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Bronchoscopic cryobiopsy: Bleeding risk factors and hemostasis techniques

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Abstract

Cryobiopsy is an innovative technique used in the diagnosis of various lung diseases, including neoplasms. Unlike conventional bronchoscopic methods, it yields larger and higher-quality tissue samples for histopathological analysis. Compared to surgical lung biopsy, it may offer a safer and more suitable alternative for high-risk patients. The diagnostic yield of the procedure is high, while the incidence of severe or life-threatening complications remains low.

Keywords: Cryobiopsy; Complications; Bleeding Risk Factors; Hemostatic Methods

1. Introduction

The incidence of severe complications associated with fiberoptic bronchoscopy is low [1-5]. In a retrospective study [2] involving 23,862 patients who underwent diagnostic and therapeutic procedures, serious complications and mortality occurred in 0.637% and 0.013% of cases, respectively. In another cohort of 3,473 individuals [5], cardiopulmonary arrest was reported in one patient (0.03%).

Bleeding is one of the major complications associated with interventional bronchoscopic techniques, including cryobiopsy of endobronchial and peripheral lung tumors. It can be life-threatening, making the identification of risk factors related to both the patient and the procedure particularly important [6-14]. A simple and reproducible way to assess its severity is by evaluating the hemostatic methods required to control it [15]:

- *Mild bleeding* — requires only aspiration, without the need for additional interventions.
- *Moderate bleeding* — controllable with endoscopic methods and/or the administration of cold saline or vasoconstrictive medications.
- *Severe bleeding* — requires further interventions such as bronchial artery embolization, blood transfusion, intubation, or admission to an intensive care unit

2. Risk factors for bleeding

The reported incidence of hemorrhagic complications associated with fiberoptic bronchoscopy varies, with the percentage of severe and life-threatening events being low [16-18]. In a multicenter retrospective cohort study [17] involving 520,343 patients, massive bleeding was observed in 194 cases. The risk associated with therapeutic bronchoscopies was significantly higher than that for diagnostic procedures (0.059% vs. 0.031%, $P < 0.001$; mortality: 0.012% vs. 0.003%). Age over 65 years, tracheal bleeding, blood loss exceeding 500 mL, and the presence of shock were identified as independent negative prognostic factors.

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The riskiest diagnostic procedure is transbronchial lung biopsy for peripheral lung neoplasms and diffuse parenchymal lung diseases [19,20]. Techniques such as bronchoalveolar lavage (BAL), brush biopsy, and transbronchial needle aspiration under endobronchial ultrasound guidance (EBUS-TBNA) are considered relatively safe by many authors, with significantly lower rates of bleeding reported**,** even in high-risk patients [6,21]. There are concerns about a potentially higher incidence of hemorrhagic events with bronchoscopic cryobiopsy, a method used for diagnosing interstitial lung diseases as well as central and peripheral lung neoplasms [22,23].

Concomitant malignant disease, liver and kidney failure, and immunosuppression, especially following lung transplantation, are among the identified risk factors for bleeding during fiberoptic bronchoscopy [11-14, 24].

Transbronchial lung biopsy should be performed with caution in patients with pulmonary hypertension**,** according to some authors [25,26]. Hypothetically, increased perfusion pressure in the pulmonary capillary network may elevate the risk of bleeding during this bronchoscopic procedure [27]. In addition, pulmonary hypertension may lead to right ventricular dysfunction and a higher incidence of cardiopulmonary complications [26,28].

A meta-analysis of nine studies comprising 1,699 patients [28] found that transbronchial lung biopsy is not associated with an increased risk of bleeding, arrhythmias, or hypotension, at least among patients with mild to moderate pulmonary hypertension included in the analysis. However, these patients are at higher risk of periprocedural hypoxia and may require prolonged mechanical ventilation**.**

Retrospective and prospective studies [29,30] have shown that routine coagulation testing does not always predict bleeding events. The British Thoracic Society [15] recommends assessing platelet count, hemoglobin level, and coagulation parameters only when clinical risk factors for coagulopathy are present. These include anticoagulant use, liver disease, renal failure, a history of increased bleeding tendency, active bleeding, or the need for preprocedural blood transfusion. Current guidelines [15,31] suggest that the lower platelet count threshold for performing bronchoalveolar lavage (BAL) is $>20 \times 10^9$/L (some experts recommend $>30 \times 10^9$/L), and for lung biopsy, $>50 \times 10^9$/L.

Antiplatelet agents and anticoagulants increase the periprocedural risk of bleeding during biopsy or transbronchial needle aspiration (TBNA). In a prospective study [8] involving 604 patients undergoing fiberoptic bronchoscopy (FBS) with TBNA, the incidence of bleeding was significantly higher among those receiving clopidogrel with aspirin (100%) or clopidogrel alone (89%) compared with the control group (3.4%). Other studies [9,32] have not found an increased risk of bleeding in patients taking aspirin alone. Based on current evidence [15,31], clopidogrel should be discontinued 5–7 days prior to the procedure, while low-dose aspirin may be continued.

Regarding anticoagulants, warfarin should be discontinued 5 days before bronchoscopy, with a target INR <1.5 prior to the procedure [15,31]. For patients taking direct oral anticoagulants (DOACs), this period ranges from 1 to 5 days, depending on the specific agent and the patient's creatinine clearance [33]. The need for periprocedural bridging with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) depends on the patient's thromboembolic risk: it is not required in low-risk patients, may be considered in those with intermediate risk, and is mandatory in high-risk patients [15,31,33].

3. Management of bleeding

Local application of ice-cold saline and vasoconstrictive agents aims to stimulate hemostasis in the presence of bleeding [34]. Doses and dilutions of epinephrine vary among sources. Potential side effects include hypertension, coronary vasospasm, and arrhythmia, with the risk being higher when the drug is administered into the distal airways [15]. Tranexamic acid inhibits the conversion of plasminogen to plasmin by blocking its lysine-binding sites. It is effective in treating hemoptysis caused by various pulmonary diseases such as cystic fibrosis, carcinoma, and others, and can be administered intravenously or via nebulization [35].

A randomized, double-blind study [36] involving 130 patients with bleeding during bronchoscopy unresponsive to ice-cold saline compared the efficacy of topical epinephrine (up to 3 applications, maximum dose 0.2 mg in 2 ml, 1:10,000) with tranexamic acid (up to 3 applications, maximum dose 100 mg in 2 ml). The results showed no significant difference in hemostatic efficacy between the two agents. Higher success rates were observed in cases of moderate bleeding compared to severe bleeding. Importantly, no adverse reactions to topical vasoconstrictors were reported.

The use of additional methods depends on the bleeding site, the availability of equipment, and operator experience. Local ablative techniques such as argon plasma coagulation or laser coagulation (Nd:YAG or diode lasers) are options for managing bleeding secondary to endobronchial biopsy of central lesions [34].

Placement of a balloon catheter/bronchial blocker proximal to the biopsy site [Figure 1], with immediate inflation following transbronchial lung biopsy, can prevent blood from entering the central airways [37]. Some experts use the two-bronchoscope technique to manage bleeding during biopsies of peripheral lesions or lung parenchyma [38]. In addition, intubation with a rigid bronchoscope or an endotracheal tube is necessary to provide better airway control in case of massive bleeding, according to some authors [22].

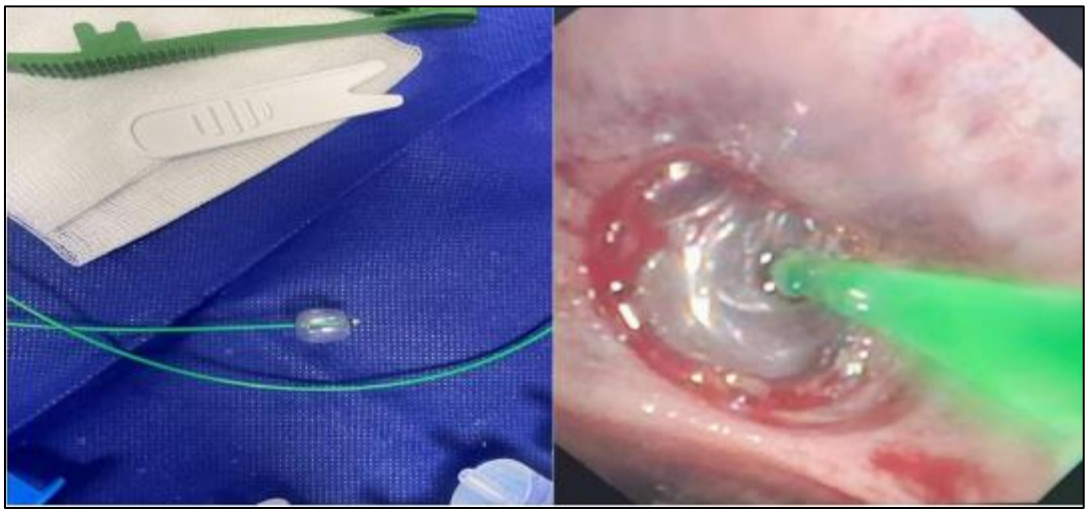

Figure 1 Placement of ballon catheter

4. Bleeding following cryobiopsies of endobronchial lesions

According to current studies [22, 39-41], the most common complication following the cryobiopsy of central tumors is mild to moderate bleeding, with most reports showing no statistically significant difference compared to bleeding after endobronchial forceps biopsy.

In a randomized trial of 593 patients [22], the incidence of bleeding was higher in the cryobiopsy group. However, there was no difference in the number of hemostatic interventions required. Argon plasma coagulation was applied in 13 patients following cryobiopsy and in 8 patients following forceps biopsy, while tamponade was used in two patients from each group. All remaining bleeding episodes were successfully managed with ice-cold saline and vasoconstrictor agents. Surgical intervention was not required, and no fatalities occurred due to complications. In all endoscopic procedures, patients were intubated with a rigid bronchoscope or an endotracheal tube to ensure airway control during the procedure.

An increased risk of bleeding when more than three cryobiopsies were taken was reported in another study [42]. In addition, a significant difference in diagnostic yield was observed between the first and second biopsies, while the third and fourth biopsies were found to be redundant. Based on the results, the authors concluded that two cryobiopsies represent the optimal balance between achieving a definitive diagnosis and minimizing the risk of complications.

5. Bleeding following transbronchial cryobiopsies

Various factors that may influence the incidence of bleeding during transbronchial cryobiopsies have been analyzed. These include the use of radial probe endobronchial ultrasound (RP-EBUS) [43-45], cryoprobe size and freezing time [45], intubation with an endotracheal tube or rigid bronchoscope [43], and the application of balloon catheters/bronchial blockers [46].

When cryobiopsy is performed in conjunction with RP-EBUS, large blood vessels can be visualized, potentially reducing the risk of bleeding. Additionally, if a guide sheath (GS) is used and remains in place after the biopsy, it can serve as a tool for tamponade [43-45, 47].

In a study by Nakai et al.[48], all bleeding episodes were controlled using the two-bronchoscope technique. After removing the cryoprobe with the frozen tissue sample along with the first bronchoscope, the assistant immediately positions the second bronchoscope at the biopsy site. The authors point out several advantages of the method: first, it

facilitates hemostasis in anatomically challenging areas, such as the upper lobe bronchi and segment B6, where balloon catheter placement is often difficult, second, it allows for real-time endoscopic assessment of the amount of bleeding and immediate administration of hemostatic agents, and third, since there is no risk of balloon migration, further endoscopic hemostasis can be combined with postural change.

Bronchoscopic cryobiopsy is an established method for the diagnosis of diffuse parenchymal lung diseases, with a lower reported complication rate and mortality compared to surgical lung biopsy [49]. In a prospective randomized trial [44] comparing transbronchial cryobiopsy and transbronchial forceps biopsy, a higher incidence of clinically significant bleeding was observed in the cryobiopsy group. Additional hemostatic interventions were required in 16% of patients in this group, compared to 4.2% in the forceps biopsy group. The authors emphasize the importance of intubation with a rigid bronchoscope or endotracheal tube, as well as prophylactic placement of a balloon catheter proximal to the biopsy site as methods for better airway control and reducing the risk of bleeding.

In the reported series by DiBardino et al. [50], most procedures were performed using a laryngeal mask (21 patients, 84%), without fluoroscopic guidance (15 patients, 60%), and without prophylactic use of bronchial blockers. Furthermore, no standardized local protocol was implemented to guide the procedure. In the non-fluoroscopy group, clinically significant bleeding occurred in three patients, and pneumothorax was observed in two cases. According to the authors, the use of fluoroscopic control may reduce the risk of such complications by preventing biopsies taken too close to or too far from the pleura.

6. Conclusion

Hemorrhage is a major complication associated with cryobiopsy of central and peripheral lung neoplasms. Although the incidence of severe and life-threatening bleeding is low, larger prospective studies are needed to identify risk factors and standardize the procedure across centers.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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