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REVIEW ARTICLE

Quality standards for cryobiopsy

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ABSTRACT

Transbronchial cryobiopsy (TBLC) is a technique on the rise in the diagnostic workup of diffuse interstitial lung diseases (DPLD), recently being included in the European Respiratory Society Guidelines as an acceptable alternative to surgical lung biopsy (SLB), which had thus far been considered the gold standard. In this article, we review what is known to optimize the procedure, including patient selection, contraindications, possible complications and transbronchial cryobiopsy technique.

Keywords: Bronchoscopy. Cryobiopsy. Interstitial lung disease. Transbronchial cryobiopsy.

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INTRODUCTION

Transbronchial cryobiopsy (TBLC) is a technique on the rise in the diagnostic workup of diffuse parenchymal lung diseases (DPLD), recently being included in the European Respiratory Society Guidelines as an acceptable alternative to surgical lung biopsy (SLB)[1], which had thus far been considered the gold standard when histopathological data was deemed necessary to reach a diagnosis. Cryoprobes, long insulated catheters with blunt metal tips that rapidly cool to extremely cold temperatures via the Joule-Thomson effect, were first introduced in the late 1960s to remove endobronchial abnormal tissue from large airways by multiple freeze-thawing cycles[2]. In time, more advanced flexible cryoprobes were developed that could be used for procedures on more peripheral tissue and eventually led to the introduction of TBLC in the late 2000s. Since then, probes have become gradually smaller (from 2.4-1.9 mm to 1.7-1.1 mm) and have also been employed in other procedures such as in endobronchial ultrasound (EBUS) mediastinal sampling[3], though the scope of this article is limited to TBLC in the diagnosis of interstitial lung diseases (ILD).

TRANSBRONCHIAL CRYOBIOPSY TECHNIQUE: THE BASICS

Although the procedure is quickly gaining momentum, the technique used to perform TBLC in diffuse lung disease varies between centres. Oftentimes this is due to a varied availability of expertise and equipment. Procedure standardization is lacking[4], as are strong randomized studies concerning the various aspects of the procedure. It should be noted that even though standardization of certain aspects of the procedure would likely guarantee a higher quality standard in TBLC, it is highly unlikely that a single approach will be reached in clinical practice since some elements depend on local organization and expertise and, as discussed further on, some strategies increase diagnostic yield, but also risk of complications, thus opening a debate regarding the risk/benefit ratio of those approaches.

In most centres, TBLC is performed via flexible bronchoscopy in patients intubated with an endotracheal tube or rigid bronchoscope under deep sedation or general anesthesia[2]. The probe is advanced to the parenchymal periphery under fluoroscopic guidance to ensure suitable probe-to-pleura distance. When the target is reached, the probe is activated for several seconds and, as the tip freezes during activation, surrounding parenchyma freezes and adheres to the tip of the probe. The flexible bronchoscope and probe are then extracted *en bloc* from the airway. The tip of the probe is placed in saline solution to ensure thawing of the sample, which then should be very delicately detached from the probe to guarantee an artefact-free sample. The sample is then fixated in formalin to be processed.

PATIENT SELECTION

Accurate patient selection is pivotal in ensuring an acceptable risk/benefit ratio. To begin with, a multidisciplinary discussion should determine whether the procedure is required for a correct diagnosis[1]. If so, the patient must

be considered fit to undergo deep sedation or general anaesthesia, antiplatelet and/or anticoagulation therapy should be discontinued as appropriate[5] and contraindications should be considered.

Bleeding diathesis increases the risk of major bleeding and therefore international normalized ratio (INR) ≥ 1.50, platelets <50.000/mmc and impossibility to discontinue anticoagulation or antiplatelet drugs are considered the only absolute contraindications to the procedure[6]. Traditionally, forced vital capacity (FVC) < 50% and/or diffusing lung capacity for carbon monoxide (DLCO) < 35-30%, and/or body mass index (BMI) > 35, and/or age above 75 years, and/or pulmonary hypertension (systolic pulmonary artery pressure > 40-45 mmHg), and/or clinically significant cardiac disease, and/or coagulation disease have been considered relative contraindications to the procedure[2,7,8]. In obese patients, the main issues appear to be the difficulty in airway management and ventilation[7] and a higher risk of bleeding[9], while worse lung function tests and pulmonary hypertension potentially expose the patient to a higher morbidity and mortality risk in case of pneumothorax and bleeding respectively. Cardiac disease entails a generally higher anaesthesiologic risk.

It must be noted that, aside from bleeding diathesis, all contraindications are relative and patients with these traits have mostly been excluded from studies on a theoretical basis. In fact, a recent study suggests that TBLC appears safe in those in whom SLB is at high risk of complications according to their age, BMI, lung impairment, and cardiac comorbidities[10]. Furthermore, the mortality rate of TBLC is very low (1.3% 90-day absolute mortality rate[11], 0.3% 60-day mortality rate due to adverse events[8]), especially when compared to SLB which has a general 2-6% 90-day mortality rate, with a 30-day mortality rate as high as 18.8% in patients ultimately diagnosed with idiopathic pulmonary fibrosis (IPF)[12].

BIOPSY TARGET SELECTION

In DPLD, biopsy target selection is guided by CT scan images and procedural factors, although the optimal target selection for biopsy remains unclear. As the cryoprobe samples peripheral lung tissue, areas with the most extensive sub-pleural lesions should be targeted and more fibrotic lesions should be avoided, though to date no studies prove the effect of these criteria on diagnostic yield.

The right lower lobe is the most convenient for accessing and placing a bronchial balloon or blocker and as DPLD often begins in the lower lobes this appears to be the most frequently chosen target[2]. In target selection, a reportedly higher risk of pneumothorax with TBLC in the middle lobe[13] and upper lobes, especially the left upper lobe[14] should also be taken into account.

In series, there is a significant variability in the number of samples and whether they are obtained in a single segment, multiple segments within the same lobe, or multiple lobes of the same lung. Performing two biopsies with a cryoprobe may be associated with an increased diagnostic yield in DPLD if these samples are obtained from two different segments[15], with diagnostic yield increasing from

69% to 96% with a second biopsy from a different segment[16]. Therefore, when feasible, TBLC should be performed in two different segments (either of the same lobe or of different lobes).

Cone beam CT guidance and novel navigation systems are being studied as a means to increase diagnostic accuracy of TBLC[17,18].

ANAESTHESIA AND AIRWAY MANAGEMENT

Cryobiopsy can be performed via flexible bronchoscopy without advanced airway management, through laryngeal mask, endotracheal tube and rigid bronchoscopy. Most series report rigid bronchoscopy or intubation with an endotracheal tube as it assures a rapid re-entry into the airway after each biopsy is performed and allows easier management of bleeding. Deep sedation or general anaesthesia is warranted to increase patient tolerance and reduce cough which can facilitate pneumothorax and complicate efforts to control bleeding[8]. General anaesthesia requires positive pressure or jet ventilation, as the patient is incapable of maintaining adequate spontaneous ventilation, potentially increasing the risk of pneumothorax as opposed to deep sedation, though no studies have directly compared these two strategies.

CRYOPROBE SIZE AND FREEZE-TIME

Sample volume and absence of artefacts are the main improvements of cryobiopsies in comparison to transbronchial forceps biopsies, ensuring a higher diagnostic yield in DPLP[19]. The size of the cryobiopsy histological samples influences the diagnostic yield and a sample size of five mm in diameter is suggested as sufficient[20]. Thus, determining how to obtain a satisfactory-sized sample is key.

New single-use cryoprobes have been developed with outer diameters of 1.1 mm, 1.7 mm and 2.4 mm to replace the previous re-usable 1.9 mm and 2.4 mm probes. A recent study has shown no statistically significant difference between the 1.9 mm and 1.7 mm probes in terms of diagnostic yield (both pathological and multidisciplinary), adverse events (bleeding and/or pneumothorax) and sampling adequacy (alveolated tissue, artefacts and biopsy size)[21]. The smaller 1.1 mm cryoprobe has thus far been used mainly to sample peripheral lesions[22] but has been proven feasible and safe also in diffuse lung diseases[23], though data concerning diagnostic yield in DPLD is lacking.

In animal studies, there is significant correlation between cryobiopsy size and probe activation time, with a biopsy area of four–five mm^2 after two seconds of 1.9 mm cryoprobe activation and up to seven–nine mm^2 after a five-second activation[24]. According to animal studies, the optimal TBLC freezing time with a 1.9 mm probe is initially three seconds, as it is associated with minimal complications and large artefact-free biopsies[24] but freeze time up to seven-ten seconds is reported[21] and cryoprobe size and required freezing time are inversely proportional, with no definitive studies on probe activation time in TBLC. Freezing time is the main factor determining biopsy size[2], with recent evidence suggesting probe size does not affect diagnostic

yield or sample size[21]. It should be noted that, especially in fibrotic areas, resistance to cryoprobe sampling can be increased, thus not allowing long freeze times.

In conclusion, we agree with the authors' suggested approach of using a 1.7 mm probe to obtain a sample of at least five mm in size, by using a freeze-time around six-eight seconds[21], though further research is needed.

PROBE TO PLEURA DISTANCE

The main adverse events of cryobiopsy are bleeding and pneumothorax and both events appear linked to the probe-to-pleura distance. The risk of bleeding is thought to be greater for biopsies obtained in the more proximal regions of the peripheral lung, where vessels are not protected by cartilaginous rings and have not yet divided into terminal branches, while pneumothorax results from a biopsy so peripheral that in performing it the visceral pleura has been damaged and air is consequently allowed to enter the pleural space from within the lung. Optimal cryoprobe placement is of paramount importance in balancing these two risks, but more importantly in obtaining an adequate sample, as it is also pivotal in determining diagnostic yield.

The probe-to-pleura distance is generally estimated visually in fluoroscopy, with tactile feedback dampened compared to traditional transbronchial biopsies (TBB) using forceps. In fact, using fluoroscopy has been proven to reduce the risk of pneumothorax[25]. Lateral airways are preferable, as they allow the probe to intersect the pleura perpendicularly reducing overlap.

Reported probe-to-pleura distances vary from within one cm from the pleura to between one and two cm from the pleura. Ravaglia et al.[21] reported a diagnostic yield of 93.3-100% using a probe-to-pleura distance of one cm, with 32% incidence of pneumothorax and 15% requiring drainage, as compared to a diagnostic yield of 80% in a study by Kropsky et al.[26] with a one-two cm probe-to-pleura distance, with no pneumothorax cases requiring drainage. It can be inferred that sampling immediately subpleural parenchyma potentially increases diagnostic yield in DPLD (although no direct comparison between probe-to-pleura distancing has been described), but a higher risk of pneumothorax is the price to pay. The CHEST Guideline and Expert Panel Report suggests biopsy with the tip of the cryoprobe located one cm from the pleura[27].

MANAGEMENT OF COMPLICATIONS: BLEEDING AND PNEUMOTHORAX

To reach a high-quality standard in cryobiopsy sampling, appropriate prevention and management of complications is key, especially considering the potential risk of major bleeding. The main technique used to control bleeding is routine placement of bronchial blockers proximal to the biopsied segment[7,25]. Before performing the biopsy, it should be verified that the blocker completely seals the bronchus when inflated. The bronchial blocker is then inflated after each biopsy to control emergent haemorrhage while the bronchoscope is out of the airway and deflated under visual control after the bronchoscope has been reintroduced. In the event of significant bleeding, the blocker can be

reinflated to tamponade the haemorrhage while at the same time protecting the rest of the lungs from blood overflow. Bronchial blockers can easily be inserted into the rigid bronchoscope, but have also been placed externally to an endotracheal tube[28] and with a laryngeal mask[29].

Management of pneumothorax entails erect X-rays and clinical monitoring to assess presence and entity of air in the pleural space. X-rays can be performed routinely (for example two hours after the procedure) and/or in case of symptoms suggesting pneumothorax (chest pain, dyspnoea). Providing oxygen (> 28%) lowers the partial pressure of nitrogen, which may accelerate the rate of absorption of air from the pleural cavity[30]. No specific guideline regarding when to drain cryobiopsy-related pneumothorax exists as existing guidelines for spontaneous pneumothorax are mostly used in deciding the appropriate treatment. Importantly, pneumothorax after TBLC always affects a pathological lung, with a lower likelihood of spontaneous recovery. This should be taken into account when evaluating chest drainage in these patients.

CHALLENGES AND FUTURE

Transbronchial cryobiopsy is a technique on the rise in the diagnosis of ILD. Though many studies have been conducted and published, methodological concerns have been raised and wide variation in procedure limit comparability between studies and the possibility to pool results, which would be convenient as studies often comprise a limited number of patients/procedures. Improving the quality of reports and working towards randomized controlled trial level evidence is pivotal to optimize the procedure and further prove its strength and safety in the diagnosis of ILD.

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