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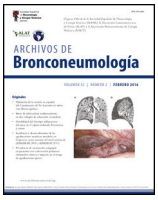

Scientific Letter

Safety and Feasibility of Transbronchial Cryobiopsy in Mechanically Ventilated Patients

To the Director,

Patients admitted to the Intensive Care Unit (ICU) who require invasive mechanical ventilation (IMV) due to undiagnosed diffuse pulmonary infiltrates (DPI) represent an important challenge. Obtaining a lung biopsy might be required in some cases, but the most appropriate sampling technique is not established.[1] Empirical treatment is often indicated based on clinical, radiological and microbiological results, but sometimes a definitive diagnosis cannot be established. Surgical lung biopsy (SLB) allows an adequate lung specimen to be obtained and provides good diagnostic yield of diffuse lung infiltrates of unclear aetiology, although is also associated to high risk of complications.[1–3] Transbronchial lung biopsies (TBLB) is less invasive than SLB but diagnostic yield of samples obtained with this method is variable, due to their small size and the presence of artifacts produced by forceps.[4,5]

The use of cryoprobe to perform TBLB (TBLC) enables higher diagnostic yield due to larger and better quality samples compared to conventional forceps[6,7] and a statement for standardisation of the procedure has been published.[8]

Therefore, TBLC in patients under IMV could improve the diagnostic yield of DPI. Limited data is available regarding the safety of TBLC in this group of patients.[9,10] The aim of this study was to evaluate the feasibility and safety of TBLC in patients under IMV with DPI.

A multicentre, prospective, observational feasibility study conducted in 3 university hospitals. All centres had broad experience performing TBLC. The study was approved by the Ethics Committees of the involved hospitals. ClinicalTrials.gov identification NCT02611297.

Patients aged 18 years or older with respiratory insufficiency requiring IMV due to persistent undiagnosed DPI were included. Eligible patients were those without heart failure who did not have a diagnosis after chest scan, blood tests, microbiological and cytological studies from BAL or PB, as well as any additional studies required. Patients with coagulation disorder, severe emphysema, pneumothorax, need for positive end-expiratory pressure (PEEP) >12 cmH_2O and/or PaO_2/FiO_2 < 100 mmHg were excluded.

The decision to indicate TBLC was made by the medical team of each hospital. Patient's legal representative was provided with all possible information and was asked to sign informed consent.

Procedures were performed at the bedside using a conventional bronchoscope and a flexible cryoprobe (model 20416-032, Erbokryo CA, Erbe, Germany). The cryoprobe was placed into the pre-selected segment. Freezing was applied for 4–5 s. A minimum of two TBLCs were obtained. Procedures were performed without fluoroscopy control and tactile sensation was use to place the probe 1–2 cm from the pleura.

Prior to the procedure, the orotracheal tube (OTT) was replaced by an armoured tube (Bronchoflex 8.5 mm, Rüsh, Teleflex Medical, Durham, NC, USA), which has a lateral channel used to insert an haemostatic balloon (Model B5-2C, Olympus Medical Systems Corp., Tokyo, Japan).[11,12]

Bronchoscopy was performed at FiO_2 1 and without PEEP. During the freezing and pulling out time (6 s in total), the ventilator was paused. Both bronchoscope and cryoprobe were removed at the same time after each biopsy. Ventilation was reinitiated and the balloon was inflated immediately after each biopsy. Bronchoscopic examination was performed to check possible bleeding during balloon deflation.

Haemodynamic variables, ventilator parameters and blood gases were collected before, during and after the procedure. Bleeding was classified as: grade 0 (no bleeding); grade 1 (mild bleeding); grade 2 (moderate bleeding requiring bronchial occlusion-collapse and/or instillation of cold saline); or grade 3 (severe bleeding not controlled endoscopically, causing haemodynamic or respiratory instability). Chest radiography was also performed post-TBLC. Histological diagnosis was established by each centre pathologist.

Seventeen patients (10 women, 65 [51–76] years old) underwent TBLC. Patient characteristics are summarised in Table 1. Median FiO_2 before performing TBLC was 0.6 (0.5–0.9) and median PaO_2/FiO_2 was 162.3 mmHg (119–265). After the procedure, no significant changes were found in FiO_2, PaO_2/FiO_2 blood gas or ventilator parameters (tidal ventilation, peak and plateau pressures) (Table 1). Duration of the procedure was 15 min [13–80].

We obtained a total of 49 biopsies (median of 3 [2–4] biopsies per patient). All samples contained alveoli and lung parenchyma suitable for histological analysis. We were able to establish a specific diagnosis in 8 patients (53.3%) (Table 2). Regardless the specific diagnosis, cryobiopsies were considered clinically useful in 14 patients (82.5%), leading to change in therapeutic actions and/or stablishing prognosis (82.3%).

Regarding complications, the change of OTT was associated with transient hypoxemia in 5 patients (29.4%) and hypotension in 1 (5.9%), neither of which required vasoactive drugs. 4 patients (23.5%) had mild to moderate bleeding that was controlled with conventional bronchoscopic techniques. 1 patient (5.9%) presented a severe haemorrhage requiring selective intubation of the contralateral lung for 24 h. During the procedure, 2 patients (11.8%) experienced temporary oxygen desaturation and arterial hypotension that did not require vasoactive drugs and that was completely recovered within the next 30 min. No pneumothoraces were observed. Ten patients (58.8%) died during hospitalisation in the ICU. The deaths occurred in a median of 8 days (5–17) after cry-

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Table 1
Patients' ventilator settings, gas exchange and haemodynamic status at baseline, during procedure and after 30 min.

Variable	Baseline	During procedure	30 min after procedure	*P* value
PaO_2/FIO_2 (mmHg)	162 [119–265]		157.5 [107.63–266.08]	0.363
Plateau pressure (cm H_2O)	25 [20–28]	25 [17.75–33]	27 [22.5–28]	0.230
PEEP (cmH_2O)	6 [5–10]	3 [0–5]	6 [5–10]	0.751
TV (ml/kg/PBW)	380 [327.75–420]	400 [360–460]	380 [310–430]	0.327
SaO_2 (%)	97 [96–100]	99 [93.75–100]	98 [97–99]	0.414
pH	7.39 [7.34–7.43]		7.38 [7.29–7.42]	0.084
PaO_2 (mmHg)	103.5 [81.23–128]		97.5 [80.15–179.63]	0.730
$PaCO_2$ (mmHg)	49.5 [42–57.93]		52.5 [47–68]	0.140
Heart rate (bpm)	81.5 [70–90]	85.5 [75.5–98.5]	82.5 [69.25–93]	0.116
MAP (mmHg)	80.3 [71–86.5]	76.5 [69.25–89.25]	77 [68.73–85]	0.633

Values are expressed as median (interquartile range) for quantitative variables and absolute number (percentage) for qualitative variables. INR: international normalised ratio; PEEP: positive end expiratory pressure; TV: tidal volume; PBW: predicted body weight; bpm: beats per minute; MAP: mean arterial pressure.

Table 2
Histopathological diagnosis of transbronchial lung biopsies obtained with cryoprobe.

Diagnosis	Patients (%)
Specific diagnosis	8 (47.1)
Organised pneumonia	5 (29.4)
Vasculitis	1 (5.9)
Carcinomatous lymphangitis	1 (5.9)
NSIP	1 (5.9)
Unspecific diagnosis	9 (52.9)
Acute DAD	2 (11.8)
Fibrotic DAD	3 (17.6)
Non-specific changes	4 (23.5)

NSIP = non-specific interstitial pneumonia; DAD = diffuse alveolar damage.

obiopsies were obtained and were considered non-related to the procedure.

Therefore, this prospective study provides similar data to previous retrospective series showing that in IMV patients with DPI, TBLC is a feasible technique to obtain lung specimens for histologic evaluation.

In addition, TBLC could be an option in this clinical scenario by providing a more appropriate benefit-risk balance compared to conventional forceps, by obtaining better quality biopsies but with a lower risk and less cost than surgical procedures.[13] In fact, TBLC has been proposed as a promising option to improve diagnostic yield in DPI, compared to conventional forceps biopsy.[6,14,15] Interestingly, TBLC enabled a specific diagnosis to be established in 8 patients (53.3%) and directly asked, the responsable intensivists considered the biopsy result to be "clinically useful" in 14 patients (82.3%), driving to therapeutic and/or prognostic changes. These rates are better to that reported for conventional TBLB.[4,5]

In addition, safety concerns must be considered carefully. OTT exchange was performed prior to TBLC in order to allow placing a preventive haemostatic bronchial blocker. Only 6 patients experienced mild complications related to the OTT exchange. 1 case presented severe bleeding after the biopsy requiring selective intubation for less than 24 h. Arterial blood samples obtained 30 min before and after the procedure did not show significant reduction in PaO_2 without increasing FiO_2. 10 patients died during the following days-weeks after TBLC, but none of the deaths were related to the procedure.

This study has limitations. First, it was designed to explore the feasibility of TBLC, thus precluding sound conclusions regarding the diagnostic capability. TBLC diagnostic yield needs further study, including comparison with SLB or eventually necropsy. Second, TLBC is not a fully standardised procedure and some of the technical aspects (OTT exchange, haemosthatic blocker) might change in future. In this study, procedures followed the recommendations established at the statement for patients with DPI.[8] Finally, the number of cases included is limited as this study was intentionally designed as a feasibility study.

In conclusion, TBLC is a feasible procedure in mechanically ventilated ICU patients. Cryobiopsies provided lung samples that allowed specific diagnosis and useful clinical information in most cases. Therefore, TBLC in this group of patients seems to provide an adequate balance between risks and benefits. Further research is needed to establish the diagnostic value of transbronchial lung cryobiopsies in mechanically ventilated patients.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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