Safety of Bronchoscopy in Patients with Echocardiographic Evidence of Pulmonary Hypertension

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Key Words

Transbronchial biopsy · Endobronchial biopsy · Endobronchial ultrasound-guided transbronchial needle aspiration · Echocardiogram · Systolic pulmonary artery pressure

Abstract

Background: Bronchoscopy with transbronchial and endobronchial biopsy and transbronchial needle aspiration is an important diagnostic tool in the pulmonologist's armamentarium. Safety in patients with pulmonary hypertension is controversial and many bronchoscopists consider this as a contraindication for the procedure. **Objectives:** To evaluate safety of bronchoscopy in patients with echocardiographic pulmonary hypertension and to compare with patients without it. **Methods:** Retrospective analysis of patients who underwent bronchoscopic transbronchial biopsy, endobronchial biopsy and/or endobronchial ultrasound-guided transbronchial needle aspiration. Patients were divided into two groups based on echocardiographic results: control group with systolic pulmonary artery pressure <36 and a group with elevated systolic pulmonary artery pressure (eSPAP) ≥36. **Results:** One-hundred and ninety patients met the study criteria. Patients in the control group were younger

with a lower incidence of chronic kidney disease. There was no difference in prevalence of congestive heart failure, obstructive airway disease, malignancy, liver disease, coagulopathy, use of antiplatelet agent or anticoagulant drugs. Incidence of minor bleeding due to bronchoscopic biopsies was 4.8% in both groups ($p = 1.00$). Incidence of major bleeding was similar in the groups (one patient in each group). In the control group, one patient had pneumothorax and another required prolonged mechanical ventilation (>4 h). In the eSPAP group, two patients required prolonged mechanical ventilation. There was no procedure-related mortality or sedation complications in the cohort. **Conclusion:** Our study provides additional support that in patients with echocardiographic evidence of pulmonary hypertension, transbronchial and endobronchial biopsies and endobronchial ultrasound-guided transbronchial needle aspiration are safe procedures.

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Introduction

Fiberoptic flexible bronchoscopy (FFB) is an indispensable tool in the evaluation, diagnosis and management of malignant as well as benign pulmonary condi-

tions. Despite its widespread use, FFB-related complications exist. Minor complications include mild laryngospasm or bronchospasm, hypoxia, epistaxis and injury due to the trauma of nasal passage, minor bleeding, and methemoglobinemia. Serious complications include major bleeding, pneumothorax, cardiac arrhythmias, acute respiratory failure and death. Rate of complications varies from 0.5 to 7%. In patients undergoing transbronchial biopsy (TBBx), major complications have been reported in up to 6.8–10% [1]. In some studies, TBBxs were avoided in 'high-risk' patients including those with pulmonary hypertension (PH), uremia and thrombocytopenia [1, 2]. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is used in conjunction with TBBx to further enhance the diagnostic yield of the procedure [3]. EBUS-TBNA carries a lower risk for serious complications when compared to TBBx, with up to 1.2% of patients having serious complications [4]. Endobronchial biopsy (EBBx) is often performed for central airway lesions, and biopsy-related hemorrhage can be seen in around of 1% of the cases [5].

PH is often considered by pulmonologists as an absolute or relative contraindication for FFB due to the higher risk for bleeding, despite contradictory data in the literature [1]. In addition, there is an increased morbidity and mortality with anesthesia in patients with PH. One study, with a large proportion of patients undergoing minor surgical procedures and regional anesthesia, showed perioperative complications in 29% of patients with non-severe PH [6]. A retrospective study of 90 patients suggested that FFB can be safely performed in patients with mild to moderate PH. However, only 24 patients with PH underwent TBBx and 7 patients had TBNA in the study, potentially affecting the study power. Associated comorbid conditions that could contribute to procedure-related morbidity were also not considered [7].

Echocardiogram is a reasonable noninvasive method for screening patients for PH. There is conflicting data regarding the reliability of echocardiographic assessment of systolic pulmonary artery pressure (sPAP) to accurately predict severity of PH [8]; Greiner et al. [9] showed that Doppler echocardiography had good diagnostic sensitivity (87%), specificity (79%) and accuracy (85%) for a sPAP cutoff value of 36 mm Hg. Another study showed an association of sPAP with prognosis in patients with PH [10].

Delays in FFB may delay diagnosis and treatment of the disease and could affect severity and final prognosis of patients [11]. If patients are deemed high risk for a FFB, there will be reluctance to perform more invasive proce-

dures and patients may also refuse a procedure due to anticipated risks.

The aim of our study was to evaluate bronchoscopy-related complications in patients with echocardiographic evidence of PH. We specifically evaluated patients who underwent bronchoscopic TBBx, EBBx or EBUS-TBNA.

Material and Methods

Study Design and Setting

This was a retrospective review of all adult patients who underwent FFB with TBBx, EBBx and EBUS-TBNA between January 2012 and July 2015 at our institution. All procedures were performed by pulmonologists and pulmonary fellows in the endoscopy suite or in the operating room. Sedation and anesthesia were provided by the anesthesiologist in all cases. The study was approved by the hospital institutional review board, and the need for informed consent was waived.

Methods

We included all adult patients who underwent FFB with TBBx, EBBx and/or EBUS-TBNA who had echocardiogram available. Exclusion criteria: (a) patients who underwent FFB without TBBx, EBBx or EBUS-TBNA, (b) patients with no available echocardiogram or unable to estimate sPAP.

Baseline characteristics and presence of comorbid conditions like congestive heart failure, chronic kidney disease, obstructive airway disease, coagulopathy, malignancy or liver disease were obtained. Information regarding use of antiplatelet or anticoagulant medications and laboratory parameters were collected. Procedural data included use of general anesthetics or conscious sedation, type of procedure and type of complications. Prolonged mechanical ventilation was defined as need for mechanical ventilation for more than 4 h following the procedure. At our institution, all EBUS-TBNA are performed by one pulmonologist, in the operating room and under general anesthesia.

Definition of Bleeding

There is no consensus regarding exact definition of minor and major bleeding associated with bronchoscopic biopsy and it is often difficult to precisely calculate blood losses during the procedure. For our study, minor bleeding was defined as bleeding which stopped spontaneously or was controlled with instillation of local epinephrine without further intervention or blood transfusion. Major bleeding was defined when additional interventions were required like balloon tamponade, embolization of blood vessel, surgical intervention or blood transfusion.

Definition of Echocardiographic PH

Consensus regarding echocardiographic cutoff value of sPAP to accurately predict PH is not available. A recent report showed a good diagnostic sensitivity (87%), specificity (79%) and accuracy (85%) of Doppler echocardiography for a sPAP cutoff value of 36 mm Hg [9]. We classified our patients into two groups: those with sPAP of <36 (control group) and patients with sPAP ≥36 (elevated sPAP group or eSPAP group).

Table 1. Characteristic of patients and pertinent laboratory findings

	Control group (n = 83)	eSPAP group (n = 107)			p
	sPAP 18–35	sPAP 37–40 (n = 31)	sPAP 41–55 (n = 40)	sPAP >55 (n = 36)	
Age, years	54.0±13.4	57.2±14.6	59±11	57.8±15	0.03
Gender, male	35 (42%)	15	17	20	0.88
Body mass index	26.9±6.2	24.8±4.9	27.1±8.5	24.3±6	0.14
Comorbid conditions					
Congestive heart failure	8 (10%)	1	6	8	1.00
Chronic kidney disease	6 (7%)	6	10	8	0.02
Obstructive airway disease	33 (40%)	12	22	24	0.77
Coagulopathy	3 (3%)	2	4	0	0.73
Malignancy	22 (27%)	5	13	12	0.87
Chronic liver disease	15 (18%)	8	10	7	1.00
Medications					
Aspirin	12 (14%)	10	12	3	0.28
Clopidogrel	2 (2%)	2	0	0	1.00
Anticoagulation use	1 (1%)	0	0	0	1.00
Pertinent laboratory findings					
Hemoglobin, mg/dl	11.2±2.2	10.4±1.8	10.5±2.5	10.93±2.6	0.07
International normalized ratio	1.1±0.3	1.14±0.19	1.11±0.16	1.14±0.26	1.00
Partial thromboplastin time	31.8±11.0	31.7±5.7	29.6±6	33.6±6.4	0.87
Thrombocytopenia (<150 × 10 ⁹ /l)	9 (11%)	7	10	8	0.052

Subgroup Analysis

Due to the retrospective analysis, we were not able to assess the adequacy of FFB biopsies. To minimize this bias, we evaluated the total number of biopsies performed in each patient and compared the two groups. In addition, TBBx required presence of alveolus/lung tissue in pathology specimens.

Statistical Analysis

Results are expressed as counts (percentage) for discrete variables and as mean ± SD for continuous variables. For demographic data and clinical characteristics of patients, nominal variables are expressed using χ^2 test or Fisher's exact test for categorical variables and Student's *t* test or Mann-Whitney *U* test for continuous variables. Statistical significance was defined as *p* < 0.05. Data analysis was conducted using SPSS v15.0.

Results

One-hundred and ninety patients met the inclusion criteria, 83 in the control and 107 in the eSPAP group. Patients in the control group were younger (54.0 ± 13.4 vs. 58.3 ± 13.5 years; *p* = 0.03). Patients with eSPAP had higher incidence of chronic kidney disease (23 vs. 7%; *p* = 0.02) compared with control group. We found no difference in gender, body mass index, incidence of comorbid conditions, use of antiplatelet or anticoagulant medications or baseline coagulation profile. Median time be-

tween echocardiogram and FFB was similar (10 days in control group vs. 9 days in eSPAP group; *p* = 0.77). Evaluation of patient characteristics at different cutoffs of sPAP revealed no differences in the groups (table 1).

Review of possible etiologies for PH in our patients revealed the following conditions: chronic obstructive airway disease (COPD) in 55%, interstitial lung diseases (ILD) in 34%, human immunodeficiency syndrome in 27%, portal hypertension due to liver cirrhosis in 18%, chronic left heart failure in 14%, collagen vascular disease in 11% and obstructive sleep apnea, sarcoidosis, end-stage renal disease in less than 10%. Many patients had more than two conditions associated with PH.

Outcome Analysis

Sixty-nine of 83 (83%) patients in the control group and 91 of 107 (85%) in eSPAP group underwent TBBx (84.2% of the cohort). EBBx was performed in 49 patients (25.7% of the cohort) and EBUS-TBNA in 35 patients (18.4% of the cohort). Four patients in the control group had minor bleeding compared to 5 patients in the eSPAP group (*p* = 1.00). There was no difference in incidence of major bleeding (1 patient in each group; *p* = 1.00). One patient in the study had pneumothorax. We found similar incidence of prolonged mechanical ventilation (1 patient in control group vs. 2 in the eSPAP group; *p* = 1.00). None

Table 2. Comparison of type of sedation and complications during bronchoscopy

Variable	Control group (n = 83)	eSPAP group (n = 107)	p
<i>Type of anesthesia</i>			
General	41 (49%)	46 (43%)	0.46
Conscious sedation	42 (51%)	61 (57%)	
<i>Complications</i>			
Minor bleeding requiring intervention	4	5	1.00
Major bleeding	1	1	1.00
Pneumothorax	1	0	0.44
Prolonged mechanical ventilation (>4 h)	1	2	1.00

of patients in the study required mechanical ventilation beyond 24 h. There were no arrhythmic events or procedure-related mortality in our cohort (table 2).

Subgroup Analysis

Subgroup analysis evaluating number of biopsies per patient per procedure found no difference in the median number of TBBx [6 biopsies per procedure in the control (range 2–11) vs. 6 biopsies per procedure in the eSPAP group (range 2–9); $p = 0.53$], EBBx [4 biopsies per procedure in the control (range 2–8) vs. 4 biopsies per procedure in the eSPAP group (range 2–14); $p = 0.21$] and EBUS-TBNA [3 passes per procedure in the control (range 3–7) vs. 6 passes per procedure in the eSPAP group (range 3–10); $p = 0.12$] (table 3). Summary of the procedures performed did not reveal any significant difference between the 2 groups (table 4).

The main indication for EBUS-TBNA was evaluation for possible malignancy or sarcoidosis in both groups. Despite the nonsignificant difference in lymph node biopsies in EBUS-TBNA, the diagnostic yield was similar, 30% in the control group and 24% in the eSPAP group.

Discussion

We demonstrate that FFB is safe in patients with echocardiographic evidence of PH. Furthermore, we found no increased risk for prolonged mechanical ventilation, cardiac arrhythmias or mortality. Major complications due to FFB are rare and reported mainly with TBBx [4]. Safety of FFB has also been evaluated in patients with other conditions such as COPD, acute myocardial infarction,

renal insufficiency, coagulopathy and malignant space-occupying brain lesions. In general, those studies suggested that FFB can be safely performed with a low incidence of procedure-related complications [12–14].

The potential increase risk for complications in patients with PH undergoing FFB are due to cardiovascular compromise due to right ventricular dysfunction leading to cardiac arrhythmia, ischemia and hemodynamic compromise. In addition, due to chronic venous PH, dilation of submucosal bronchial veins and their plexuses exist making bleeding potentially more common [7, 12]. There are few studies looking specifically at complications of FFB in this selective group of patients, and most guidelines in FFB have no specific recommendations for PH. Furthermore, there is no consensus regarding which levels of pulmonary artery pressure are considered safe for TBBx or TBNA.

In a prospective study by Neuman and colleagues [15], they reported an increased incidence of hypoxemia during TBBx in 40 patients with COPD and PH. No increase in bleeding was found and overall the procedure was safe.

Another prospective study in 50 patients with ILD and no clinical or radiographic evidence of PH who underwent TBBx revealed PH (defined as sPAP >30 mm Hg or evidence of right-sided chamber enlargement) in 44% of the patients. They found no significant difference in bleeding between the PH and the control group [16].

Diaz-Guzman et al. [7] reported the safety of FFB in 90 patients with mild and moderate PH, but this study was limited by the retrospective nature and few patients undergoing TBBx. In our patients, COPD and ILD were common, and our data support these studies regarding the safety of FFB.

Hemodynamic complications after bronchoscopy are uncommon with an incidence of cardiac arrhythmia of 1% [17]. In a large review of 107,969 bronchoscopies, the incidence of complication due to local anesthesia was 0.3–0.5%, pneumothorax and pneumomediastinum 1–6%, and mortality rate 0.1–0.2% [18].

Pulmonary arterial hypertension is characterized by a progressive increase in pulmonary arterial pressure (PH defined as mean pulmonary arterial pressure ≥ 25 mm Hg at rest or 30 mm Hg during exercise) in association with variable degrees of pulmonary vascular remodeling, vasoconstriction, and in situ thrombosis. Chronic PH leads to progressive right ventricle systolic pressure overload resulting in gradual right ventricular dysfunction. The increase in pulmonary vascular resistance gradually worsens right ventricular failure. Decreased venous return compromises right ventricular preload and pulmonary blood flow. Patients with PH undergoing sedation and

Table 3. Comparison of number of bronchoscopic biopsies or passes

Procedure	Control group	eSPAP group	p
TBBxs per patient, median (range)	6 (2–11)	6 (2–9)	0.53
Number of patients who underwent TBBx	69	91	z score –0.623
EBBx per patient, median (range)	4 (2–8)	4 (2–14)	0.21
Number of patients who underwent EBBx	25	24	z score –1.25
EBUS-TBNA passes per patient, median (range)	3 (3–7)	6 (3–10)	0.12
Number of patients who underwent EBUS-TBNA	10	25	z score –1.563535

anesthesia represent a unique perioperative challenge due to changes in preload and afterload induced by fluid shifts, changes in autonomic nervous system and medications administered during the procedure [19, 20]. Hypercarbia, hypoxia, acidosis and noxious stimuli from pain and airway stimulation can also increase pulmonary arterial pressure [19, 21]. Increased perioperative morbidity and mortality of adult patients with PH has been well described in patients undergoing cardiac and noncardiac surgery [22]. In our study, close to 50% of patients with PH underwent FFB under general anesthesia and positive pressure ventilation without complications.

Due to unique challenges attributed to PH patients undergoing bronchoscopic biopsy, this has been an area of concern [23, 24]. Schulman et al. [25] reported an incidence of 15% for moderate hemorrhage in patients with mean pulmonary arterial pressure higher than 16 mm Hg.

We additionally accounted for other predictors of procedure-related morbidity and mortality such as prevalence of underlying congestive heart failure, liver disease, renal failure, or use of antiplatelet/anticoagulant agents. We also compared for differences in the number of biopsies performed in each patient.

There are several limitations in our study. First, there might be a selection bias because this is a retrospective study in a single center. Second, we were not able to correlate echocardiographic findings of PH with right-side cardiac catheterization. Third, echocardiograms were not performed on the same day of FFB; however, 54% patients in the control and 60% in the eSPAP group had echocardiogram done within 2 weeks of bronchoscopy. Furthermore, the total number of major complications was very low; using a stricter cutoff for the interval between echocardiogram and FFB would not have changed the outcomes. Fourth, in view of the retrospective nature of the study, we are not able to comment on the technique and adequacy of sampling of each pulmonary biopsy. We compensated by reviewing number of biopsies for each

Table 4. Comparison of bronchoscopic procedures

Procedures	Control group SPAP <36 (n = 83)	eSPAP group SPAP ≥36 (n = 107)	p
EBUS-TBNA only	3	4	1.00
EBBx only	11	8	0.22
TBBx only	50	66	0.88
EBUS-TBNA + TBBx + EBBx	2	6	0.46
EBUS-TBNA + TBBx	5	12	0.30
TBBx + EBBx	12	7	0.08
EBUS-TBNA + EBBx	0	3	0.25

patient and review of pathology report. Fifth, patients in our control group were younger than patients with PH.

Our study is the largest case control study evaluating the outcomes of bronchoscopic biopsies in patients with PH while accounting for important comorbid conditions and medications that could potentially contribute to procedure-related morbidity and mortality.

Conclusions

Our study demonstrates that bronchoscopic TBBx, EBBx and EBUS-TBNA with either conscious sedation or general anesthesia can be safely performed in patients with echocardiographic diagnosis of PH. Careful perioperative planning of the procedure and sedation can minimize any potential complication.

Financial Disclosure and Conflicts of Interest

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the manuscript. No financial support was used for the study. The authors declare that they have no competing interests.

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