullae. In another study, a 22-gauge transbronchial biopsy needle was introduced into the bullae and AB applied using a different technique [20]. Methods of application and techniques are summarized in Table 2.

Potential Complications

According to the available evidence, application of AB for lung volume reduction is minimally invasive and well tolerated by patients. In the first report of intrabullous application of AB, Kanoh et al. [7] observed fever and cough on the day of the procedure. Kobayashi et al. [8] did not report any severe complications among 4 patients. Zoumot et al. [17] performed intrabullous application of 240 mL of AB in 5 patients; and 1 of them was hospitalized after 8 days with pneumonia, and 2 patients suffered acute exacerbation of COPD on days 4 and 9 after the procedure. This could be related to the high volume (240 mL) of AB injected. They received appropriate antibiotics and a 7-day course of prednisolone. All patients were discharged after full recovery after a brief period of hospitalization [17]. Mizumori et al. [5] suggested that transient pneumonia should develop within 1–3 days after BioLVR for the treatment to be successful. He reported that patients recovered rapidly following antibacterial treatment with intravenous piperacillin-tazobactam 4.5 g thrice a day and a single dose of methylprednisolone 125 mg. He also observed fever, tachycardia, and hypoxemia immediately after the procedure. Eosinophilia was noted a few weeks after the resolution of pneumonia [5].

Bakeer et al. [6] reported a 14.5% incidence of pneumonia with AB and 12.5% of COPD exacerbation with fibrin glue application after the procedure among patients with heterogeneous emphysema. All patients recovered with standard medical treatment, and there was no incidence of pneumo-

Table 2. Synopsis of application methods in the literature

Author	Target	Anesthesia	Procedure
Kanoh S.[7]	Intrabullous	LA	10 mL AB + 3 mL of fibrinogen and thrombin solution
Kobayashi H.[8]	EA	-	AB followed by thrombin solution procedure was repeated to several different areas
Kanoh S.[9]	EA	LA	4 mL AB followed by 2 mL (2,000 units) of thrombin solution. Similar procedures were repeated to other left upper segments at up to 5 times.
Zoumot[17]	Intrabullous	Moderate sedation	240 mL of blood was instilled intrabullous in 60-mL aliquots, followed by 10 mL of normal saline. The position of the working channel is verified fluoroscopically.
McNulty[18]	Intrabullous	Conscious sedation	240 mL of AB was instilled under fluoroscopy. Similar technique with reference 17.
Mizumori[5]	EA	LA + light sedation	3–4 mL AB + followed by thrombin solution (2,500 units) was repeated in 4 to 6 regions mainly in the anterior segment of the target lobe (1 course). The same procedure was repeated at intervals of several days until significant and obvious infiltration (pneumonia) was observed in the emphysematous area. A total of 1 to 4 courses of treatment (median value 2) were needed to obtain sufficient infiltration in each procedure.
Bakeer[6]	EA	LA + conscious sedation	30 mL AB injected through 1 port of the triple lumen catheter, + 3 mL tranexamic acid (Cyklokapron® 100 mg/mL), and 3 mL calcium chloride 10% (2.04 mmol of calcium) injected through the other port of the catheter. After injection, the catheter was kept in position for 4-8 minutes, the specific duration was previously determined according to the clotting time of each patient. The balloon was then deflated, and the catheter was withdrawn. The procedure was repeated to the next targeted segment.
Atta ME.[19]	EA	LA	10 mL of AB + 5 mL tranexamic acid (Cyklokapron® 100 mg/mL) was injected. The bronchoscope remained in the wedge position (for an average of 1-2 minutes) until the coagulation process was completed.
Mohamed[20]	Intrabullous	LA + moderate sedation	A 22-gauge transbronchial biopsy needle (ECHO-HD, 22-EBUS P, Echotip, Ultra, COOK, Ireland) was inserted through the working channel of the bronchoscopy into the affected segmental bronchus, and a maximum of 10 mL AB was infused into the bulla.
Radwan[21]	EA	LA + light sedation	A small diameter catheter (OLYMPUS PR-2B) was introduced through the working channel of the bronchoscope. When its tip appeared about 2-3 cm beyond the tip of bronchoscope, 10 mL AB and 5 mL tranexamic acid (Cyklokapron® 100 mg/mL) were injected, and then the 10 mL of prepared gel foam (Cutanplast® pieces and 10 mL of normal saline) was injected through the catheter. The bronchoscope was kept in wedge position till the coagulation process was completed (for an average of 1-2 minutes), and to prevent regurgitation of the prepared combination. Group 1: in the feeding bronchus; Group-2: in the most affected 4 subsegments, 2 on each side.

AB: autologous blood; EA: Emphysematous area; LA: local anesthesia

thorax. Atta et al. [19] applied this method in 20 patients with bullous emphysema in 2017; no serious adverse events were observed, and the patients were discharged from the hospital on the same day after BioLVR treatment. Transient, minor, and procedure-related adverse events attributable to bronchoscopy were observed, including cough (10%), hemoptysis (20%), and sore throat (5%) [6].

In another study performed in 2017, the mean duration of the procedure was 19.75±3.64 minutes, was very well tolerated, and no serious complications were observed. All patients were discharged from the hospital on the same day [20]. At the 3-month follow-up, no serious complications such as pneumonia, lung abscess, or bronchopleural fistula were noted. There was no mortality reported at 3 months. Radwan et al. [21] did not report serious adverse events during or after the procedure. Hemoptysis occurred in 53.3% of the patients, 73.3% developed cough, and 23.3% experienced low-grade fever because of the injected blood and the inflammatory reaction. No mortality was reported in this study, and there was no incidence of pneumonia or pneumothorax [21].

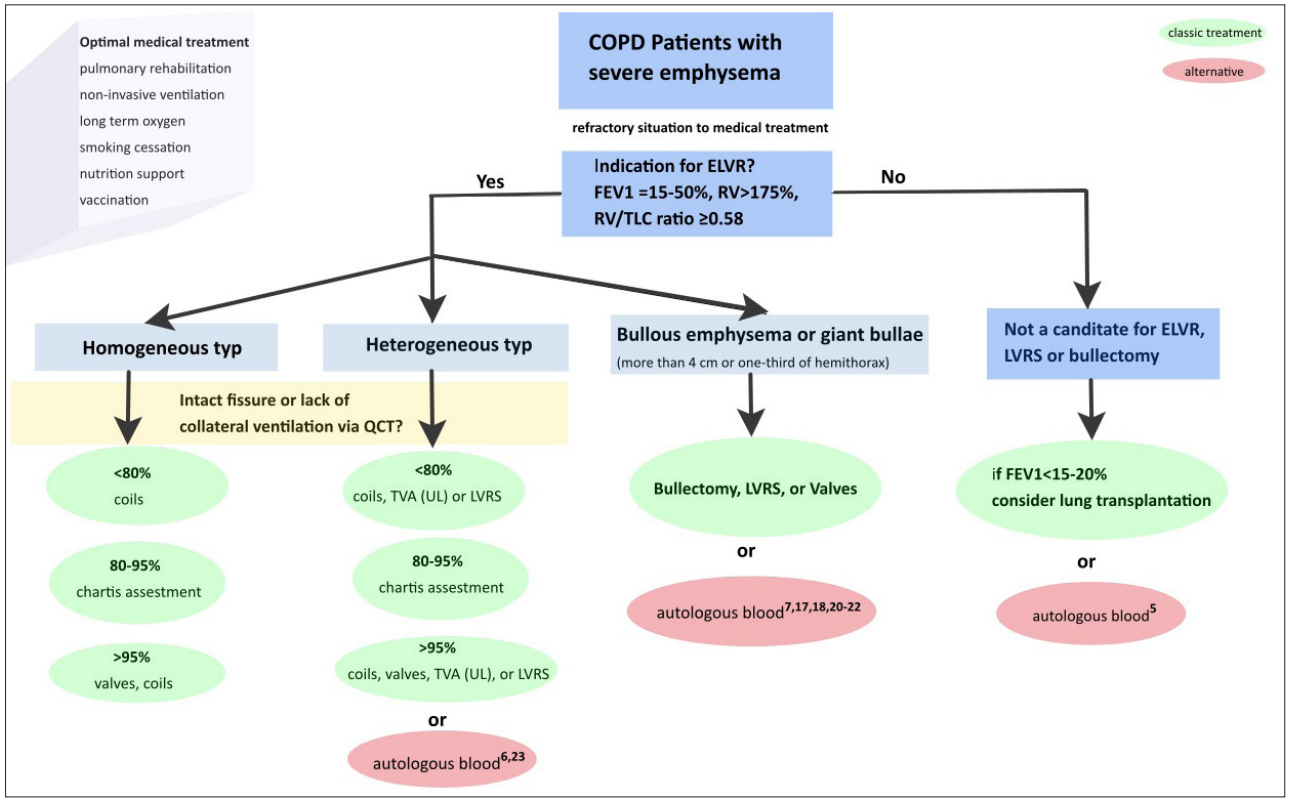

Figure 2. Treatment algorithm and possible place of autologous blood application for patients with severe emphysema

DISCUSSION

Emphysema, a type of COPD, is often difficult to treat with the currently available therapeutic modalities. Lung volume reduction surgery, including bullectomy, lobectomy, local excision, and drainage of bullae have been established to be beneficial, especially in patients with giant bullous lesions. However, in some patients, surgical intervention may not be feasible due to comorbid disease, the likelihood of postoperative complications, or patient refusal. Caution needs to be exercised with non-invasive mechanical ventilation in these patients because it may lead to a secondary pneumothorax [24]. Recently, minimally invasive therapeutic modalities have been developed using ELVR techniques (valve, coil, thermal vapor, airway stent, and lung denervation) for the treatment of emphysema [1]. However, these procedures involve highly specific patient selection and strict exclusion criteria. For instance, valve procedures are not applicable to patients with collateral ventilation, and coil treatment is contraindicated in patients with paraseptal emphysema and bullous lesions. ELVR with valve procedures may be the sole therapeutic option in patients with giant bullous lesions without collateral ventilation [25]. Severe impairment in pulmonary function and quality of life occurs due to patient refusal for surgery, resulting in limited treatment options. In such complex clinical scenarios, BioLVR with AB appears to be a good therapeutic option. The treatment algorithm and the possible place of AB applications in patients with severe emphysema are given in Figure 2.

Fissure integrity with the absence of collateral ventilation is not required for successful BioLVR therapies aimed at inducing a proinflammatory or profibrotic response [17]. These treatment modalities resulted in favorable outcomes in patients with heterogeneous and bullous emphysema and giant bullous lesions. Favorable outcomes were also observed in a small group of patients with homogenous emphysema [5]. In general, the available clinical evidence is limited to case reports and small case series. Particularly, among patients with large bullous lesions, a reduction in the size of the bullae has resulted in improved pulmonary function, quality of life, and increased walking capacity per several studies [7, 17, 18, 22]. Similar improvement in outcomes was also observed in patients with LAM [8, 9].

A major limitation of these studies is the relative lack of information regarding long-term outcomes. The minimum time required to evaluate the effect of treatment is 6 to 8 weeks, the time required for the development of inflammatory reaction and remodeling of lung tissue [4]. The longest period of follow-up was by Mizumori et al. (18 months) and by Kemp et al. (36 months) [5, 22]. Although Mizumori et al. [5] observed that some pulmonary function parameters returned to baseline values at 18 months; improvement in blood gas parameters, increase in exercise capacity, and quality of life was found to be sustained. Kemp et al. [22] reported that the improvement in FEV1, RV, and RV/TLC values were sustained at the end of 36 months. This difference may be because of the application of AB using different techniques. Considering the low-cost and easy implementation of ELVR techniques, repeat AB application may also be carried out. However, the possible benefit from repeat applications needs to be evaluated in large-scale studies. AB application has also been established to be beneficial in the treatment of persistent and postoperative air leaks, pneumothorax, and for pleurodesis. It is associated with a lower incidence of complications com-

pared with other techniques [26-28]. AB application is cheap, effective, and underutilized [29].

Another important issue is the difference in AB application techniques. Although the volume of AB and drugs used in combination for coagulation are variable, the treatment is based on the development of an inflammatory reaction. The inflammatory reaction is important for treatment success with the development of transient pneumonia on chest radiographs. Mizumori et al. [5] reported that infusion of 2 mL of AB and 1,000 units of thrombin solution 4 times during a single course of treatment led to inadequate inflammation. Administration of 4 mL of AB 4 to 6 times with 2,500 units of thrombin during a single course of treatment was more effective and resulted in an adequate inflammatory reaction. The administration of 240 mL of AB in 60 mL aliquots into giant bullous lesions was reported to be sufficient to trigger an inflammatory response [17, 18]. The volume of a standard blood donation is 440 mL; 240 mL of AB application is suitable to avoid adverse effects, such as hypotension. Technical differences pose a difficulty in evaluating the efficacy and safety of this procedure; hence, standardization is urgently needed to increase applicability.

In terms of safety of the procedure, pneumothorax and mortality have not been reported [5-9, 19-21]. Usually, mild, procedure-related complications are observed, including cough (10%-73.3%), hemoptysis (20%-53.3%), fever (23.3%), COPD exacerbation (3.3%-40.0%), and pneumonia (14.2%-20.0%) [6, 17, 19, 21]. These complications are controlled with standard medical treatments. Considering that the procedure is aimed to trigger an inflammatory reaction, the extent of optimal inflammatory response is unknown. There is also little information on the severity of post-procedure pneumonia or pneumonitis. There are no guidelines regarding the appropriate time to intervene in the event of an excessive inflammatory reaction. The administration of prophylactic corticosteroids may reduce inflammation and the incidence of complications; however, the benefit or possible negative impact on the effectiveness of the procedure is not fully known. It may be appropriate to consider the administration of pneumococcal and influenza vaccines prior to the procedure to reduce the incidence of possible complications, although there are no data to support this practice. Prophylactic antibiotics and steroids are frequently used by clinicians considering the high risk of potential complications, such as COPD exacerbation and pneumonia.

Following the ELVR foam sealant procedure, which decreased the volume by triggering an inflammatory response, most patients experienced an acute inflammatory reaction owing to mucosal irritation during the first few days of treatment [30]. This was defined as transient fever, pleuritic chest pain, fatigue, shortness of breath, high C-reactive protein and fibrinogen levels, and leukocytosis. This reaction was usually self-limiting and rapidly resolved with supportive treatment within 24 to 96 hours [30]. Prophylactic antibiotic and steroid treatments for 7 days are recommended for all the patients prior to treatment to reduce the intensity of the acute inflammatory response post procedure [30, 31]. The importance of such prophylaxis in AB applications is not yet known; however, considering the similar mechanisms of therapeutic effect, expert opinion may be followed.

Overall, ELVR leads to improvement in functional capacity, blood gas parameters, anxiety and depression scores, and quality of life [1, 3, 23, 32]. BioLVR applications performed with AB result in functional improvement, improvement in the quality of life, decrease in functional dyspnea scores, and reduction in the size of bullae [5-9, 17-22]. This modality of treatment may be an option for patients with large bullous lesions who refuse volume reduction surgery or other ELVR procedures. Similar to coil procedures, it may also help patients to buy time and may act as a bridge to lung transplantation [33]. Further large-scale studies are needed in the future to standardize the technique of AB application.

CONCLUSION

Endoscopic lung volume reduction with AB needs to be studied in larger groups of patients in the future to evaluate its efficacy. The application of AB may prove to be an alternative and low-cost technique for lung volume reduction in patients with hyperinflated lung diseases. It may also be effective in the treatment of large bullae where standard ELVR application or surgery is contraindicated. The lack of standardization of the procedure appears to be a major limitation.

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