Archivos de Bronconeumología 57 (2021) 772–785

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

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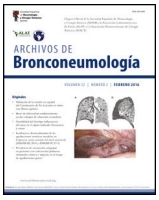

Scientific Letter

Transbronchial Cryobiopsy of Peripheral Pulmonary Lesions Guided With Real-Time Transthoracic Ultrasonography

Criobiopsia transbronquial de lesiones pulmonares periféricas guiada en tiempo real con ultrasonografía transtorácica

Dear Editor,

The diagnosis of peripheral pulmonary lesions (PPL) is important, especially when it is required to confirm or exclude malignancy. We present what we believe to be the first two cases of PPL diagnosed by transbronchial cryobiopsies guided by real-time transthoracic ultrasound and assisted by radial endobronchial ultrasound (r-EBUS).

The first patient was a 76-year-old male, a heavy ex-smoker with a peripheral left mass on chest X-ray. Thoracic computed tomography (CT) revealed a lingular solid mass with 38 mm larger diameter, based on pleura adjacent to the anterior thoracic wall (Fig. 1A) compatible with primary lung neoplasia. Chest ultrasound examination showed a nodule of 26 mm of maximum depth with pleural contact, mobile with respiratory movements and partially covered by the adjacent rib, leaving a narrow intercostal space for examination. Standard bronchoscopy with a thin bronchoscope, showed no endobronchial lesions so the endoscopic examination was carried out with r-EBUS. A 1.4 mm radial ultrasound probe (Olympus Co, Japan) was advanced through the lingula bronchi until the hypoechoic heterogeneous nodule was visualized and then we tried to reproduce the path with the 1.9 mm cryoprobe (ERBE CA, Germany) (Fig. 1B). Prior to transbronchial sampling, the transthoracic ultrasound (convex transducer, F2.5 MHz D9.9, MINDRAY Co, China) was applied on the anterior chest wall (Fig. 1C) and was able to visualize, in real time, the transbronchial cryoprobe going through the mass and avoiding the pleura (Fig. 1D and supplementary video 1A). Curiously, applying freezing decreased the ultrasound image of the probe, except for the tip (supplementary video 1B), and allowed for the visualization of the tissue freezing process. Biopsies (4 samples, 1.1 × 0.9 × 0.3 cm) were positive for adenocarcinoma.

The second case was a 39-year-old female who presented with fever and unresolved pneumonia which had resisted antibiotic therapy for a period of two months. The patient had no history of smoking and her physical examination revealed only bilateral basal fine crepitations. Thoracic CT showed bilateral basal consolidation opacities with positive air bronchogram. Microbiological examination for sputum and bronchoalveolar lavage samples were negative, including the tuberculosis work-up. For the diagnosis of the underlying pathology, the patient was subjected to r-EBUS assisted transbronchial cryobiopsy guided with transthoracic ultrasound. During the procedure, the radial probe was advanced through the lateral segment of the left lower lobe until the lesion was visible. Then, the 1.9 mm flexible cryoprobe was advanced to the target location. Simultaneously, the transthoracic ultrasound was applied on the chest wall and was able to detect the lesion. The transthoracic ultrasound was helpful in confirming that the cryoprobe was located within the lesion and distant from the pleura to avoid pneumothorax. Four transbronchial cryobiopsies were obtained and the histopathological examination revealed cryptogenic organizing pneumonia.

Conventional bronchoscopy has a low diagnostic value for PPL which may be less than 20% for nodules smaller than 2 cm in diameter.[1] Also, it should be noted that not all PPL can be seen by fluoroscopy, in addition to the presence of radiation hazards for the patient and the operators. Although CT guided percutaneous biopsy is a reliable technique for the diagnosis of these lesions, it is associated with a high risk of pneumothorax[2] and is therefore usually indicated when transbronchial procedures have proved unsuccessful. Chest ultrasound guided percutaneous biopsy is an equally long-established method but requires appropriate case selection in advance.[3] The pleural contact length made by the mass or nodule, for example, influences diagnostic yield. Chest ultrasound and CT guided percutaneous biopsy were not considered a convenient alternative because of the ultrasound findings in our first case and because of diagnostic suspicion in the second one. Moreover, these techniques do not allow for the obtention of cryobiopsy samples.

Recent updates to bronchoscopic methods have aimed to increase the diagnostic value for PPL. Electromagnetic navigation bronchoscopy has achieved an accuracy of up to 81.7%, however, it is associated with high economic costs.[4] R-EBUS has emerged as a safer method in comparison to CT-guided biopsy but the yield of r-EBUS remains lower than that of CT-guided biopsy, due in part to the smaller sample size.[5,6]

The safety and feasibility of cryoprobes in combination with r-EBUS has also undergone a preliminary evaluation for the diagnosis of PPL and compared with forceps biopsies. Transbronchial cryobiopsy with r-EBUS assistance can obtain a better diagnostic yield and significantly larger samples.[7,8] Cryobiopsy could even increase the detection rate of epidermal growth factor receptor (EGFR) mutations in non-small-cell lung cancer in comparison to other tissue sampling techniques.[9] However, a meta-analysis[10] reported a pneumothorax average incidence of 10% after transbronchial biopsies with a cryoprobe in interstitial lung disease. Bleeding during cryobiopsy is common and the risk is greater than with conventional forceps biopsies. Moderate bleeding after cryo-biopsy was observed in 65 cases of 383 patients in 12 studies (16.9%).[10]

A main drawback regarding r-EBUS is the absence of real-time vision for biopsy. In this case report, we describe a novel technique for the biopsy of malignant and benign PPL near to pleura using transthoracic ultrasound guidance for cryobiopsies. The particular advantages of real-time guidance with external thoracic ultrasound are the ability to guide the biopsy tool directly to the lesion without C-arm fluoroscope, using echotexture to avoid necrotic areas, preventing injury to surrounding vascular structures and the pleura and to permit the exclusion of the pneumothorax.[11] For instance, in the diagnosis of interstitial lung diseases, distances of the cryoprobe to the pleura of less than 1 cm are associated with a significantly increased risk of pneumothorax,[12] while biopsies obtained too proximally to the middle third of the lung without ultrasound assistance increase the risk of severe bleeding.

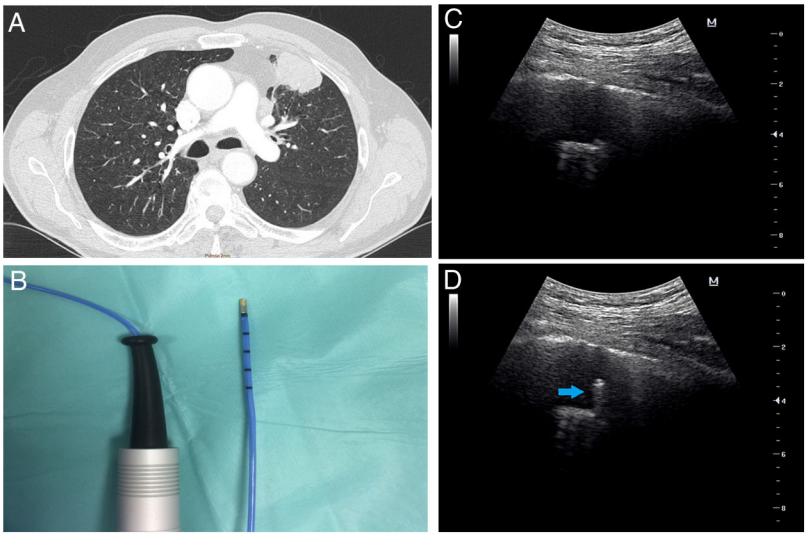

Fig. 1. (A) Chest CT image shows a lingular mass with pleural contact and bronchus sign. (B) Flexible cryoprobe indicated for transbronchial biopsy. Outer diameter 1.9 mm, length 900 mm. (C) Transthoracic ultrasound image before performing transbronchial biopsy of the mass. (D) Transthoracic ultrasound image during the performance of transbronchial biopsy, which locates the cryoprobe within the lung mass (arrow).

Also, we hypothesize that guided real-time transthoracic ultrasound can increase the diagnostic yield of r-EBUS in a way that is similar to real-time convex EBUS transbronchial needle aspiration[13] when compared with non-real-time EBUS.[14] Nevertheless, in comparison with CT-guided biopsy, our technique may have the disadvantage of requiring two operators, one for bronchoscopy and the other for performing transthoracic ultrasound. Even though, thoracic ultrasound offers other advantages, including the lack of ionization radiation, low cost, flexibility, reproducibility of the examination and bedside availability.[15]

In conclusion, the combination of transthoracic ultrasound and flexible cryoprobe add to r-EBUS procedure the potentiality of vision-guided transbronchial cryobiopsies for PPL lesions with pleural contact. Using percutaneous chest ultrasound has enabled us to guide the cryoprobe to the target lesion to obtain accurate samples. Further benefits are visual confirmation that it is freezing the tissue, visualization of the distance to the pleura to prevent pneumothorax and the use of the color Doppler to avoid highly vascularized areas.

Our initial experience requires prospective validation in a larger patient cohort to confirm the reliability and reproducibility of these results combining transbronchial cryobiopsy with percutaneous chest ultrasound.

Funding

This study was partially supported by grants AEER 2016, SEPAR 120/2016 and FUCAP 2017.

Conflict of interest

The authors have reported to Archivos de Bronconeumología that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2020.10.015.

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https://doi.org/10.1016/j.arbres.2020.10.015

Should pulse oximeter saturations be included in the risk stratification for chronic obstructive pulmonary disease proposed by GesEPOC?☆

¿Debe incluirse la Saturación basal de oxígeno en la estratificación de riesgo de la enfermedad pulmonar obstructiva crónica propuesta por GesEPOC?

To the Editor:

The 2017 edition of the Spanish Chronic Obstructive Pulmonary Disease Guidelines (GesEPOC) establishes a treatment algorithm based on the stratification of patient risk at 2 levels, low risk and high risk, according to three criteria: lung function, dyspnea grade, and history of exacerbations[1]. This stratification was initially based on a theoretical framework designed to determine the probability of the patient presenting an unfavorable clinical course. Since the publication of the algorithm, several studies have evaluated its prognostic capacity and endorsed its usefulness in this respect[2,3].

Chronic respiratory failure is associated with a higher mortality rate in patients with chronic obstructive pulmonary disease (COPD)[4]. Peripheral oxygen saturation (SpO2) is easy to determine by pulse oximetry, and values <92% correlate with the presence of severe hypoxemia[5,6]. On this premise, we conducted a retrospective study of patients with stable COPD monitored in a pulmonology clinic to analyze whether including the SpO2 measurement in the conventional GesEPOC risk criteria would improve the prognostic capacity of the algorithm. Consecutive patients with a diagnosis of COPD[7] and a history of smoking (cumulative consumption >10 pack-years) were included. The following variables obtained at the first visit were recorded: lung function, body mass index (BMI), mMRC dyspnea grade, resting SpO2 (determined by the physician in clinically stable patients, breathing room air, at rest, and prior to physical examination), and history of exacerbations prior to inclusion, taking into account both moderate (requiring outpatient treatment with antibiotics and/or steroids) and severe (requiring emergency or hospital admission) exacerbations. Patients were classified as high risk and low risk according to the current GesEPOC criteria[1] (in the presence of any of the following criteria the patient would be categorized as high risk: FEV1% <50%, dyspnea ≥2 if treated, 2 or more moderate exacerbations or ≥ 1 severe exacerbations the previous year), and this was compared with a classification in which high-risk patients were categorized as SpO2 <92% (high risk-SpO2 <92%) and SpO2 ≥92% (high risk-SpO2 ≥92%). A Cox regression survival analysis was performed to compare the two classifications: model 1 was obtained with the conventional GesEPOC classification; and model 2 included the variable SpO2 in the classification. The models were adjusted for age and comorbidity measured with the unadjusted Charlson index. The Akaike information criterion (AIC) was obtained for model comparison. Adjusted survival curves were obtained. Data collection was approved by the Santiago-Lugo Research Ethics Committee.

Overall, 710 patients were included, of whom 632 were men (89%), with a mean age of 68.3 ± 9.6 years, post-bronchodilator FEV1% 50.5 ± 17.2, and BMI 28.3 ± 5.2 kg/m^2. One quarter (25.9%) were active smokers and the pack-year index was 59.3 ± 30.7. The Charlson comorbidities index was 1.98 ± 1.41. In total, 522 patients were classified as high risk (73.5%) and 188 (26.5%) as low risk. The mean SpO2 was 93.1 ± 4.6%. One hundred and sixty-four (23.1%) had SpO2 <92%, of which 155 were high risk. Mean follow-up time was 53.9 ± 26.7 months.

Overall mortality during follow-up was 25.8%, with significant differences between the low-risk group and the high risk group (10.1% vs 31.5%: $P < .0001$, respectively). The high risk-SpO2 group <92% had a mortality rate of 54.2%, compared with 21.9% in the high risk-SpO2 group ≥92% ($P < .0001$). In the Cox regression analysis, compared to the low-risk group, high-risk patients with SpO2 <92% have a greater risk of mortality (HR: 4.79; 95% CI: 2.90–7.91; $P < .001$) than high-risk patients with SpO2 ≥92 (HR: 1.7; 95% CI: 1.02–2.80; $P < .001$) (Table 1; model 2) (Fig. 1).

In our study, the addition of the SpO2 variable to the conventional GesEPOC criteria improves its prognostic capacity and classifies patients more precisely in terms of their mortality risk.

Factors, such as impaired ventilation-perfusion, dysregulation of respiratory center drive, or inspiratory muscle dysfunction due to pulmonary hyperinflation, contribute to the development of hypoxemia in COPD patients, impacting negatively on their life expectancy[8–11]. A cut-off point of SpO2 ≥92% is highly sensitive for ruling out respiratory failure, while SpO2 ≤88% is highly specific for confirming it[5,6]. Taking a pragmatic approach, and to avoid excluding any patient with respiratory failure, we selected a value of SpO2 <92%[5]. Thus, not all patients would meet the criteria for initiating long-term oxygen therapy (LTOT), so an intense bronchodilator therapy, sustained smoking abstention, and early onset of respiratory rehabilitation would hypothetically improve baseline SpO2 values[12–15] and consequently, life expectancy. In line with the concept of personalized treatment proposed by GesEPOC, our approach may of particular interest in high-risk individuals with SpO2 <92% in whom the recommended initiation therapy would be a long-acting β2-agonist inhaled corticosteroid, as would correspond to the COPD-asthma phenotype. These subjects may benefit from early initiation of dual bronchodilation, despite the clinical impact that could be achieved with an inhaled corticosteroid. Furthermore, although this was not an objective of the study, we must point out that 9 patients in the low-risk group had SpO2 <92%. While this accounted for a very low percentage of patients, we believe that further studies that characterize these individuals in more depth may be needed to assess the clinical relevance of this finding.

Our study has limitations and essentially serves to generate debate. It is a retrospective study, conducted in a single center. The number of low-risk patients was very low, as SpO2 could not be used as a variable in these subjects. We cannot rule out that many of these patients were prescribed LTOT during follow-up, which could have influenced the reported mortality figures. Patients could not be stratified according to SpO2 ranges to avoid reducing statistical power. Despite these limitations, we believe that our results could be a stim-

☆ Please cite this article as: Figueira Gonçalves JM, Golpe R, Ramallo Y, García Talavera I, Dacal D. ¿Debe incluirse la Saturación basal de oxígeno en la estratificación de riesgo de la enfermedad pulmonar obstructiva crónica propuesta por GesEPOC? Arch Bronconeumol. 2021;57:774–776.