Transbronchial cryobiopsy in fibrosing interstitial lung disease: modifications of the procedure lead to risk reduction

Lars Hagmeyer,[1] Dirk Theegarten,[2] Jeremias Wohlschläger,[3] Thomas Hager,[2] Marcel Treml,[1] Simon Dominik Herkenrath,[1] Khosro Hekmat,[4] Matthias Heldwein,[4] Winfried J Randerath[1]

[1]Clinic for Pneumology and Allergology, Center of Sleep Medicine and Respiratory Care, Hospital Bethanien Solingen, Solingen, Germany
[2]Institute for Pathology and Neuropathology, University Hospital Essen, Essen, Germany
[3]Institute for Pathology, Diakonissen Hospital Flensburg, Flensburg, Germany
[4]Clinic for Cardiac and Thoracic Surgery, University Hospital Cologne, Cologne, Germany

Correspondence to
Dr Lars Hagmeyer, Clinic for Pneumology and Allergology, Center of Sleep Medicine and Respiratory Care, Hospital Bethanien Solingen, Solingen 42699, Germany; lars.hagmeyer@klinik-bethanien.de

Received 20 May 2018
Revised 5 February 2019
Accepted 11 February 2019
Published Online First 9 March 2019

To cite: Hagmeyer L, Theegarten D, Wohlschläger J, *et al*. *Thorax* 2019;**74**:711–714.

ABSTRACT

Sixty-one subjects with fibrosing interstitial lung disease were prospectively analysed to determine the efficacy of transbronchial cryobiopsy (CryoTBB) and the effect of procedural modifications which were introduced after an interim analysis of the first 19 subjects. The modifications significantly reduced complication rates from 84% to 14% (p<0.001). 30-day-mortality was 2%. The algorithm with initial CryoTBB and surgical lung biopsy (SLB) as optional step-up procedure was feasible. CryoTBB led to a confident diagnosis in 46/61 subjects (75%). Only 21% out of all subjects were forwarded for SLB. As the modified CryoTBB reduced but not eliminated the risk of severe complications, tissue sampling should be limited to patients where confident diagnosis enables life prolonging therapy. Trial registration number: NCT01714518.

INTRODUCTION

Surgical lung biopsy (SLB) is the gold standard for tissue sampling in fibrosing interstitial lung disease (ILD).[1 2] However, this well-established sampling procedure is afflicted with a relevant morbidity and mortality.[3]

In recent years, the transbronchial cryobiopsy (CryoTBB) has played an increasing role worldwide.[4]

A diagnostic algorithm has been published, proposing that CryoTBB may be performed as an initial step with SLB as an optional step-up procedure when findings remain inconclusive. However, comparably to previous trials, high complication rates have been documented.[5]

In this study, we first analysed whether the CryoTBB-associated complication rate could be reduced by procedural modifications which were introduced after an interim analysis of the first 19 subjects, whose results were previously published.[5] Second, we aimed to further validate the proposed algorithm. Third, we investigated whether an additional SLB following inconclusive CryoTBB findings leads to a change in the clinical diagnosis.

MATERIAL AND METHODS

Study design and patients

Prospective diagnostic trial: Inclusion criteria were: first diagnosis of fibrosing ILD with the indication for lung tissue sampling according to the guidelines;[1] subject willing to follow the CryoTBB and SLB algorithm if indicated, informed consent for study participation. Exclusion criteria were: invasive diagnostic procedures not feasible; diffusion capacity of the lung for carbon monoxide (DLCO) <50%. After the occurrence of a number of relevant CryoTBB-associated complications, an interim analysis of the first 19 subjects was performed, leading to modifications of the CryoTBB procedure for the following 42 patients. Data from both groups were comparatively analysed.

The trial was approved by the institutional review board, University Witten/Herdecke, Germany (ClinicalTrials.gov: NCT01714518).

Transbronchial cryobiopsy

Flexible bronchoscopy was performed as described previously via a tracheal tube (Bronchoflex 104100, Rüsch, Germany) using a flexible 1.9 mm cryobiopsy probe (Erbe, Tübingen, Germany).[5] Biopsies were sampled from different ipsilateral segments, which were prespecified based on high-resolution CT. After the first 19 subjects, modifications of the procedure were introduced which comprised endobronchial placement of a prophylactic bronchus blocker balloon (RÜS 330600, Rüsch, Germany), reduction of freezing time (from 4–5 s to 3–4 s) and biopsy number (from 4–5 samples to 2–3 samples). Prior to each biopsy, the bronchus blocker balloon was placed in the lobe to be biopsied. The balloon was routinely inflated after each biopsy as the bronchoscope was removed together with the cryoprobe and was deflated after reintubation with the bronchoscope.

Bleeding complications were classified as described previously[5] in a modified manner according to the guidelines of the British Thoracic Society (BTS).[6] The modifications of the BTS bleeding classification affected the criteria 'bronchus blocker usage' and 'quantification of blood volume'. The prophylactic usage of the bronchus blocker balloon was not included in the evaluation of bleeding severity. However, reinflation of the balloon after its prophylactic use was classified as severe bleeding. Bleeding severity is defined solely by therapeutic interventions in the BTS guidelines. It is stated 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 addition to the BTS criteria bleeding, complications with a quantity of >100 mL were categorised as 'severe bleeding'.

Table 1 Anthropometric and lung function data of patient groups before and after modification of cryobiopsy procedure

	Female (n, %)	Age (years)	BMI (kg/m²)	TLC (%pred)	FVC (%pred)	DLCO (%pred)	DLCO/VA (%pred)
Premodification (n=19)							
	7 (37%)	66±11	28±3	73±19	80±16	61±13	91±16
Postmodification (n=42)							
	18 (43%)	66±11	29±6	77±17	82±18	64±18	84±22
P value	0.656	0.845	0.168	0.307	0.680	0.817	0.123

Mean±SD deviation and p values for between group comparisons are shown.
BMI, body mass index; DLCO, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; TLC, total lung capacity; VA, alveolar volume; %pred, per cent of predicted value.

Pneumothoraces, bleeding complications, sedation hangover, cardiac events, fibrosis exacerbations and 30-day mortality were documented.

Surgical lung biopsy

SLB was performed by video-assisted-thoracoscopy. Two sampling areas were prespecified and were identical to the areas targeted by CryoTBB.

Pathological evaluation

The histopathological pattern was assessed and classified into one of three diagnostic confidence levels (>95%: definite, 70%–95%: probable, <70%: possible). In the presence of an UIP pattern, the ATS/ERS/JRS/ALAT diagnostic criteria were applied.[1] All findings were discussed in a multidisciplinary discussion.

Statistical analysis

Anthropometric and lung function data are given as mean±SD. All other results are presented using descriptive statistics, giving absolute numbers and percentages. Continuous data were tested for normality using the Shapiro-Wilk test. In case normal distribution could be assumed, the two groups were compared using the independent samples t-test, otherwise the Mann-Whitney U test was applied. Differences of complication rates were analysed for statistical significance by the two-proportions z-test. An inter-rater and intra-rater analysis of the three independent pathologists' assessments of cryobiopsy samples was performed. This was restricted to the group of 42 patients postprocedural modifications to focus on samples obtained under comparable circumstances. Their individual analyses of the predominant histopathological pattern were used to calculate Fleiss' Kappa. Intra-rater reliability, using the Cohen's Kappa statistic, was tested for one pathologist, who reassessed the cryobiopsy samples at a later time-point while being blinded to his former evaluations.

RESULTS

Sixty-two patients were enrolled and data from 61 subjects (25 female, age 66±11 years, BMI 29±6 kg/m²) were analysed due to one withdrawal of consent. Mean forced vital capacity (% of predicted) was 81%±17% and mean DLCO was 63%±17%.

The 42 postmodification subjects showed similar anthropometric and lung function characteristics as compared with the 19 subjects from the premodification cohort (table 1).

Comparing the premodification and postmodification data, a significant reduction of the CryoTBB associated overall complication rate (84% [95% CI 62-94%] vs 14% [7-28%], p<0.001), bleeding rate (79% [57-91%] vs 0% [0-8%], p<0.001), sedation hangover (16% [6-38%] vs 0% [0-8%], p<0.010) and myocardial infarction (11% [3-31%] vs 0% [0-8%], p=0.033) were determined, while for premodification, there were 7 (37%) cases with bleeding volume >100 mL (range 120–350 mL), 11 (58%) and 5 (26%) with xylometazoline and epinephrine application, respectively, these events did not occur at all postmodification (all p<0.001). There was also a reduction—although not significant—of the pneumothorax rate (26% [12–49%] vs 12% [5–25%], p=0.160) and 30-day mortality (5% [1-25%] vs 2% [0-12%], p=0.559) (table 2). After SLB in one subject an overnight stay on intensive care unit was recorded due to prolonged

Table 2 Number and rate of CryoTBB-associated complications with at least possible causal relation

	Total complication rate	Sedation hangover	Pneumothorax	Bleeding moderate	Bleeding severe	Myocardial infarction	Fibrosis exacerbation with death
Premodification (n=19)[5]							
	16 (84%) [62–94%]	3 (16%) [6–38%]	5 (26%) [12–49%]	7 (37%) [19–59%]	8 (42%) [23–64%]	2 (11%) [3–31%]	1 (5%) [1–25%] 29d* (UIP/IPF)
Postmodification (n=42)							
	6 (14%) [7–28%]	0 (0%) [0–8%]	5 (12%) [5–25%]	0 (0%) [0–8%]	0 (0%) [0–8%]	0 (0%) [0–8%]	1 (2%) [0–12%] 21d* (UIP/IPF)
P value	<0.001	<0.010	0.160	<0.001	<0.001	0.033	0.559

95% CI given in square brackets.

CryoTBB, transbronchial cryobiopsy; d*, days after intervention; IPF, idiopathic pulmonary fibrosis; UIP, usual interstitial pneumonia; UIP/IPF, histopathology results: UIP; clinical diagnosis: IPF.

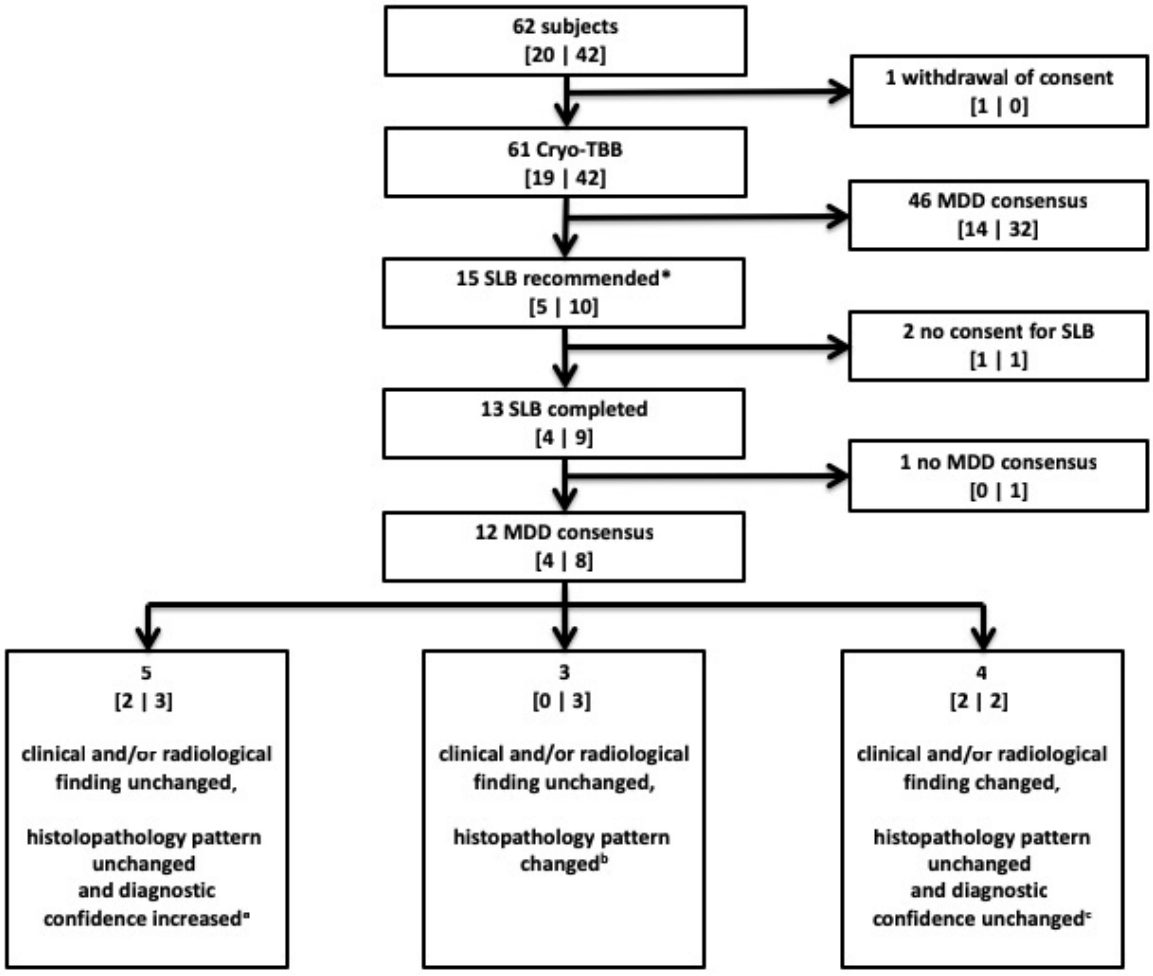

Figure 1 Enrolment and outcomes. Numbers from the premodification (left) and postmodification group (right) are separated by a vertical bar and given in square brackets. *Due to insufficient diagnostic confidence or dissent in multidisciplinary discussion. (a) Pathological evaluation of tissue samples from SLB described the same histology pattern as of CryoTBB. The diagnostic confidence of histology findings (prespecified classification as definite, probable, possible) after SLB was increased as compared to CryoTBB. (b) Pathological evaluation of tissue samples from SLB described a different histology pattern as of CryoTBB. (c) Pathological evaluation of tissue samples from SLB described the same histology pattern as of CryoTBB. The diagnostic confidence of histology findings (prespecified classification as definite, probable, possible) after SLB remained unchanged as compared to CryoTBB. CryoTBB, transbronchial cryobiopsy; MDD, multidisciplinary discussion; SLB, surgical lung biopsy.

postoperative respiratory and cardiovasculatory instability. No further relevant complications were observed after SLB.

In the 42 postmodification subjects, 106 CryoTBB samples were obtained in total (right upper lobe: 10, left upper lobe: 10, middle lobe: 13, right lower lobe: 57, left lower lobe: 16) and the range of the samples' diameter was 3–11 mm. The Fleiss' Kappa value for assessment of inter-rater reliability of cryobiopsy samples was 0.73 (95% CI 0.64 - 0.81). Cohen's Kappa for intra-rater reliability was 0.85 (0.71 - 0.99).

The results from CryoTBB led to a confident clinical diagnosis in 46 subjects (75%) (figure 1). The histopathological pattern was categorised as definite or probable in 41 subjects (67%) and as possible or ambiguous in 20 subjects (33%) (table 3).

The clinical diagnosis remained unclear in 15 subjects. Thirteen subjects gave their consent for the recommended SLB, in 12/13 subjects a conclusive clinical diagnosis could be achieved after SLB. SLB results led to a change of the recorded histopathological pattern in three subjects and to an improved confidence in five subjects. In four subjects, no change of pattern and no improved confidence were recorded (figure 1).

DISCUSSION

The modification to the CryoTBB procedure led to a relevant reduction in the overall complication rate, but did not reduce the likelihood of a confident clinical diagnosis (76% vs 74%). Reducing the number of biopsies and the freezing time resulted in a lower rate of pneumothoraces (12% vs 26%). The blocker balloon led to a reduction of endobronchial blood volume, sedation hangover and endobronchial application of vasoconstringents. In the premodification group, myocardial infarction occurred in two cases where the systemic effect of epinephrine may have resulted in relevant coronary ischaemia.

An expert statement on the safety and utility of CryoTBB-transbronchial cryobiopsy has been published recently.[7] The safety data from our study provide additional insight and demonstrate the need for further evidence-based standardisation of the procedure.

This is the first prospective study to systematically analyse the 30-day mortality following CryoTBB. In a meta-analysis, the 30-day mortality after SLB in fibrosing ILD has been

Table 3 Histopathological findings of transbronchial cryobiopsy

	Definite	Probable	Possible	Σ
Usual interstitial pneumonia	3	9	6	18
Non-specific interstitial pneumonia	10	4	0	14
Respiratory bronchiolitis interstitial lung disease	3	1	0	4
Organising pneumonia	4	2	0	6
Hypersensitivity pneumonitis	2	1	3	6
Sarcoidosis	1	0	0	1
Lymphoma	1	0	0	1
Σ	24	17	9	50
Ambiguous				11*
Σ				61

*In all 11 cases, representative lung tissue samples with interstitial alterations could be obtained. However, the interstitial pattern could not be categorised by the pathologist leading to the classification 'ambiguous'.

determined to be about 3%.[5] In our study, 30-day mortality after modification of the CryoTBB procedure was 2%. Twelve cases of CryoTBB associated deaths have been reported in the literature.[5 8–11] These data demonstrate the importance of a strict and rational risk-benefit decision for or against lung tissue sampling regarding both procedures, CryoTBB and SLB. Tissue sampling should be limited to patients where a confident diagnosis enables life prolonging therapy.

The feasibility of an algorithm, where CryoTBB is performed as the initial step with SLB as an optional step up procedure, could be demonstrated in this study.

A confident diagnosis could be reached in 75% of the analysed CryoTBB cases. In these cases, no further invasive diagnostic procedure was necessary.

Inter-rater and intra-rater reliability for the determination of the predominant histopathological patterns of the cryobiopsy samples was good to excellent.

To the best of our knowledge, this is the first prospective study analysing results of CryoTBB and SLB in subjects who underwent both procedures. There is a clear diagnostic impact of CryoTBB. SLB still remains an important step-up procedure, especially to allow the initiation of antifibrotic treatment in suspected idiopathic pulmonary fibrosis,[2] but the number of SLBs may be substantially reduced in the future.

The study is limited by the low number and the non-randomised controlled design. As morbidity/mortality of SLB is equal to higher compared with CryoTBB and as SLB induces pneumothorax by the approach itself, a randomised controlled design (SLB/CryoTBB or previous-CryoTBB/new-CryoTBB) would result in a higher risk than in clinical routine. Due to the low number of enrolled subjects, conclusions from this study should be drawn with caution.

CONCLUSION

The complication rate of CryoTBB can be reduced by modification of the procedure. There is a relevant risk of CryoTBB associated acute exacerbation of ILD. 30-day mortality may be lower or equal than after SLB.

CryoTBB leads to a confident clinical diagnosis in 75% of cases taking away the need for further invasive diagnostic procedures.

Contributors LH: substantial contributions to conception and design, analysis and interpretation of data, drafting the article and finalising the version to be published taking responsibility for the integrity of the work as a whole, from inception to published article. DT, JW, TH: acquisition of data, analysis and interpretation of data, revising the article critically for important intellectual content, final approval of the version to be published. MT, SDH: acquisition of data, analysis and interpretation of data, drafting statistics section and revising the article, final approval of the version to be published. KH, MH: acquisition of data, analysis and interpretation of data, revising the article, final approval of the version to be published. WJR: substantial contributions to conception and design, analysis and interpretation of data, drafting the article and finalising the version to be published.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Raghu G, Collard HR, Egan JJ, *et al*. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011;183:788–824.
2 Raghu G, Remy-Jardin M, Myers JL, *et al*. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018;198:e44–68.
3 Han Q, Luo Q, Xie J-X, *et al*. Diagnostic yield and postoperative mortality associated with surgical lung biopsy for evaluation of interstitial lung diseases: a systematic review and meta-analysis. *J Thorac Cardiovasc Surg* 2015;149:1394–401.
4 Iftikhar IH, Alghothani L, Sardi A, *et al*. Transbronchial lung Cryobiopsy and video-assisted thoracoscopic lung biopsy in the diagnosis of diffuse parenchymal lung disease. A meta-analysis of diagnostic test accuracy. *Ann Am Thorac Soc* 2017;14:1197–211.
5 Hagmeyer L, Theegarten D, Treml M, *et al*. Validation of transbronchial cryobiopsy in interstitial lung disease - interim analysis of a prospective trial and critical review of the literature. *Sarcoidosis Vasc Diffuse Lung Dis* 2016;33:2–9.
6 Du Rand IA, Blaikley J, Booton R, *et al*. British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE. *Thorax* 2013;68(Suppl 1):i1–44.
7 Hetzel J, Maldonado F, Ravaglia C, *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.
8 Casoni GL, Tomassetti S, Cavazza A, *et al*. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. *PLoS One* 2014;9:e86716.
9 Sriprasart T, Aragaki A, Baughman R, *et al*. A single us center experience of transbronchial lung Cryobiopsy for diagnosing interstitial lung disease with a 2-Scope technique. *J Bronchology Interv Pulmonol* 2017;24:131–5.
10 Dhooria S, Mehta RM, Srinivasan A, *et al*. The safety and efficacy of different methods for obtaining transbronchial lung cryobiopsy in diffuse lung diseases. *Clin Respir J* 2018;12:1711–20.
11 Cooley J, Balestra R, Aragaki-Nakahodo AA, *et al*. Safety of performing transbronchial lung cryobiopsy on hospitalized patients with interstitial lung disease. *Respir Med* 2018;140:71–6.