The cool new kid on the block: Lung cryobiopsy

Transbronchial lung biopsy (TBLB) using biopsy forceps was initially introduced in the mid-1960s for sampling peripheral lung lesions or tissue.[1] However, despite the perfection of this technique over several decades, it still has the disadvantages of retrieval of small-sized, mainly centrilobular lung tissue samples and the inadvertent introduction of artifacts in the biopsied tissue (mainly bleeding and crush artifacts). These factors complicate laboratory processing and histopathological analysis in the diagnosis of diffuse parenchymal lung disease (DPLD).[2,3] Even when combined with clinical examination and high-resolution computed tomography (HRCT), TBLB therefore only achieved a diagnosis in ~30% of patients with suspected DPLD.[4,5] Despite these drawbacks, TBLB has often been attempted prior to surgical lung biopsy (SLB), which is regarded as the 'gold standard', owing to patient preference and to avoid more costly surgery and its attendant complications, including high morbidity (bleeding, prolonged air leak, persistent thoracic pain, cardiac arrhythmias, infectious complications).[6,7] An alternative was to sample the lung using percutaneous image-guided biopsy. However, this method is also associated with suboptimal yield in DPLD (~45%),[8] and pneumothorax rates are high (20 - 45%).[9] TBLB and image-guided biopsy are therefore techniques with a poor diagnostic yield, significant complication rates, especially with image-guided percutaneous needle biopsy, and a high associated rate of onward referral for SLB.

The poor performance of TBLB and other approaches has now been superseded by a new technique, peripheral transbronchial lung cryobiopsy (TBLC). Historically, the first bronchoscopic cryobiopsy procedure was described in 1978,[10] where it was used for debulking tumours occluding the lumen of larger airways.[11] More recently, we have seen a reintroduction of cryoprocedures for diagnostic purposes.[12] The technology leverages the Joule-Thomson effect, which describes the rapid expansion of compressed gas when forced through a valve. This rapid expansion leads to a drastic drop in the temperature of the gas, resulting in the adherence of moist lung tissue to the tip of the probe, which is then pulled back to retrieve a lung biopsy sample. The ERBECRYO 2 equipment currently used to perform the cryobiopsies uses pressurised carbon dioxide at 45 bar to cool the probe tip to ~–80°. The diameter of the cryoprobe (1.1 mm, 1.7 mm, 1.9 mm or 2.4 mm) and the freezing time are the two key determinants of the size of the biopsy specimens obtained. Most guidelines recommend that the procedure be performed under anaesthesia via a secured airway (usually an armoured endotracheal tube or rigid bronchoscopy). The two main complications of this procedure are bleeding (mitigated with bronchial balloon blockers) and pneumothorax. However, in busy pulmonology units and respiratory divisions, and often in the hospital setting of overworked anaesthetic departments, the need for anaesthesia and endotracheal intubation represents a huge barrier to undertaking the procedure, not to mention increasing costs substantially. So, can this procedure be undertaken safely using conscious sedation (as is performed with TBLB)?

In this issue of *AJTCCM*, Mohanrao *et al.*[13] address this critical question. They performed TBLC on 87 patients with suspected DPLD in tandem with forceps biopsy from the same segments, under conscious sedation. The TBLC procedure in this study was performed using a 1.9 mm Erbe cryoprobe with a 4 - 5-second freezing time. An Arndt bronchial blocker was used along with topical therapy (adrenaline) to control bleeding. They showed that TBLC had a significantly superior diagnostic yield compared with TBLB (*n*=69/87 (79.3%) v. *n*=27/87 (31.0%)) when combined with multidisciplinary discussion. However, oxygen desaturation was observed in 30/87 patients (34.5%) during the TBLC procedure, while none of the patients experienced desaturation during TBLB. Pneumothorax developed in 12 of the patients (13.8%), of whom 11 required high-flow oxygen therapy and 1 insertion of an intercostal drain with a 3-day hospital stay. Moderate bleeding mandating the use of a bronchial blocker and/or topical treatment occurred in most of the patients (~72%), with no reported incident of major bleeding.

The authors must be commended on performing this interesting but difficult study. What are the implications of the findings? Although most guidelines recommend performing TBLC via a secured airway using an endotracheal tube or rigid bronchoscopy, the authors have shown that it can be done under conscious sedation in a specific context. However, the bleeding rate was much higher than in other studies, ~75% v. ~25%. The possible reasons include undiagnosed pulmonary hypertension, as the patients were not screened for this; coughing, as patients were not deeply sedated; and the most common diagnosis in this series being hypersensitivity pneumonitis, in contrast to other studies, which may have contributed to the increased incidence of bleeding. The pneumothorax rate was also higher than what has traditionally been reported with TBLB, but this could simply represent an additive effect: the study design did not allow for the accurate quantification of adverse events, especially pneumothorax, as it would be difficult to ascertain exactly when the event occurred, i.e. during TBLB or TBCB. The major advance of this study is confirmation that conscious sedation may be compatible with low severe bleeding rates, as the main reason for using endotracheal intubation is to maintain a safe airway in the event of major bleeding. Significantly, more recent data on cryobiopsy using a 1.1 mm sheathed cryoprobe support use with a laryngeal mask airway without bronchial blockers,[14] adding to the confidence in this approach. Another advantage of the study by Mohanrao *et al.*[13] was the resource-poor setting; TBLC was useful in patients with DPLD, but also, surprisingly, in those with tuberculosis (although it is not clear whether the diagnosis was made using Xpert or was purely histological).

Another conundrum facing those of us in the field is the order in which bronchoscopic investigations should be performed, i.e. when one has access to endobronchial ultrasound-guided transbronchial fine-needle aspiration (EBUS-TBNA), TBLB and TBLC. Our approach is to perform EBUS first in all patients with suspected DPLD who have significantly enlarged mediastinal lymph nodes. All patients with a non-diagnostic mediastinal lymph node biopsy on rapid on-site evaluation should proceed to TBLB during the same procedure. Given the additional logistical challenges, costs and risks associated with TBLC, this procedure is reserved for patients with a non-diagnostic EBUS/TBLB and for patients with DPLD with a high likelihood of a non-bronchocentric disease process such as pathologies associated

with non-definite usual interstitial pneumonia, and nonspecific interstitial pneumonia patterns on HRCT – the bottom line is that this decision will be centre specific and dependent on capacity. Furthermore, choosing between TBLB and TBCB may depend on several other factors, including patient preference and available resources. TBLC will also be useful for the ~15% of patients who remain unclassifiable in large series who are too sick for SLB. However, there are still several unanswered questions. One is, could a similar diagnostic yield be achieved with the smaller 1.1 mm sheathed probe (with a slightly higher freezing time of ~7 seconds), while keeping bleeding and pneumothorax rates similar to forceps-linked TBLB? Second, which area on HRCT should be biopsied, and should more than one region be biopsied? These issues will need to be resolved in future studies.

It should be noted that TBLC is not a panacea, and ~20% of patients in Mohanrao *et al.*'s[13] series still had an inconclusive diagnosis. While TBLC has a better yield than TBLB, it is not perfect and is still a technique complementary to SLB. Patients should therefore be selected by multidisciplinary teams, and the procedure should be performed in close co-operation with cardiothoracic surgeons. Indeed, interventional pulmonology remains a hot topic, and TBLC is certainly the new 'coolest kid on the block'!

A Esmail, MD, FCP (SA)
Centre for Lung Infection and Immunity, Division of Pulmonology, Department of Medicine and UCT Lung Institute, University of Cape Town; South African MRC/UCT Centre for the Study of Antimicrobial Resistance, University of Cape Town, South Africa
ali.esmail@uct.ac.za

K Dheda, MB BCh (Wits), FCP(SA), FCCP, PhD (Lond), FRCP (Lond)
Head: Division of Pulmonology, Department of Medicine, University of Cape Town, South Africa; Professor of Mycobacteriology and Global Health, London School of Hygiene and Tropical Medicine, United Kingdom; Director: Centre for Lung Infection and Immunity, University of Cape Town Lung Institute, South Africa

1. Andersen HA, Fontana RS, Harrison EG Jr. Transbronchoscopic lung biopsy in diffuse pulmonary disease. Dis Chest 1965;48:187-192.
2. Colby TV. The pathologist's approach to bronchoscopic biopsies. Pathologica 2010;102(6):432-442.
3. Leslie KO, Gruden JF, Parish JM, Scholand MB. Transbronchial biopsy interpretation in the patient with diffuse parenchymal lung disease. Arch Pathol Lab Med 2007;131(3):407-423. https://doi.org/10.7196/10.5858/2007-131-407-TBIITP
4. Berbescu EA, Katzenstein A-LA, Snow JL, Zisman DA. Transbronchial biopsy in usual interstitial pneumonia. Chest 2006;129(5):1126-1131. https://doi.org/10.7196/10.1378/chest.129.5.1126
5. Shim HS, Park MS, Park IK. Histopathologic findings of transbronchial biopsy in usual interstitial pneumonia. Pathol Int 2010;60(5):373-377. https://doi.org/10.7196/10.1111/j.1440-1827.2010.02528.x
6. Blackhall V, Asif M, Renieri A, et al. The role of surgical lung biopsy in the management of interstitial lung disease: Experience from a single institution in the UK. Interact Cardiovasc Thorac Surg 2013;17(2):253-257. https://doi.org/10.7196/10.1093/icvts/ivt217
7. Nguyen W, Meyer KC. Surgical lung biopsy for the diagnosis of interstitial lung disease: A review of the literature and recommendations for optimizing safety and efficacy. Sarcoidosis Vasc Diffuse Lung Dis 2013;30(1):3-16.
8. Peng M, Xu W-B, Shi J-H, et al. [The diagnostic value of CT-guided percutaneous needle lung biopsy in diffuse parenchymal lung diseases]. Zhonghua Jie He He Hu Xi Za Zhi 2012;35(3):171-175.
9. Huo YR, Chan MV, Habib AR, Lui I, Ridley L. Pneumothorax rates in CT-guided lung biopsies: A comprehensive systematic review and meta-analysis of risk factors. Br J Radiol 2020;93(1108):20190866. https://doi.org/10.7196/10.1259/bjr.20190866
10. Rodgers BM, Talbert JL. Clinical application of endotracheal cryotherapy. J Pediatr Surg 1978;13(6D):662-668. https://doi.org/10.7196/10.1016/s0022-3468(78)80111-0
11. Mathur PN, Wolf KM, Busk MF, Briete WM, Datzman M. Fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. Chest 1996;110(3):718-723. https://doi.org/10.7196/10.1378/chest.110.3.718
12. Babiak A, Hetzel J, Krishna G, et al. Transbronchial cryobiopsy: A new tool for lung biopsies. Respiration 2009;78(2):203-208. https://doi.org/10.7196/10.1159/000203987
13. Mohanrao KS, Chakraborti A, Saini JK, et al. Afr J Thoracic Crit Care Med 2023;29(3):e799. https://doi.org/10.7196/AJTCCM.2023.v29i3.799
14. Thiboutot J, Illei PB, Maldonado F, et al.; Interventional Pulmonary Outcomes Group. Safety and feasibility of a sheath cryoprobe for bronchoscopic transbronchial biopsy: The FROSTBITE Trial. Respiration 2022;101(12):1131-1138. https://doi.org/10.1159/000526876

Afr J Thoracic Crit Care Med 2023;29(3):e1494.
https://doi.org/10.7196/AJTCCM.2023.v29i3.1494