Endobronchial ultrasound-guided transbronchial needle aspiration is feasible, safe, and reaches a 90 % diagnostic yield in patients with hypoxemic acute respiratory failure

Maxens Decavèle, Valérie Gounant, Jocelyne Fleury Feith, Michel Febvre, Jean-Marc Naccache, Antoine Parrot, Muriel Fartoukh

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Online Supplement (with 1 Table and 2 figures)

Patients and methods

Selection of the patients

Patients were selected from a prospective cohort [1] that comprehensively describes all EBUS-TBNA procedures performed in Tenon hospital, a tertiary university teaching hospital in Paris, France. Over the study period (May 2011-May 2015), the database comprised 842 records almost exclusively performed in the respiratory department, a referral center for lung cancer. Of those latter, 9 were performed in the ICU.

Methods and Sampling Procedures

EBUS-TBNA equipment was a 6.7 mm outer diameter, real-time, bronchoscope (BF-UC-160F; Olympus Ltd., Tokyo, Japan) with a 7.5-MHz linear ultrasound transducer set on a 50 mm maximal penetration. Specimens were obtained using a 22-gauge dedicated needle (Figure 1) equipped with a stylet (ViziShot NA-201SX; Olympus Ltd). EBUS-TBNA was performed by three interventional pulmonologists (V.G., M.F., JM.N.), whereas ROSE was performed by a single experienced lung cytologist (J.F.). The diagnosis obtained with EBUS-TBNA was based on cytological material examination; all specimens were reviewed by J.F. The representative nature of the aspirations was established by the presence of characteristic lymph node cells [2]. Only when representative, cytological samples were either positive if they carried a diagnosis, or negative if only lymphocytes were observed. The final diagnosis was based on EBUS-TBNA samples and all other diagnostic procedures.

Because of its large diameter, the bronchoscope was inserted either orally or through the endotracheal tube, whether the patients were breathing spontaneously or mechanically

ventilated. EBUS was performed under conscious sedation (mild sedation) or general anesthesia [3]. As recommended, local anesthesia (2% lidocaine) was systematically administered to further minimize cough [4]. Mild sedation included hydroxyzine, bolus of midazolam or propofol with domperidone and atropine.

Statistical analysis and ethical considerations

Demographics, clinical variables, and laboratory findings are reported as median (interquartile range) and the absolute and relative frequencies are used for categorical variables, unless stated otherwise. Statistical analysis was performed with Stata 10.1 software (StataCorp, College Station, Texas).

The samples were collected according to French legislation and the ethical rules of our institution at the time the experiments were carried out. All patients or relatives were informed and gave consent

Results

Patient's characteristics

During the study period, 9 patients (8 males; age 62 years [18-42]; IGS2 22 [18-42]) underwent an EBUS-TBNA procedure, 5 [2-8] days after ICU admission. Table 2 displays the patients' characteristics during the procedure. The reasons for ICU admission were acute respiratory failure (ARF, n=5), asphyxiating hemoptysis (n=1) and abundant hemoptysis (n=3, including 2 hemoptysis after bronchial biopsy). The median SOFA score was 2 [2-4] and vasopressors were ongoing for 2 patients (22%) on the day of EBUS-TBNA.

Radiological findings

All patients had undergone a median of 2 [1-3] CT-scan before EBUS was performed. The CT scan patterns were reviewed by V.G. Lung or pleura were involved in all patients.

Mediastinal and hilar lymphadenopathy were observed in 8 patients, whereas an isolated mediastinal lymphadenopathy was observed in the remaining (patient 4). The size of lymph nodes punctured ranged between 5 and 35 mm. Noteworthy, a fluorine-18fludeoxyglucose (18F-FDG) positron emission tomography (PET)/CT had been performed in 4 patients within the preceding 30 days, demonstrating at least one hypermetabolic lymph node with a maximal standardized uptake value (SUVmax) ranging from 3.7 to 8.5.

Prior diagnosis procedures and rationale for EBUS-TBNA recourse

Bronchoscopic lower respiratory tract samplings (tracheal aspirate TA, or bronchoalveolar lavage BAL) were obtained in all patients for usual pathogens and mycobacteria. Three patients had a positive bacterial culture (*Enterococcus faecalis*, n=1; *Proteus mirabilis*, n=1; *Serratia marcescens*, n=1), and all were negative for mycobacteria. In addition to conventional lung sampling procedures, other tissue samples were obtained before EBUS-TBNA was performed, including gastroduodenal (n=3), skin (n=3), or accessory salivary gland (n=1) biopsies, and thyroid fine needle aspiration (n=1). In addition to life-threatening hemoptysis complicating lung biopsies (patients 2, 4, 6, 7), the severity of the underlying pulmonary disease (patients 1, 5 and 8) and the accessibility to the paratracheal region (patient 9) also participated to the intensivists' decision for performing EBUS.

Diagnosis accuracy and safety of EBUS-TBNA

Excluding the patient 6 for whom all aspirations were non-representative of the node structure, EBUS-TBNA was representative of lymph node structure in 69% of the cases (41 of 59 aspirations). When necessary, molecular testing was performed on EBUS-TBNA samples (patients 4 and 9). Strikingly, central pulmonary embolism was distinctly observed by EBUS in one patient (patient 4).

There were no complications, except minor bleedings at the puncture site (patients 7 and 9) that were merely controlled by local instillation of cold serum or adrenaline.

Discussion

If the role of EBUS-TBNA or esophageal ultrasound-guided fine needle aspiration (EUS-FNA) has been traditionally limited to non emergent settings, its expanding applications and performances may concern intensivists, regarding the recent reports of esophageal EUS-FNA in critically ill patients [5-7].

Safety

The safety of EBUS/EUS-FNA has been widely assessed in large series [8, 9], complications being very rarely reported [10-13]. In a recent prospective quality improvement registry [9] enrolling more than 1300 non-critically ill patients undergoing EBUS-TBNA, the rate of complications was 1.4%, including pneumothorax (n=7; 0.5%), sustained hypoxemia (n=4; 0.3%), bleeding (n=3; 0.2%) and respiratory failure (n=3; 0.2%). In multivariate analysis, TBLB performed during the procedure was the only factor associated with the occurrence of pneumothorax. However, complications (especially pneumothorax) of TBLB may average 15% in critically ill cancer or mechanically ventilated patients [14, 15] when performed during fiberoptic bronchoscopy. Similarly, the complications related to CT-guided biopsy are frequent and may be fatal [16, 17]. Finally, open lung biopsy (OLB) exhibits very high complications rates ranging from 20 to 56%, when performed in mechanically ventilated patients with undiagnosed diffuse pulmonary infiltrates [18, 19]. Altogether, the side effects of TBLB, CT-guided or OLB should be confronted to the vulnerability of critically ill patients, particularly hematological patients [20].

In our series, EBUS-TBNA was a diagnostic technique of particular value in selected patients (patients 2, 4, 6 and 7) who were estimated to be at high risk of bleeding during conventional lung sampling procedures. In particular, for the patients 3 and 7, the real time visualization of a vessel through the lymph node (station 4 and 7, respectively) prompted the operator to avoid

the vessel during the puncture or to puncture another lymph node. In the same way, EBUS-TBNA was also a precious alternative diagnostic procedure in patients suffering of severe respiratory insufficiency (patients 1, 3 and 5) in whom the occurrence of a pneumothorax was feared.

Diagnostic yield

In our series, the diagnostic yield of EBUS-TBNA was higher than that reported with conventional lung samples procedures in critically ill patients, especially TBLB either isolated or combined with BAL [14, 21, 22], or CT-guided mediastinal biopsy [23]. Finally, EBUS-TBNA yield approached that of open lung biopsy in mechanically ventilated patients [18].

Even if such information may be interpreted with caution [24], ROSE may certainly have participated to the high diagnostic rate, by improving the quality of the samples [1, 24, 25]. Moreover, EBUS demonstrated exceptional accuracy in some cases of diagnostic deadlock (patient 3), by providing the diagnosis of angiosarcoma, without any worsening of the critical respiratory state.

Feasibility

Endotracheal tube placement or laryngeal mask may be useful to perform EBUS-TBNA under general anesthesia (GA). Passing the EBUS scope is roughly equivalent to passing a standard fiberoptic bronchoscope except that, depending on the diameter, it may significantly impact on pressures and volumes. If passed through a ♯8.5 endotracheal tube, EBUS occludes 66% of the cross-section. The occlusion reaches 74% and 80% for ♯8 and ♯7.5 tubes, respectively. In patient 6, kink or secretions may have completed the tube obstruction that constrained the operator to remove intermittently the EBUS scope to allow mechanical ventilation. So, we recommend at least a ♯8 tube. No ventilatory complications were reported with the ♯8.5 endotracheal tube or the laryngeal mask.

A second limitation resides in the fact that lymph node stations 5, 6, 8 and 9 are not accessible by EBUS approach for anatomical reasons (Figure 2). In addition, the diameter of the scope prevents the access to the station 14. However the access to the areas 5, 6, 8 and 9 can be recovered by associating an esophageal ultrasound-guided (EUS) phase likewise approved as a safe procedure [26].

Finally, the extent of sedation (minimal, moderate, deep, GA) for the procedure is not specifically defined, and may depend on the duration and the complexity of the procedure as well as the tolerance of the patient [4]. A target-controlled infusion of sedation may bring particular benefits (patient 9) by reducing the hemodynamics side effects of the sedation [27] and should be evaluated.

To summarize, advances in ultrasound technology enhance the area of diagnostic applications in daily clinical practice. In the ICU setting, EBUS-TBNA is a safe procedure, associated with a good and rapid diagnosis yield at bedside, so that it might be preferable to TBLB, when the hilum and/or mediastinum are involved. Finally, EBUS-TBNA appears as an elegant diagnostic solution with minimal risks in vulnerable patients. Further studies are needed to confirm these promising results.

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Table of the Online Supplement

Table 2. Diagnostic steps before EBUS-TBNA and patients' characteristics during procedure

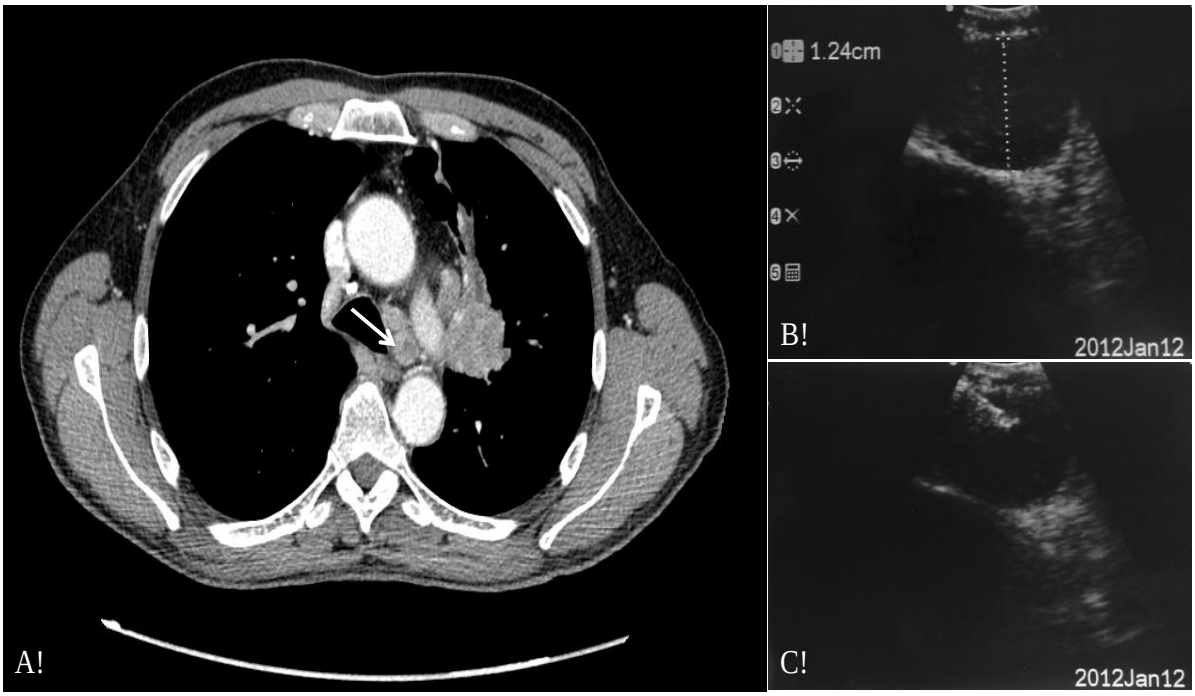
Patient Gender/age	Respiratory Support	Lung samples before EBUS, n						Puncture station	TEP SUVm	Vasopressor	Sedation	PA[a]	Heart Rate /min	Respiratory Rate /min	PaO_2 mmHg	Duration /min
		BA	*BAL*	*PP*	*BB*	*TTB*	*OTLB*									
Patient 1 M/70	**ET-MV/FiO_2:0.6** VT: 450 ml PEEP: 7 cmH_2O	1	1	1	2	1	-	7	3.7	Norepinephrine	**General anesthesia** Midazolam Sufentanil	No	93	30	150 FiO_2:0.6	35
Patient 2 M/65	**Nasal Oxygen** 4 l/min	-	-	-	1	-	-	4L 11L	-	No	**Mild sedation** Hydroxyzine	No	77	16	76 O_2: 4 l/min	25
Patient 3 F/35	**Nasal Oxygen** 6 l/min	1	1	1	-	-	1	12R	6.5	No	**Mild sedation** Midazolam	No	92	32	75 O_2: 6 l/min	30
Patient 4 M/34	**Nasal Oxygen** 9 l/min	-	-	-	1	-	-	4R	8.5	No	**Mild sedation** Midazolam Propofol	No	96	30	94 O_2: 9 l/min	25
Patient 5 M/64	**Nasal Oxygen** 3 l/min	1	1	-	1	-	-	7 11L	-	No	**Mild sedation** Hydroxyzine	No	87	22	76 O_2: 3 l/min	30
Patient 6 M/58	**ET-MV/FiO_2:0.4** VT: 450 ml PEEP: 5 cmH_2O	1	2	-	1	1	-	4R 7	5.1 4.6	Adrenaline	**General anesthesia** Propofol Sufentanil	Yes	155	26	85 FiO_2:0.4	40
Patient 7 M/73	**Nasal Oxygen** 4 l/min	1	1	-	1	-	-	4R 10R	-	No	**Mild sedation** Hydroxyzine	No	74	24	87 O_2: 4 l/min	35
Patient 8 M/68	**ET-MV/FiO_2:0.35** VT: 450 ml PEEP: 5 cmH_2O	1	-	1	1	-	-	4R	-	No	**General anesthesia** Midazolam Sufentanil	No	92	25	81 FiO_2:0.35	40
Patient 9 M/39	**LM-MV** VT: 400 ml PEEP: 5 cmH_2O	-	-	1	-	-	-	4R	-	No	**General anesthesia - TCI** Propofol Remifentanil	No	103	24	-	35

Abbreviations. EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration; PA: platelet antiaggregant; BA: bronchial aspiration; BAL: bronchoalveolar lavage; PP: pleural puncture; BB: bronchial biopsy; TTB: CT-guided transthoracic biopsy; OTLB: open thorax lung biopsy; PET: positron emission tomography; SUVm: maximal standard uptake value; M: male; F: female; R: right; L: left; TCI: target-controlled infusion; Duration: duration of the procedure.

[a] acetylsalicylic acid

Figures of the online supplement

Figure 1. Imaging of EBUS lymph node identification and puncture



Arrow indicates the lymphadenopathy in station 4L (figure A), measuring 12mm with EBUS (figure B). The figure (C) shows the real-time needle penetration into the lymph node.

EBUS: endobronchial ultra sound.

Figure 2. Anatomical depiction of lymph node stations

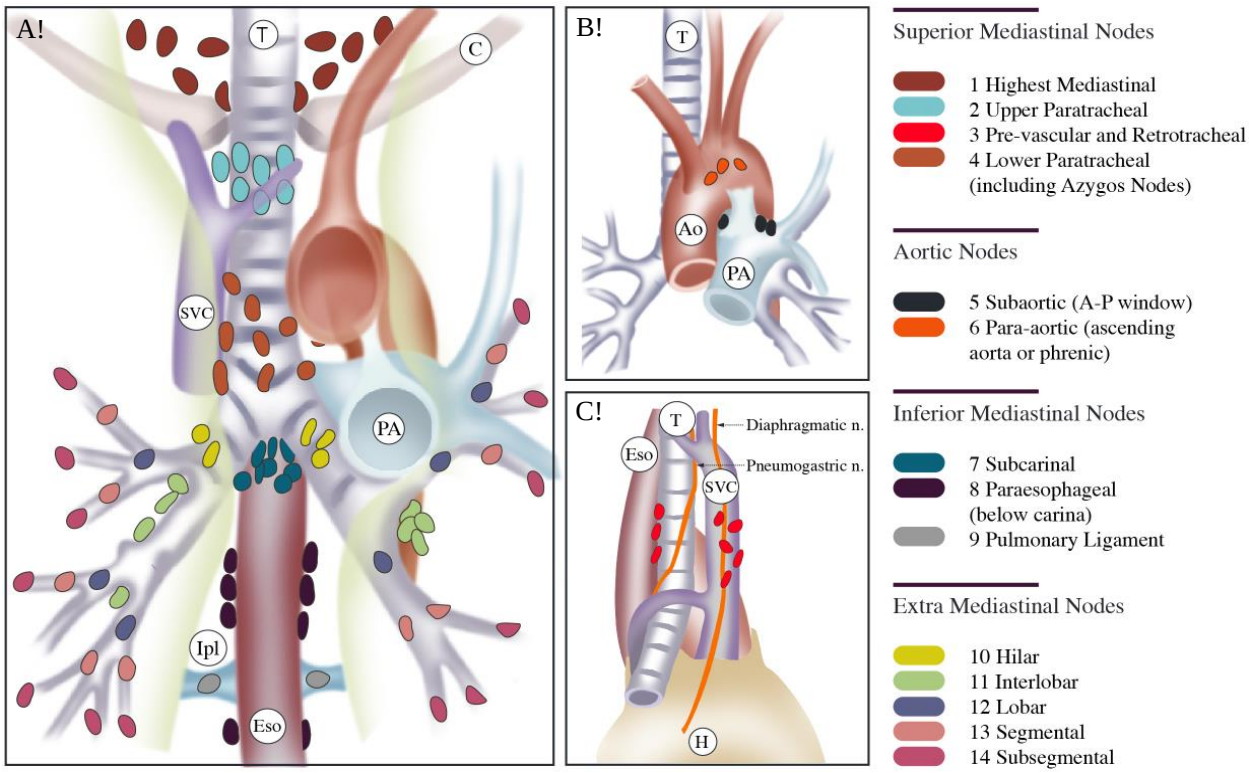


Figure A, B and C represent respectively the anterior, posterior and right lateral view of the mediastinum. Stations 2, 3, 4, 7 10 and 11, 12, 13, are accessible with EBUS, as opposed to stations 5, 6, 8, 9 and 14. Adapted from references [36] and [37].

T: trachea; C: clavicle; SVC: superior vena cava; Ao: aorta; PA: pulmonary artery; Ipl: inferior pulmonary ligament, Eso: esophagus; H: heart; n.: nerve.