Safety and Tolerability of Nonbronchoscopic Lavage in ARDS*

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Study objective: This study compared the safety profiles of bronchoscopic lavage with nonbronchoscopic lavage in the investigation of patients with acute lung injury (ALI) or ARDS.

Design: Single-center, randomized, cross-over study.

Setting: General ICU in the United Kingdom.

Participants: Fourteen patients with ALI or ARDS.

Interventions: Bronchoscopic BAL and nonbronchoscopic BAL 1 h apart.

Measurements and results: Hemodynamic and ventilatory parameters were recorded during and for 1 h following each procedure. On average, bronchoscopic lavage took longer to perform than nonbronchoscopic lavage (7 min and 6 s vs 2 min and 28 s, p < 0.001). During the procedures, bronchoscopic lavage increased heart rate and systolic BP more than nonbronchoscopic lavage (23% vs 10% [p < 0.01] and 18% vs 7% [p < 0.01]). Three patients had ST-segment depression during bronchoscopic, and one patient had ST-segment depression during nonbronchoscopic lavage (p = 0.298). Bronchoscopic lavage reduced minute ventilation by 63 ± 17.3%, while nonbronchoscopic lavage only reduced it by 36 ± 21.9% (p < 0.001). PaCO₂ rose more after bronchoscopic lavage than after nonbronchoscopic lavage.

Conclusion: Nonbronchoscopic lavage is associated with less marked physiologic derangements than bronchoscopic lavage. Further studies are required to validate the hypothesis that nonbronchoscopic lavage may be safer in patients with unstable coronary heart disease or head injury/raised intracranial pressure who are at risk from unpredictable fluctuations in hemodynamic and ventilatory profiles.

Key words: acute lung injury; ARDS; BAL; bronchoscopy

Abbreviations: ALI = acute lung injury; B-BAL = bronchoscopic BAL; Cdyn = dynamic compliance; CI = confidence interval; Fio₂ = fraction of inspired oxygen; HR = heart rate; IQR = interquartile range; MABP = mean arterial BP; N-BAL = nonbronchoscopic BAL; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; Raw e = expired airway resistance; SBP = systolic BP; Spo₂ = pulse oxygen saturation; VAP = ventilator-associated pneumonia; V˙e = minute ventilation

Nonbronchoscopic BAL (N-BAL) has been proposed as an alternative to bronchoscopic BAL (B-BAL) in the diagnosis of ventilator-associated pneumonia (VAP).1 This technique provides similar sensitivity and specificity for the diagnosis of VAP as bronchoscopic sampling.2,3 It does not require bronchoscopic equipment and the presence of a trained bronchoscopist, thus reducing costs compared to B-BAL. By using sterile, single-use catheters, it also eliminates the potential risks of cross-infection between patients.4

Although bronchoscopy is usually well tolerated in critically ill patients with acute lung injury (ALI) or ARDS, acute changes in hemodynamic status, deterioration in oxygenation, alterations to lung compliance, and even cardiac arrest have been reported.5 Despite the increasing use of N-BAL in both clinical and research practice, the tolerability and safety profile of N-BAL has not previously been formally evaluated. The aim of this study was to compare the acute hemodynamic and pulmonary changes associated with N-BAL and B-BAL to determine if N-BAL is a safer alternative to bronchoscopic lavage.
Materials and Methods

The Local Research Ethics Committee approved this study. Authorization for inclusion in the study was required from two senior doctors who were independent from the study investigators. Written informed assent was obtained from the next of kin, and when possible retrospective written informed consent was obtained from patients.

This study was conducted on the Intensive Care Unit at Birmingham Heartlands Hospital between January and October 2002. This is a general adult ICU with approximately 750 admissions per year. Patients were screened for the presence of ALI/ARDS according to the American-European consensus criteria. Patients were eligible for inclusion if ALI/ARDS had developed in the previous 48 h and required bronchoscopy as part of routine clinical care. Patients with any of the following criteria were excluded from participation: fraction of inspired oxygen (FiO2) ≥ 0.8 and pulse oxygen saturation (SpO2) ≤ 90%; active bronchospasm; myocardial infarction within the previous 48 h; unstable arrhythmia; mean arterial BP (MABP) < 65 mm Hg despite vasopressor treatment; platelet count < 20,000/mm3; prothrombin time > 15 s; suspicion of raised intracranial pressure; endotracheal tube < 7.5 mm in diameter; or refusal for participation from next of kin.

Study Design

The study was randomized across-over trial. Patients were randomized in blocks of two using a computer-generated random number table to either B-BAL then N-BAL or N-BAL then B-BAL. Procedures were performed a minimum of 1 h apart. Patients received ventilation using a Galileo ventilator (Hamilton Medical; South Croydon, Surrey, UK) in volume-controlled mode using a square waveform. During the study, tidal volume was preset to 8 mL per kg ideal body weight (calculated by standard formula) and a ventilator rate of 14 breaths/min. Positive end-expiratory pressure (PEEP) settings were not changed. The FiO2 was increased to 1.0 for 10 min prior to the procedure. The pressure alarm limit was increased to 50 cm H2O during the procedure. Sedation (morphine and midazolam) was increased prior to the procedures until patients were unresponsive to painful stimuli (Ramsay sedation score 6). The adequacy of sedation was confirmed immediately prior to each procedure. Further boluses of sedation (midazolam, 2 mg) were administered during the procedure if the heart rate (HR) or systolic BP (SBP) rose by >30% from baseline. Vasopressor infusions (if required) were titrated prior to each procedure to achieve the MABP > 80 mm Hg. Muscle relaxants, topical anesthesia, and nebulized bronchodilators were not used. The bronchoscope or catheter was inserted down the endotracheal tube through a swivel connector with a perforated diaphragm to minimize resistance in the ventilator circuit. The pressure transducer is automatically “zeroed” to correct for changes in ambient temperature and electronics. Data for minute ventilation (Ve), PEEP, peak inspiratory pressure (PIP), dynamic compliance (Cdyn), and expired airway resistance (Raw e) were calculated by averaging 60 s of breath-by-breath recordings.

The effect of N-BAL and B-BAL on oxygenation was studied in two parts. The immediate effects were studied by recording SpO2 before, during (lowest value recorded), and 1 min after the respective procedures while patients were receiving an FiO2 of 1.0. Pulse oximetry readings were recorded simultaneously with blood gas sampling using a finger probe (Nellcor; Puritan Bennett; Pleasanton, NJ) probe attached to a Merlin monitor. The pulse oximeter displays an average SpO2 from the preceding 5-s beat-by-beat analysis. Only readings associated with a clear pulse waveform were recorded. The alveolar-arterial gradient (713 × FiO2) − (PaO2) − (FiO2 × Paco2/0.8) was compared to measure the short/medium-term effects (15 to 60 min) to allow for the differences in inspired oxygen concentration according to the study protocol.

Analysis

Based on earlier work by Papazian,9 it was calculated that 14 patients would be required to detect a 20% difference in HR between procedures with 90% power at a significance level of 0.05. Data were entered into the computer (Microsoft Access; Microsoft; Redmond, WA) and analyzed (SPSS 10.0; SPSS; Chicago, IL). Data were tested for normality using the Shapiro-Wilk test. Normally distributed data were analyzed using repeat-
ed-measure analysis of variance for changes over time, and paired $t$ tests were used to compare between techniques. Nonparamet-

ric data were analyzed using Friedman and Wilcoxon signed-rank tests. Differences between categorical data were analyzed using a

Fisher exact test. Data are expressed as mean $\pm$ SD or median (interquartile range [IQR]) according to the distribution of the data. Significance values were corrected using the Bonferroni method to allow for multiple comparisons; $p < 0.05$ was consid-

ered significant. Where significant differences were detected, the 95% confidence interval for the difference was also presented.

**RESULTS**

Fourteen patients (6 male) were recruited for the study. Mean age was 69.1 $\pm$ 6.5 years, APACHE II was 20.3 $\pm$ 3.0, and PaO$_2$/FiO$_2$ ratio was 22.7 $\pm$ 5.2 mm Hg. Two patients were known to have pre-

existing ischemic heart disease. B-BAL took longer to perform than N-BAL (7 min and $6 \text{s vs } 2 \text{ min and } 28 \text{ s}; 95\%$ confidence interval [CI], $2 \text{ min } 57 \text{ s to } 6 \text{ min } 27 \text{ s}; p < 0.001$). There was no difference in

volume of the lavage return between techniques (N-BAL, 62 $\pm$ 20 mL; B-BAL, 54 $\pm$ 20; $p = 0.348$).

During the procedure, B-BAL caused a 23% increase in HR and an 18% increase in SBP compared to baseline, while N-BAL only caused a 10% increase in HR (95% CI, 4.9 to 21.2%; $p = 0.002$) and a 7% increase in SBP (95% CI, 1.7 to 20.8%; $p = 0.005$). HR and BP returned to baseline after 1 min of both techniques and remained stable for the following 60 min (Table 1). Baseline sedation with midazolam was increased from, on average, 7.6 to 10.3 mg/h prior to the first lavage procedure. Four patients during the B-BAL procedure required an average additional bolus of midazolam, 2.5 mg, due to coughing or increases in BP/HR $>30\%$ from baseline. No patients required additional sedation during the N-BAL procedure ($p = 0.198$). Three patients had significant ST-segment depression ($>1 \text{ mV}$) during B-BAL, and one patient had significant ST-segment depression during N-BAL ($p = 0.298$). The B-BAL patients with ST-segment depression had required additional sedation during the procedure. One of the B-BAL patients had a history of stable ischemic heart disease.

Both B-BAL and N-BAL caused a reduction in V$\dot{e}$ during the procedure. B-BAL reduced V$\dot{e}$ by

### Table 1—Changes in Respiratory Mechanics During N-BAL and B-BAL*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>During</th>
<th>1 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-BAL</strong></td>
<td></td>
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<tr>
<td>HR, beats/min</td>
<td>89 (15)</td>
<td>107 (20)†‡</td>
<td>100 (17)†‡</td>
<td>92 (14)</td>
<td>88 (29)</td>
<td>92 (23)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>122 (21)</td>
<td>151 (35)†‡</td>
<td>114 (24)</td>
<td>106 (25)</td>
<td>110 (19)</td>
<td>115 (16)</td>
</tr>
<tr>
<td>V$\dot{e}$, L/min</td>
<td>7.8 (1.2)</td>
<td>2.9 (1.4)†‡</td>
<td>7.4 (1.7)</td>
<td>8.2 (2.3)</td>
<td>8.1 (1.3)</td>
<td>7.9 (1.2)</td>
</tr>
<tr>
<td>PaCO$_2$, mm Hg</td>
<td>41.8 (9.9)</td>
<td>56.8 (7.8)†‡</td>
<td>49.4 (9.9)†‡</td>
<td>47.1 (9.1)</td>
<td>45.2 (7.8)</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.44 (7.33–7.75)</td>
<td>7.31 (7.22–7.39)</td>
<td>7.38 (7.26–7.45)</td>
<td>7.43 (7.28–7.47)</td>
<td>7.44 (7.21–7.48)</td>
<td></td>
</tr>
<tr>
<td>P($\text{A-a}$)O$_2$, mm Hg</td>
<td>205.9 (54.7)</td>
<td>447.6 (81.3)†</td>
<td>387 (61.6)†‡</td>
<td>330.5 (86.6)†</td>
<td>285.8 (90.4)</td>
<td></td>
</tr>
<tr>
<td>PIP, cm H$_2$O</td>
<td>33.6 (6.2)</td>
<td>40.1 (5.2)†‡</td>
<td>35.6 (6.0)</td>
<td>34.1 (3.3)</td>
<td>34.6 (8.1)</td>
<td>34.1 (5.6)</td>
</tr>
<tr>
<td>PEEP, cm H$_2$O</td>
<td>7.7 (2.6)</td>
<td>7.3 (2.5)</td>
<td>7.9 (2.7)</td>
<td>8.0 (2.5)</td>
<td>7.9 (2.9)</td>
<td>7.7 (2.7)</td>
</tr>
<tr>
<td>Cdyn, mL/cm H$_2$O</td>
<td>38.1 (9.0)</td>
<td>35.6 (18.1)</td>
<td>32.8 (9.0)</td>
<td>33.4 (9.7)†</td>
<td>33.7 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Raw, mL/cm H$_2$O</td>
<td>22.3 (8.3)</td>
<td>25.1 (10.3)</td>
<td>24.8 (11.2)</td>
<td>22.7 (6.8)</td>
<td>22.4 (7.1)</td>
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<tr>
<td><strong>N-BAL</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>89 (19)</td>
<td>97 (16)†</td>
<td>89 (15)</td>
<td>89 (16)</td>
<td>89 (17)</td>
<td>89 (18)</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>114 (14)</td>
<td>128 (26)†</td>
<td>117 (17)</td>
<td>110 (16)</td>
<td>109 (14)</td>
<td>113 (15)</td>
</tr>
<tr>
<td>V$\dot{e}$, L/min</td>
<td>7.5 (1.1)</td>
<td>4.6 (1.6)†</td>
<td>6.8 (1.6)</td>
<td>8.2 (1.3)</td>
<td>8.2 (1.3)</td>
<td>8.1 (1.3)</td>
</tr>
<tr>
<td>PaCO$_2$, mm Hg</td>
<td>44.1 (9.1)</td>
<td>49.4 (8.1)†</td>
<td>46.3 (8.9)</td>
<td>44.9 (7.8)</td>
<td>44.1 (9.0)</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.45 (7.24–7.48)</td>
<td>7.42 (7.25–7.25)</td>
<td>7.44 (7.29–7.48)</td>
<td>7.45 (7.30–7.50)</td>
<td>7.46 (7.38–7.49)</td>
<td></td>
</tr>
<tr>
<td>P($\text{A-a}$)O$_2$, mm Hg</td>
<td>260.0 (57.4)</td>
<td>451.4 (99.1)†</td>
<td>381.5 (77.5)†</td>
<td>313.2 (72.2)</td>
<td>259.2 (69.1)</td>
<td></td>
</tr>
<tr>
<td>PIP, cm H$_2$O</td>
<td>33.4 (6.1)</td>
<td>39.6 (10.2)†</td>
<td>40.9 (8.3)†</td>
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<td>29.2 (8.8)†</td>
<td>24.2 (8.0)</td>
<td>24.3 (7.7)</td>
<td>23.2 (6.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) or median (IQR). P($\text{A-a}$)O$_2$ = alveolar-arterial oxygen pressure difference.

†$p < 0.05$ compared to baseline.

‡$p < 0.05$ compared to N-BAL.
63 ± 17.3% compared to baseline, while N-BAL only reduced it by 36 ± 21.9% (95 CI, 14.3 to 40.8%; p = 0.005). PaCO₂ rose following the procedure to a greater extent for B-BAL than N-BAL 1 min after the procedure (56.8 ± 7.8 mm Hg vs 49.4 ± 8.1 mm Hg; 95% CI, 4.1 to 9.8 mm Hg; p = 0.005) and remained elevated for up to 30 min after the procedure (Table 1). This caused respiratory acidosis in the B-BAL group (1 min after procedure: median B-BAL pH 7.31 [IQR, 7.22 to 7.39] vs N-BAL pH 7.42 [IQR, 7.25 to 7.25] p = 0.01). Although compliance fell and resistance rose after each procedure, there was no significant difference between techniques (Table 1). There was minimal loss of PEEP during the procedures: B-BAL, 0.24 cm H₂O; N-BAL, 0.59 cm H₂O N-BAL (p = 0.2).

There was no difference in baseline FIO₂ requirements prior to each procedure: B-BAL, 0.46 ± 0.07%; N-BAL, 0.56 ± 0.12 (p = 0.1). During the procedure, mean oxygen saturations were lower in the B-BAL group compared to the N-BAL group (95.1 ± 5.9% vs 97.1 ± 3.0%; 95% CI, 0.1 to 4.8%) (p = 0.4). Two patients had clinically significant desaturations (SpO₂ < 90%) in the B-BAL group, while no patients in the N-BAL group did (Fisher exact test, p = 0.54). The alveolar-arterial gradient rose after each procedure and remained elevated up to 60 min after each procedure before returning to baseline, although there was no difference between B-BAL and N-BAL groups (Table 1). There were no episodes of significant bleeding in this study.

**Discussion**

This randomized, cross-over study in ALI or ARDS patients receiving mechanical ventilation has shown that compared to bronchoscopic procedures, nonbronchoscopic techniques reduced the physiologic derangement associated with BAL and took less time to perform. BAL has an important role in the clinical investigation of patients receiving mechanical ventilation presenting with diffuse infiltrates and in patients with ALI/ARDS. The procedure facilitates direct sampling of the alveolar space for cytologic and microbiological examination. In addition to providing clinically valuable information, BAL studies have provided important insights into the pathophysiology of the early and later phases of ALI/ARDS.

Nonbronchoscopic-administered BAL is used as the technique of choice in children receiving mechanical ventilation and neonates, in whom the small diameter of the endotracheal tube or absence of a suction channel in smaller bronchoscopes precludes bronchoscopic lavage. In this population, N-BAL has been shown to yield reproducible results for total cell count and cytokines. N-BAL also overcomes the problems encountered by some ICUs in organizing B-BAL out of routine working hours. Equipment costs are considerably less for N-BAL than B-BAL. N-BAL requires $5 (US) of equipment, as opposed to approximately $40,000 (US) for a bronchoscopy setup. In the adult population, N-BAL has been used in critically ill patients for the diagnosis of infections in immunocompromised and immunocompetent patients. The sensitivity and specificity for the two techniques appear similar across several studies: B-BAL, 42 to 95% and 45 to 100%; N-BAL, 63 to 100% and 66 to 93%, respectively. Furthermore, the N-BAL equipment is single-patient use, which may reduce the risk of bronchoscopy-associated cross-infection between patients.

The acute hemodynamic responses to B-BAL have been well characterized. Tachycardia, bradycardia, hypertension or hypotension, increase in cardiac output, and an increase in oxygen consumption have all been described in this patient group. In one study of 111 patients with ARDS, 1 patient had a cardiac arrest during the procedure and subsequently died. The effect of B-BAL on silent myocardial ischemia in these patients has been less extensively investigated. In sedated, although spontaneously breathing elderly patients, Matot et al reported the presence of silent myocardial ischemia in association with tachycardia, hypoxemia, and hypertension in 17% of patients during diagnostic bronchoscopy. In a similar study, Davies et al found evidence of ST-segment depression or development of bundle-branch block in 15% of their patients undergoing bronchoscopy. It has been suggested that the mechanism behind the hemodynamic changes is a reflex sympathetic discharge caused by mechanical irritation of the larynx and bronchi. This is supported by studies that have shown that the use of topical anesthesia, IV sedation and analgesia, and calcium antagonists and β-blockers can partially attenuate the cardiovascular response to bronchoscopy, although these agents are not used universally in clinical practice. In the present study, 21% of patients undergoing B-BAL and 7% of patient undergoing N-BAL showed signs of myocardial ischemia assessed using changes in CM₅ ST segment. Although this failed to reach statistical significance, we cannot exclude that this may have been due to a type II error as this variable was not included as our primary outcome when performing the power calculation. The pronounced difference in hypertension and tachycardia between groups supports the belief that patients undergoing B-BAL are at a greater risk of myocardial ischemia. N-BAL would appear to cause less cardiovascular instability.
than B-BAL, which may confer advantages over B-BAL in the hemodynamically unstable patient, or patients at increased risk of myocardial ischemia.

The reduction in VE during B-BAL is similar to the findings of other investigators who report a 50% and 56% fall in VE, respectively. This is likely to occur due to increased leakage from the ventilator circuits, greater obstruction of the endotracheal tube by the bronchoscope than catheter, and effects of airway suction. The combination of the greater reduction in VE and longer procedure duration compared to N-BAL are likely to explain the short-lived development of a respiratory acidosis in the B-BAL group but not in the N-BAL group.

The alveolar-arterial gradient rose after each procedure and remained elevated up to 60 min after each procedure before returning to baseline. We found a small (2%), although statistically significant fall in oxygen saturations in the B-BAL group during the procedure compared to the N-BAL group despite a similar return in lavage fluid volume. Deterioration in oxygenation after BAL has been well described and has been reported to last for up to 24 h after BAL in the critically ill patient. The etiology of the deterioration in oxygenation has not been clearly elucidated. We suggest that in our study the greater and more prolonged reduction in alveolar ventilation may have contributed to the lower oxygen saturations observed during the procedure in the B-BAL group. However differences in oxygen consumption and ventilation/perfusion mismatching as a consequence of the greater alterations in hemodynamic changes associated with B-BAL and thus reduced the extent of the cardiorespiratory changes associated with B-BAL and thus reduced the differences between the bronchoscopic and non-bronchoscopic techniques. Second, it was not possible to blind the investigators performing the procedure or collecting the physiologic data to which may have unwittingly introduced some bias. The data on respiratory mechanics were, however, collected electronically, and analysis was performed with blinding maintained to avoid potential bias. Finally, ethical considerations precluded us undertaking this evaluation in patients with the most severe derangements of physiology. Caution should therefore be exercised in extrapolating these findings to this patient group.

Despite the growing use of N-BAL as a diagnostic and research tool, to our knowledge, this is the first study to examine the safety profile of N-BAL. Although the differences between B-BAL and N-BAL reported in the present study are modest, N-BAL would appear to offer physiologic advantages to B-BAL. As N-BAL appears to be comparable to B-BAL for the diagnosis of VAP, we hypothesize that this technique could be used in preference to B-BAL in patients at risk from tachycardia, hypertension, and a rising PaCO₂, such as those with unstable coronary heart disease or head injury/raised intracranial pressure. If B-BAL is used, consideration should be given to the addition of systemic or topical analgesia and/or neuromuscular relaxation to attempt to blunt the adverse effects of B-BAL on hemodynamic stability and respiratory profiles.

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