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## Mini Review

# Usefulness of Transbronchial Cryobiopsy in Interstitial Lung Disease

## Review

Interstitial lung disease (ILD) is a term that describes a group of more than 200 lung disorders that show varying degrees of inflammation and fibrosis of the pulmonary interstitium. The etiology and pathophysiology of many of these disorders still remains poorly understood and is the topic of ongoing research and debate. The diagnostic approach to ILD can be complex and often requires a multidisciplinary team approach with involvement of a pulmonologist, radiologist and pathologist. A lung biopsy is often needed to determine the particular subcategory of interstitial lung disease. Unfortunately, conventional transbronchial biopsy with forceps has a very poor diagnostic yield in ILD. A large review of 801 patients showed a diagnostic yield of less than 30% [1]. Surgical lung biopsy is considered the “gold standard” but has a high mortality with several studies showing a mortality of 1.7% to 4.2% in elective cases and 16% to 17.5% in urgent cases [2–6]. In the last several years, the introduction of bronchoscopic transbronchial cryobiopsy has been an exciting development in this regard. This particular diagnostic intervention has the potential to provide diagnosis in ILD with a safety profile closer to conventional transbronchial biopsy and a diagnostic yield approaching surgical lung biopsy.

The cryobiopsy apparatus consists of a cryo-generator that contains Nitric Oxide or Nitrous Oxide gas. Cryo-generators with Carbon Dioxide as the cryogen are also available and are less costly than Nitric Oxide or Nitrous Oxide based systems. A flexible cryoprobe ranging in diameter from 1.9 to 2.6 mm is connected to the generator. A foot paddle allows the operator to release the gas from the generator to exit at the tip of the probe. Utilizing Joule-Thompson effect of fluids, the rapid expansion of gas exiting at the tip of the probe causes a rapid drop in temperature and freezes the tissue surrounding the tip of the probe. Freezing times from 3–6 seconds are generally considered adequate. Care is taken to keep the probe 5–10 mm away from the pleural lining on the fluoroscopic view to avoid advertent freezing of the visceral pleura which could cause a pneumothorax. The probe and scope are then pulled back gently

removing the frozen tissue attached at the tip of the cryoprobe. An endobronchial blocker has been used by some operators to control bleeding but its use is not universal or standardized [7]. As opposed to conventional transbronchial biopsy with forceps, cryobiopsy provides a larger specimen with the area of sample ranging from 11.11 mm<sup>2</sup> to 64.2 mm<sup>2</sup> as compared to 0.58 mm<sup>2</sup> to 20.88 mm<sup>2</sup> for conventional transbronchial biopsy sample size [8–12]. Moreover, there is avoidance of crush artifact leading to better preservation of tissue architecture.

The larger sample size and preservation of tissue architecture translates into a better diagnostic yield as well. A systematic review and meta-analysis of 11 studies (731 patients), showed a diagnostic yield from 74 to 98% when transbronchial cryobiopsy findings were interpreted in isolation, with a pooled estimate of 83%. Diagnostic yield ranged from 51 to 98% when the results were reviewed within a multidisciplinary discussion with a pooled estimate of 79% [13].

The safety profile of transbronchial cryobiopsy seems to be favorable, although the risk of pneumothorax and bleeding are higher than conventional transbronchial biopsy. In the systematic review and meta-analysis published by Johnson KA et al., the pooled estimate for pneumothorax and moderate to severe bleeding were 12% and 39% respectively [13].

Ranaswamy A et al., published a retrospective review comparing conventional transbronchial biopsy and cryobiopsy [14]. Fifty six patients underwent flexible bronchoscopy under conscious sedation and had conventional transbronchial biopsies followed by transbronchial cryobiopsy. Forty five patients (80.4%) had a definitive pathologic diagnosis. In twenty six patients (46.4%), both types of biopsies yielded the same diagnosis. Transbronchial cryobiopsy added a diagnosis in 11 patients (19.6%) while only 4 patients (7.1%) had a diagnosis established only by conventional biopsy. The diagnostic yield of cryobiopsy was higher in hypersensitivity pneumonitis (HP) and non-specific pneumonitis (NSIP) when compared to conventional biopsy. Only two patients needed subsequent surgical biopsy.

A retrospective analysis of 447 cases with ILD undergoing transbronchial cryobiopsy and/or surgical lung biopsy showed no significant difference between the diagnostic yield of

cryobiopsy vs video-assisted thoracoscopic (VATS) lung biopsy (82.8% vs 98.7%,  $p=0.013$ ) [15]. There was a significant decrease in number of hospital days with cryobiopsy when compared to VATS lung biopsy (2.6 d vs 6.1 d,  $p<0.0001$ ). The mortality rates were 2.7% for surgical biopsy as opposed to 0.3% for cryobiopsy.

With a diagnostic yield approaching that of surgical lung biopsy and an acceptable safety profile, it is possible that bronchoscopic transbronchial cryobiopsy will obviate the need for surgical biopsy in many cases of interstitial lung diseases. An interim analysis of a prospective trial found that in 38 out of 51 patients (75%), a surgical biopsy was deemed unnecessary following a cryobiopsy [16].

With further studies showing the feasibility and usefulness of transbronchial cryobiopsy, it is hoped that this diagnostic intervention will become an integral part of the diagnostic algorithm of interstitial lung diseases. Transbronchial cryobiopsy is still an evolving diagnostic modality that requires development of a standardized procedural technique and protocols to manage complications, particularly bleeding. This is especially important as variations in technique as well as the target patient population can result in widely different diagnostic yields and complications rates. These questions can be explored with a prospective randomized clinical trial [17].

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