The utility of transbronchial cryobiopsy performed under conscious sedation for interstitial lung diseases in a resource-constrained setting

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Background. Transbronchial biopsy (TBB) with a cryoprobe, also known as transbronchial lung cryobiopsy (TBLC), has become a well-established modality for sampling lung parenchyma. TBLC is performed under general anaesthesia in the majority of centres, utilising rigid or flexible bronchoscopy. In resource-constrained settings, however, most diagnostic bronchoscopies, including TBB, are performed under conscious sedation with flexible bronchoscopy without the presence of a specialist anaesthetist.
Objectives. Given the paucity of evidence on TBLC performed under conscious sedation for interstitial lung diseases (ILD), specifically in a resource-constrained setting, we aimed to describe its utility in a pilot study.
Methods. We prospectively enrolled the first 20 patients who underwent TBLC for ILD at a large tertiary hospital in South Africa. All TBLCs were performed under conscious sedation using a cryoprobe. Patients were actively monitored for complications. The final diagnosis and decision regarding need for a surgical biopsy were made at a multidisciplinary meeting that included at least two specialist pulmonologists with an interest in ILD, a thoracic radiologist, and an anatomical pathologist with an interest in ILD.
Results. Three patients experienced complications. Two (10%) developed a pneumothorax (neither required any intervention). Bleeding that required 10 minutes of tamponade with the endobronchial blocker was observed in one case. This patient experienced no haemodynamic or respiratory compromise and was discharged the same day. There were no complications arising from the use of conscious sedation. A definitive diagnosis was made in 17/20 (85%) of the patients.
Conclusion. TBLC performed at an experienced bronchoscopy centre using a cryoprobe under conscious sedation with a dedicated sedationist was safe and well tolerated. Furthermore, it had a high diagnostic yield, and surgical lung biopsy was avoided in 85% of the patients.

Keywords. Cryobiopsy, interstitial lung disease, conscious sedation.

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Study synopsis

What the study adds. There is a paucity of evidence for the use of transbronchial lung cryobiopsy (TBLC) for the diagnosis of interstitial lung diseases (ILD) in resource-constrained settings, especially when performed under conscious sedation. In this pilot study, TBLC performed under conscious sedation was safe and well tolerated, and had a high diagnostic yield.
Implications of the findings. TBLC under conscious sedation can safely be rolled out in resource-constrained settings as a first-line diagnostic procedure when lung tissue needs to be obtained in patients with ILD, as its yield is comparable to TBLC under general anaesthesia. It potentially avoids surgical lung biopsy in >80% of cases, together with the need for general anaesthesia.

Transbronchial biopsy (TBB) with a cryoprobe, or transbronchial lung cryobiopsy (TBLC), has become a well-established modality for sampling lung parenchyma.[1] In fact, in 2022 European Respiratory Society guidelines on TBLC in the diagnosis of interstitial lung diseases (ILD) it was suggested that TBLC could be the first-line investigation to obtain histopathological data in a patient with undiagnosed ILD, rather than surgical lung biopsy (SLB), particularly if patients are unfit to undergo SLB.[2]

With TBLC, lung parenchyma is subjected to cryofixation by a liquid cryogen to sample tissue for histological examination. The main advantage over traditional forceps TBB is the size of the biopsy specimen (4 - 5 times larger) and the absence of crush artifacts.[3] A recent systematic review and meta-analysis reported a diagnostic yield of ~80% for TBLC.[4] However, in the largest retrospective study to date (*N*=1 024), a definitive diagnosis was achieved in >90% of cases. TBLC is generally considered a safe procedure, with clinically

significant bleeding (4%) and pneumothorax (6%) being the most common complications reported.[5]

TBLC is performed under general anaesthesia in most centres, with a rigid or flexible bronchoscope.[2,3] In resource-constrained settings, however, the majority of diagnostic bronchoscopies, including TBB and endobronchial ultrasound-guided transbronchial needle aspiration, are performed under conscious sedation without the presence of a specialist anaesthetist.[6]

Given the paucity of evidence on TBLC performed under conscious sedation for ILD, specifically in a resource-constrained setting, we aimed to describe its utility in a pilot study.

Methods

Study design and participants

We prospectively enrolled the first 20 patients who underwent TBLC for ILD at Tygerberg Hospital in Cape Town, South Africa. The institution is a 1 380-bed referral hospital that provides tertiary service to ~3.5 million people. The capturing and deidentification of data were approved by the Stellenbosch University Health Research Ethics Committee (ref. no. N16/02/020).

Patient selection

Adults aged >18 years with suspected ILD were selected for TBLC following discussion in a multidisciplinary team (MDT) meeting comprising pulmonologists and radiologists. Patients required diffuse interstitial pulmonary infiltrates for consideration. In these cases, the MDT meeting deemed histopathology necessary to make or confirm a definitive diagnosis, which was not possible with the available clinical, radiological, serological and other laboratory data. Potential cases were reviewed with the bronchoscopist to ensure accessibility to the affected areas. Pulmonary hypertension (right ventricular systolic pressure >40 mmHg on echocardiogram), bleeding diathesis, lack of patient consent and haemodynamic instability were outright exclusion criteria.

Basic demographic and clinical data

Demographic information included age (years) and sex. Smoking status, defined as current smoker, non-smoker and ex-smoker (smoking cessation >6 months prior to the day of procedure), was documented for all. Comorbidities and HIV status were also recorded.

Bronchoscopy and procedural sedation

All procedures were performed in an experienced centre with a dedicated bronchoscopy suite and by a single pulmonologist with >20 years of experience in bronchoscopy. A flexible bronchoscope with a 3.2 mm working channel was used, and an oral bite guard (Fig. 1) was inserted for oral intubation. Supplementary oxygen was given via nasal prongs at 5 - 15 L/min.

Conscious sedation was achieved with a combination of fentanyl (100 µg/2 mL) with a bolus of 50 µg followed by 25 - 50 µg boluses as needed, and propofol (200 mg/20 mL) with a 0.5 - 1 mg/kg intravenous loading dose followed by 0.5 mg/kg increments every 3 - 5 minutes as required, targeting an Observer's Assessment of Alertness/Sedation (OAAS) scale of 2 - 3 (Table 1).[7] A dedicated and experienced member of the team served as the sedationist, ensuring that the required level of sedation was achieved on the OAAS scale.

Fig. 1. Patients were orally intubated via a plastic bite guard. Supplementary nasal oxygen was routinely administered.

Table 1. Observer's Assessment of Alertness/Sedation (OAAS) scale

5	Awake and responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Response only after name is called loudly and/or repeatedly
2	Response only after name is called loudly and after mild shaking
1	Does not respond when name is called and after mild shaking

An endobronchial blocker (7.0 Fr/65 cm Arndt Endobronchial Blocker Set (Cook Medical, USA) (Fig. 2) was attached with an adjustable loop to the distal tip of the bronchoscope and introduced into a segment or subsegment of the targeted lobe. The balloon was inflated, and its position was endoscopically confirmed (Fig. 3).

All TBLC specimens were taken from the same lobe (different segments or subsegments); in no patient was more than one lobe sampled. The target lobe and segment(s) were identified prior to the procedure at a combined meeting that was attended by at least three specialist pulmonologists.

A cryoprobe attached to the controller (ERBECRYO 2; Erbe Elektromedizin GmbH, Germany) was inserted past the deflated

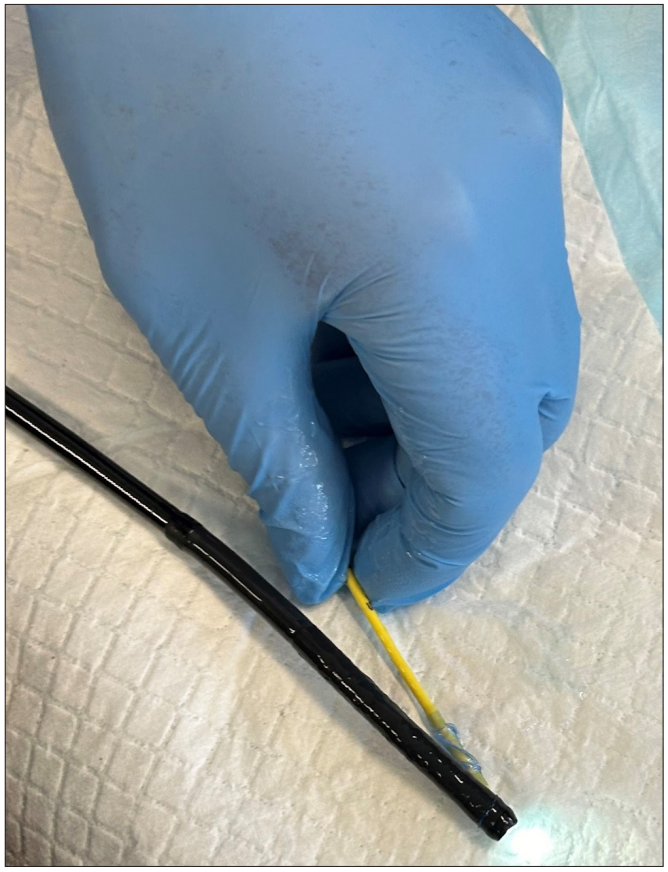

Fig. 2. A bronchial blocker (7.0 Fr/65 cm Arndt Endobronchial Blocker Set) was attached to the distal tip of the bronchoscope prior to insertion. The balloon was only inflated once the target segment was identified.

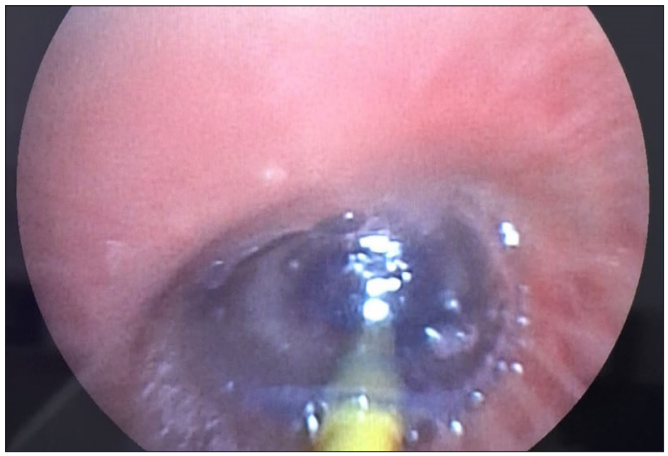

Fig. 3. The balloon was inflated, and its position was endoscopically confirmed.

balloon to the periphery of the lung, and its position was confirmed using fluoroscopy (Fig. 4). The operator aimed to keep the probe at least 2 cm away from the visceral pleura and used fluoroscopy to guide the cryoprobe into different subsegments. During the first procedure, a 1.1 mm flexible probe with a sheath (Erbe Elektromedizine GmbH, Germany) was used, and specimens were retrieved through the sheath. For the following 19 cases, a 1.7 mm flexible probe (Erbe Elektromedizine GmbH, Germany) was used. A freezing time of

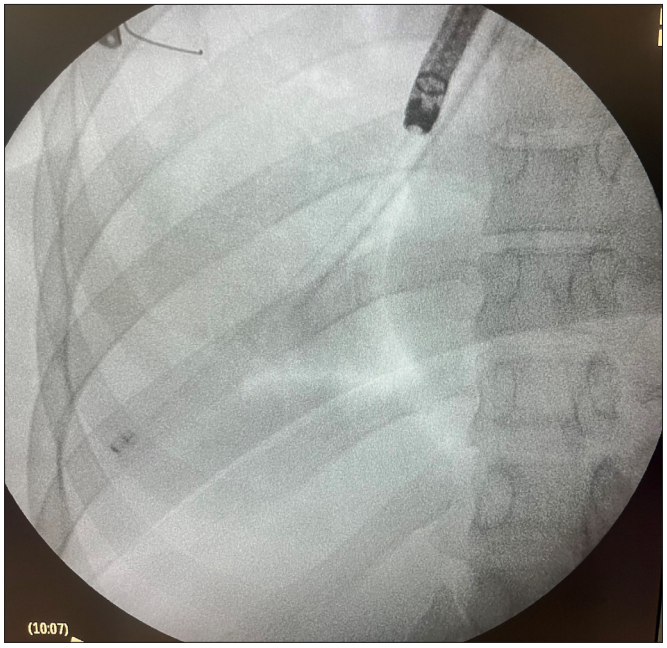

Fig. 4. An example of fluoroscopy. In this case the operator retracted the probe by 2 - 3 cm prior to confirming its position again and performing the biopsy.

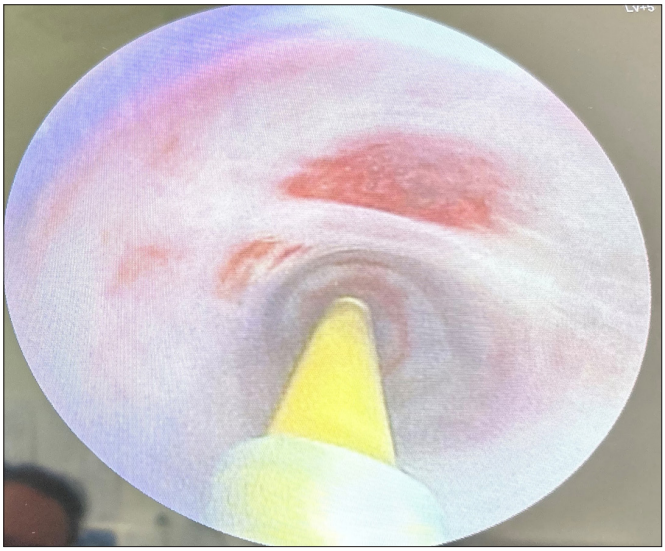

Fig. 5. An example of the endoscopic view when the tip of the bronchoscope is placed against the balloon to inspect for bleeding (in this case very minor).

6 - 10 seconds was applied, after which the bronchoscope together with the TBLC specimen was removed *en bloc*. A dedicated balloon operator inflated the bronchial blocker as soon as this manoeuvre was completed, tamponading the target segment or subsegment. Once the specimen was retrieved from the tip of the probe, the endoscopist reintubated the patient and rapidly navigated the bronchoscope back to the target segment, using the bronchial balloon blocker as a physical guide. The bronchoscope camera was placed against the balloon to inspect for bleeding distal to the inflation point (Fig. 5). The balloon was only deflated if it was deemed safe to do so (no excessive bleeding). The procedure was repeated until at least five

macroscopically acceptable samples (>5 mm) were obtained (Fig. 6). Finally, the endoscopist inspected the segments in which the TBLCs were performed and only removed the bronchoscope once no active bleeding was observed. The endoscopist (experienced in rigid bronchoscopy) had a rigid bronchoscope readily available and prepared for each case to ensure prompt response in the event of an emergency. During the recovery period, patients were positioned with the lung from which the biopsy was taken in the dependent position.

Post-procedural care and monitoring for complications

A transthoracic ultrasound scan was used to exclude a pneumothorax, and in all cases in which a pneumothorax could not be excluded, a chest radiograph was obtained. A pneumothorax was deemed significant if any intervention (e.g. chest tube insertion) was required. Likewise, any bleeding that required more than tamponade by means of the endobronchial blocker was documented as significant. All procedural complications (including those potentially related to conscious sedation) were documented.

Assessment of diagnostic yield

The final diagnosis, and a decision regarding the need for a step-up SLB if TBLC was non-diagnostic, were made at a multidisciplinary meeting that included at least two specialist pulmonologists with an interest in ILD, a thoracic radiologist, and an anatomical pathologist with an interest in ILD.

Statistical analysis

All descriptive numerical data with a normal distribution were described using means and standard deviations, whereas non-normal data were described using medians and interquartile ranges (IQRs). Categorical data were described using frequencies and percentages. The Statistical Package for Social Sciences version 29 (SPSS) (IBM, USA) was used to analyse the data.

Results

Baseline demographics and patient characteristics

A total of 20 patients underwent TBLC from June 2023 to May 2024. Seven (35%) were male, and the median (IQR) age of the patients was 46 (22) years. Comorbidities included hypertension (*n*=9), diabetes mellitus (*n*=5), HIV infection (*n*=4) and previous pulmonary tuberculosis (*n*=5). Nine patients (45%) were active smokers, 3 (15%) were ex-smokers and 8 (40%) were non-smokers. No patient had overt pulmonary hypertension.

Complications

Three patients experienced complications. Two (10%) developed a pneumothorax after the procedure. Neither required any intervention, but one was kept in hospital for 1 day for observation before discharge. Bleeding that required 10 minutes of tamponade with the endobronchial blocker was observed in one case. The patient experienced no haemodynamic or respiratory compromise and was discharged the same day. There were no direct complications as a consequence of conscious sedation or recurrent airway intubation. Notably, no patient required conversion to a general anaesthetic, needed vasopressor support, had vocal cord injury, or experienced any post-procedural aspiration-related sequelae.

Diagnostic yield

The MDT agreed on a clinical, radiological and histological diagnosis in 17 cases (85%) (Table 2). In one case, histological examination revealed a nonspecific interstitial pneumonitis pattern with features of respiratory bronchiolitis, which was not consistent with the high-resolution computed tomography (HRCT) findings, and in two cases

Fig. 6. Examples of transbronchial cryobiopsy specimens obtained with a 1.7 mm probe.

Table 2. Diagnoses confirmed with transbronchial lung cryobiopsy (*N*=17)

Diagnosis	Subtype	*n*
Hypersensitivity pneumonitis	Non-fibrotic	3
	Fibrotic	3
	Mixed	1
NSIP	Cellular	1
	Fibrotic	1
RB-ILD		1
Tuberculosis		2
Pulmonary alveolar proteinosis		2
Lung cancer	Adenocarcinoma	1
Lymphoma	Marginal zone	1
	Nodular sclerosing Hodgkin's lymphoma	1

NSIP = nonspecific interstitial pneumonia;
RB-ILD = respiratory bronchiolitis-interstitial lung disease.

the TBLC histological specimen was considered insufficient to make a clear diagnosis. An SLB was performed in one of these cases, which diagnosed adenocarcinoma with a micropapillary and lipidic pattern.

Discussion

In this pilot cohort, we found TBLC performed under conscious sedation to be well tolerated with few complications. Furthermore, it had a high diagnostic yield when a 1.7 mm cryoprobe was used, and enabled us to avoid SLB in the majority of cases. The overall diagnostic yield from our TBLC cohort was 85%, which is higher than in many comparable studies in the existing literature.

The largest meta-analysis, by Rodrigues *et al*.,[4] described a pooled diagnostic yield of 77%, rising to 81% in more experienced centres that had performed >70 procedures. The type of sedation is not specifically described, but the majority of centres perform conventional TBLC under general anaesthesia with a definitive airway, allowing more rapid and easy access to the airway after each sample. When looking at TBLC performed under conscious sedation, diagnostic yields ranged from 67% to 90%.[8-10] Notably, the study by Salton *et al.*[8] reported a diagnostic yield of 90%, but only included 11 patients. Our results, which are similar to those at high-volume centres, may be attributable to the level of experience of the primary operator, but do lend support to more frequent use of this technique going forward, especially in resource-constrained settings. Training personnel in advanced bronchoscopic techniques, as well as strengthening the MDT with members who have specialised in thoracic radiology and pathology, will further build up this service.

The most common complications in our study were pneumothorax not requiring intervention (10%) and moderate bleeding (5%), which are comparable with rates reported in the literature. In Rodrigues *et al*.,[4] the reported pooled incidence was 5.6% (95% confidence interval (CI) 3.8 - 8.2) for pneumothorax requiring chest tube insertion and 10% (95% CI 6.8 - 14.3) for significant bleeding (7% for centres with >70 TBLCs). A further 1.4% of patients (95% CI 0.9 - 2.2) experienced an acute exacerbation of ILD after TBLC,[4] which was not seen in our cohort, possibly owing to patient selection as well our limited sample size. Our patients did not experience any form of complication related to the use of conscious sedation, and its use did not limit the number of samples taken. Notably, there were no deaths in our cohort.

Smaller individual studies similar to ours, with sample sizes ranging from 12 to 100, had pneumothorax incidences of 13 - 20%, with small proportions of patients requiring chest tube insertion.[8-10] These studies did not routinely use fluoroscopy, however, and although it has been postulated that use of fluoroscopy reduces the risk of pneumothorax, this has not been consistently shown in the literature. Probe size is also thought to play a role, with the smallest 1.1 mm cryoprobe being shown to have the lowest risk for pneumothorax.[11]

Bleeding rates vary widely and significantly between studies, with another meta-analysis reporting ranges from 0% to 70%, with a mean incidence of 27%.[12] Discrepancies may arise as a result of differences in defining the severity of bleeds, the size of probes used, the number of samples, and the presence of pulmonary hypertension. Even when considering these factors, the bleeding rate in our cohort was similar to that described by Johannson *et al.*[12] Timely diagnosis in patients with ILD is a key component of an effective management strategy.[4] When standard diagnostic pathways, including clinical evaluation, serological or bronchial lavage findings and correlation with HRCT imaging of the chest and followed by an MDT meeting of pulmonologists and chest radiologists, do not yield a diagnosis, histopathological sampling may be deemed necessary. With the current safety profile, it appears that in appropriately selected patients and in experienced centres, TBLC under conscious sedation is feasible and safe as a first-line histopathological sampling procedure, particularly in resource-constrained areas where general anaesthesia is not readily available.

A key strength of our pilot study was confirmation that the practice of performing TBLC under conscious sedation can be continued, particularly in resource-constrained settings. Limitations include the relatively small sample size, and the fact that one (experienced) endoscopist performed all 20 procedures, which limits extrapolation beyond a large-volume centre and procedures performed by experienced bronchoscopists.

Conclusion

TBLC performed at an experienced bronchoscopy centre using a 1.7 mm cryoprobe under conscious sedation with a dedicated sedationist is safe and well tolerated, and has a high diagnostic yield. Using the proposed technique, accessibility to TBLC may be significantly and feasibly increased in our resource-constrained environment.

Data availability. The datasets generated and analysed during the present study are available from the corresponding author (CFNK) on reasonable request.

Declaration. The research for this study was done in partial fulfilment of the requirements for ADB's MPhil (Pulmonology) degree at Stellenbosch University.

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Author contributions. ADB and CFNK contributed to the design and data analysis. ADB collected the study data. ADB, NS and CK wrote the first draft of the manuscript, which was reviewed and edited by all co-authors.

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Conflicts of interest. None.

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