

Transbronchial cryobiopsy in diffuse parenchymal lung disease

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ABSTRACT

The evaluation of patients with diffuse parenchymal lung disease is best achieved by a multidisciplinary team approach combining clinical, radiological, and pathological information. Although a lung biopsy may be necessary to firmly establish a diagnosis, safely obtaining adequate tissue specimens in such patients remains challenging. Traditional bronchoscopic forceps biopsies are not recommended for most idiopathic interstitial pneumonias due to their low diagnostic yields, whereas a surgical lung biopsy increases the risk for serious complications, including a small but real risk of an exacerbation of the underlying interstitial lung disease and death. Bronchoscopic cryosurgical techniques (i.e., cryobiopsy) is being increasingly used as an attractive compromise between the two, due to its ability to be performed under conscious sedation and its ability to obtain larger tissue fragments without crush artifacts. Although promising and increasingly employed at some academic centers, it remains untested in rigorous systematic studies. This article will review the existing literature on the diagnostic role and safety of transbronchial cryobiopsy in patients with diffuse parenchymal lung diseases.

Key words: Transbronchial cryobiopsy, cryobiopsy, interstitial lung disease, diffuse parenchymal lung disease

INTRODUCTION

The evaluation of patients with diffuse parenchymal lung diseases (DPLD), particularly the idiopathic interstitial pneumonias (IIP), often requires a multidisciplinary team approach. A surgical lung biopsy may be necessary for a confident diagnosis, particularly in patients with atypical clinical/radiological presentations.¹ However, surgical lung biopsies carry a risk of serious complications, with a 30-day mortality ranging from 2.7% to 12% in patients with interstitial lung disease (ILD)^{2,3}, and the short-term mortality rate from

either thoracotomy or video-assisted thoracoscopic surgery has been as high as 21.7% in patients with idiopathic pulmonary fibrosis (IPF).⁴

Bronchoscopic transbronchial forceps biopsy had been considered a safer alternative to surgical lung biopsy and can be diagnostic for several respiratory disorders (e.g., sarcoidosis) presenting as a diffuse parenchymal lung process.⁵ The procedure is typically performed in the outpatient setting with a low incidence of serious complications that include pneumothorax and significant bleeding which occur at a rate of 0.1 to 0.04%.⁶ However, the specimens obtained by transbronchial forceps biopsies are often nondiagnostic due to the small size of specimens and crush artifacts.⁷ The diagnostic yield of transbronchial

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lung biopsies varies significantly according to the radiographic pattern,⁸ but can be as high as 60-90% in selected disorders, such as sarcoidosis and lymphangitic carcinomatosis.⁸⁻¹⁰ However, for most fibrotic lung diseases, the diagnostic yield is considerably lower at 20-30%.^{8,9,11} Transbronchial lung biopsy is thus not recommended when attempting to histologically confirm IPF or the other IIPs.¹²

One alternative that is being increasingly used for the evaluation of diffuse parenchymal lung diseases is the flexible cryoprobe, which has been primarily used for the biopsy or ablation of visible endobronchial lesions.¹³ The advantage of cryobiopsies includes the ability to obtain a larger tissue sample, with preservation of the underlying lung parenchymal architecture, similar to a frozen section, but the potential disadvantages include more substantial bleeding. Additionally, because the sample is larger, the tissue cannot be withdrawn through the bronchoscopic channel and the whole bronchoscope must be withdrawn with each cryobiopsy, potentially losing an insecure airway if bleeding occurs. Although systematic controlled trials comparing cryobiopsies to forceps biopsies or thoracoscopic lung biopsies for idiopathic interstitial pneumonias are lacking, multiple centers have started reporting their experience with transbronchial cryobiopsies. Here, we review the existing literature on the diagnostic yield and safety of transbronchial cryobiopsies in the evaluation of diffuse parenchymal lung diseases.

METHODS

The MEDLINE and PubMed search of the English literature was performed between 1970 and 2014 using the keywords “transbronchial cryobiopsy,” “cryobiopsy,” “interstitial lung disease,” and “diffuse parenchymal lung disease” in combination. The results were reviewed and summarized.

CRYOTECHNOLOGY

Cryoprobes are available as rigid, semi-rigid, or flexible catheters of 50, 60, or 90 cm in length with variable tip diameters of 1.9, 2.4, and 5.5 mm (Erbokryo CA, ERBE, Germany). Utilizing the Joule-Thomson

effect, compressed gas (e.g., nitrous oxide, carbon dioxide, nitrogen, argon) is allowed to rapidly expand within the metallic tip which instantaneously drops the temperature locally to -70 to -196 ° C. The subfreezing temperature leads to adhesion of the tissue to the probe which can then be removed. Cessation of flow and a pressure decrease are followed by release of heat and defrosting.¹⁴ The tissue can be released from the probe during the freeze-thaw cycle. Cellular and vascular injury can result in tissue necrosis,¹⁴ but the diagnostic quality of the histopathology obtained is not significantly affected, even with longer freezing periods.¹⁵⁻¹⁷

PROCEDURAL ASPECTS OF THE TRANSBRONCHIAL CRYOBIOPSY

The cryoprobe is introduced through the working channel of a flexible bronchoscope, under fluoroscopic guidance, into the desired location, until slight resistance is met. The tip is then cooled for 3-6 seconds causing adherence of the frozen tissue to the cryoprobe.^{13,18-22} The longer the freeze cycle, the larger the size of the biopsy. The probe is then firmly pulled back separating the frozen biopsy sample from the native lung. Care must be taken not to pull the cryoprobe and the biopsy sample (which is typically larger than the working channel) through the bronchoscope to avoid damaging the bronchoscope and losing the sample. Thus, the entire bronchoscope has to be removed with the frozen tissue at the probe's tip as a single unit. To minimize the need to repeatedly renavigate through the nose or mouth into the lower airways, most experts recommend a secure endotracheal airway with deeper sedation as necessary. This allows the bronchoscope to be rapidly reintroduced after the biopsy to clear blood and wedge into the biopsied subsegment to tamponade any active bleeding. Since bleeding can be immediate and compromise visualization of the airways, some have routinely applied a Fogarty balloon proximal to the biopsied subsegment to immediately occlude the airway and provide better control of bleeding.^{18,23,24} Upon completion of the procedure, a chest x-ray is recommended to exclude pneumothorax unless fluoroscopy is able to confidently exclude this complication.

DIAGNOSTIC YIELD OF TRANSBRONCHIAL CRYOBIOPSY

Cryosurgical techniques were initially used for biopsy and debulking of airway diseases.²⁵ The efficiency and advantages of the cryoprobe in obtaining the samples from lung parenchyma have been actively explored by multiple centers in the recent years as summarized in Table 1.

A major advantage of cryo-transbronchial biopsy is that the samples obtained are larger,^{13,17,19,21,26} have a higher percentage of alveolar tissue, and are typically without crush artifacts (atelectasis and intra-alveolar hemorrhage) that are frequently seen in forceps biopsy samples.^{19,21,26} More alveolar tissue^{13,17,19,21,26} correlates with a better diagnostic yield,^{17,18} but the histologic quality is also superior, being free of cryospecific artifacts and having an overall higher artifact-free area.^{15,16} Additionally, the high-quality detection of cytoplasmic and nuclear antigens suggests the potential benefit of doing additional immunohistochemistry investigations.²¹ Thus, cryo-techniques appear to offer higher quality tissue specimens from the pathologists' perspective, and likely increase the diagnostic value.^{26,27}

When specifically applied to patients with diffuse lung diseases, the cryobiopsy specimens were also significantly larger with a median sample area of 15.11 mm² (2.15-54.15 mm²) compared to 5.82 mm² (0.58-20.88 mm²) by forceps. Tissue architecture from the cryobiopsy was described to be preserved which facilitated diagnosis.¹⁷ Compared to a historical diagnostic rate of 30% from traditional forceps transbronchial biopsies, the yield of cryobiopsies was increased up to 80%.^{11,13,28} The higher diagnostic yield was attributed to the larger samples allowing for more contiguous alveolated lung and small airways. It is important to note that the results might be limited by the observational nature of the study, as well as the small sample.^{13,19}

The yield does vary depending on the underlying diagnosis, but appears to be generally higher than

what has been previously reported for conventional forceps biopsies. For example, in a retrospective study of 52 patients the diagnostic yield was 83% for sarcoidosis, 89% for organizing pneumonia, 86% for hypersensitivity pneumonia, and 67% for UIP.^{11,28} One possible explanation is the ability to obtain small airways to view granulomas or other characteristic changes close to the bronchial walls,²⁰ as well as a large enough alveolar tissue samples to capture the patchwork pattern of fibrosis in UIP.²⁰

In a prospective series of patients with fibrotic diffuse parenchymal lung diseases with nondiagnostic imaging using the cryobiopsy technique, adequate biopsies were obtained in 68 cases (99%) with a diagnostic yield in fibrosing interstitial pneumonia of up to 93%.¹⁸ Using cryobiopsy identified more UIP cases (47 patients, 73%) when compared to forceps biopsies performed on a similar population in a previous study (12 patients, 30%) by the same investigators.²⁸

Furthermore, the first randomized controlled study (n=77) comparing transbronchial forceps to cryobiopsies in patients with suspected ILDs reported 74.4% histopathological diagnoses in the cryoprobe group versus 34.1% in the conventional-forceps group (p<0.001).²¹ The most frequent histologic diagnosis observed in the cryoprobe group was nonspecific interstitial pneumonia (NSIP) with the characteristic histopathologic pattern of chronic inflammatory or cellular infiltrates. Again, the higher diagnostic yield of cryobiopsy in identifying more IIP was attributed to the larger size and higher quality of samples in comparison with the conventional forceps group.²¹

One of the major limitations in most of these studies is the lack of pathology from surgical lung biopsy as the histologic gold standard to compare the accuracy of transbronchial cryobiopsy. Hagemeyer et al²² performed the latest retrospective study on 32 patients with suspected ILD who underwent transbronchial cryobiopsy. Of those subjects, 8 patients underwent both transbronchial cryobiopsy and surgical lung biopsy. They found a good correlation between cryobiopsy and surgical lung biopsy in 7 of the 8 patients. In these 7 cases, surgical lung biopsy confirmed the

Table 1 Studies of transbronchial cryobiopsy in patients with diffuse parenchymal lung diseases

Study	Design	Patient numbers	Diagnosis	Diagnostic yield	Number of biopsies	Size (mm ²)	Pneumothorax	Bleeding	Death
Hagmeyer 2015 ²²	Retrospective study Cryobiopsy vs. surgical biopsy	32, 8 with surgical lung biopsy	21(66%) IIP 11(34%) Non-IIP	78% (25/32) 70% in IIP 92% in non-IIP	2-4 per procedure	NA	6 (19%)	25 (78%)	2(6.25%) Acute exacerbation of IPF after surgical lung biopsy
Pajares 2014 ²¹	Randomized controlled study Forceps vs. Cryobiopsy	77	12(30%)NSIP 7(18%) UIP 19 not diagnostic	74.4% (29/39)	3.7 (mean) per procedure	14.7±11 Mean diameter 4.1 ±1.5 mm	3 (7.7%)	22 (56.4%)	None
Griff 2014 ²⁰	Retrospective study Cryobiopsy	52	9 (17%) UIP 32 (62%) Non-UIP (10 Sarcoidosis, 6 HP, 8 COP) 4 not adequate	79% (41/52)	1-2 per procedure	NA Mean diameter 6.9±4.4 mm	None	None	None
Casoni 2014 ¹⁸	Prospective study Cryobiopsy	69	47(75%) UIP 16(25%) Non-UIP 5 not diagnostic 1 not adequate	76% (52/69)	3 (median) per procedure	43.11 (11.94-76.25)	19 (28%)	1 (1.4%)	1(1.4%) Acute exacerbation of IPF, massive pneumothorax.
Fruchter 2014 ¹⁹	Retrospective study Cryobiopsy	75	21(28%) NSIP 22(29%) IIP 11(14%) COP 7(9%) UIP 2 not diagnostic	70% (52/75) possible 28% (21/75) probable	3(mean) per procedure	9 (6-18)	2 (2.6%)	3 (4%)	None
Kropski 2013 ¹³	Retrospective study Cryobiopsy	25	7(28%) UIP 12(48%) Non-UIP 1 normal 5 not diagnostic	80% (20/25)	2 per procedure	64.2 (1.5-136.7)	None	None	None
Babiak 2009 ¹⁷	Retrospective study Forceps vs. cryobiopsy	41	15 (37%) UIP 24 (59%) Non-UIP 2 surgical biopsy	95% (39/41)	At least 1 biopsy per procedure	15.11 (2.15-54.15)	2 (4.87%)	None	None

suspected histological results obtained by cryobiopsy which were mostly in the UIP pattern. In the majority of patients, the pathology obtained from cryobiopsy was considered adequate and was consistent with the suspected clinic/radiologic diagnosis, and thus no further investigations (i.e., surgical lung biopsy) were felt to be necessary following the multidisciplinary review.²² Cryobiopsy seems to be a promising diagnostic tool based on previous studies. But even surgical lung biopsies have some element of uncertainty, and the diagnostic yields in patients with DPLD need to be

interpreted with caution.

SAFETY

Safety is one of the most important concerns when introducing new techniques and technologies. With regard to transbronchial cryobiopsy, bleeding is a major concern due to the technique itself, in which the bronchoscope has to be withdrawn from the airways in entirety with each biopsy. As expected, the

previously discussed studies excluded patients with coagulation disorder (thrombocytopenia < 50,000 cells/mm³, international normalized ratio > 1.5, and activated partial thromboplastin time > 50 s) and pulmonary hypertension estimated by pulmonary systolic arterial pressure above 40 mmHg.^{18,21}

The safety of the technique was assessed in a randomized controlled study comparing transbronchial forceps to cryobiopsies. The study demonstrated no statistically significant difference in overall bleeding complications (39 patients in cryoprobe group vs. 38 patients in the conventional forceps group, $p=0.068$), but did show a trend of bleeding complications that required bronchoscopic interventions (22 patients in the cryoprobe group vs 13 patients in conventional-forceps group, no p value reported).²¹

Hagmeyer et al²² reported very high rates of bleeding complications which were graded moderate in 25% and severe in 53%. However, bleeding could be stopped by bronchoscopic wedging and instillation of epinephrine. In a randomized study of 77 patients, more patients in the cryobiopsy group had bleeding complications requiring bronchoscopic procedures, such as bronchial occlusion/collapse. In this study, the number of samples was not associated with the increased bleeding risk, but it appeared that the size of the biopsy sample may be a factor.²¹ Some studies minimized the consequence of bleeding by the routine preventive use of an occlusion balloon catheter placed immediately after the biopsy.^{18,23,24} Nevertheless, the cryobiopsy is potentially useful in the diagnosis of selected patients with diffuse parenchymal lung disease, but possibly at the cost of more serious bleeding complications.

Several studies have also demonstrated a higher incidence of pneumothorax after transbronchial cryobiopsy.^{18,21,22} Casoni et al¹⁸ demonstrated a significant higher rate of pneumothorax which might be associated with the study population being limited to fibrotic lung diseases and attempted biopsies at subpleural areas. The Hagmeyer study²² also reported a higher incidence of pneumothorax at 43% (3/7 patients) in patients under general anesthesia and on invasive

ventilation versus 12% (3/25 patients) in patients under conscious sedation and spontaneous breathing. Of note, estimates of the risk of pneumothorax associated with traditional transbronchial biopsy typically range from 0 to 5%, with higher rates up to 16% in mechanically ventilated patients.²⁹⁻³²

SUMMARY

Although the role of transbronchial cryobiopsy is still not established as a standard tool in the investigation of interstitial lung disease, the data presented favor and justify its consideration on a case by case basis until more definitive ongoing studies provide more information. The diagnostic yield overall appears to be superior to previous experience with bronchoscopic forceps biopsies, particularly for the IIP, but is at the cost of increased risk for bleeding and pneumothoraces. This new technique is not likely applicable to all patients or all centers, and mastery of this procedure and management of its complications will likely be an important factor in the safety and feasibility of the procedure. However, with new therapies available for fibrotic lung diseases^{33,34}, making a confident diagnosis of idiopathic interstitial pneumonias is increasingly pertinent, and cryobiopsies are a potential compromise between surgical lung biopsies that are often not possible in patients with advanced lung diseases and the low diagnostic yield of the traditional transbronchial forceps biopsies.

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