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Validation of transbronchial cryobiopsy in interstitial lung disease – interim analysis of a prospective trial and critical review of the literature

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Abstract. *Background:* Transbronchial Cryobiopsy (Cryo-TBB) represents a new approach for sampling lung tissue in interstitial lung disease (ILD). *Objectives:* Comparing the reliability of Cryo-TBB results and the procedure's complication rates with the procedure of surgical lung biopsy (SLB). *Methods:* ILD subjects with the need of lung tissue sampling are analyzed in this prospective trial. To determine the relevance of procedure-related complications the pooled data from the ongoing and previous Cryo-TBB studies were compared with pooled data from previous SLB studies in an interim analysis. In our own cohort we analyzed how often Cryo-TBB results lead to a definite diagnosis without the need for a SLB. In subjects who underwent both procedures it was determined how often SLB confirmed Cryo-TBB findings. *Results:* Analyzing the pooled data of the ongoing study (19 subjects) and our own retrospective study (32 subjects), in 38/51 subjects (75%) SLB was deemed to be unnecessary following Cryo-TBB. In 12/13 subjects an SLB was performed confirming Cryo-TBB results in 92%. 30 day-mortality was 1.9%, bleeding occurred in 78%, pneumothorax in 22%. 2 subjects showed a myocardial infarction. Complication rates are comparable to previous Cryo-TBB studies. Analysis of the pooled data from the literature showed an overall 30-day mortality of 0.7% for Cryo-TBB and 3.3% for SLB. *Conclusions:* Cryo-TBB may be a reliable diagnostic tool in ILD, dispensing the need for a SLB in most cases. Severe complications may occur less frequently than in SLB. Modifications of the procedure may lead to further risk reduction. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 2-9)*

Key words: bronchoscopy, histopathology, surgical lung biopsy

Abbreviations

COP	cryptogenic organizing pneumonia
Cryo-TBB	transbronchial cryobiopsy
DLCO	diffusing capacity or transfer factor of the lung for carbon monoxide
HP	hypersensitivity pneumonitis
HRCT	high resolution computed tomography
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
NSIP	non-specific interstitial pneumonia
SLB	surgical lung biopsy
TBB	transbronchial forceps biopsy
UIP	usual interstitial pneumonia

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Introduction

Transbronchial cryobiopsy (Cryo-TBB) is a new bronchoscopic approach for sampling of lung tissue. Previous studies reported a high diagnostic yield due to less compression artifacts and a 5-10 fold increase in sample size in comparison to conventional transbronchial forceps biopsy (TBB) (1-2). The diagnostic value of Cryo-TBB in patients with interstitial lung disease (ILD) has not yet been studied. Previous studies have shown the superiority of the procedure in comparison to conventional TBB (3-4). In the mentioned studies all subentities of ILD with the indication for lung tissue sampling were included. The feasibility of a surgical lung biopsy (SLB) was not part of the inclusion criteria nor were the entities excluded where the low risk procedure of conventional TBB might have been sufficient (granulomatosis, organizing pneumonia, lymphangiosis carcinomatosa, etc.).

To determine the importance of Cryo-TBB in ILD patients, in our study the diagnostic value is evaluated in patients where a SLB should be recommended as opposed to a conventional TBB according to the guidelines (5). This is especially the case for differentiating between fibrosing non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) and for the ILDs which are unclassifiable via high resolution computed tomography (HRCT) (6-7). It could be shown in a retrospective study that for this indication, Cryo-TBB led to a definite clinical diagnosis following interdisciplinary case evaluation in about 70% without the need for a SLB. In cases where the results of Cryo-TBB were equivocal, an additional SLB confirmed the suspected diagnosis following Cryo-TBB in 89% of subjects (8).

Cryo-TBB and SLB are invasive procedures with relevant mortality and morbidity. Because of ethical concerns in our prospective trial, subjects are not forwarded for a SLB in cases where Cryo-TBB results lead to a definite clinical diagnosis. In cases where the Cryo-TBB results are inconclusive, a SLB is performed as a step-up procedure according to the guidelines. To prevent a bias in data interpretation, subjects are only included where a SLB is feasible (available patient consent for a potential SLB, acceptable risk assessment based on lung function impairments) (9).

It is the aim of the study to determine whether Cryo-TBB results can lead to a definite clinical diagnosis without the need for a SLB. In cases where histological Cryo-TBB findings are felt to be inconclusive, it has to be studied whether an additional SLB leads to a change in histological findings and clinical diagnosis. Furthermore, the reproducibility of the pathological results needs to be evaluated. The peri-interventional complication rates of Cryo-TBB and SLB have to be compared. In the on-going study, within 24 months of recruitment relevant peri-interventional complications have been observed and lead to an interim analysis in order to evaluate the diagnostic value of Cryo-TBB. A critical literature review was performed to analyze procedural differences and complication rates in Cryo-TBB and SLB studies.

Methods

The prospective trial was approved by the institutional review board, University Witten/Herdecke, Germany and was initiated in October 2012 (ClinicalTrials.gov NCT01714518). In all subjects, an ILD pattern is present on HRCT and additional investigations including clinical data, serologic markers and bronchoalveolar lavage do not result in a definite clinical diagnosis. When an interdisciplinary case evaluation leads to the recommendation of SLB according to the guidelines (5), subjects are eligible for recruitment into the study. Following recruitment, lung tissue is sampled by Cryo-TBB as the initial intervention and SLB is performed as a step-up procedure in subjects where histological findings following Cryo-TBB remain unequivical and/or do not lead to a definite clinical diagnosis. All histological findings are discussed in an interdisciplinary case evaluation. Pseudonymized Cryo-TBB samples and SLB samples are all independently analyzed by the pathologist. For all samples the diagnostic reliability is assessed as well as the concordance of Cryo-TBB and SLB samples in patients who undergo both procedures. The results of the interim analysis were compared with retrospective data from our center, which have been previously published (8). After a critical review of the literature, complication rates of the on-going study have been compared with previous studies investigating Cryo-TBB or SLB in ILD

patients. Bleeding complications have been classified in a modified manner according to the guidelines of the British Thoracic Society (BTS) (10). There is no statement in the BTS Guidelines how to characterize bleeding severity considering the quantity of bleeding (ml). The bleeding severity is only defined by the therapeutic interventions. The BTS Guidelines state that the majority of bronchoscopic bleeding complications are mild to moderate with only 3% estimated at being more than 100 ml. According to this data, in the ongoing and in the retrospective study (8) bleeding complications with a quantity of >100 ml were categorized as "severe bleeding". For the analysis descriptive statistical calculations have been applied.

Flexible bronchoscopy is performed under sedation (Midazolam and Disoprivan) using a cuffless 7.5-bronchoscopy tube (Rüsch, Teleflex Medical, Kernen, Germany) with an integrated second lumen for endotracheal oxygen application. The flexible cryoprobe (Erbe, Tübingen, Germany) is applied through the working channel of the bronchoscope. The biopsy is sampled under fluoroscopy control with the tip guided to a 1.0-1.5 cm subpleural position. Using liquid nitrous oxide, the cryoprobe is cooled down to a working temperature of -85 to -90° Celsius for 4-5 seconds, freezing the vital tissue in contact with the probe. The samples are extracted under freezing conditions together with the activated cryoprobe. In all patients, 3-5 transbronchial biopsies are sampled from different ipsilateral segments, which are pre-specified based on HRCT. A chest X-ray is routinely performed on all patients, in order to exclude an iatrogenic pneumothorax. Specimens are processed and stained using standard histological techniques (Haematoxylin-Eosin, Elastica-van Gieson and Prussian-Blue).

Results

Within a period of 24 months, 7 female and 12 male subjects were recruited to the study (median age 67 years (range 39-80); median forced vital capacity 80 % predicted (range 51-105); median diffusion capacity of the lung for carbon monoxide corrected for hemoglobin 61 % (range 48-97). In 15/19 (78%) subjects, a definite diagnosis could be established following Cryo-TBB, thereby dispensing of the need for a SLB. Four of 19 (22%) subjects were forwarded for SLB because of equivocal findings after Cryo-TBB. The Cryo-TBB findings were confirmed by SLB in two of these four cases with the same reliability and in the other two with a higher reliability (Table 1). In no case did the results of the SLB lead to a change in the clinical diagnosis. Pooled data of the ongoing study (19 subjects) and retrospective data (32 subjects) showed that in 38/51 (75%) subjects, histological findings after Cryo-TBB prevented the need for a SLB (prospective study: NSIP (5), UIP (7), OP (2), RB-ILD (1), unclassifiable fibrosis (1), retrospective study: NSIP (9), UIP (6), OP (3), sarcoidosis (1), RB-ILD (1), excluded ILD (2), unclassifiable fibrosis (2)). In 12 of the remaining 13 subjects a SLB was conducted, the Cryo-TBB results were confirmed in 11 of these 12 (92%) subjects. In one subject, the histological findings changed following SLB (probable NSIP changed to definite UIP pattern) (Table 1).

In 2/19 subjects a myocardial infarction occurred as primary manifestation of coronary heart disease. One of these two cases was aggravated by an acute exacerbation of ILD with a lethal outcome. The 30-day-mortality rate was 5.3%. Pooling the data with the analysis of our retrospective study revealed a 30-day-mortality rate of 1/51 subjects (1.9%). 15/19 (79%) subjects showed endobronchial bleeding (seven moderate, eight severe; classified according to the BTS guidelines (10). In 5/19 (26%) subjects a pneumothorax occurred with four being treated by chest drainage.

A critical literature review showed that there are 5 studies which analyzed Cryo-TBB in ILD patients (3 retrospective, 2 prospective, 25-75 subjects, overall 294 subjects) (Table 2). Our ongoing study is the first prospective study analyzing results from Cryo-TBB and SLB in patients who underwent both procedures. The comparison with previous Cryo-TBB studies showed that the study populations are similar in terms of age and lung function impairments (Table 2). Analysis of the Cryo-TBB procedures revealed that the number of samples per patient, the cryoprobe's freezing time and diameter differed between the studies (Table 2).

Pooling the data of all studies the 30-days-mortality in ILD patients after Cryo-TBB is 2/294 (0.7%). The 30-days-morbidity after Cryo-TBB can hardly be determined. The classification of bleeding complications is heterogeneous and has not been

Table 1. Consistency of histological findings after SLB and Cryo-TBB in all 12 subjects who underwent both procedures

Subject	SLB consensus	Cryo-TBB consensus	Consistent results
R4	definite UIP	probable NSIP, possible UIP	no
R6	definite UIP	unclassifiable fibrosis, minimal changes, possible UIP	Yes
R8	postbronchiolitic fibrosis, possible NSIP, inconsistent with UIP	possible NSIP, inconsistent with UIP	Yes
R12	definite UIP	possible UIP	Yes
R13	probable HP, possible sarcoidosis, inconsistent with UIP	probable HP, possible sarcoidosis, inconsistent with UIP	Yes
R14	OP, inconsistent with UIP	probable OP, inconsistent with UIP	Yes
R31	definite UIP	possible UIP	Yes
R32	bronchiolocentric fibrosis, possible UIP	possible UIP	Yes
P2	definite UIP	possible UIP	Yes
P5	probable UIP	possible UIP	Yes
P9	probable UIP	probable UIP	Yes
P12	NSIP, inconsistent with UIP	NSIP, inconsistent with UIP	Yes

Legend: HP = hypersensitivity pneumonia; NSIP = non specific interstitial pneumonia; P = subjects from prospective study (ClinicalTrials.gov NCT01714518); R = subjects from retrospective study (8); UIP = usual interstitial pneumonia

standardized in previous studies. The range of reported bleeding complication rates is 0-87%. Pneumothorax was reported in 0-28% of the cases (Table 3).

Pooling the data of all studies analyzing SLB in ILD patients, the overall 30-day-mortality is 3.3% (range 0-17%). Where reported, morbidity after SLB was quantified at 0-66% (overall morbidity 14%), with acute exacerbations documented in 1.1% (11), 3.9% (12) and 5% (9) (Table 4).

Discussion

Data of the ongoing study suggest that Cryo-TBB may have a high diagnostic value in ILD patients. In subjects where a SLB was indicated, Cryo-TBB helped to reduce the number of SLB by 78%. Results from Cryo-TBB are reliable, as SLB confirms results from Cryo-TBB in > 90%. Data in this field are lacking. There are only a few studies that have analyzed Cryo-TBB and only six of these specifically in ILD patients (1, 3-4, 8, 13-14). To date there is no study where Cryo-TBB results could be validated with the results of SLB samples in patients who underwent both procedures.

Cryo-TBB induced acute exacerbations of ILD are rare and the mortality is low. Overall, there are two reported cases in the literature with an acute exacerbation - both subjects where the histological findings described a UIP pattern (Table 3). These two cases showed a lethal course and represent the only reported procedure related deaths within 30 days. Mortality after Cryo-TBB is probably lower than after SLB. The rate of procedure-induced acute exacerbations is documented in only a few Cryo-TBB and SLB studies. It remains unclear whether in some subjects acute exacerbations were classified as pneumonia. Documented exacerbations seem to be less frequent after Cryo-TBB than after SLB. One reason may be that most acute exacerbations observed after SLB occur in the contralateral lung due to the intraparenchymal shear forces induced by mechanical unilateral ventilation used when performing a SLB. The broad range of morbidity rates following SLB can be explained by the heterogeneous designs of most studies. No standards have been applied for the definition of postoperative morbidity and in some

Table 2 - Synopsis of Cryo-TBB studies (study design, anthropometry of subjects, modalities of Cryo-TBB procedure)

Author (reference)	Study design (recruitment time)	Number of Cryo-TBB subjects	Age	Forced vital capacity percent predicted	Diffusion capacity, percent, corrected for hemoglobin	number of samples per patient	Cryotime (Seconds)	Diameter cryoprobe (mm)	Bronchoscopy approach
Babiak et al. 1	retrospective (6 months)	41	not reported	not reported	not reported	1,8	approximately 4	2,4	sedation, spontaneous breathing, bronchoscopy tube
Kropski (4)	retrospective (10 months)	25	mean value 57 (range 27-75)	mean value 75 (standard deviation 17)	mean value 66 (standard deviation 25)	2	4	1,9	sedation, spontaneous breathing, bronchoscopy tube
Casoni et al.13	prospective (18 months)	63	median 60 (range 29-77)	median 81 (range 50-123)	median 55 (range 29-86)	1,1	5-6	2,4	sedation, spontaneous breathing, rigid bronchoscopy
Pajares et al. 3	prospective (35 months)	39	mean value 60 (standard deviation 10)	mean value 78 (standard deviation 15)	mean value 68 (standard deviation 20)	3,6	3-4	2,4	sedation, spontaneous breathing, bronchoscopy tube
Fruchter et al. 14	retrospective (29 months)	75	mean value 56 (range 17-81)	not reported	not reported	3	approximately 4	2.4	sedation, spontaneous breathing
Hagmeyer et al. 8	retrospective (15 months)	32	mean value 65 (range 45-83)	mean value 75 (range 40-120)	mean value 52 (range 17-108)	2,6	4-5	2,4+1,9	sedation, spontaneous breathing, bronchoscopy tube (25 patients); general anesthesia, rigid bronchoscopy (7 patients)
Hagmeyer et al. (Clinical Trials.gov NCT 01714518)	prospective (16 months)	19	median 67 (range 39-80)	median 80 (range 51-105)	median 61 (range 48-97)	3,9	4-5	1,9	sedation, spontaneous breathing, bronchoscopy tube

studies only severe and/or directly procedure-related complications were reported. It is unclear whether there are differences in the analyzed cohorts (subentities of ILD, functional impairments, etc.) and in the perioperative management.

Morbidity after Cryo-TBB and after SLB is hard to compare, due to differences in procedural approaches. Bleeding complications are very rare after SLB but typical in Cryo-TBB. During a SLB, a pneumothorax is induced on the site of the surgical

Table 3. Synopsis of reported complications in Cryo-TBB studies

Author (reference)	Number [%] of bleeding complications (severity)	Number of pneumothoraces (%)	Number of myocardial infarctions	Number of acute exacerbations (ILD histology)	Number of deaths within 30 days (ILD histology)
Babiak et al. (1)	0 (reported no tamponade, no double lumen tube, no surgery)	2 (4,87%)	0	not reported	not reported
Kropski (4)	0	0	0	not reported	not reported
Casoni et al. (13)	1 (prolonged bleeding despite of blocking balloon)	19 (28%), chest tube necessary in 14 cases (20%)	0	1 (UIP)	1 (UIP)
Pajares et al. (3)	12 [31%] (bleeding requiring suction to clear but no other endoscopic procedures) 22 [56%] (bleeding requiring endoscopic procedures (bronchial occlusion-collapse and/or instillation of ice-cold saline)	3 (8%)	0	not reported	0
Fruchter et al. (14)	3 [4%] (cold saline instillation)	2 (2.6%)	0	0	Not reported
Hagmeyer et al. (8)	8 [25%] (moderate) 17 [53%] (severe)	6 (19%), chest tube necessary in all cases	0	0	0
Hagmeyer et al. (ClinicalTrials.gov NCT01714518)	7 [36%] (moderate) 8 [42%] (severe)	5 (26%) , chest tube necessary in 4 cases (21%)	2 (first manifestation of coronary heart disease)	1 (UIP)	1 (UIP)

Legend: UIP = usual interstitial pneumonia

approach and a chest tube is inserted at the end of the intervention in every subject. Postoperative pneumothorax is therefore not documented as a complication after SLB, but is part of the procedure. Following Cryo-TBB, insertion of a chest tube because of pneumothorax is necessary in 0-21%. Complications such as pneumonia, persistent pleural fistula, neuropathic pain and empyema have been described only in SLB studies. In the on-going study, myocardial infarction occurred in two cases after Cryo-TBB. Ischemic events have not yet been described in other Cryo-TBB studies. After SLB Lettieri et al. reported two myocardial infarctions and one stroke (15), Blackhall et al. reported a case of intestinal ischemia with lethal outcome (12).

Bleeding complications are frequently seen in Cryo-TBB; there are two publications focusing on bronchoscopic techniques to stop bleeding after Cryo-TBB (16-17). Where standardized classifications for bleeding complications are applied in the studies, bleeding is often classified as moderate or severe. In Cryo-TBB studies, classification of bleeding complications is heterogenous. Blocking devices are used frequently as part of clinical routine (13, 16), suggesting that bleeding complications have to be classified as severe according to the BTS classification. There is no reported case of severe bleeding leading to surgical interventions, blood transfusion, admission to a critical care unit, resuscitation or death.

Table 4. Synopsis of SLB studies (number of included subjects, 30-days-mortality, 30-days-morbidity)

Author	Number of subjects included study	30-days-mortality (%)	30-days-morbidity (%)
Ferson PF (18)	75	12%	23 (31%)
Bensard DD (19)	43	2%	7 (16%)
Bentzon N (20)	9	11%	3 (33%)
Molin LJ (21)	37	3%	5 (14%)
Mouroux J (22)	66	6%	7 (11%)
Zedgi R (23)	64	5%	7 (11%)
Rena (24)	58	0%	2 (3%)
Ayed AK (25)	61	2%	9 (15%)
Blewett CJ (26)	32	0%	0
Utz JP (27)	60	17%	Not reported
Yamaguchi M (28)	30	0%	3 (10%)
Lettieri CJ (15)	83	5%	7 (8%)
Tiitto L (29)	76	5%	7 (9%)
Park JH (9)	200	4%	51 (26%)
Guerra M (30)	53	2%	5 (9%)
Zhang D (31)	418 (complications analyzed in 335 patients)	1%	24 (7%)
Luo Q (32)	32	0%	21 (66%)
Blackhall V (12)	103	5%	14 (14%)
Morris D (33)	66	2%	19 (29%)
Samejima J (11)	285	0%	20 (7.0%)
Overall	N = 1765	Overall 30-day-mortality 58/1765 (3.3%)	Overall 30 day morbidity 234/1705 (14 %)

Analyzing the procedural modalities of Cryo-TBB in all studies, data suggest that a lower number of samples per patient may be afflicted with a lower risk of bleeding and that a less peripheral position of the cryoprobe (13) and a shorter freezing time may be afflicted with a lower risk of pneumothorax (Table 2 and 3). In the on-going study, these data lead to a modification of the procedural setting with a standard of two samples per patient and a freezing time of 3-4 seconds. To waive the endobronchial application of adrenaline may reduce the risk of cardiac events.

This is the first prospective study to analyze results from Cryo-TBB and SLB in patients who underwent both procedures. Findings from Cryo-TBB are probably reliable, meaning that the procedure may become an attractive minimally invasive procedure in place of a SLB in many patients. Cryo-TBB is probably afflicted with a lower risk of mortality and morbidity than SLB. Complication rates may be reduced by modification of the procedural setting of Cryo-TBB.

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