

TRANSBRONCHIAL CRYOBIOPSY IN DIFFUSE PARENCHYMAL LUNG DISEASE. A NEW STAR IN THE HORIZON

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INTRODUCTION

Surgical lung biopsy is still considered the gold standard to obtain enough lung tissue in the clinical context of diffuse parenchymal lung disease. Tissue samples obtained are large enough for morphological analysis and also very difficult patterns may be identified. Transbronchial lung biopsy is not useful to identify complex morphological patterns and mainly is not recommended as a diagnostic tool in patients with suspected idiopathic pulmonary fibrosis (IPF). This statement is included in the majority of textbooks' chapters or review articles dealing with the diagnostic work-up of diffuse parenchymal lung diseases and surgical lung biopsy is suggested as an important diagnostic step also in recently published guidelines (1)

However this affirmation, after a deeper analysis, seems to be "axiomatic" and not responding to the problems that clinicians and patients might meet in the real life every day.

• **Surgical lung biopsy is associated to significant risks and complications.** The procedure has a 2-4% mortality at 90 day that may be even higher in patients that will have a final diagnosis of IPF (mortality mainly due to acute lung injury) (2,3).

Other complications include infection, prolonged air leak (6-12%) and complain of continuing pain at 7-12 months in more than fifty per cent of patients (3-5). These complications may be reduced if the selection of patients is very strict excluding unstable subjects, patients with low lung function or subjects older than 65. The paradox that could be generated by the axiomatic affirmation above mentioned is that physicians might require an invasive diagnostic procedure that can generate complications that are even worse than the disease at last identified. Therefore the decision to submit a patient to surgical lung biopsy is always difficult and need to be discussed in details of course with the patient her/himself. In clinical practice surgical lung biopsy is used in less than 10-15% of cases in contrast with the guidelines that suggest the use of this bioptic approach in all the cases in which CT scan pattern is not conclusive (i.e. in more than 40% of cases).

• **The interobserver variability between expert pathologists when assessing lung specimens obtained by surgical lung biopsy is not as high as expected (6,7).** This observation reflects the fact that histological classifications and patterns (nowadays defined on the basis of simple stains such as Hematoxylin-Eosin) are not yet clearly reproducible regardless the dimension of the lung samples provided. The paradox that could be created by surgical lung biopsy (as a tool able to supply material for morphological analyses) is that the material provided by the invasive tool might generate not clear information to add on top an al-

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ready not so clear context. In other words are we sure that bigger is the lung tissue sample more clear is the information obtained? Up to now this question is still without a formal and assessed answer, mainly when difficult patterns are considered (UIP, NSIP, overlapping patterns....). Or do we know exactly the minimum size of lung tissue containing the morphological information useful for a diagnosis? Again the answer to this crucial question is not yet known.

- **Data provided by conventional transbronchial lung biopsy are usually considered useful to exclude a disease (mainly sarcoidosis or carcinomatous lymphangitis) and not to confirm a diagnosis of UIP pattern or of other “idiopathic” patterns (NSIP, DIP, ...)(1).** This point of view is not easy to defend. First of all the diagnosis of sarcoidosis or carcinomatous lymphangitis is usually not in the differential diagnostic list of patients in which the first diagnosis to consider is IPF, mainly due to the different high resolution CT scan patterns in these different disorders. Furthermore the UIP pattern might be recognized, unfortunately in a very low percentage of cases, also in these tiny specimens, having this pattern in TBB samples a very high predictive value. In a recent study Tomassetti S, et al (8) observed also that nonspecific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP) are patterns that could be identified in tiny samples but this identification is linked to a very low negative predictive value. In conclusion the diagnostic role of TBB in diffuse lung diseases observed in immunocompetent patients is significant in a few specific disorders (sarcoidosis, carcinomatous lymphangitis, organizing pneumonia,...) but it is limited (a very low sensitivity) in UIP and of no value in other forms of so-called “idiopathic interstitial pneumonia” (NSIP, DIP,)

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These difficulties appear even increased after the publication of large studies that have documented the detrimental effects of the use of steroids, N-acetyl cysteine and azathioprine in patients with IPF and, viceversa, the beneficial influence of pirfenidone and nintedanib in the same group of pa-

tients. (9-11) A light on the horizon may help to solve at least part of these impediments. The use of cryoprobes for bronchoscopic procedures was described as early as 1977 (12). More recently, cryoprobes have been used to obtain lung tissue (13-21). The cryosurgical equipment operates by the Joule-Thompson effect, which dictates that a compressed gas released at high flow rapidly expands and creates a very low temperature. The cooling agent is applied under high pressure (45 bar) through the central canal of the probe (Erbokryo CA, ERBE, Tübingen, Germany). Carbon dioxide (CO₂) or nitric oxide are the cooling agents commonly used. The gas at the tip expands due to the sudden difference in pressure relative to the atmospheric pressure, resulting in a drop in temperature at the tip of the probe (minus 80-89°C). Flexible cryoprobes utilized for TBB can have different diameters: 1.9 and 2.4 mm. Transbronchial cryobiopsies of lung tissue are carried out during flexible bronchoscopy. The patients are deeply sedated with intravenous propofol with or without remifentanyl and intubated with a spiral armored endotracheal tube or a rigid tube. Oxygen is insufflated continuously through the tube. Spontaneous breathing is maintained during the whole procedure or, if patients are paralyzed by the use of non-depolarizing blocking agents, jet ventilation is used. Oxygen saturation, blood pressure, ECG and transcutaneous carbon dioxide partial pressure are monitored continuously. The bronchopulmonary segment for biopsy is determined prior to the procedure based on the high resolution CT of the chest. A Fogarty balloon is positioned at the entrance of the preselected segmental bronchus. The cryoprobe is introduced into the selected area under fluoroscopic guidance via flexible bronchoscope. A distance of approximately 10-20 mm from the thoracic wall and a perpendicular relation between the thoracic wall and the probe, are considered optimal. Once brought into position, the probe is cooled for approximately 3-6 s. The frozen tissue attached to the probe's tip is removed by pulling the cryoprobe together with the bronchoscope. The number of biopsies taken is usually 2-6. A chest radiograph or an ultrasonographic evaluation after the procedure are performed when a pneumothorax is clinically suspected (pain, oxygen need). Multiple recent studies have confirmed the feasibility and safety of this approach in various patient populations including

patients with fibrotic diffuse lung diseases, immunocompromised hosts, lung transplant recipients and even patients with focal opacities. The samples obtained by cryoprobes are bigger than that obtained by conventional transbronchial lung biopsy and without crash artifacts. The size of specimens obtained varies from one study to the other (from 11 mm² to almost 75 mm²) as well as the number of specimens obtained and probably also the distance from the pleura from which the tissue was retrieved (more or less 1 cm) and the "stiffness" of the lungs submitted to biopsy. This could explain, in part, the different rate of pneumothorax reported (varying from a significant 28% to 5%) (10,11). Bleeding has not been reported with high frequency and the use of Fogarty balloon may even reduce more this complication. The diagnostic yield of this technique in patients with diffuse parenchymal lung diseases has been reported to exceed the 80% and mainly it has been feasible in recognizing the UIP pattern. Furthermore in UIP pattern interobserver variability between pathologists has similar values to that described when surgical lung biopsy specimens are analyzed (18). Its value in the context of a multidisciplinary diagnosis seems to be similar to that observed when surgical lung biopsy is involved.

UNSOLVED QUESTIONS AND CONCLUSIONS

Transbronchial lung cryobiopsy is an innovative method to obtain lung tissue. It is carried out under deep sedation/general anesthesia, in patients intubated with orotracheal tube or rigid bronchoscope. Samples are usually of 4-6 mm of maximum diameter and complex pathologic patterns may be recognized: UIP, NSIP, DIP, etc. This is because larger samples are retrieved without crash artifacts, peripheral structures of the secondary pulmonary lobule are recognized (mainly pleura but also interlobular septa and veins) and immunohistochemical investigations are easier to perform on these samples. Transbronchial cryobiopsy might, therefore, be considered an alternative to surgical lung biopsy in patients with DPLDs and particularly in subjects with f-DPLDs (18), elderly patients, or subjects with comorbidities. However the procedure has not yet been standardized so far and data regarding the optimal way to obtain lung tissue has not yet assessed.

The biopsies are obtained under fluoroscopic guidance but the distance of the cryoprobe tip from the pleura varies (less than 1 cm or even 2 cm in different studies). The biopsies are obtained in the same segment in some studies or from different segments of the same lobe in others. Also the freezing time and the size of the probe are not equal varying from 3 to 6 seconds and 2.4 to 1.9 mm respectively. Data on the utility or inutility to obtain lung samples from different lobes in the same emithorax are still missing. The best way to prepare histological slides from the samples obtained by cryoprobe, the improvement of diagnostic yield and specificity using immunohistochemical methods or even molecular biology procedures have not been tested (22-24). Larger and multicenter trials evaluating the different technical aspects [cooling using carbon monoxide or nitrous oxide; biopsies < 1 cm from the thoracic wall or more centrally located; number of samples to obtain; comparison between different probes (1.9 vs 2.4 probes), the utility of biopsies in different segments or even different lobes, etc] and the clinical impact of this method on the final multidisciplinary diagnosis will better clarify the clinical utility of this diagnostic tool and will allow to standardize it (25). Finally trials comparing transbronchial cryobiopsy and surgical lung biopsy could be very informative but ethical reasons are an almost insurmountable obstacle to carry them out.

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