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CASE SERIES

Autologous Blood Patch Pleurodesis for Secondary Spontaneous Pneumothorax: A Narrative Review, a Retrospective Case Series and State of Play in the UK

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ABSTRACT

Introduction: Treatment of prolonged air leak due to secondary spontaneous pneumothorax is challenging. Autologous blood patch pleurodesis (ABPP) is a treatment option. Previous evidence is reliant on single-centre series and underpowered trials and is mostly described in air leaks post cardiothoracic intervention. There are no United Kingdom (UK) wide data.

Methods: Members of the UK Pleural Society were surveyed for their practice and for patients who underwent blood patch. There were 16 respondents from 333 members. Twelve had performed the procedure, and six had kept records and could submit data. Basic demographics, intervention and clinical details of patients were then collected. The study was sponsored by the Audit Department of Northumbria Healthcare NHS Foundation Trust (reference 8124), and Caldicott Clearance for data sharing was provided by the Trust's Information Goverance Board (reference C4221). There was no requirement for informed consent.

Results: Data for 12 patients that received ABPP between 2014 and 2022 in six respiratory centres were assessed. The aetiology of the secondary pneumothoraces was mostly due to chronic obstructive pulmonary disease and end-

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stage interstitial lung disease. The patients had a median age of 75 years. The median air leak time before ABPP was 17 days. A total of 50–100 ml of blood was used for ABPP. Five patients had two attempts at ABPP. Air leak resolved in six patients (50%). Four patients had pleural apposition prior to ABPP. Four patients were diagnosed with hospital-acquired pneumonia following ABPP.

Conclusion: This is the only UK-wide retrospective case series of ABPP of 'medical' patients with secondary pneumothorax. There is widespread variation in care. No formal conclusions can be drawn, and much larger robust datasets are required. An application has been made to the European Respiratory Society to incorporate ABPP within the International Collaborative Effusion database.

Keywords: Blood patch; Pleurodesis; Autologous blood patch; Pneumothorax

Key Summary Points
Autologous blood patch pleurodesis is a simple intervention for persistent air leak.
Previous evidence mostly focuses on post-surgical prolonged air leak.
This UK survey shows widespread variability in autologous blood patch pleurodesis use.
Autologous blood patch pleurodesis can be effective in treating prolonged air leak, but this patient group experiences high levels of morbidity and mortality.
Ongoing collaboration is required to increase knowledge of the efficacy and risks of autologous blood patch pleurodesis.

INTRODUCTION

Pneumothorax is traditionally defined as primary spontaneous (in patients with no apparent lung disease or history of trauma) or secondary spontaneous (in patients with pre-existing lung disease, or in those above 50 years of age with significant smoking history and no trauma) [1]. The aetiology of secondary spontaneous pneumothorax (SSP) is usually the rupture of blebs or emphysema-like structures. This results in an air leak: flow of air into the pleural space, through a tract either from the lung (alveolar-pleural fistula) or in central airways (bronchopleural fistula) [1, 2]. The management of any pneumothorax is patient centred. In SSP, if a pleural intervention is indicated, this is usually a small or large bore drain or even ambulatory devices [3]. The purpose of any intervention is to allow the air in the pleural space to drain whilst allowing time for the disruption in the pleura to heal and for the air leak to settle. In those with a prolonged air leak (defined as ongoing air leak after 5–-7 days, with a prevalence of 20–40% in patients with SSP), various management strategies can be employed [4, 5]. National guidelines suggest an early referral to cardiothoracic services for surgery (which might incorporate pleurectomy, abrasion, pleurodesis or bullectomy, which might not be appropriate for all patients due to underlying severe fibrotic lung disease or end-stage chronic obstructive lung disease to cite just two examples) [5]. Endobronchial valves can also be used, although these still require patients to be fit for a general anaesthetic or deep sedation [6]. Non-surgical approaches include the use of talc, tetracycline and autologous blood to try seal the air leak and achieve pleurodesis, or the use of ambulatory bags to allow the patient to mobilise and allow the leak to heal by itself over a longer time period [7, 8]. Talc pleurodesis has the highest success rates but requires visceral and parietal pleural apposition, which might not occur if an air leak remains high. Autologous blood patch pleurodesis (ABPP) involves instilling blood from the patient into his/her own pleural space. It is an option in patients with secondary pneumothoraces and a prolonged air leak who are not fit for surgical and bronchoscopic approaches, and in whom talc might have failed to enable air leak cessation or in whom there are large areas of pleural non-apposition [9].

There is no published case series in patients with SSP undergoing ABPP from the United Kingdom (UK) and no consensus on how to perform ABPP. In this article, we describe how to perform the procedure, the results of the first UK-wide survey of ABPP practice and a resultant retrospective case series. We also provide a narrative review of the clinical context of and available literature of ABPP.

UK-WIDE SURVEY OF PRACTICE

An online survey, created on GoogleForms (blood pleurodesis survey – Google Forms, Electronics Supplementary Material (ESM) Appendix 1) was distributed to 333 members of the UK Pleura Society. The UK Pleural Society was created in 2018 and brings together doctors and nurses with an interest in pleural disease [10]. Results were analysed descriptively. Sixteen responses (5%) were recorded, all from different institutions. Seventy-five percent had performed the procedure 0–6 months ago and 46.2% more than 12 months ago. All the physicians had instilled varying amounts of blood (range 60–120 ml). Some had kept records and could contribute to a retrospective case series.

RETROSPECTIVE CASE SERIES

Methods

A retrospective case series was not deemed research by the Health Research Authority (Fig. 1 in ESM Appendix 1), and no formal ethical approval was required for the sharing of anonymised data. The study was sponsored by the Audit Department of Northumbria Healthcare NHS Foundation Trust (reference 8124), and Caldicott Clearance for data sharing was provided by the Trust's Information Goverance Board (reference C4221). There was no requirement for informed consent. The case series was performed according to the CARE guidelines [11] (ESM Appendix 1). A case record form (ESM Appendix 1) was used for those identified in the survey who had kept records. Basic demographics, details of intervention before and after ABPP and of the ABPP itself, and outcomes were collected. Prolonged air leak was defined as an air leak of more than 5 days.

RESULTS

Twelve patients underwent ABPP between November 2014 and August 2022, from six different units. These are listed in ESM Appendix 1, as well as how the procedure was performed.

Demographics are summarised in Table 1.

One patient had an initial attempt at conservative management [79-year-old male, with metastatic colorectal cancer and chronic obstructive pulmonary disease (COPD), developing a pneumothorax 48 h into admission due to pleural metastases]. One patient had a needle aspiration which failed (72-year-old male with COPD and heart failure). All 12 had a chest drain inserted (11 12 Fr small bore drains and 1 28 Fr drain). Seven patients had an additional drain inserted (either additionally or as replacement for the initial drain); these were: one 12 Fr, one 16 Fr, two 18 Fr, one 24 Fr and two 28 Fr drains. Six patients had a third drain inserted (five 28 Fr and one 24 Fr). When the prolonged air leak was diagnosed (air leak after more than 5 days), none was thought fit for surgery. Talc pleurodesis was tried in two patients first. The median length of time of the prolonged air leak before blood instillation was 17 days (IQR 18.5, mean 18 days). Digital suction and/or digital leak devices were in use in only one patient (Thopaz – Medela), and leak was measured at 2000 ml/min. For all the others, three chest drains bubbled only on coughing, three had gentle bubbling with respiration/talking and in five there was vigorous continuous bubbling.

Table 2 below describes the specifics around the ABPP procedures.

Table 3 below describes the characteristics between the responders to the first ABPP and those who did not (non-responders).

The success rate of the first ABPP was 50% (6 patients) over a median of 5 days (IQR 4). For the non-responders, one died of a hospital acquired pneumonia. Two underwent talc

Table 1 Patient characteristics with SSP undergoing ABPP

Total number of cases	12		
Sex	8 males (67%)	4 females (33%)	
Median age (years)	75	IQR 11	
Side of pneumothorax	4 left sided	8 right sided	
Mean height (cm)	169		
Mean weight (kg)	58.6	Mean BMI 20.6	
Underlying lung disease	COPD 6, end-stage fibrotic lung disease 5, diffuse carcinomatosis 4, bronchiectasis 1		
Smoking status	7 ex-smokers	2 current smokers	3 never smokers
Cannabis smoking status	10 never smoked cannabis (unknown 2)		
History of pneumothorax	4 (3 on the ipsilateral side, 1 on the contralateral side)		
Family history of pneumothorax	No in 10, unknown status in 2		

ABPP autologous blood patch pleurodesis, *IQR* interquartile range, *SSP* secondary spontaneous pneumothorax, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease

pleurodesis (had not received talc before), and the leaks resolved. Two underwent endobronchial valve placement under deep sedation rather than general anaesthetic, and one underwent thoracoscopic wedge resection and bullectomy; those air leaks settled.

DISCUSSION

This is the first description of a case series of patients with SSP from the UK undergoing ABPP. There is significant variance in initial management of SSP, instillation of talc, volume of blood instilled and timing of instillation. This is consistent with the two most recent published reviews on the topic. The first one by Muruganandan et al. in 2017 included 18 studies in the final analysis [12]. Only 2 of the 18 studies were graded as moderate quality. The second review by Shafiq et al. was more recently published [9]. Seven studies were assessed, including two randomised controlled trials. The authors again found widespread variation in how patients were selected, the definition of prolonged air leak (from 2 to 7 days), the amount of pleural apposition before ABPP instillation and the volume of blood instilled (between 50 and 100 ml). There was almost no clamping of the drain post ABPP, with elevation of the chest drain above the patient commonplace. ABPP tended to be performed between 2 and 7 days after chest tube placement, whose sizes were between 20 and 28 Fr. There was also

Table 2 Specifics of the ABPP procedures

Median length of time to ABPP (days)	17 (IQR 18.5)
Blood volume instilled for first ABPP (ml)	50 (4 patients), 80 (2), 100 (6) (mean 80)
Success of first ABPP (cessation of leak within 5 days)	50% (6 patients) over a median of 5 days (IQR 4)
Blood volume instilled for second ABPP (ml)	50 (2 patients), 100 (3 patients)

ABPP autologous blood patch pleurodesis

Table 3 Comparison of responders and non-responders to first ABPP

	Responders (*n* = 6)	**Non-responders (*n* = 6)**
Median age (years)	75 (IQR 24)	73.5 (IQR 8)
Median weight (kg)	48.6 (IQR 5.9)	56.5 (IQR 14.1)
Smoking status	4 ex-smokers, 2 current, 1 never	3 ex-smokers, 1 current, 2 never
Co-morbidities	COPD (3), cancer (2), fibrosis (2)	COPD (4), fibrosis (2)
Volume of blood (ml)	50 (2), 80 (2), 100 (2)	50 (1), 80 (2), 100 (3)
Duration of prolonged air leak before ABPP (days)	7 (IQR 11)	18 (IQR 12)
Pleural apposition (more than 75%)	Present in 3 (50%)	Present in 1(16%)
Median length of stay (days)	27 (IQR 32)	41(IQR 19)
Complications	3 pneumonias	1 pneumonia

ABPP autologous blood patch pleurodesis, *COPD* chronic obstructive pulmonary disease

a trend towards a shortened length of stay with ABPP. Thus, there are multiple unanswered research questions, and the authors suggest large randomised trials.

There are several proposed mechanisms of action for ABPP. ABPP may cause a pleural inflammatory response resulting in adhesions between the visceral and parietal pleura [13] as evidenced by transient fever and raised inflammatory markers described in some patients following ABPP [14, 15]. It has been suggested that the volume of blood used may fill the intrapleural space obliterating the space created by a pneumothorax [16], although volumes of blood used are small compared with the volume of pneumothorax. ABPP may exert a patch effect with coagulated blood mechanically sealing visceral pleural defects. This is the most likely mechanism given the lack of pleural adhesions seen following successful ABPP in animal models [17] and that prolonged air leak ceases with ABPP far quicker than could be explained by inflammatory pleurodesis [13, 15, 18].

The two largest series in patients with SSP are from from Koegelenberg et al. [19] and Aihara et al. [20]. Koegelenberg et al. analysed 46 episodes of SSP with prolonged air leak (mean duration prior to ABPP 22 days). ABPP was successful in 72% of cases, with 52% resolving within 24 h. Adverse events included three episodes of spontaneously resolving transient fevers and three empyemas which required antibiotics and further drainage [19]. Aihara et al. reviewed 59 pneumothoraces in 34 patients with interstitial lung disease, over 12 years. ABPP was used on 22 occasions, and the air leak resolved in 73% of cases [20]. There have been two randomised controlled trials of ABPP in SSP. Ibrahim et al. randomised 47 patients with a SSP and a prolonged air leak (defined at 3 days) to ABPP (50 ml of blood) versus conservative management [21]. Only approximately 30% of patients in each group had full pleural apposition. The success rate of ABPP was 78.3% versus 8.3% in the conservative group. They also showed a 5-day reduction in time to cessation of air leak and length of hospital stay. Pleural infection occurred in nine patients, and the authors suggested that ABPP should be performed aseptically. The other randomised trial is a study looking at dosage of blood comes from Cao et al. (a randomised, single-blinded cross-over study) which showed that 1 ml/kg is perhaps the optimal dose, but the study involved only 44 patients with advanced chronic obstructive pulmonary disease [22]. However, Andreetti et al. showed a statistically difference in duration of drainage between 50 and 100 ml, in favour of 100 ml. The study was done in patients post lobectomy and has not been replicated since [16]. There is

thus no consensus on how much blood to instil. When specifically assessing SSP, Evman et al. analysed 31 patients who underwent ABPP with a first episode of SSP and ongoing air leak after 3 days [23]. Within 24 h, 94% of the air leaks had resolved and the chest tubes could be removed. The authors highlighted the economic benefit of ABPP as the length of stay was reduced by approximately 3–4 days. Ando et al. performed a small prospective observational study of 11 patients with 17 secondary pneumothoraces, all of whom had a prolonged air leak [24]. Overall, 50 ml of blood enabled cessation of prolonged air leak in ten cases (59%). Six of these had pleural apposition. There were no reported side effects.

In our case series, the drain size was varied due to physicians' choice and experience. The volume of blood instilled was approximately 1 ml/kg in three patients; the others had more than 1 ml/kg of blood instilled, most commonly 100 ml in five patients as per Rinaldi's protocol [25]. Pleural apposition was present in only 4 of 12 patients, reflecting the supposition that ABPP is useful in those without apposition.. The duration of air leak before ABPP was 7 days (IQR 11 days) for those who responded to the first ABPP and 18 days (IQR 12 days) for those not responding.

This study has numerous limitations. The survey was disseminated to a UK-wide group of pleural specialists, and not everyone who has done an ABPP might have been part of the society. The series is subject to recall bias, and a number of centres had done an ABPP but not kept records. Thus, only a small number of patients were included in the study. Due to these small numbers, meaningful statistical interpretation is not possible, and we have limited ourselves to descriptive methods only as no conclusions can be drawn. There are also variations in practice in chest drain sizes, duration of prolonged air leak before ABPP attempt and methodology of the ABPP itself. Due to those limitations, we also cannot provide enough evidential on how to choose ABPP as a procedure, except for what is already described in the literature [25].

CONCLUSIONS

We present the first description of ABPP in SSP in patients from the UK. We show variability in practice, and larger, multicentre datasets are required.

Clinical Research Collaborations within the European Respiratory Society were established in 2013 and encompass a number of areas of respiratory medicine [26]. Through this initiative, the International Collaborative Effusion (ICE) database was launched in 2017 and centres were invited to contribute retrospective data on four separate disease entities: chylothorax, eosinophilic pleural effusion, non-specific pleuritis and non-malignant effusions secondary to cardiac, renal or hepatic dysfunction [27].

Through this collaboration, we plan to launch a multicentre retrospective study of ABPP, inviting centres to enter all cases within the past 10 years (the appropriate coding searches will be need to done within each hospital) with a standardised case record form, a clear definition of prolonged air leak, outcomes and recurrence rates. This should not only give us a unique insight into worldwide practice of ABPP but also create a network of interested centres, and possibly form the basis of a network for future studies in ABPP. Those future studies should have strict inclusion and exclusion criteria, have multiple interventional arms looking at dosage of instilled blood, duration of air leak and chest tube size for example and should be conducted in multiple centres for widespread applicability.

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Prior presentation. Part of the data has been presented as a poster at the Winter British Thoracic Society Meeting, London, November 2022.

Data availability. The raw data is can be shared upon consideration of a reasonable request.

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