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Criobiópsia no Diagnóstico das Doenças Pulmonares Intersticiais

Transbronchial lung cryobiopsy for the diagnosis of Interstitial Lung Diseases

RESUMO

No diagnóstico e tratamento da doença pulmonar intersticial (DPI), a criobiópsia pulmonar transbrônquica (TBLC) fornece informações significativas com um razoável perfil de segurança, especialmente em centros experientes. A criobiópsia pulmonar transbrônquica configura-se como um método diagnóstico inicial menos invasivo que reduz a morbimortalidade relacionada à abordagem cirúrgica, garantindo um bom diagnóstico. Assim como para a biópsia cirúrgica, também para a TBLC o rendimento diagnóstico histopatológico é uma medida simples de eficácia da biópsia, mas sua contribuição para o diagnóstico final de DPI deve ser harmonizada com outras variáveis no contexto da discussão em equipe multidisciplinar. Os estudos que avaliaram o impacto da informação histopatológica obtida por TBLC em comparação com a cirurgia mostrou que no contexto da discussão multidisciplinar, a TBLC fornece informações significativas que aumentam a confiança no diagnóstico, orientar decisões de tratamento e refinar corretamente a previsão prognóstica. A TBLC tornou-se o passo diagnóstico inicial em muitos centros experientes, reservando a procedimento cirúrgico à pequena minoria dos casos em que não foi possível identificar um padrão histológico específico com a abordagem transbrônquica. Estudos avaliando TBLC como procedimento de segunda etapa em casos com primeira TBLC não diagnóstica estão atualmente em andamento. Os dados sobre o desempenho diagnóstico e o perfil de segurança da TBLC derivaram de estudos recentes estudos levam ao endosso deste método inovador de biópsia para o diagnóstico das DPIs por todas as principais sociedades respiratórias. A experiência do centro continua importante para alcançar resultados precisos e para realizar um procedimento seguro. A padronização da técnica está avançando, enquanto vários centros estão trabalhando em como implementar e padronizar o treinamento, e estão procurando sistemas de orientação mais precisos. Na era da medicina de precisão, a TBLC representa uma forma segura e precisa de obter tecido, abrindo caminho para uma nova abordagem para classificação de DPIs e tratamento alvo.

PALAVRAS-CHAVE

Criobiopsia pulmonar, criobiópsia transbrônquica, doença pulmonar intersticial.

ABSTRACT

In the diagnosis and management of ILDs, TBLC provides significant input with a reasonable safety profile, particularly in experienced centers.

Transbronchial lung cryobiopsy is configured as a less invasive initial diagnostic method that reduces morbidity and mortality related to the surgical approach, ensuring a good diagnostic yield. As for SLB also for TBLC histopathological diagnostic yield is a simple measure of biopsy efficacy, but its contribution to the final ILD diagnosis must be harmonised with other variables in the context of multidisciplinary team discussion. The studies that evaluated the impact of histopathologic information obtained by TBLC compared to surgery showed that in the context of MDT discussion TBLC provides meaningful information that increase the diagnostic confidence, guide treatment decisions, and correctly refine prognostic prediction.

TBLC has become the initial diagnostic step in many experienced centres, reserving the surgical procedure to the small minority of the cases in which it has not been possible to identify a specific histological pattern with the transbronchial approach. Studies evaluating TBLC as a second step up procedure in cases with first non-diagnostic TBLC are currently ongoing.

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ST declares speaker's fees from Roche, Boehringer-Ingelheim, PulmoniX and ERBE. VL declares no conflict of interest.

The data on the diagnostic performance and safety profile of TBLC derived from recent studies lead to the endorsement of this innovative biopsy method for the diagnosis of ILDs by all major respiratory societies. Center's experience remains important to achieve accurate results and to perform a safe procedure. Standardization of the technique is improving, while several centers are working on how to implement and standardize training, and are searching for more accurate guiding systems.
In the era of precision medicine TBLC represent a safe and accurate way to obtain lung tissue, paving the road to a new approach to ILDs classification and target treatment.

KEY WORDS

Lung cryobiopsy, transbronchial lung cryobiopsy, interstitial lung disease.

MAIN TEXT

Interstitial lung diseases (ILDs), also referred to as diffuse parenchymal lung diseases, are a diverse group of lung diseases classified together because of similar clinical, radiological, physiologic or pathologic characteristics. In this heterogenous group are included welldefined clinical-radiologic-pathologic entities, with different prognoses and therapeutic options. Idiopathic pulmonary fibrosis (IPF) is the most lethal and one of the most frequent ILDs that pulmonologists encounter in their clinical practice.[1] The distinction of IPF from the others fibrotic ILDs is of utmost importance to predict the prognosis, choose timely the more appropriate therapy and plan for non-pharmacological treatments such as lung transplant listing.[2] Recent data suggest that IPF and fibrotic ILDs nonresponsive to standard management may have similar prognosis and similar response to antifibrotic drugs.[3-5] Despite this observation, the distinction between ILDs with a pathogenesis mainly inflammatory and immune mediated, such as nonspecific interstitial pneumonia, connective tissue diseases, hypersensitivity pneumonitis, and those mainly driven by senescence and degenerative mechanisms such as IPF is still very important to make appropriate treatment decisions including immunomodulation for the former and antifibrotic only for IPF.[2,6]

Multidisciplinary team (MDT) discussion is the reference standard for ILDs diagnosis and the discussion may provide a definite or provisional diagnosis. The diagnostic work-up of ILDs, in fact, includes accurate history, physical examination, respiratory function tests, high resolution computed tomography (HRCT). When the clinical-radiological diagnosis is made with low confidence invasive procedures are indicated to obtain lung tissue.[7] In the scenario of uncertain clinical-radiological diagnosis lung biopsy has shown to provide important information that help clinicians to refine the MDT diagnosis, the prognostic prediction and the treatment decision.[8]

Historically the two techniques used to sample ILDs have been regular forceps transbronchial biopsy (TBBx) and surgical lung biopsy (SLB). TBBx is a safe technique but with a low diagnostic yield limited by small specimens, sampling errors and crush artefacts. Although highly specific (80-100%), TBBx is poorly sensitive (10-30%) for the diagnosis of usual interstitial pneumonia (UIP) and its use in the differential diagnosis of fibrotic ILDs has been abandoned.[9] SLB allows large tissue samples to be obtained with a high diagnostic yield (>90%), but the procedure is burdened with appreciable costs and risks, with a mortality rate around 2% within 90 days, and several possible postoperative complications (infections, prolonged airway leak, respiratory failure, and, chest pain). In addition, due to age, comorbidity, disease severity and respiratory failure, a fair proportion of subjects are not eligible for this procedure.[10,11]

In this scenario transbronchial lung cryobiopsy (TBLC) represents a less invasive alternative to surgical lung biopsy (SLB) for the diagnosis of interstitial lung diseases (ILDs), with a diagnostic yield close to that of SLB (approximately 80% for TBLC compared to >90% for SLB).[12] Cryoprobes have proved more effective than forceps biopsies in retrieving sufficient tissue for histological diagnosis without crush artefacts.[13] Furthermore, mortality and other complications have been reported to be significantly fewer in TBLC than in SLB (mortality 0.3% for TBLC compared to 2% for SLB).[12] As a result, TBLC has grown fast in recent years, and a considerable body of evidence accumulated in the literature leading to several documents and guidelines, until the recent publication of the European Respiratory Society Guidelines that endorsed the clinical use of TBLC in the diagnosis of ILDs.[5,14-16] The recently published ERS guidelines evaluated the role of TBLC in obtaining tissue-based diagnosis in patients with undiagnosed ILDs, aiming to provide evidence-based clinical practice recommendations for its application. Advantages and disadvantages of TBLC, with respect to diagnostic confidence, diagnostic yield, diagnostic accuracy, adverse events and patientimportant outcomes, were assessed and compared with those of SLB. The first recommendation was made for patients eligible to surgery, for whom the panelists suggested that performing TBLC in centers with experience is indicated. The recommendation was based on two prospective studies with

indirect comparison and several study without any comparison, no randomized controlled trials (very low quality of evidence). The most rigorous study evaluating TBLC diagnostic accuracy for ILDs diagnosis was conducted by Troy et al. who reported a histopathological agreement between TBLC and SLB of 70·8% (weighted k 0·70, 95% CI 0·55-0·86) and a diagnostic agreement at MDT discussion of 76·9% (k 0·62, 0·47-0·78). For TBLC with high or definite diagnostic confidence at MDD (39 [60%] of 65 cases), 37 (95%) were concordant with SLB diagnoses. In the 26 (40%) of 65 cases with low-confidence or unclassifiable TBLC diagnoses, SLB reclassified six (23%) to alternative high-confidence or definite MDD diagnoses.[17] Not all the studies with a similar design have been similarly successful. It seems that centers with a low volume of activity performing studies with a very low number of cases can't achieve the same agreement, with a kappa of agreement between TBLC and SLB ranging between 0.22 and 0.46 across Europe and Canada.[18,19]

Several large studies have evaluated the utility of TBLC in the MDT diagnosis of ILDs showing that the histopathologic information obtained by TBLC equals SLB in terms of increase in diagnostic confidence for the diagnosis of IPF. Our group was the first that evaluated how TBLC could improve the diagnostic confidence in a comparison study between TBLC and SLB. In this preliminary study we reported that the percentage increase in IPF diagnosis made with a high level of confidence in MDT increased from 29% to 63% before and after adding TBLC results, and from 30% to 65% before and after adding SLB results.[20] Hetzel and coworkers corroborated these results with a second prospective international study conducted on 128 TBLC in ILDs showing a percentage increase in confidence (i.e. confident diagnosis or provisional diagnosis with high confidence) from 60.2% after clinico-radiological discussion and BAL to 81.2% when adding TBLC results.[21]

Given that the histopathologic information provided by lung biopsy is part of the MDT diagnosis, one way to assess the reliability of an MDT diagnosis reached with TBLC compared to SLB is to evaluate and compare the prognosis of different fibrotic ILDs (mainly IPF versus non-IPF). We explored this issue in a large monocenter study that showed that the distinction between IPF and other interstitial lung diseases made by MDT diagnosis on the basis of TBLC biopsy had clear prognostic significance, with a 5-year transplant-free survival of 68% (95% CI 57-76) in patients with an MDT idiopathic pulmonary fibrosis diagnosis based on TBLC compared with 93% (87-96) in patients without an idiopathic pulmonary fibrosis diagnosis based on TBLC (hazard ratio 5·28, 95% CI 2·72-10·04; p<0·0001). This distinction remained statistically significant in a multivariate analysis controlling for age, sex, smoking status, comorbidities, pulmonary function, and highresolution CT patterns (p=0·02). The prognostic separation provided by an historical comparison group of SLB was similar.[22]

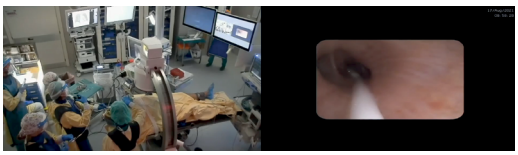
One of the advantages of TBLC compared to surgery is the better safety profile. This allows to get tissue information in a wider spectrum of patients including those that can't undergo surgery. The recent ERS guidelines have endorsed this view, but underlying the importance of a carefully balanced decision that takes into account the advantages of reaching a more confident diagnosis to the disadvantages of increased risk of severe adverse events in this subgroup of fragile patients.[14] This recommendation was based on very low quality of evidence. Limited evidence from high-volume centers suggests safety in high risk patients, but the risk of accelerating disease in patients who are critically ill or have rapidly progressive ILDs may be unacceptably high. Very few studies have shown that the diagnostic yield of TBLC in patients with under diagnosed ILD not considered to undergo SLB is similar to patients eligible to undergo SLB, with a safety profile similar to less severe patients.[23] For this reason the advantage of potentially increasing diagnostic certainty should be weighted in each individual patient.

One question that remains unanswered is whether a second cryobiopsy should be performed as a step-up procedure in cases with inconclusive cryobiopsy results at first attempt. The ERS guidelines recommend SLB as a step-up procedure based on few studies on SLB and on the complete

lack of studies investigating cryobiopsy (very low quality of evidence). The patient representatives who provided input in the guidelines agreed that they expected that, if initial TBLC is not informative, most patients would opt for step-up SLB rather than second TBLC as subsequent diagnostic. Yet, this should be decided upon on a case by case level.[14] Several experienced centers are now exploring novel guiding system for TBLC in ILDs diagnosis. We can hypothesize that adding more sophisticated guiding methods may further increase the diagnostic yield of this technique and possibly open a new perspective also on the opportunity to re-biopsy patients with cryo instead of going to a step-up surgery.[24-26] Studies addressing this issue are eagerly needed.

Another field requiring further investigation is the standardization of training for TBLC. Training is very important to achieve operator competency, as diagnostic yield increases and adverse events decrease with experience. Introducing TBLC in less experienced centers may result in higher rates of complications. TLCB technique standardization is improving, and it has been five years since the publication of the first statement by experts in the field proposing some recommendations (requisite equipment, personnel, indications / contraindications, risks and training requirements) with the aim of facilitating uniform practice and providing a guide for those wishing to introduce this technique.[27] TBLC should be performed in intubated patients under deep sedation or general anesthesia. It can be used a flexible endotracheal tube or a rigide bronchoscope. It is recommended to use fluoroscopy to guide biopsy. In order to control bleeding and prevent central airway blood flooding it is recommended to preventively use an endobronchial blocker or a Fogarty balloon. It is advisable to obtain two samples from two different sites in order to enhance the diagnostic yield and to avoid larger probes (2.4mm) that may be associated with a higher rate of pneumothorax and without significantly increasing the diagnostic yield.[28] A postprocedural chest X-ray or ultrasound examination should be performed to assess for the occurrence of pneumothorax either immediately (if desaturation, persistent cough and/or thoracic pain are present) or 2 h after the end of the procedure if the patient is asymptomatic.[29]

TBLC can be easily implemented in referral centers for ILDs with a solid background in rigid bronchoscopy, and is rapidly spreading around the globe. The added value of TBLC for ILDs diagnosis rests in the better safety profile for patients and lower costs compared to SLB, that makes tissue sampling widely available, holding great potential for advancing in the understanding of ILDs pathogenetic mechanisms. Pathogenic studies on ILDs have been limited by the shortage of lung tissue, in fact biopsy was often not performed even when potentially useful, due to the perceived risks of SLB. TBLC opens a new scenario in the most propitious time for lung research. Thanks to novel profiling technologies and to the availability of TBLC samples, the research can now shift toward the analysis of tissue. For decades research hypothesis was based on animal models, clinical analogies between different diseases, or biologic plausibility with limited validation in humans. Today, a paradigmatic shift in lung research is pointing toward precision medicine and the availability of lung tissue along with the emergence of high profiling technologies are critical in this new era where transcriptomics is becoming the golden opportunity for research.[30]



Video 1. How to perform TBLC in ILDs

ACESSE O VÍDEO AQUI!

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