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Efficacy of an Autologous Blood Patch for Prolonged Air Leak: A Systematic Review

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ABSTRACT

BACKGROUND Prolonged air leak after pulmonary surgery remains a clinical challenge and sometimes needs surgical reintervention. An autologous blood patch (ABP) may provide a noninvasive method to stop air leak. Its value, however, is debatable. The aim of this systematic review is to synthesize evidence regarding the efficacy of ABP in patients with prolonged air leak.

METHODS A comprehensive search for published studies was performed in the Medline database, Embase, and the Cochrane library. Randomized controlled trials, case-control studies, and case series in which a postoperative ABP was performed were included. Findings from these studies were tabulated and data were synthesized graphically (PROSPERO registration number CRD42020157591).

RESULTS A total of eight studies was included in the analysis, comprising 151 patients. Studies demonstrated heterogeneity in ABP timing and practice, and an intermediate to high risk of bias was scored. The majority of studies demonstrated a beneficial effect of the ABP, with a high rate of success of more than 89%. One randomized trial did not find a difference in time to cessation of air leak after ABP compared with conservative tube thoracostomy. The overall complication rate was 10%.

CONCLUSIONS Quality of included studies is limited owing to lack of comparison groups. Synthesized data in this review demonstrate a high rate of successful procedures and acceptable complication rates, and seems encouraging enough to justify a large randomized clinical trial on the use of ABP for patients who have prolonged air leak after thoracic surgery.

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Persistent air leak (PAL) after pulmonary surgery is a challenging problem. According to The Society of Thoracic Surgeons (STS) and the European Society of Thoracic Surgeons (ESTS) present guidelines, PAL is defined when lasting more than 5 days.[1] There is a wide variation in the incidence, prevention, and treatment of PAL. It is among the most common complications after pulmonary surgery, with a reported incidence rate of 8% to 10%.[2,3] Persistent air leak is associated with an increased length of hospital stay and significant morbidity, which subsequently leads to increased costs.[4,5] Preventive measures during surgery include fissureless surgical technique and application of sealant or glue, but they may not completely prevent PAL.[6,7]

When PAL occurs, it can be treated by surgical repair, prolonged tube thoracostomy, endobronchial valves, or instillation of sealants. The injection of autologous blood through the thoracostomy tube, referred to as an autologous blood patch (ABP), may provide a simple and inexpensive treatment modality. An autologous blood patch is common in a wide variety of clinical practices, although its benefit is debated by others. The discussion is generally dominated by believers and nonbelievers. Several studies have reported the beneficial effect of

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ABP, especially in patients with a spontaneous pneumothorax, although that has not led to exclusive application of this technique in clinical practice.[8] Therefore, insight into the available benefit of an ABP after surgery is required, and merging of data may put the available evidence in a balanced perspective.

This systematic review evaluates the role of ABP in patients with postoperative PAL after either lobectomy, segmentectomy, wedge resection, or lung volume reduction surgery (LVRS). It aims to review published data to determine safety and efficacy of ABP as an additional treatment to stop air leak compared with conservative tube thoracostomy treatment.

METHODS

STRATEGY FOR SEARCH OF ARTICLES AND SELECTION CRITERIA. A comprehensive search for published studies was performed in Embase and Medline databases (OvidSP software; Ovid Technologies, New York, NY), from inception to November 1, 2020, using a Boolean search term combination (Supplemental Material). The Cochrane library was also searched. Given the expected low number of published studies, the search terms were limited to intervention and patient and no search strings for comparison and outcome were added. Reference lists of selected studies were assessed for additional studies. The Grey literature database System for Information on Grey Literature (SIGLE) and the Clinical Trials Registries (clinicaltrials.gov) were searched for relevant records of unpublished studies. Original studies on the use of ABP at least 5 days after parenchymatous pulmonary resection (lobectomy, segmentectomy, wedge resection, LVRS) that were published in English with at least 3 patients meeting the criteria were selected. Studies including patients with (secondary) spontaneous pneumothorax or pleural effusions were not included given the distinct origin of this disease entity. Selection of studies was performed independently by two of the authors (N.H. and E.J.H.). Discrepancies were discussed until consensus was reached.

ANALYSIS AND DATA SYNTHESIS. Data regarding type of surgery, volume of the blood patch (in milliliters), details on the application procedure, duration of PAL, age, success rate, time to air leak cessation, type of resection, complication rate, and type of complication were extracted from all studies if available independently by two authors (N.H. and E.H). Discrepancies were discussed until consensus was reached. Data were merged and mean was calculated for duration of PAL. A median could not be calculated as individual patient data were generally not reported. For both the RCT as well as the noncontrolled intervention studies, data were extracted and interpreted against findings from the other included studies. A meta-analysis was not considered appropriate given the heterogeneity and quality restraints of included studies. The primary endpoint was cessation of air leak enabling drain removal. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting the results.[9]

REGISTRATION. The study design was registered and published at the International Prospective Register of Systematic Reviews (PROSPERO),[10] registration number CRD42020157591.

RESULTS

SEARCH RESULTS. A total of 76 studies were retrieved by the search in the Medline database and 158 were selected from Embase (Figure 1). An additional 23 studies were found in the Cochrane Library. Duplicates were removed (n = 90), as well as conference abstracts (n = 74). After screening title and abstract, another 76 studies were excluded (Figure 1). The remaining 17 studies were assessed by full text for eligibility. We excluded one study owing to application of ABP during the initial operative procedure, and in two studies, data could not be extracted. One study performed an ABP on the third postoperative day in combination with a pneumoperitoneum and was therefore excluded. Eight studies were eligible for inclusion, of which the main characteristics are listed in Table 1 for the nonrandomized studies[11-16] and in Table 2 for the randomized controlled studies.[17,18] No additional studies were added after cross-referencing.

QUALITY ASSESSMENT AND RISK OF BIAS. The majority of included studies were cohort studies series and only three controlled intervention studies were included, of which one used a historic cohort for comparison of efficacy of ABP and was therefore regarded as a cohort study.[11] Appraisal of internal validity, using a standardized approach, was feasible for the randomized controlled trials (RCTs) using the Cochrane Risk of Bias Tool (Figure 1).[19] The study by Shackcloth and colleagues[18] demonstrated an intermediate risk of bias, whereas the study by Ploenes and associates[17] carried a high risk of bias due to insufficient methods and outcome reporting (Figure 2A). Both studies did not perform a sample size calculation. Quality assessment of the cohort studies was analyzed using the Methodological Items for Non-Randomized Studies (MINORS) score.[20] This analysis revealed major limitations regarding the quality of included cohort studies in terms of consecutive inclusion, prospective data registration, assessment of endpoint, and calculation of sample sizes (Figure 2B).

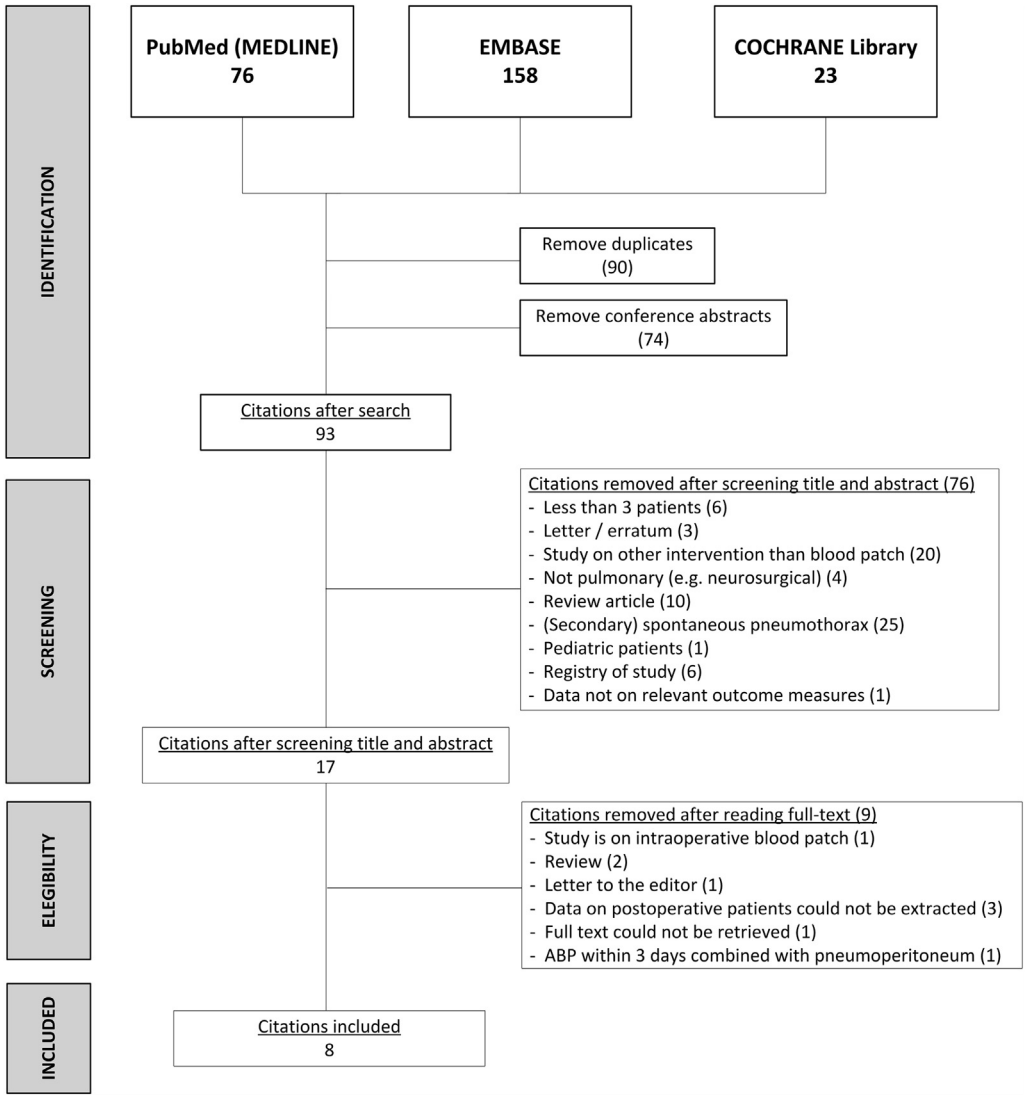

FIGURE 1 Flow chart of study identification and selection for eligibility. (ABP, autologous blood patch.)

PATIENTS AND PROCEDURE. From eight studies, 151 patients were included in the current study. The age of included patients was between 22 and 83 years. There were 93 male patients and 48 female patients (one study did not report sex). Most patient were treated for a malignancy and underwent lobectomy. A minority was treated with volume reduction surgery or wedge resection. Data on pulmonary health status and comorbidities were generally not reported. The median time to intervention from start of the air leak varied mostly between 5 and 11 days in the different studies; only one study performed an ABP after a mean of 16.3 days after initial surgery. The method of ABP application was overall rather similar among the studies. Blood was drawn from the patient's vein in a nonheparinized syringe and subsequently instilled into the thoracostomy tube under sterile conditions. The amount of instilled blood varied between 24 mL and 250 mL, but was most often in the range of 100 to 150 mL (Figure 3). Clamping of the thoracostomy tube was performed in only two studies.[14,17] In all studies, the chest tube was suspended over a drip stand above the level of the patient's chest after instillation to allow air to exit and the blood to remain in the thoracic cavity. The duration of this maneuver, if reported, varied between 30 minutes and 24 hours. Rotation of the patient to optimize distribution of the instilled blood patch through the thoracic cavity was performed

TABLE 1 Details of Included Nonrandomized Studies

Author	Year	Study Type	Patch Vol. (mL)	No. Pts.	Age (range)	Days to ABP	Range	Resection Type	Siphon	Success Rate (%)	Days to Success	2nd ABP	Complications	Reop.	Remarks for RCTs
Andreetti[11]	2007	Cohort	50-100	40	66.9 (NR)	6	0	40 lobectomies	NR	100	1.8	0	None	0	50 vs 100 mL, compared to historical cohort
Droghetti[12]	2006	Cohort	50-150	21	61 (22-83)	11[a]	5-13	14 mass resections, 4 LVRS, 2 decort.[b]	6 h	100	0.9	4	2 fever, 1 PPE	0	…
Dye[13]	2020	Cohort	45-140	19	67.9 (50-78)	7	4-19	15 mass resection; 4 LVRS	NR	89	NR	7	Not consistently reported	1	…
Lang[14]	2004	Cohort	50	11	56 (31-82)	7	6-11	8 mass resections, 2 WR for blebs	No	100	0.7	0	1 pneumonia, 2 low-grade fever with positive culture	0	…
Oliveira[15]	2010	Cohort	24-200	10	NR	9	5-12	10 mass resections	30 min-24 h	90	1.6	1	Not specified	1[c]	…
Rivas de Andrés[16]	2000	Cohort	50-250	6	55 (36-66)	16.3[a]	10-23	6 mass resections[d]	24 h	100	1	0	None	0	…

[a]Mean; [b]Empyema; [c]Reoperation due to tumor-involved resection margin; [d]Four lobectomies, one wedge, one segmentectomy. ABP, autologous blood patch; AF, atrial fibrillation; decort., decortication; LVRS, lung volume reduction surgery; No. Pts., number of patients; NR, not reported; PPE, prolonged pleural effusion; RCT, randomized controlled trial; Reop., reoperation; Vol., volume; WR, wedge resection.

in 6 of 8 studies. Bed rest was prescribed in two studies for 40 minutes and 2 hours, respectively, and duration was not reported in the other studies. Antibiotic prophylaxis was not administered.

RESULTS

The efficacy of ABP varied between included studies. Most studies demonstrated a beneficial effect of the ABP, with a high rate of success of more than 89% (Table 1). For the studies that demonstrated a beneficial effect of an ABP, the mean time to air leak cessation was 1.6 days (Figure 4). A second or third application of ABP was performed in four studies if the initial ABP failed (in 20 of 70 patients). The second ABP led to cessation of air leak in 90% of these patients. The study by Ploenes and associates[17] was the only study that did not demonstrate a beneficial effect of an ABP compared with tube thoracostomy treatment alone. This study was an RCT in which 10 patients underwent an ABP on the fifth and sixth day of PAL and 14 patients were continuously treated with tube thoracostomy.[21] All patients demonstrated cessation of air leak after a median interval of 9 days (range, 2 to 20), but this was not different between study groups. Therefore, this RCT did not provide evidence indicating benefit of ABP and recommended operative closure instead.

Another RCT, by Shackcloth and colleagues[18], randomized 20 patients to either instillation of 120 mL autologous blood or tube thoracostomy alone. The thoracostomy alone group crossed over to the ABP group if the air leak was still present on the 10th postoperative day.[18] Two of the patients who underwent conservative management showed cessation of PAL, whereas 77% of patients in the ABP group were free of PAL within 48 hours. Eventually, all patients had cessation of air leak within 5 days, sometimes after the application of a second ABP.

The optimal volume of ABP was studied by Andreetti and colleagues.[11] They included 25 patients with PAL who were randomly assigned to two groups in which either 50 mL or 100 mL autologous blood was instilled. These groups were compared with a retrospective cohort of the last 15 patients showing PAL.[11] They found that air leak ceased faster in patient who received 100 mL ABP compared with patients who received 50 mL ABP (1.5 vs 2.3 days).[11]

Complications were reported in 9 patients (10%) from six studies comprising 93 patients who were treated with an ABP. The majority (7 of 9) of these complications were Clavien-Dindo grade I or II. There were 6 patients who had fever, and pneumonia was reported in 1 patient. One case of empyema was reported, which could be treated by drainage and antibiotic treatment.[18] One patient had prolonged pleural

TABLE 2 Details of Included Randomized Controlled Studies

Author	Year	Study Type	Patch Vol. (mL)	No. Pts.	Age (range)	Days to ABP	Range	Resection Type	Siphon	Success Rate (%)	Days to Success	2nd ABP	Complications	Reop.	Remarks for RCTs
Ploenes[17]	2020	RCT	100	I, 10; C, 14	I, 65.5 (50.4-78); C, 66.6 (56.2-79.1)	5	0	I, 5 lobectomy, 5 W/ LVRS; C, 7 lobectomy, 1 bilobectomy, 6 W/ LVRS	NR	I, 7/10; C, 11/14	I, 9 (5-23); C, 9 (2-20)	NR	None	3[a]	No sample size calculation performed.
Shackcloth[18]	2006	RCT	120	I, 10; C, 10	I, 63 (61-72); C, 64 (53-70)	5	0	20 lobectomies	2 h	100	I, 0 (0-2); C, 6 (4-7)	I, 3; C, 5	I, 1 empyema; C, 2 fever[b]	0	Patients in group C crossed over after 10 days.[c] No sample size calculation performed.

[a]Three patients from either group underwent revision surgery; [b]After cross over; [c]Air leak ceased spontaneously in 2 patients in control group. ABP, autologous blood patch; C, control group; I, intervention group; LVRS, lung volume reduction surgery; No. Pts., number of patients; NR, not reported; RCT, randomized controlled trial; Reop., reoperation; Vol., volume; W, wedge.

effusions (more than 200 mL per day) for which the patient was discharged with a Heimlich valve.[12] None of the patients needed surgery for postprocedural complications.

COMMENT

Persistent air leak can be treated by a variety of interventions. This systematic review evaluated the current evidence regarding the use of ABP and found that most studies reported a beneficial effect. Data from this systematic review provide support for the beneficial effect of ABP, as it may contribute to rapid cessation of PAL and considering that the alternative is surgical reintervention. Persistent air leak remains one of the most common complications after pulmonary surgery.[4,5,22] The associated morbidity and prolonged hospital stay demand effective treatment.[4,5] Although smaller studies have reported the beneficial effect of ABP for both patients with spontaneous pneumothorax and postsurgical patients, its use in clinical practice has not been widely embraced hitherto.[8,23]

This study has systematically reviewed the literature for the efficacy of ABP for patients after thoracic surgery. By excluding all patients who underwent ABP for other causes, such as spontaneous pneumothorax, and only including patients who underwent a parenchymal resection, findings from this study can be applied to clinical surgical practice directly. Data were included from 8 studies on 151 patients, of whom 122 underwent ABP for PAL.

The use of ABP was first described by Robinson in 1987.[23] In 25 patients with chronic or recurrent spontaneous pneumothorax, a notable 85% resolved after instillation of 50 mL of autologous blood into the thoracic cavity. Its use was first described in a postoperative patient in 1992 by Dummier and associates.[24] Although allegedly effective, its mechanism of action is not well understood. It has been hypothesized that instillation of blood into the thoracic cavity may either function as pleurodesic agent or may function as a patch at the site of air leak. The rapid mechanism of action, as described by cessation of air leak within minutes, substantiates the likelihood of the latter mechanism. It is unclear whether pleural adhesions do develop as data on the intrathoracic appearance after ABP are lacking. An animal study by Mitchem and colleagues[25] compared the effects on the pleural surface of rabbits, after administration of autologous blood, doxycycline and talc slurry. Although doxycycline and talc led to pleurodesis and adhesions, autologous blood exhibited no significant pleurodesis 30 days after instillation. That supports the “patch” hypothesis of ABP, but would also allow safe salvage surgery in the event of PAL after ABP.

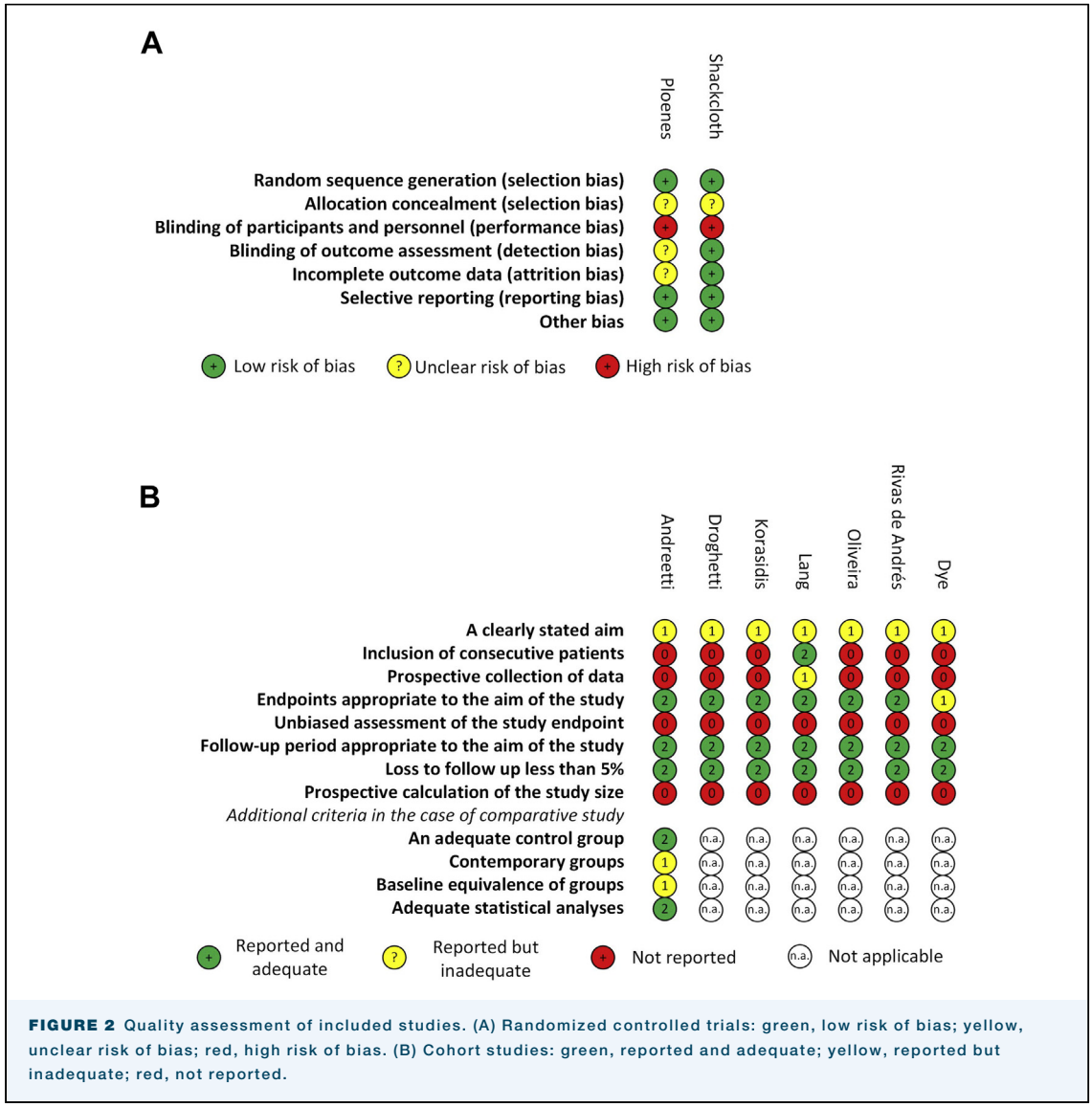

FIGURE 2 Quality assessment of included studies. (A) Randomized controlled trials: green, low risk of bias; yellow, unclear risk of bias; red, high risk of bias. (B) Cohort studies: green, reported and adequate; yellow, reported but inadequate; red, not reported.

The ABP application is not yet a uniform procedure, nor is there a best practice consensus. Although most studies have described a foremost similar procedure of ABP and all included studies share the same key elements, it is unclear which steps in the application and what volume of ABP are essential to achieve an optimal effect. The majority of studies emphasize that changes in position of the patient may aid in distribution of blood throughout the pleural cavity, although evidence for this step is not provided. On the contrary, a study with radiolabeled tetracycline has shown that distribution of fluid is uniform within seconds of instillation within the thoracic cavity.[26] Another study using 99mTc-sestamibi labeled talc on the distribution of talc suspension during treatment of malignant pleura effusion demonstrated that rotation did not affect the dispersion of talc suspension.[27] Moreover, the clotting time of blood within 2 to 8 minutes renders further distribution of the ABP beyond this timeframe unlikely. Studies regarding the optimal volume of ABP are limited. Only one study, included in this review, compared 50 mL vs 100 mL ABP and found a statistically significant reduction in time to deal the leak, time to chest drain removal, and time to hospital discharge in the 100 mL ABP group.[11] The appearance of a tension pneumothorax after ABP has been reported in the literature, but did not occur in the patients from the included studies.[28] Most studies explicitly mention the precautionary measure of flushing the drain directly after instillation of the ABP with saline to prevent clotting in the drain.

STUDY LIMITATIONS. When interpreting the data, there are several issues that should be addressed. The included studies were performed between 2000 and 2018. Most studies were performed before the introduction of video-assisted thoracoscopic surgery, limiting the availability of recent data in an era in which a shift toward minimally invasive procedures has been made. The review is limited by the quality of the available data in the individual studies and heterogeneity of performed ABP procedures. Although two RCTs were included, most included studies were of a retrospective nature and often noncomparative, which increased the risk of selection and reporting bias. The quality assessment for both interventional as well as noninterventional demonstrated an intermediate to high risk of bias, which should be taken into account. For both RCTs, no sample size calculation was performed, which may limit power, especially when no differences between groups has been demonstrated. It cannot be determined which patients have been selected to undergo ABP, and which patients may not have been treated by ABP despite the appearance of PAL. Therefore, this study cannot provide any insight into patient selection for ABP and into factors that may improve or hamper the effect of ABP, such as the size of the air leak.

Clinical background of enrolled patients could not be analyzed in the current review as data on comorbid conditions such as chronic obstructive pulmonary disease or interstitial lung disease as well as data on type of surgery were generally not reported in the included studies. Similarly, the size of air leak was not consistently reported in the included studies, although some studies used a (modified) classification as reported by Cerfolio and associates.[29] Alternatively, objective quantification could be achieved by the use of a digital air leak meter incorporated within the drainage system. Moreover, there were no data on the chest radiographic appearance of the residual lobe.

It is not inconceivable that an ABP may be less successful in patients in whom the lobe remains fully collapsed despite drainage and suction. However, none of the studies provided information on this issue. Furthermore, the reportedly high rate of successful ABP applications is suggestive of a selective reporting. There was only one study that did not demonstrate a beneficial effect of an ABP compared with tube thoracostomy treatment alone; therefore, it is not inconceivable that other studies in which a negative effect of ABP was demonstrated were not published. A multicenter RCT with a higher number of patients may strengthen the earlier findings from smaller cohorts studied and may help to translate findings to clinical practice.

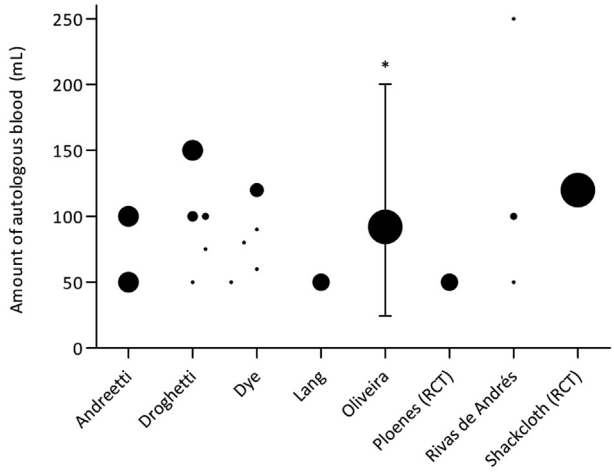

FIGURE 3 Amount of autologous blood instilled through chest tube. Size of dot represents number of patients. *Mean and range. (RCT, randomized controlled trial.)

CONCLUSION. Findings from this systematic suggest a beneficial effect of an ABP for patients who have PAL after thoracic surgery. The procedure appears to achieve high rates of air leak cessation against an acceptable complication rate, but heterogeneity of data and intermediate to high risk of bias limit validity of data. The evidence is encouraging and might serve as a foundation for future direct comparison studies or larger studies where the true effectiveness of ABP can be assessed.

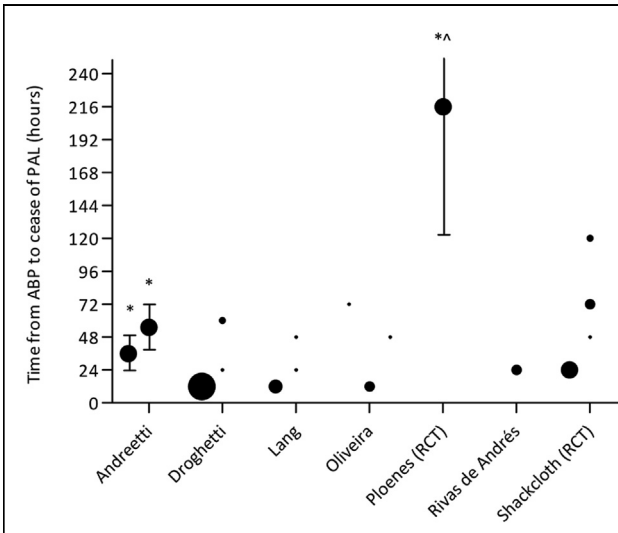

FIGURE 4 Time from application of autologous blood patch (ABP) to cessation of persistent air leak (PAL) in included studies. Size of dot represents number of patients. Only studies supplying individual patient data are included. *Median time and range. ^Upper range is 552 (not depicted). (RCT, randomized controlled trial.)

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