Transbronchial Lung Cryobiopsy for Interstitial Lung Disease Diagnosis

A Perspective From Members of the Pulmonary Pathology Society

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• Transbronchial lung cryobiopsy involves using a cryoprobe rather than forceps to obtain a bronchoscopic biopsy. Recent studies have shown that transbronchial cryobiopsy provides a larger specimen than conventional transbronchial forceps biopsy, and that the interobserver agreement in the interpretation of cryobiopsy specimens is comparable to that of a surgical lung biopsy. This is encouraging, and transbronchial lung cryobiopsy clearly has a role in the workup and diagnosis of interstitial lung diseases. However, very few patients who have been studied underwent both transbronchial lung cryobiopsy and surgical lung biopsy, and the available data suggest that the diagnostic accuracy of cryobiopsy may not be similar to that of surgical lung biopsy. Further study is needed before transbronchial lung biopsy can be recommended as a replacement for surgical lung biopsy.

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The current American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association guidelines recommend surgical lung biopsy (SLB) in combination with multidisciplinary discussion among a team comprising experienced clinicians, radiologists, and pathologists to reach a consensus diagnosis is the standard of care for the diagnosis of interstitial lung diseases (ILDs) including idiopathic pulmonary fibrosis.[1] When practitioners are confronted with a diagnosis of ILD, a comprehensive clinical evaluation performed by the pulmonologist needs to be correlated with the interpretation of a high-resolution computed tomography by the thoracic radiologist. When a combination of the clinical context and thoracic imaging is inadequate to provide a confident diagnosis, the pulmonologist must consider a role for a transbronchial biopsy and/or SLB.

Transbronchial lung biopsies using regular flexible forceps have a limited role in the diagnosis of ILDs except in the granulomatous and alveolar filling/airspace diseases because of the limited size of the biopsy, the associated small chance of sampling sufficient diagnostic information, and artifacts associated with the technique. Transbronchial lung biopsy is a relatively noninvasive technique and safe, with pneumothorax being the most common complication (seen in 2% to 10% of cases) and bleeding seen in less than 2% of cases. Transbronchial biopsy with jumbo forceps can provide

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Studies Reporting Use of Transbronchial Lung Cryobiopsy (TBLC) in Diagnosis of Interstitial Lung Diseases				
	Prospective/ Retrospective	No. of Patients Who Underwent Cryobiopsy	Mean Specimen Area or Diameter of Biopsies	Diagnostic Yield on Pathology (Including Clinical and Radiology Data)
Babiak et al,[14] 2009	Retrospective	41	15.11 mm^2 (area)	95%
Fruchter et al,[10] 2013	Retrospective	15	9 mm^2 (area)	80%
Kropski et al,[11] 2013	Retrospective	25	64.2 mm^2 (area)	80%
Casoni et al,[9] 2014	Prospective	69	43.11 mm^2 (area)	High coincidence: 52 (76%)
Pajares et al,[3] 2014	Randomized prospective	77	14.7 mm^2 (area)	74%
Griff et al,[6] 2014	Retrospective	52	6.9 mm (diameter)	79%
Fruchter et al,[7] 2014	Retrospective	75	9 mm^2 (area)	70%
Hernandez-Gonzalez,[4] 2015	Retrospective	33	4 mm (diameter)	79%
Hagmeyer et al,[5] 2015	Retrospective	32	. . .	72%
Gershman et al,[8] 2015	Retrospective	300	. . .	. . .
Tomassetti et al,[2] 2016	Prospective	58	. . .	IPF 29 (50%) NSIP 7 (12%) HP 6 (10%) DIP/RBILD 2 (4%) Other 9 (15%) No consensus 3 (5%) Unclassifiable 2 (4%)

Abbreviations: DIP, desquamative interstitial pneumonia; HP, hypersensitivity pneumonitis; IPF, idiopathic pulmonary fibrosis; NSIP, nonspecific interstitial pneumonia; RBILD, respiratory bronchiolitis–associated interstitial lung disease; SLB, surgical lung biopsy.

larger specimens with fewer artifacts, but is associated with a greater incidence of bleeding.

To date, SLB is considered the most reliable method to provide diagnostic and prognostic information in cases of ILD for which this information cannot be obtained using less-invasive methods. However, SLB requires endotracheal intubation, general anesthesia, chest tube placement, and a few days' hospitalization and is associated with increased cost and risks, including 2% to 6% reported mortality. There is a need for a technique for lung biopsy that is less invasive than SLB but provides more tissue than traditional transbronchial biopsy to aid the clinical team in making a diagnosis.

Transbronchial lung cryobiopsy (TBLC) has been proposed as a less invasive alternative to SLB in patients with ILD. Recent studies have highlighted its safety and diagnostic accuracy in ILD and have suggested that it may be possible for TBLC to replace SLB (Table).[2–11] Results from the available studies to date are encouraging, but more prospective data are needed before cryobiopsy can replace SLB for the diagnosis of ILDs.

Cryoprobes for bronchoscopic procedures were first described in 1977 and have been used in the palliative treatment of obstructing endobronchial tumors.[12] More recently, cryoprobes have been used to obtain lung tissue during flexible bronchoscopy. The cryosurgical equipment operates by the Joule-Thomson effect, where compressed gas released at high flow rapidly expands and creates a very low temperature. The cryoprobe is introduced into the selected area under fluoroscopic guidance and is cooled for approximately 3 to 6 seconds. The frozen tissue attached to the probe's tip is retracted along with the cryoprobe and bronchoscope, which is then thawed and later fixed in neutral buffered formalin. The number of biopsies obtained during a procedure is variable, but usually ranges between 3 and 6. A chest radiograph is performed after the procedure to evaluate for pneumothorax. A Fogarty balloon can be used to control the bleeding.

The characteristics of samples obtained via TBLC vary from those of samples obtained via standard methods in several important aspects. Transbronchial lung cryobiopsy yields larger and better-preserved specimens as compared with transbronchial biopsies, but smaller specimens than surgical lung biopsies. In TBLC, the collapse artifact seen in transbronchial biopsy and SLB is prohibited to a large extent, leading, for example, to more open alveolar spaces and open peribronchiolar lymph vessels, which can be visualized by immunohistochemical D2-40 stain. Thus, the morphology is a closer representation to the in vivo situation with TBLC.[13] Most series require at least one fragment of alveolated lung parenchyma to be classified as an adequate specimen. However, the size of the biopsies in TBLC (range, 9–64.2 mm^2) is substantially smaller than the size of those in SLB, making it harder for the pathologist to come up with a definite and confident diagnosis in what is an already difficult diagnostic area of pathology, where the pattern of the disease at low power is crucial. Transbronchial lung cryobiopsy specimens are from a relatively more central location when compared with the peripheral SLB specimens. Additionally, TBLC provides a sample from a

Extended			
κ Coefficient (Pathologists)	Complications, No. (%)	Comparison With Surgical Lung Biopsy	Comparison With Transbronchial Biopsy
. . .	Pneumothorax, 2 (5)	No	Yes
. . .	Significant bleeding, 1 (6)	No	Yes
. . .	No significant complications	No	No
0.83 (usual interstitial pneumonia pattern)	Pneumothorax, 19 (28) Chest tube drainage, 14 (20) Prolonged bleeding, 1 (1.4) Death, 1 (1.4)	No	No
. . .	Mild bleeding, 12 (31) Moderate bleeding, 22 (56) Pneumothorax, 3 (8)	No	Yes
. . .	No significant complications	No	No
. . .	Pneumothorax, 2 (2.6) Mild bleeding, 3 (4)	No	No
. . .	Pneumothorax, 4 (12) Mild bleeding, 3 (9) Moderate bleeding, 7 (21)	No	No
0.80	Pneumothorax, 6 (19) Moderate bleeding, 8 (25) Severe bleeding, 17 (53)	8 patients (underwent both TBLC and SLB)	No
. . .	Pneumothorax, 15 (5) Chest tube drainage, 6 (2) Bleeding, 16 (5)	No	Yes (complications similar in both groups)
0.59 (TBLC) 0.86 (SLB)	Pneumothorax, 19 (33) Chest tube drainage, 15 (25) Death, 1 (2)	Yes, retrospective (59 patients with SLB; 4 patients underwent both TBLC and SLB)	No

single site, unlike the multiple and peripheral samples obtained from different lobes in SLB. These factors may affect the diagnostic ability of the pathologists in making a diagnosis of a particular pattern, specifically a usual interstitial pneumonia pattern. An important and as yet unanswered question is whether the pattern seen in the smaller sample from the single focus obtained via TBLC is truly representative of what one would see if multiple biopsies from multiple lobes were obtained.

Studies have shown that pneumothorax (2.6%–33% of cases) and significant bleeding (1.4%–56% of cases) can be seen in patients undergoing TBLC. Mortality and complication rates for TBLC lie somewhere in between those observed for transbronchial biopsy and those observed for SLB.

Recent studies have also shown that a definite and confident diagnosis can be obtained in a substantial proportion of patients undergoing TBLC, but a closer look at the data from these studies shows that TBLC cannot yet be recommended as a replacement for SLB for the diagnosis of ILDs. In what is probably the most rigorously conducted study on the performance characteristics of TBLC, Tomassetti et al[2] reported their experience with 58 TBLC and 59 SLB cases and noted that the interobserver agreement in idiopathic pulmonary fibrosis diagnosis after a multidisciplinary discussion for TBLC was comparable with that for SLB. However, akin to the concept of precision versus accuracy in physics, a high interobserver agreement is not the same as high diagnostic accuracy. This study was not designed to, and did not, compare the diagnostic accuracy of TBLC with that of SLB. Fewer patients (39% versus 50%) were diagnosed with idiopathic pulmonary fibrosis on SLB, raising the question as to whether it is possible that larger and multifocal tissue sampling allowed the visualization of specific patterns, permitting the pathologists to make an alternate diagnosis in a higher proportion of the SLB cases.

There are no studies primarily designed to compare the performance characteristics of TBLC and SLB in a prospective blinded fashion, but a closer examination of the reported data on patients who underwent both these procedures suggests that the diagnostic accuracy of TBLC is likely not comparable with that of SLB. Four patients in the series reported by Tomassetti et al[2] underwent both SLB and TBLC. The diagnoses were congruent for TBLC and SLB for 3 patients; the fourth patient was diagnosed to have unclassifiable fibrosis by TBLC and chronic hypersensitivity pneumonitis by SLB. Eight patients in the series reported by Hagmeyer et al[5] underwent both SLB and TBLC. The TBLC diagnoses in this series, even when congruent with the SLB diagnoses, were consistently reported with a much lower diagnostic confidence than the SLB diagnoses.

Finally, the current studies are limited by the almost exclusive performance of the procedures by expert bronchoscopists with vast experience in performing TBLC, and the inclusion of pathologists who are experts in pulmonary pathology and, more specifically, in ILDs. It is unclear if the performance characteristics of TBLC in the hands of less-experienced bronchoscopists and pathologists will be comparable with those of the experts reported in the current literature, an important consideration because the vast majority of lung biopsies are performed by community pulmonary physicians and read by nonacademic community pathologists whose primary area of interest and expertise is not ILDs.

In conclusion, although the emerging data on transbronchial cryobiopsy are encouraging and TBLC definitely has a role in the diagnosis of ILD in a subset of patients, particularly those considered to be at a high risk of complications from SLB, TBLC cannot be recommended as a replacement for SLB at this time. Prospective studies demonstrating comparable diagnostic accuracy of the 2 procedures in the multidisciplinary context are needed, although the practical difficulty of performing these studies may be a limiting factor.

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