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Journal

Respiratory Investigation Volume 58, Issue 1, January 2020, Pages 68-73

Published

27 Mar 2017

URL

https://doi.org/10.1016/j.resinv.2019.09.004

The new procedure of bronchoalveolar lavage using a balloon catheter in diffuse lung disease

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Abstract

Background: Various procedures for bronchoalveolar lavage (BAL) have been developed. BAL need the snugly wedge between the bronchoscope with the inner surface of the bronchus. Whether or not BAL can even be performed in the targeted position cannot be determined until just before the procedure. We examined bronchoalveolar lavage performed using a balloon catheter in order to evaluate the stability of the procedure itself and the quality of the specimen obtained.

Methods: The tip of a disposable balloon catheter was passed through the orifice of the B^5a bronchus, and the balloon was expanded at the B^5a. A 50-ml syringe of saline was instilled, and gentle hand suction was performed. This procedure was repeated 2 more times (total 150 ml).

Results: In all 13 patients of this study, the balloon of the catheter was inflated at the B^5a. The median recovery rate was 34.92%±13.22%. These values were comparable to previously obtained BAL data (control group, N=56) from our facility. The bronchoalveolar lavage fluid (BALF) findings and final diagnosis, with the exception of one undiagnosed case, were consistent. Overall, four patients suffered an adverse event during BAL (hypoxemia). All cases were dealt with by increasing the oxygen flow rate, and the event did not affect the subsequent examinations.

Conclusions: Using a balloon catheter made it possible to perform BAL at the intended bronchus. The quality of the obtained specimen was also acceptable.

Keywords: bronchoalveolar lavage, balloon catheter, diffuse lung disease, bronchoscopy.

Abbreviations: BAL; bronchoalveolar lavage, BALF; bronchoalveolar lavage fluid, HRCT; high-resolution computed tomography.

Introduction

Bronchoalveolar lavage (BAL) is a diagnostic tool applied worldwide in patients with respiratory illnesses, including interstitial lung disease. However, there is considerable variability in the procedures. BAL is performed with a fiberoptic bronchoscope in a wedge position within the selected bronchopulmonary segment. The American Thoracic Society guideline suggests that the BAL target site be chosen based on high-resolution computed tomography (HRCT) performed before the procedure rather than choosing a traditional BAL site (i.e. the right middle lobe or lingula) [1]. Some reports suggest that HRCT may be useful for selecting the site for lavage [2, 3]. Further complicating matters is the fact that whether or not BAL can even be performed in the targeted position cannot be determined until just before the procedure.

The anatomic lung volume of a medial or lateral segment of the middle lobe is estimated to be 152 ml (Segment 4) and 125 ml (Segment 5) [4], and a subsegment represents 50% of a segment (76 and 62.5 ml, respectively). Therefore, depending on the location of the wedge, the amount of saline solution required may vary. In general, the total instilled volume of saline should be no less than 100 ml. Three to five sequentially instilled aliquots are generally used [1]. However, the total volume of saline and the size of the individual aliquots are affected by the size of the available syringe, which varies among countries.

More BAL data must be accumulated through common procedures. To that end, it is important to inject a fixed amount of saline solution at a fixed place. In order to resolve this nonuniformity associated with BAL, a method using a balloon catheter was developed. We examined the safety and whether or not BAL can be performed at a predetermined site (B^5a bronchus as the superior/medial segment of the right middle lobe or lingula).

Materials and Methods

Patients

Patients referred for bronchoscopy to the Division of Medical Oncology and Respiratory Medicine, Shimane University Hospital, from September 2017 to August 2018 were potential candidates for this study. All patients older than 18 years who gave their informed consent were enrolled. The study was approved by the local ethics committee (approval number: 2819, approval date: August 28, 2017) and was performed in accordance with the principles of the 2013 Declaration of Helsinki.

The inclusion criteria were diffuse lung disease with a shadow in the B^5a area, and a transbronchial lung biopsy able to be performed at the same time as BAL. The exclusion criterion was combined blood disorders showing abnormalities in the white blood cell fraction. Patients receiving treatment with steroids, immunosuppressive drugs, biological preparations and antineoplastic agents were also excluded. The control group comprised patients referred for BAL in B5 from April 2014 to August 2017. From this period, we started analyzing and recording BAL by the cytospin method in our facility.

Bronchoscopic procedures

Experienced bronchoscopists performed the procedures with the assistance of at least two physicians and one nurse working in a bronchoscopy suite. Diagnostic Olympus flexible videobronchoscopes with a 2.8-mm working channel were used. Monitoring included electrocardiogram, SpO_2 and noninvasive blood pressure. Before starting bronchoscopy, patients received supplemental oxygen through a nasal cannula at a flow rate of ≥2 L/min, adjusted to maintain the SpO_2 at ≥90%. Nebulization of lidocaine was performed by Jackson's spray. All patients received an intravenous bolus injection of midazolam (1-4 mg).

Additional bolus doses of midazolam were administered at the discretion of the bronchoscopists.

BAL using a balloon catheter

We used a disposable balloon catheter (B7-2C®; Olympus, Tokyo, Japan). BAL was always performed first. Three 50-ml syringes were prefilled with warmed sterile saline (50 ml, 50 ml, and 50 ml in successive syringes) (Fig. 1a). The catheter tip was passed through the B^5a bronchus, and the balloon was expanded while viewing (Fig. 1b, c). When the bronchoscopist was ready, the first syringe of saline was instilled by the bronchoscopy assistant (Fig. 1d). Gentle hand suction was then performed by the assistant using the same port and the 50-ml syringe. Airway collapse was avoided whenever possible by the assistant. This procedure was then repeated two more times, with a maximal volume of 150 ml used in our specific technique. The volume of BALF was recorded and filtered into sterile 50-ml centrifuge tubes through a double layer of sterile gauze swab in order to remove mucus plugs. The BALF from the 50-ml injection was labeled BALF 1. Similarly, that from the 100-ml injection was labeled BALF 2 and that from the 150-ml injection BALF 3.

The BALF analysis

BALF was pelleted by centrifugation at 500 *g* at 4 °C for 5 min. The cells were resuspended in culture medium (RPMI-1640), and counting was performed using an automated cell counter (The Cell Counter model R1®; Olympus). Cells were then plated onto a clearly defined area of a glass slide by cytocentrifuge (CytoSpin 4®; Thermo Fisher Scientific, MA, USA). Differential cell counts were performed via cytocentrifugation with May-Grunwald-Giemsa staining and enumeration at 400 cells. Blood contamination was defined as cases in

which (1) contact bleeding was described in the medical record and (2) where erythrocytes were confirmed in the BALF (Microscope ×400).

Statistical analyses

Statistical analyses were performed using the GraphPad Prism 7 software program (GraphPad Software, La Jolla, CA, USA). Qualitative variables were reported as frequencies and percentages and quantitative variables as means and standard deviations. For comparisons between two groups, normally distributed data were compared using an unpaired *t*-test. Fisher's exact test was used for categorical data. Three-group comparisons were performed using the Kruskal-Wallis test, Tukey's multiple comparisons test and Dunn's multiple comparisons test. Statistical significance was defined as a p value <0.05. This study was an exploratory study. The sample size became the number that could be registered within the research period. For the comparison group, we examined all cases that had previously been analyzed by the same BALF analysis method in the past at our institution. We excluded cases with even one missing data point.

Results

Using the B^5a bronchus for a wedge was possible in all cases, which was decided before starting the procedure. We did not perform BAL in the same patient (irrespective of whether a balloon catheter was used). By adhering the bronchoscope tip to the balloon, it was possible to observe the peripheral bronchus from the balloon (Fig. 1d). The collapse of the bronchus and flow of the bubble when suction was applied were also observed.

Characteristics of subjects

A total of 13 patients were included in the study. The control group included 56 patients (Table 1). There were no current smokers among our subjects using the balloon catheter. While a previous report described an effect of respiratory function on the recovery volume, no difference in the function between subject and control was observed. The conclusive diagnosis was idiopathic lung fibrosis (N=3), connective tissue disease affecting the lungs (N=3), hypersensitivity pneumonitis (N=3), non-specific interstitial pneumonia (N=2), lipoid pneumonia (N=1) and unknown (N=1) (Table 2). We comprehensively diagnosed indications by transbronchial lung biopsy tissues, surgical biopsy tissues, radiologic findings, antibody test and clinical findings. Consistency was found between the BALF and the final diagnosis with the exception of one undiagnosed case.

BALF characteristics

The subjects had a median recovery amount of 51.07±19.67 ml and recovery rate of 34.92%±13.22%, while the control group had a mean recovery amount of 61.40±24.08 ml and recovery rate of 40.99%±16.08%. When a catheter was used, no specimens showed blood contamination (Table 3). The BALF increased as the amount of saline instilled increased (BALF 1: 11.23±4.46 ml, BALF 2: 17.77±7.37 ml, BALF 3: 23.38±10.12 ml; Figure 2a). The cell concentration of the BALF did not change greatly and remained fairly constant (BALF 1: $16.76\pm19.37\times10^4$/ml, BALF 2: $18.59\pm17.57\times10^4$/ml, BALF 3: $17.54\pm19.64\times10^4$/ml; Figure 2b). The cell fraction of each BALF sample had a high proportion of neutrophils in BALF 1. There were no significant differences in macrophages, lymphocytes or eosinophils between BALF 2 and BALF 3 (Figure 3).

Adverse events

Overall, four patients suffered an adverse event during BAL (hypoxemia). All cases were dealt with by increasing the oxygen flow rate, and the event did not affect the subsequent examinations.

Discussion

We proposed new BAL method using a balloon catheter to obtain a more accurate and clean specimen. Our use of a balloon catheter made it possible to study the BALF at the same branch level. We believe that this approach will supply more reliable data than conventional method because it prevents procedure-based variations in findings.

The advantages of using a balloon catheter include a guaranteed reliable wedge at the site planned before the procedure. Because wedge of using a balloon catheter does not become a forced wedge, the possibility of blood contamination is markedly reduced. Regarding the BALF collection volume, a previous report stated that at least 30% should be secured **[5]**. The catheter method also achieved a recovery rate of ≥30%, as recommended for evaluations. Although the recovery rate was not significantly different from that of the control group, it should be noted that it tended to be lower than that of the control group. In particular, in cases in which the recovery rate was low, the catheter tip might have contacted the bronchial wall, suggesting that the port of the tip was blocked. In clinical practice, this problem can easily be resolved by shifting the location for balloon inflation to a more central site. However, locations other than B^5a could not be selected in the clinical protocol. On the other hand, if the lung shadow is limited and pinpoint sample collection is desired, a sample can be collected for analysis, even though it may have an adverse effect on recovery. We limited the wedge to B^5a in order to facilitate analyses; however, from the viewpoint of guaranteeing a wedge, this may be more effective for bronchial locations with a difficult approach.

We performed individual evaluations of samples instead of mixing BALF. On BAL examinations using three 50-ml aliquots, the mean surfactant protein A level in the second lavage was 2.0- and 2.4-fold of that in the first and third lavages, respectively **[6]**. Other reports have similarly reported that dilution occurs if the saline volume is increased **[7, 8, 9, 10]**. The number of cells obtained in our study plateaued, with a peak at the second sampling. The first BALF sample contained more neutrophils than BALF2 and BALF3, suggesting that the alveolar findings may not be reflected correctly because the cells from the tracheal epithelium are mixed into the first recovery fluid sample. It may therefore be useful to inject saline and collect first saline for the purpose of washout. There were no significant differences in the cell fraction between BALF 2 and BALF 3 in this study. Similar results to existing reports were obtained using a balloon catheter.

As a limitation associated with BAL using balloon catheter, it is expensive. With regard to this, it is unlikely that cost of balloon catheter will fall unless the technique is popularized. As with normal BAL, there is a possibility that wedge will be released if cough is strong. However, in the case of the balloon catheter, by pulling bronchoscope, the field of view can be kept wide. It's easy to see whether wedge is loose or not. There is a port in the tip of the catheter. Thus, if the catheter tip adheres to the bronchial wall, the recovery rate may be poor. The present study was associated with some limitations. It was an observational study in a single institution; thus, the findings cannot be widely generalized. Second, we compared the characteristics to historic data from our facility because we could not plan a concurrent controlled trial.

Conclusion

Using the balloon catheter made it possible to perform BAL reliably at a predetermined bronchus. The quality of the obtained specimen was also acceptable. This approach is expected to help to ensure the uniformity of the BAL procedure.

Acknowledgements

None.

Statement of Ethics

Subjects have given their written informed consent. The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

Takeshi Isobe have received honoraria from Boehringer-ingelheim, Astrazeneca, Pfizer.

Funding Sources

This study was funded by Merck Sharp & Dohme (MSD). The company had no control over the interpretation, writing, or publication of this work.

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Figure Legends

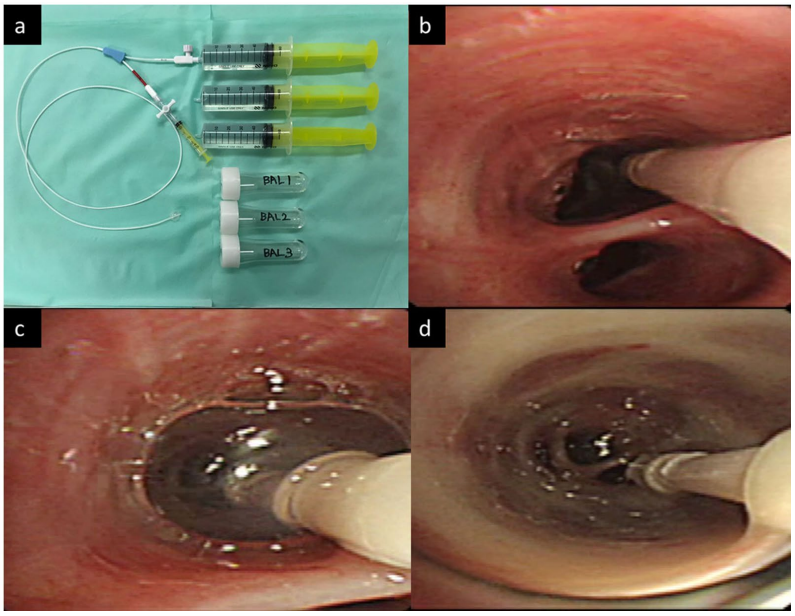

Fig. 1. Legend text. Our BAL setup (a). The catheter tip was passed through the B5a bronchus (b). The balloon was expanded (c). By adhering the bronchoscope tip to the balloon, we were able to observe the peripheral bronchus from the balloon (d).

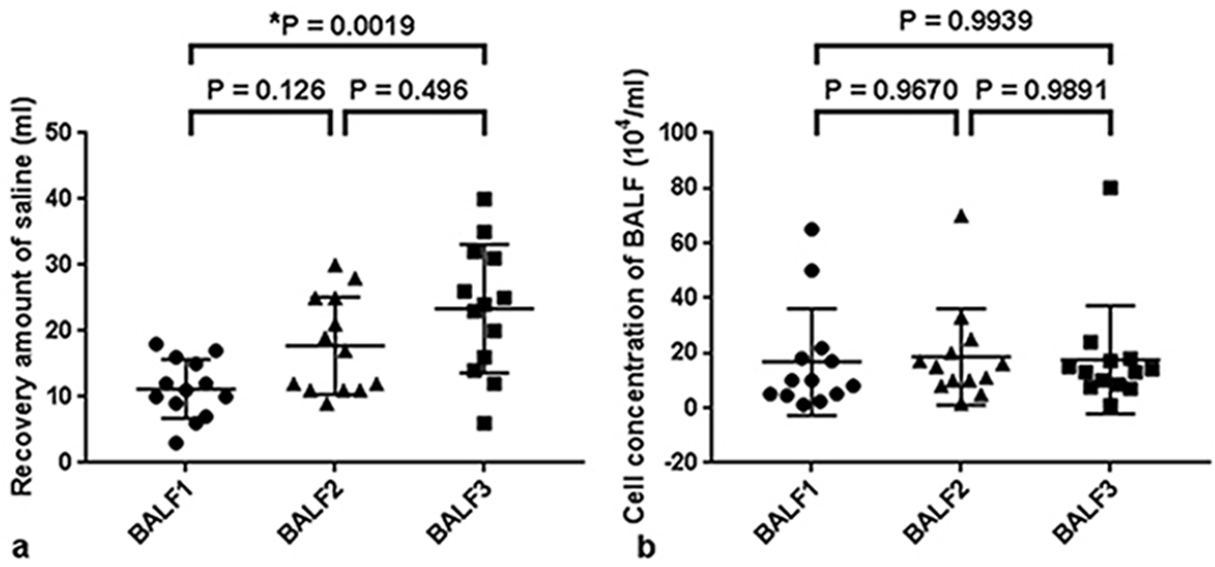

Fig. 2. Legend text. Recovery amount (a) and cell density (b) in each BAL fluid sample. *$P <$ 0.05.

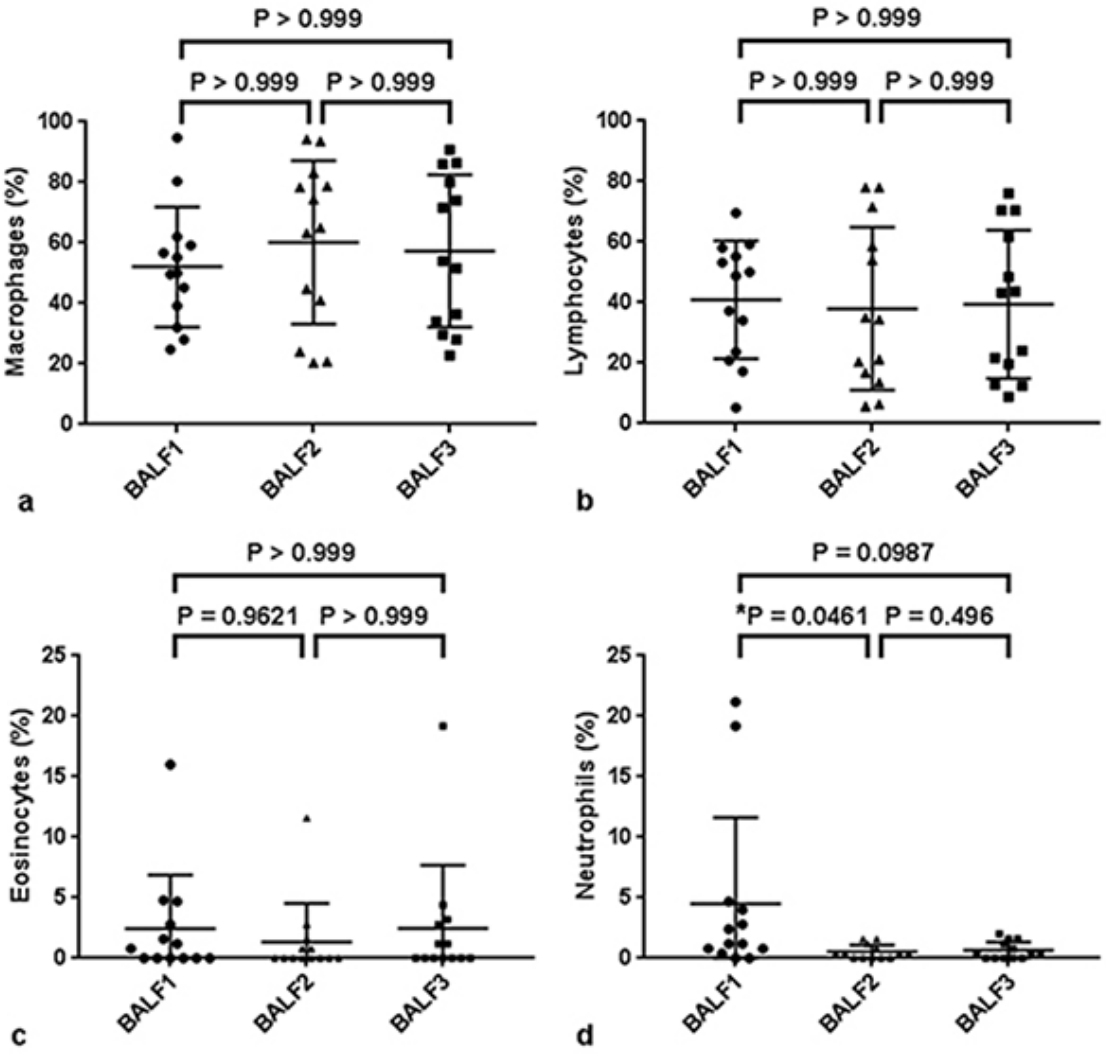

Fig. 3. Legend text. The cell fraction of each BAL fluid sample. Macrophages (a), lymphocytes (b), eosinophills (c) and neutrophils (d). *$P < 0.05$.

Table 1 - Characteristics of subjects.

Characteristics	Subjects（*n*=13）
Mean age, years	72.31±9.2
Male/Female, *n*	3/10
Smokers, *n*	
Never	2
Former	11
Current	0
VC, %	83.87±18.93
FEV_1, %	87.04±14.61
FEV_1/VC, %	81.96±8.50

Values are means ± standard deviations unless otherwise indicated.

VC, vital capacity; FEV1, forced expiratory volume in 1s.

Table 2 - Indications for bronchoscopy

Characteristics	Subjects（*n*=13）
IPF	3
CTD	3
HP	3
NSIP	2
Lipoid Pneumonia	1
Not diagnosed	1

Values are *n*. IPF, idiopathic plumonary fibrosis; CTD, connective tissue disease affecting the lungs; HP, hypersensitivity pneumonitis; NSIP, Non-specific interstitial pneumonia

Table 3 - BALF characteristics of subjects.

Characteristics	Subjects（*n*=13）
Recovered amount of saline, ml	52.38±19.83
Recovered rate of saline, %	34.92±13.22
Blood contamination, *n*	0

Values are means ± standard deviations unless otherwise indicated.