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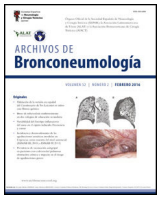

Editorial

Transbronchial Cryobiopsy Bohemian Rhapsody

"Bohemian Rhapsody", the 1975 Queen song written by Freddy Mercury, has always run up against controversy. The impossibility of classifying the song in one specific musical genre (with its balladic, operatic and hard rock passages), not to mention other details such as its length, complexity and Baroque stylings, caused a deep rift among music critics. Despite all that, the song was a huge hit for the band. Transbronchial lung cryobiopsy (TBLC) seems destined for a similar fate. A growing number of centers perform this technique. Publications and series have increased exponentially over the past decade. TBLC has an increasing presence at congresses and in specialized courses. The scope and performance of TBLC have proven to be far superior to those of its predecessor, the transbronchial forceps biopsy, as shown in a recent study conducted with 124 patients subjected to TBCB and forceps-TBB in the same bronchoscopic procedure.[1]

But as with "Bohemian Rhapsody", TBLC's apparent success is also marred by pitfalls and controversies. The official ATS/ERS/JRS/ALAT clinical practice guideline published in 2018 does not include this procedure in the algorithm for idiopathic pulmonary fibrosis (IPF), and indicates surgical lung biopsy (SLB) as the only valid histological sampling method for cases in which a reliable diagnosis cannot be established with clinical–radiological information alone.[2] Nonetheless, part of the panel of experts was enthusiastic about the outcomes of TBCB, and in the vote for the recommendation there was a tie between those in favor and against. Consequently, it was not included in the algorithm. Paradoxically, despite the split decision, the guidelines did not discourage continued use of TBLC in centers that have experience with the technique, but advised those lacking this experience to wait until they gather more evidence. Our opinion is that this message is difficult to interpret in clinical practice. The concerns expressed about TBLC mainly have to do with the absence of standardization, safety and the low number of studies in direct comparison with SLB.

However, substantial advancements have been made in standardization, as established in recent documents and agreements by experts on the technical aspects key to guarantee the efficacy and safety of the technique, such as freezing time, the recommended number and size of biopsies, the use of bronchial blockers for hemostatic control, and other recommendations.[3,4]

As for the lingering doubts regarding the head-to-head comparison with SLB, the recent publication of two studies is worth mentioning. In them, TBLC and SLB were sequentially performed on the same patient. In the first study (Romagnoli et al., Cryo-PID Study), 21 patients from centers in France and Italy sequentially underwent both sampling methods in the same procedural time. The histological diagnosis was established by an independent expert pathologist, who analyzed the samples blinded to clinical information. In this study, despite the high yield of TBCB (diagnostic yield of 81%, only three TBLC's were considered non-diagnostic), the correlation with results of the SLB was poor (diagnostic concordance between techniques of 8/21, 38%, kappa 0.22).[5] The second study (Troy et al., COLDICE Study), included 65 patients from nine Australian centers, in whom both procedures were also simultaneously and sequentially performed. The histopathological diagnosis was made by a committee formed by three expert pathologists. In this study, both techniques showed high performance (93% for TBLC, 98% for SLB). Contrary to the prior study, the concordance between the techniques to establish a histological diagnosis based on the four IPF guidelines-categories (definite, probable, indeterminate and alternative), was 70.5% (kappa 0.7). Furthermore, in this study there was correlation of 69% (kappa 0.47) between the techniques to determine the specific histological pattern or entity. Additionally, the degree of concordance between the two techniques to establish diagnosis by multidisciplinary decision (MDD) was 76.9% (kappa 0.62).[6]

In addition, a very important point highlighted in both studies is that TBLC appears to be a safe procedure, when performed at centers with previously-trained personnel. In both studies, cases of pneumothorax following TBCB were few (2/21 and 1/65 cases respectively) and no cases of severe bleeding were reported.

Both studies are a remarkable effort. Nonetheless, their overall results leave TBLC in a situation comparable to "seeing the glass half-empty or half-full" when it comes to its possible role in the diagnostic management of ILD's. Both studies have given rise to a number of questions. First, how do their designs represent real life? In the majority of clinical practice scenarios, neither the pathologist is a reputed international expert evaluating biopsies blinded to clinical information, nor is the diagnosis given by an external committee of three expert pathologists. Second, how unreliable can a histological result be if it matches the clinical orientation? In other words, regardless of the sample type, only a suitable clinical-radiological context can determine whether the histological orientation is coherent. Third, in both studies, a number of pre-selected patients were rejected for surgery or refused surgery themselves. Therefore, the question is: which is better for a "non-surgical" patient; performing a TBLC or doing nothing? The answer is probably to perform it only if the clinical-radiological evaluation generates enough doubt for the histological result to

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have a potential therapeutic and/or prognostic impact. In fact, a recently published study by Hetzel et al. shows that adding the results of a TBLC to the clinical-radiological and bronchoalveolar lavage information is key to reaching diagnostic confidence in a high percentage of non-diagnosed patients.[7]

Given this "rhapsody" of opinions on TBLC generated over the past decade, the value of clinical flexibility and the capacity to individualize decisions advocated by Wells AU[8] are worth remembering. SLB are larger and more efficacious. But they also entail greater complexity and risk, are more costly, and as shown in the study by Walsh et al., are not indicated by half of the physicians who treat ILD, even in a clinical–radiological context of low diagnostic confidence.[9] This fact seems to suggest that, despite the ATS/ERS/JRS/ALAT algorithm, referral to surgery to diagnose a chronic pathology does not appear to be an easy decision for many clinicians. Following this train of thought, Castillo et al. suggest the possibility of modifying the diagnostic algorithm through a decision on histological techniques, TBLC or SLB, based on their individualized predictive value. To do so, it is fundamental to establish the indication of one or another technique in a multidisciplinary context, in which the clinical information and radiological pattern are key factors, but other circumstances such as severity, comorbidities, local experience in different techniques, waiting lists, local results of each center in performance and safety, and costs, are also taken into account.[10] Of course, this proposal must be validated prospectively to determine its clinical usefulness.

Whatever happens in the future, and like the Bohemian ideals extolled in Queen's timeless classic, against the odds, cryobiopsy seems determined to stay the course and make a stand, with its own role and "*miseria bella*", before surgical biopsies.

References

1. Pajares V, Núñez-Delgado M, Bonet G, Pérez-Pallarés J, Martínez R, Cubero N, et al. Transbronchial biopsy results according to diffuse interstitial lung disease classification Cryobiopsy versus forceps. Multicrio study. PLOS ONE. 2020;15:e0239114.
2. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. Am J Respir Crit Care Med. 2018;198:44–68.
3. Hetzel J, Maldonado F, Ravaglia C, Wells AU, Colby TV, Tomassetti S, et al. Transbronchial cryobiopsies for the diagnosis of diffuse parenchymal lung diseases: expert statement from the cryobiopsy working group on safety and utility and a call for standardization of the procedure. Respiration. 2018;95:188–200.
4. Maldonado F, Danoff SK, Wells AU, Colby TV, Ryu JH, Liberman M., et al. Transbronchial cryobiopsy for the diagnosis of interstitial lung diseases: CHEST guideline and expert panel report. Chest. 2020;157:1030–42.
5. Romagnoli M, Colby TV, Berthet JP, Gamez AS, Mallet JP, Serre I, et al. Poor concordance between sequential transbronchial lung cryobiopsy and surgical lung biopsy in the diagnosis of diffuse interstitial lung disease. Am J Respir Crit Care Med. 2019;199:1249–56.
6. Troy LK, Grainge C, Corte TJ, Williamson JP, Vallely MP, Cooper WA, et al. Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (Coldice): a prospective, comparative study. Lancet Respir Med. 2020;8:171–81.
7. Hetzel J, Wells AU, Costabel U, Colby TV, Walsh SLF, Verschakelen J, et al. Transbronchial cryobiopsy increases diagnostic confidence in interstitial lung disease: a prospective multicenter trial. Eur Respir J. 2020;56:1901520.
8. Wells A. IPF diagnosis: flexibility is a virtue. Lancet Respir Med. 2018;6:735–7.
9. Walsh SLF, Lederer DL, Ryerson CJ, Kolb M, Maher TM, Nusser R, et al. Diagnostic likelihood thresholds that define a working diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2019;200:1146–53.
10. Castillo D, Sánchez-Font A, Pajares V, Franquet T, Llatjós R, Sansano I, et al. A multidisciplinary proposal for a diagnostic algorithm in idiopathic pulmonary fibrosis: the role of transbronchial cryobiopsy. Arch Bronconeumol. 2020;56:99–105.

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