Advances in Bronchoscopy — New and Upcoming Bronchoscopic Methods at the Dawn of the 21st Century

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Abstract

The last decade has seen the increasing application of bronchoscopic methods such as transbronchial needle aspiration in the staging of lung cancer as well as in the diagnosis of peripheral lung cancer, balloon dilatation using flexible bronchoscopy, development of new tracheobronchial stents to manage central airway obstruction, autofluorescence bronchoscopy for the early diagnosis of lung cancer and pediatric flexible bronchoscopy. There is also a better understanding in the mechanisms and management of hypoxemia during bronchoscopy such as upper airway obstruction. Recent developments include direct endobronchial ultrasound to increase the yield of transbronchial needle aspiration, high magnification bronchoscopy to assist in the diagnosis of early lung cancer and bronchoscopic lung volume reduction to gain the effects lung volume reduction surgery without the need for surgery in patients with severe emphysema. In this article the new and upcoming bronchoscopic techniques are discussed, which we believe will find a broader clinical application in the near future to manage patients in a better way.

INTRODUCTION

There has been significant progress in the field of bronchology in the last decade. These include the increasing application of transbronchial needle aspiration (TBNA) in the staging of lung cancer as well as in the diagnosis of peripheral lung cancer, balloon dilatation using flexible bronchoscopy, development of new tracheobronchial stents to manage central airway obstruction, autofluorescence bronchoscopy for the early diagnosis of lung cancer and pediatric flexible bronchoscopy.1-7 There is also a better understanding in the mechanisms and management of hypoxemia during bronchoscopy such as upper airway obstruction.8-10 The beginning of the 21st century continues to see further development and there are several applications on the horizon, waiting to be applied in clinical practice in larger populations such as direct endobronchial ultrasound (EBUS) to increase the yield of TBNA, high magnification bronchoscopy to assist in the diagnosis of early lung cancer and bronchoscopic lung volume reduction for patients with emphysema.1,3,13-14 In this article the new and upcoming bronchoscopic techniques are discussed, which we believe will find a broader clinical application in the near future to manage patients in a better way.

ENDOBRONCHIAL ULTRASOUND

EBUS may be performed either using a radial probe inserted through the working channel of the bronchoscope or using a convex probe ultrasound bronchoscope that has an ultrasound probe incorporated at it’s tip.13,15

Radial probe endobronchial ultrasound

The ultrasound probe (20 MHz frequency) is inserted through the working channel of the bronchoscope into the airways. A balloon is inflated at the tip of the probe with water, which acts as a coupling mechanism between the probe and the airway wall. This is important because air in the airways causes high impedance or resistance. Coupling may also be achieved by close contact with the airway wall, however, the view is limited to a very small sector.16 Inflation of the balloon may not be necessary when the ultrasound probe is passed into the peripheral bronchi 2 to 3 mm in diameter. Balloon equipped ultrasound probes can be inserted in bronoscopes having working channels of 2.8 mm in diameter or more. In the larger airways, the tip of the bronchoscope can be flexed to bring the balloon in better contact with the airway wall.

Layers of the airway wall13,17,18

These consists of seven layers,
1. Mucosa - this is a hyperechoic layer. The echogenicity of the mucosa is enhanced by the adjacent balloon.
2. Submucosa - this is a hypoechoic layer.
3. The cartilage has three layers,
   a. the endochondrium and the perichondrium are hyperechoic layers
   b. the internal layer between the endochondrium and the perichondrium is hypoechoic
4. The supporting connective tissue outside the cartilage appears as a hypoechoic layer
5. The adventitia surrounding the supporting connective tissue is visualized as a hyperechoic layer

**Convex probe ultrasound**

The ultrasound transducer with a frequency of 7.5 MHz is integrated at the tip of a flexible bronchoscope. It has a linear curved array transducer that scans parallel to the insertion direction of the bronchoscope. Images can be obtained by directly contacting the probe with the airway wall or by attaching a balloon on the tip and inflating with saline. The ultrasound image is processed in an ultrasound scanner and is visualized along with the conventional bronchoscopy image on the same monitor. The Doppler mode assists in the confirmation of blood vessels. This system allows the bronchoscopist to perform real-time TBNA under direct ultrasound guidance. The needle can be visualized through the optics and on the ultrasound image.

**Clinical Applications**

These include, staging of patients for lung cancer, diagnosis of unexplained benign and malignant mediastinal and hilar lymphadenopathy and assessment of the extent of tumor infiltration in the airway wall. Other techniques available for obtaining pathology specimens from the mediastinal lymph nodes include mediastinoscopy, computed tomography guided percutaneous needle aspiration, conventional bronchoscopic TBNA, computed tomography guided TBNA and transesophageal ultrasonography guided needle aspiration. All of these techniques have some limitations, which may either be variation in yield, complications, poor access to some lymph nodes, need for general anaesthesia, exposure to radiation or the referral to a service, which offers the specialised procedure. Real-time TBNA of mediastinal and hilar lymph nodes under direct EBUS guidance using the new ultrasonic puncture bronchoscope is a novel approach that is safe and has a good diagnostic yield. The potential benefits of direct ultrasound guided TBNA include, avoiding surgical procedure of mediastinoscopy by making a definitive diagnosis of mediastinal and hilar lymph node enlargement using flexible ultrasound guided bronchoscopy and its potential impact on saving health care costs.

The intactness or the integrity of the of the internal bronchial wall layers has been used to assess tumor infiltration of the airway wall. If there is no tumor infiltration into the deeper layers of the bronchial wall cancer may be treated endoscopically with a curative intent. This can be particularly important for early cancer lesions that are diagnosed using autofluorescence bronchoscopy, which may underestimate the submucosal tumor spread because the autofluorescence signal is mainly influenced by the superficial layers of the airway. In tumors invading the bronchial wall externally, comparison of computed tomography and radial probe EBUS demonstrated an accuracy of 51% and 94% respectively, a sensitivity of 25% and 89% respectively and a specificity of 80% and 100% respectively. EBUS has been used as a guide during interventional bronchoscopy to adjust stent dimensions, termination of tumor debriement near the vessels and referral for surgical intervention.

**Peripheral lesions**

When the ultrasound probe is inserted in the peripheral airways, pulmonary masses are visualized to have a hypoechoic texture compared to the surrounding tissue. They often have a sharply defined border due to the strong reflective interface produced between the aerated lung and the lesion. The zones of atelectasis adjacent to the tumor tend to be more reflective than the tumor due to the multiple interfaces between the aerated and the collapsed tumor. The images from peripheral nodules are usually clear because of sharp borders due to the strong reflection from adjacent atelectasis, whereas images of cancer are often surrounded by a dark zone due to tumor necrosis. The sensitivity of TBNA samples taken from peripheral lesions decreases with increasing distance from the hilum.

**Autofluorescence Bronchoscopy**

The proportion of individuals with bronchial carcinoma in situ in whom invasive cancer will develop is likely to be greater than 40%. Treatment of cervical dysplasia or carcinoma in situ has significantly reduced the incidence and mortality of invasive cervical cancer. By coupling sensitive diagnostic tools in the investigation of early lung cancer with new treatment modalities, such as chemoprevention and various endobronchial therapies, it is hoped that the traditionally poor prognosis for patients with lung cancer can be altered in the near future.

The role of autofluorescence bronchoscopy as a guide for endobronchial biopsy has been established for the localisation of intraepithelial neoplasia. When bronchial surface is illuminated by light, the light can be back-scattered, absorbed, transmitted, or it can induce fluorescence. White light bronchoscopy makes use of the absorption and back-scattering properties of bronchial tissues to broad-band visible light and thus provides information on the structure and morphological features such as the mucosal thickness, sheen, smoothness or vascularity. When the chromophores present in the bronchial tissue are excited by light of specific wavelengths to higher electronic states, fluorescence is emitted when the electrons return to ground level.

**Clinical Applications**

Fluorescence bronchoscopy makes use of the absorption
and fluorescence properties of chromophores in bronchial tissues to provide information on the biochemical and functional changes in the bronchial tissues. Autofluorescence bronchoscopy uses illumination by violet or blue light (400 nm or 450 nm). Normal tissue fluoresces green while precancerous or cancerous tissue fluoresce brown or brownish red.34 Autofluorescence bronchoscopy has been reported to have twice the sensitivity of white light bronchoscopy in detection of these lesions.35 However, in these studies white light bronchoscopy was performed using fiberoptic bronchoscopy. The white light flexible video bronchoscope has a miniature colour charge couple device built into its tip, which helps to deliver a clearer image. Furthermore, the images obtained with the flexible video bronchoscope do not have the graininess seen with images from the conventional fiberoptic bronchoscope. A recent study has shown a sensitivity of 72% using white light video bronchoscopy.36

During the bronchoscopic investigation of early lung cancer, the visual findings at white light and autofluorescence bronchoscopy are classified as either normal, abnormal or suspicious. At flexible video bronchoscopy areas without any visual abnormality are classified as normal; areas with increased redness and hypervascularity, swelling or thickening of the bronchial mucosa or focal thickening of a sub carina as abnormal and nodular or polypoid lesions or irregularity of the bronchial mucosa as suspicious for high grade dysplasia or cancer.30,37,38 At autofluorescence bronchoscopy, normal areas appear as green; areas with a definite brown or brownish-red color (loss of green fluorescence) are labeled as suspicious for high-grade dysplasia or cancer; and areas that are slight brown with ill-defined margins are labeled as abnormal. Abnormal lesions at white light bronchoscopy have been classified differently by some authors.30,36 Abnormal and suspicious areas both at white light bronchoscopy and autofluorescence bronchoscopy are subjected to endobronchial biopsy.36 Some undertake endobronchial biopsy of only suspicious lesions.30 Endobronchial biopsy specimens are then graded by the histopathologist as either normal, hyperplasia, metaplasia, inflammation, mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma in situ or cancer.

**High Magnification Bronchoscopy**

Increased thickening of the bronchial epithelium and increased vessel growth are thought to be related to the appearance of areas of abnormal fluorescence, suggesting roles for neovascularisation or increased mucosal microvascular growth in bronchial dysplasia. Recently, a new morphological entity, “angiogenic squamous dysplasia” has been identified in large airways by autofluorescence bronchoscopie, characterized by collections of capillary blood vessels closely juxtaposed to and projecting into dysplastic bronchial epithelium.39-41 High magnification bronchovideoscopy system enables detailed observation of dysplasia in the bronchial mucosa.3 Vascular networks with regular patterns are observed at abnormal fluorescence sites from patients with bronchitis. However, vascular networks with increased vessel growth and complex networks of tortuous vessels of various sizes have been reported in abnormal fluorescence sites having dysplasia.3 Therefore, areas of increased vessel growth and complex networks of tortuous vessels in the bronchial mucosa detected using a high magnification bronchovideoscopy at sites of abnormal fluorescence may enable discrimination between bronchitis and dysplasia.

**High magnification bronchoscopy combined with narrow band imaging**

Angiogenesis is now thought to be an early event during the pathogenesis of lung cancer.42 Microvessels, vascular networks of various grades and dotted vessels in angiogenic squamous dysplastic tissue have been observed with high magnification bronchoscopie combined with narrow band imaging.1 As capillary blood vessels in angiogenic squamous dysplastic project into the dysplastic bronchial epithelium, the dotted vessels in the narrow band -B1 images represent angiogenic squamous dysplasia capillary blood vessels. Thus, high magnification bronchoscopy combined with narrow band imaging is proposed to be a new investigatory tool to detect capillary blood vessels in ASD lesions, and is able to demonstrate the onset of angiogenesis during the multi-step carcinogenesis of the lung in heavy smokers at high risk for lung cancer.1

**Bronchoscopic Lung Volume Reduction**

Lung volume reduction surgery (LVRS) refers to elimination of emphysematous hyperinflated lung, which allows the remaining pulmonary parenchyma and the respiratory muscles to function more effectively.41 Over the past decade, LVRS has emerged as an adjunct to conventional medical treatment for end-stage emphysema.43,44 LVRS improves pulmonary function, shortness of breath, exercise capacity and hence quality of life for a few years after surgery.45 An interim analysis of the National Emphysema Treatment Trial (NETT) showed that in patients with forced expiratory volume in one second (FEV1) of no more than 20% of the predicted value and either homogeneous distribution of emphysema on computed tomography or a carbon monoxide diffusing capacity of no more than 20% of the predicted value, 30-day mortality after surgery was 16% as compared to nil mortality among patients treated medically.46 Further results published in May 2003 showed that those patients who were randomly assigned to surgery were more likely than those assigned to medical therapy to have improvement in exercise capacity and quality of life, but there was no reduction in mortality during an average of 29 months of follow up.47 Among patients with predominantly upper lobe emphysema and low exercise capacity, the risk ratio for death in the surgery group as compared with the medical group was 0.47 (p=0.005), indicating a significant benefit of surgery. Among patients with predominantly upper lobe emphysema and high exercise capacity, the risk ratio was 0.98 (p=0.7), and among those with non-upper lobe emphysema
and low exercise capacity, the risk ratio was 0.81 (p=0.49). Among patients with non-upper lobe emphysema and high exercise capacity, the risk ratio was 2.06 (p=0.02); that is, the risk of death was significantly higher in those who underwent surgery. These results suggest that surgery may reduce the risk of death among patients with upper- lobe emphysema and low exercise capacity, increase the risk among patients with non-upper lobe emphysema and high exercise capacity, and have little effect on the risk of death in the other two groups.47,48

Alternatives to surgical LVRS have been experimented in animal models.49,50 Recently preliminary results investigating an endobronchial approach to deflation of emphysematous lungs by bronchoscopic methods have been published.11,12 These results show that lung volume reduction can be achieved with bronchoscopically placed valve implants in patients with severe emphysema with acceptable short-term safety. Both these studies have used the same valve but different versions. In the study by Snell et al, the device did not reduce the radiological volume probably due to poor valve closure.51 In the modified design of the valve, four of the eight patients who underwent valve implantation showed radiographic signs of volume reduction with collapse of the target lobe after the procedure.52 The improvement in lung function was greater in patients with radiographic signs of collapse than in those without. Failure of obtaining radiological collapse in all patients has been attributed to the presence of interlobar collaterals between target and non-target lobes.

In an ex vivo study in emphysematous human lungs, direct stented passages from the large airways into the emphysematous pulmonary parenchyma has been shown to improve FEV. The hypothesis being that such passages would improve expiratory flow and respiratory mechanics.53 Results from human studies are awaited.

**Summary**

The flexible fiberoptic bronchoscope has undergone tremendous development since its invention in 1968, such as the development of the flexible video bronchoscope, the fluorescence bronchoscope, the high magnification bronchoscope and the convex probe EBUS bronchoscope. With evolution in technology, the bronchoscopist would further like to see the reduction in the size of the convex probe EBUS for potential use in the management of peripheral lesions. Having the flexibility of using a variety of ultrasound frequencies ranging from 7.5 to 20 MHz would have the potential for its application in the evaluation of airway wall and also serve as a useful guide in performing therapeutic flexible bronchoscopy. Despite being one of the most common cancers and a major cause of morbidity and mortality, we still do not have a uniform and accepted approach for the screening of lung cancer. Although, some approaches are used in select patient population, a technique to diagnose early lung cancer that is not too expensive and one which can be used by the common respiratory physician would be needed to impact the outcome. We believe that newer bronchoscopic methods combined with radiological tools will probably find an important role in a unified approach in the screening of lung cancer in high risk individuals. The preliminary results of bronchoscopic lung volume reduction are encouraging in patients with severe emphysema. Currently, it is not possible to predict in which patients collagenal ventilation will be a limiting factor. Potentially, a combined approach using valve implants and creation of direct stented passages from the airways into the emphysematous bullae may be the way to address the issue of collateral ventilation between target areas for valve implants and adjacent large bullous areas.

**REFERENCES**


