Bronchoscopic Intrabullous Autologous Blood Instillation: A Novel Approach for the Treatment of Giant Bullae

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The current standard therapy for patients with giant bullae is surgical bullectomy; however, high operative risk and comorbidities preclude surgical procedures in many patients. Autologous blood instilled directly into bullae can induce an inflammatory reaction, leading to scarring, fibrosis, and ultimately volume loss. We have treated 5 patients with this minimally invasive approach as day-case procedures using moderate sedation. Three of the 5 patients had shrinkage of the bullae, leading to large and clinically meaningful improvements in lung function, exercise capacity, and quality of life 3 months after treatment. (Ann Thorac Surg 2013;96:1488–91) © 2013 by The Society of Thoracic Surgeons

In severe cases of emphysema, areas of alveolar destruction coalesce, creating bullae that can become so large that they occupy more than 30% of the hemithorax (termed “giant bullae”). Pharmacologic therapy is of limited benefit in these situations, and non-pharmacologic methods to reduce the size of the bullae and hence reduce gas trapping and lung volumes have been developed. Surgical removal of giant bullae (bullectomy) has been a standard treatment in selected patients for many years [1], and this has been achieved by lateral thoracotomy, bilateral resections via midline sternotomy, and video-assisted thoracoscopy [2]. Patients who are symptomatic and have a forced expiratory volume in 1 second (FEV1) of less than 50% predicted have a better outcome after bullectomy [1]. Benefits result from expansion of compressed lung tissue and improved ventilatory mechanics, with short-term benefits in hypoxemia, hypercapnia, gas trapping, and dyspnea reported in the published literature (predominantly uncontrolled retrospective studies) [2]. Unfortunately, bullectomy in a significant number of patients with giant bullae is considered too high risk because of disease severity and other comorbidities. There is little evidence to support bullectomy in younger minimally symptomatic patients with giant bullae, who often decline this major surgical intervention, which requires a prolonged period off work and an extended recovery.

A variety of less invasive strategies to reduce lung volume in patients with bullous emphysema have been developed, and some may be effective for the treatment of giant bullae (one-way endobronchial valves [3], airway bypass stents [4], and percutaneous airway bypass [5]). However, benefits from the latter two approaches has only been transient, and the evidence base supporting endobronchial valves in this population is poor. Extracellular heme-bound iron from blood deposited within airways and alveoli induces oxidation and reduction reactions, leading to an inflammatory response [6]. The potential is for permanent scarring and fibrosis, and thus lung volume reduction. Kanoh and colleagues [7] used autologous blood admixed with fibrinogen and thrombin to treat a 59-year-old man with a large bulla, and they have demonstrated significant reductions in static lung volumes and dyspnea. The same group has also published encouraging results in patients with lymphangioleiomyomatosis and advanced emphysema [8]. The solution used contained thrombin and fibrinogen mixed with blood. It is unclear whether it is the clotting factors added ex vivo or the natural extracellular heme-bound iron in blood that is the primary inducer of the localized inflammatory and profibrotic reaction. We therefore prospectively investigated the clinical effect of intrabullous unaltered autologous blood instillation in a pilot study of 5 patients with giant bullae.

Technique

The procedures were performed as day cases in the bronchoscopy suite with the patients under moderate sedation. An extended working channel was passed bronchoscopically into the giant bulla. Fluoroscopy was used to guide and confirm the positioning of the tip of the extended working channel inside the target giant bulla.

HOW TO DO IT

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In 60-mL aliquots, venesection of 240 mL blood was then performed, and the blood was instilled through the extended working channel within 60 seconds of being withdrawn, followed by 10-mL normal saline flushes.

Patients
Five patients (3 male and 2 female) were recruited (age range, 43 to 78 years) between September 2011 and July 2012. Two were too sick for operation, 2 had previous pleurodeses, and 1 refused operation. At baseline, the cohort had severe airway obstruction (mean [SD] FEV$_1$ 36.4% [16.8] predicted) with severe gas trapping and hyperinflation (mean residual volume [RV] 218% [53.3] predicted). The average procedure time was 25 (6.6) minutes. There was successful deposition of the blood with no back-spill seen in any of the cases. The mean (SD) dose of midazolam required for the procedures was 2.25 [0.62] mg. The 3-month post-treatment follow-up visit occurred at a mean (SD) of 95.4 [5.8] days after the procedure.

There were large reductions in the group mean change in RV (mean [SD] −0.73 L [0.50], $p = 0.06$), and increases in FEV$_1$ (mean [SD] % change 17.3% [17.8]), reduction in St. George Respiratory Questionnaire score (mean [SD] −11.1 points [13.3]) and increase in the 6-minute walk test (6MWT).

![Figure 1](image1.png)

**Fig 1.** (A) Extended working channel. (B) The intrabullous position of the tip of the working channel is confirmed fluoroscopically.

![Figure 2](image2.png)

**Fig 2.** (A–D) Individual results at baseline and 3 months after bronchoscopic intrabullous blood instillation treatment. Red dash illustrates group means. Patient 3 was unable to complete the 6MWT; hence, results for only 4 patients are shown. (FEV$_1$ = Forced expiratory volume in 1 second; RV = residual volume; SGRQ = St. George Respiratory Questionnaire; 6MWT = 6-mi walk test.)
walk test (6MWT) distance (mean [SD] + 88 m [± 69.9]) (Fig 2). Patients 1, 2, and 4 had considerable and almost universal improvements across all outcome measures, exceeding the minimally clinically important differences by large margins. All 3 patients described their symptomatic improvements as “life-changing.” Computed tomography performed at the follow-up visit demonstrated noticeable reductions in the size of the bullae in patients 1, 2 (Fig 3), and 4 (Fig 4) with evidence of new fibrotic reactions in the bullae lining. One patient was admitted to hospital 8 days after her procedure with symptoms and roentgenographic appearances of pneumonia. She improved with nebulized bronchodilators and intravenous antibiotics for 3 days and was discharged home 5 days after admission, with subsequent complete resolution of the adverse event. Two of the other 4 patients experienced infective exacerbations of their chronic obstructive pulmonary disease on days 4 and 9, respectively, after their procedures. Both fully resolved after 7-day courses of an appropriate antibiotic and prednisolone. No adverse events were noted relative to venesection of 240 mL blood in these patients.

Comment
This novel approach using directed intrabullous autologous blood instillation into giant bullae represents a cheap, minimally invasive, and safe alternative to surgical bullectomy in patients not suitable for surgical treatment. Three of the 5 patients in our cohort had significant and dramatic improvements in quality of life, exercise capacity, and lung function.

In this pilot study, the adverse event profile was acceptable, with the only adverse events experienced involving an inflammatory reaction—a desired outcome in terms of inflammation leading to scarring. The optimal volume of blood instilled to cause the desired effect is unclear. Our data confirm that 240 mL is sufficient to trigger a response but is not a sufficiently large volume for venesection to cause side effects of hypotension. Venesection of 440 mL is routinely undertaken for blood donation and other medical reasons.

Of the 3 strong responders, 2 had end-stage inoperable disease with very poor exercise tolerance, whereas the third patient was relatively young and active but had declined the offer of a bullectomy. Nevertheless, all 3 had similarly large benefits from this minimally invasive treatment. Hence, this technique may be useful as a bridge to operation in young patients with giant bullae.

Trials with other sclerosants and profibrotic agents such as AcriSeal and thermal ablation with steam have shown that maximal benefit occurs after 6 months. We have had a similar experience with further shrinkage of bulla as shown by computed tomography in 2 patients who had longer follow-up times after exiting this trial. It is yet to be determined whether repeat intrabullous blood
instillation (for example, 3 to 6 months after the first treatment) can lead to further shrinkage of bullae.

Although essential for successful lung volume reduction using endobronchial valves, fissure integrity (as a surrogate for the absence of collateral ventilation) is not a factor in the success of treatments aiming to induce a proinflammatory profibrotic response. Bronchoscopic intrabullous autologous blood instillation falls in the latter group, and 2 of the 5 patients had incomplete fissures in the treated lung, both being strong responders.

In conclusion, the data presented suggest that bronchoscopic intrabullous autologous blood instillation into giant bullae can induce shrinkage of the bullae, leading to clinically meaningful improvements in lung function, exercise capacity, and quality of life. This treatment represents a cheap, minimally invasive, widely available, and safe technique to reduce bulla volume. It may serve as an adjunct to surgical bullectomy by delaying the need for operation or as a precursor to it. It may also be considered in the treatment of frail patients receiving maximal medical therapy who are not fit for surgical intervention when no other treatment options are available. Further basic science research is required, but the responses in these pilot study patients are sufficiently impressive to warrant a larger clinical trial.

References