Transbronchial Lung Cryobiopsy: New Options for a New Reality

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Transbronchial lung cryobiopsy (TBLC) is a new bronchoscopic procedure, which is able to improve the specimen size and diagnostic yield in comparison with transbronchial lung biopsy (TBLB) performed with a conventional forceps [1–7]. TBLB aims to obtain samples from lung parenchyma and is indicated in patients with pulmonary infiltrates or peripheral consolidations, selected according to clinical and radiological information.

Cryoprobes are used with a flexible bronchoscope and work by the Joulen-Thomson effect that occurs when a quick gas decompression generates a very low temperature compared to that of the atmosphere. The cryosystem (Erbokryo®; ERBE Elektromedizin GmbH, Tübingen, Germany) works with carbon dioxide or nitrous oxide. The fast cooling effect at the tip of the probe firmly attaches to the surrounding tissue in few seconds. Both probe and bronchoscope are then pulled out of the airways. Flexible probes 1.9 and 2.4 mm in diameter are available for cryotherapy and cryobiopsies.

Different studies have demonstrated that TBLC is a feasible technique in the hands of trained bronchoscopists and may become a viable alternative to surgical lung biopsy [1–7]. In addition, benefits observed from the use of cryoprobes include better sample preservation with less artefacts and crushing effects. This in turn improves the number of the specific histological patterns identified. Cryobiopsies also demonstrate that the fast freezing and thawing process preserves the capacity for molecular and staining studies [4, 8, 9].

However, a multidisciplinary approach and the diagnostic consensus reached by pathologists, clinicians and radiologists are still crucial in the management of this complex group of lung diseases [10]. In addition, TBLC still has several challenges to overcome.

Firstly, published studies show a variable incidence of complications, mostly bleeding and pneumothoraces. In some articles, the safety profile is comparable to that of the conventional biopsy forceps, but a higher rate of pneumothoraces and severe haemorrhage has also been described with this technique [3, 4, 11]. Pajares et al. [4], in a randomized trial comparing cryoprobes and forceps in patients with interstitial lung diseases inconsistent with usual interstitial pneumonia, found a higher diagnostic yield in the cryobiopsy group, even after histological findings had been submitted to a multidisciplinary approach. The same study found a very low rate of complications, with no differences in pneumothorax and no clinically relevant differences in the percentage of patients experiencing a pulmonary haemorrhage. Casoni et al. [3] described a high rate of pneumothorax (28%) probably associated with the cryoprobe position (closer distance to the pleura) in subjects with a radiological usual interstitial pneumonia pattern (histologically confirmed in 75% of the patients who underwent a cryobiopsy).

Secondly, TBLC requires standardization. Recently, an interesting editorial by Poletti and Hetzel [12] has highlighted that the variety of modalities, i.e., cooling agents, freezing time and distance from the pleura, is

slightly different in the published studies. In addition, bronchoscopy settings [type of ventilation, type of airway access (tracheal tube vs. laryngeal mask; flexible vs. rigid scope) and probe diameter], radiological selection and sampling protocol (number and location of biopsies) also vary in different studies. Finally, most of these studies are observational, have been carried out in single centres and include a limited number of patients.

As mentioned before, one of the most important concerns regarding TBLC is the risk of bleeding. Cryobiopsies are too big to pass through the working channel. The bronchoscope is removed together with the cryoprobe once the biopsy is obtained. Hence, there is loss of visual contact with no option to place the bronchoscope in the segment immediately after the biopsy to collapse and suck a possible haemorrhage. In the first TBLC studies, a second bronchoscope was ready and inserted immediately after biopsy had been used to keep up visual airway control, but this may still be inadequate in the context of a massive bleeding [1, 2].

Some recent studies use a bronchial haemostatic blocker (Fogarty balloon or equivalent) placed routinely before any cryobiopsy to tamponade the lobe, assist clot formation and, more importantly, prevent overspill of blood into the adjacent lobes and the contra-lateral lung. This is particularly important as impaired ventilation and gas exchange from clots formed in other areas of the lung in a patient with pre-existing lung disease is the main cause of cardio-respiratory arrest rather than the blood

loss itself. In our opinion, the use of balloon blockers is a much better option than using a second bronchoscope. However, the placement of balloon blockers may be difficult in some cases, and the technique also requires training and standardisation of the clinical practice [3, 4, 7].

The feasibility study published in this edition of *Respiration* by Franke et al. [13] describes the use of a new 1.1-mm thin cryoprobe (ERBE Elektromedizin GmbH) to perform TBLC with a 2.6-mm guide sheath to allow removal of the cryobiopsies directly through the bronchoscope working channel. The authors show in an ex-vivo animal lung that the new mini-cryoprobe obtains alveolar parenchyma specimens 2–3 times bigger than with a 1.8-mm alligator forceps. The new miniprobe might help overcome some major disadvantages of the present cryobiopsy technique, especially the need of intubation, and may facilitate bleeding control. However, in vivo and human studies are needed to demonstrate the efficacy and safety of the new probe. Our personal view is that patient safety should be the primary concern, and hence, even with this adapted technique, it may be better to have airway control with an endotracheal tube in place.

TBLC has become a reality that improves the diagnostic power of the traditional TBLB described in the seventies by Levin et al. [14]. However, large multicentre trials are required to determine the role of TBLC in the management algorithm of interstitial lung diseases. Safety concerns and comparisons with surgical biopsy are crucial aspects to be considered in the near future.

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