Interventional Pulmonology: A New Medical Specialty

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ABSTRACT: Interventional pulmonology (IP) is the newest chapter in respiratory medicine. IP includes both diagnostic and therapeutic methods. Nanotechnology, in both instrumental engineering and optical imaging, will further advance this competitive discipline towards cell diagnosis and therapy as part of the future's personalized medicine.

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It is estimated that chronic respiratory diseases cause approximately 7% of all deaths worldwide and represent 4% of the global burden of disease. Diseases once found primarily in industrialized countries, such as asthma, chronic pulmonary obstructive disease and lung cancer, are now major health problems throughout the world and threaten to overwhelm public health services. By 2020, COPD will be the third leading cause of death worldwide [1]. Against this somber prospect, respiratory medicine is an evolving specialty. Diagnostic procedures and therapeutic interventions emerged in recent decades to manage the complex spectrum of lung diseases. Interventional pulmonology was born more than 100 years ago with the first insertion of a rigid bronchoscope into the airways by Gustav Killian [2]. Over the subsequent years IP was synonymous with bronchoscopy and related diagnostic and therapeutic procedures.

Interventional pulmonology is a new medical specialty that has both a diagnostic and therapeutic impact on lung disease management

However, IP is not limited to the bronchial tree. Endobronchial ultrasound may help in reaching the mediastinal lymph nodes or masses with real-time imaging of the biopsies. Probe confocal laser endomicroscopy is a novel technology that enables, for the first time, the performance of in vivo alveoscopy, expanding the field of respiratory endoscopy to the smallest anatomic lung units. Today, the pleural cavity is investigated for diagnostic and therapeutic purposes by both non-invasive (ultrasound) and invasive methods (medical thoracoscopy, tunneled pleural catheters). IP is now reaching the field of cellular and molecular biology. Different markers of micro- and nanodimensions are being developed together with optical visual technologies with the purpose of studying the cellular changes of inflammation and malignancy. This review will focus on some of the latest developments in diagnostic and therapeutic interventional pulmonology.

COPD = chronic pulmonary obstructive disease
IP = interventional pulmonology

DIAGNOSTIC INTERVENTIONAL PULMONOLOGY

Most of the advances in diagnostic IP involved image acquisition and sampling instruments at bronchoscopy. However, some of the new imaging techniques reach the alveoli (alveoscopy) and the pleural cavity (pleuroscopy).

IMAGE ACQUISITION TECHNIQUES

"Classical" bronchoscopy is based on white light, hence the term white light bronchoscopy. The light reflected by the airway mucosa is processed by the optic fibers (flexible bronchoscope) or by a charge-coupled device (video bronchoscope) into an image projected on a screen [Figure 1]. At the end of the 20th century, diagnostic bronchoscopy began to use the autofluorescence properties of respiratory mucosa when illuminated by dedicated laser beams in an effort to improve visual diagnosis, mainly specificity. This was generated by the necessity of screening for early-stage bronchogenic lung cancer.

- Autofluorescence bronchoscopy is able to differentiate between the normal appearance of respiratory mucosa (green color) and the abnormal (brown color) [Figure 2]. Unfortunately, histological examination of these abnormalities showed the lack of specificity of autofluorescence bron-

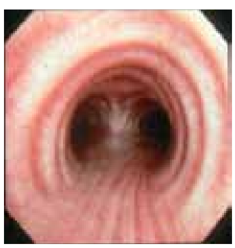


Figure 1. White light bronchoscopy image of trachea and main bronchi

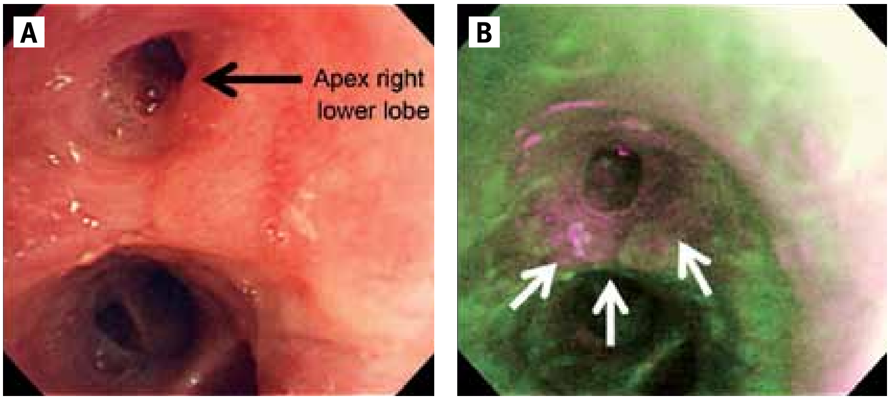


Figure 2. Autofluorescence bronchoscopy. **[B]** Areas of dysplasia (white arrows)

choscopy since the brown color was not able to differentiate between inflammatory and dysplastic/neoplastic lesions [3].

- Narrow band imaging enhances the visibility of vessels of the respiratory mucosa and may theoretically differentiate between inflammation and pathologic vascularization of tumors (by analyzing the morphology and frequency of structures). In a comparative study WLB and NBI were analyzed in 500 patients. The relative sensitivity of NBI as compared to WLB was 1.06 (P = 0.004) and the rate of false positive results 0.91 (P = 0.012) [4].

Technological advances are moving IP to the level of cellular diagnosis and therapy

- High definition (magnification) bronchoscopy is a direct-view WLB procedure using an instrument with an outer diameter of 6 mm easily insertible into the tracheobronchial tree. High definition bronchoscopy combines two systems: a video observation system for high magnification observation and a fiberoptic system for the orientation of the bronchoscope tip. This combination allows for a magnification four times that of a regular video bronchoscope to a depth of 1–3 mm. The vascular network is better viewed but the advantages of this technology over WLB are not clear.

MINIATURIZATION OF BRONCHOSCOPES

Optical fibers and video chips have become smaller since the first flexible bronchoscope was introduced by Ikeda [2]. The new instruments have diameters of 2.2–3.6 mm and are able to reach the 9th–10th order subsegmental bronchi. Using those ultrathin bronchoscopes, lesions smaller than 2 cm in diameter may be reached and biopsied. The sensitivity of ultrathin bronchoscopes for diagnosing peripheral pulmonary lesions ranges between 60% and 81% [5].

IMAGING OF ANATOMIC STRUCTURES SURROUNDING THE AIRWAYS

Technological advances enabled attachment of the ultrasound imaging modality to the bronchoscope. The endobronchial ultrasound facilitates lung cancer staging by reaching the lymph node stations in the mediastinum and lung hilar areas. Staging lung cancer before therapy and restaging after treatment is an important substitute for surgery (mediastinoscopy/tomy) [6]. Following this original indication new diagnostic opportunities were described for EBUS. Radial probes of EBUS may help in evaluating the airway involvement by tumors or assist in the placement of biopsy instruments into peripheral lung nodules [7].

NAVIGATION TECHNIQUES

Bronchoscopy is a visual technique that reaches the airways only. However, the bronchoscope facilitates diagnostic procedures at the alveolar level through transbronchial biopsies. Although this type of biopsy may be performed without guidance, it is well established that in order to improve the yield of the procedure and to minimize complications, visualization of the lung parenchyma by fluoroscopy is imperative. This is especially valid in localized pulmonary disease where the placement of forceps into the lesion is critical for accurate histologic diagnosis [8].

An extensive panel of navigation techniques was developed in recent years. The most promising is the electromagnetic navigation system [9]. An electromagnetic board is placed underneath a supine patient. The generated magnetic field pinpoints the position of a sensor probe that is inserted through the working channel of a bronchoscope. This position is projected on a three-dimensional computed tomographic reconstruction that allows the operator to see the position of the probe vis-à-vis the lesion to be reached.

WLB = white light bronchoscopy
NBI = narrow band imaging

EBUS = endobronchial ultrasound

EMERGING DIAGNOSTIC TECHNIQUES

Despite these technological advances, the diagnostic yield of biopsies performed through a bronchoscope varies significantly, due not only to the operator's experience but also to the size and the location of the lesion in the lung parenchyma. The addition of EBUS and various navigation techniques may increase the yield, but peripheral and small lesions (< 2 cm) are difficult to reach. In vivo real-time biopsy site assessment could aid in targeting the lung nodule and provide selective tissue acquisition. Two novel technologies address this challenging aspect of IP:

• Optical coherence tomography

This is an imaging technique that measures the intensity of back-scattered near-infrared light by low coherence interferometry. OCT is, in this respect, similar to the ultrasound technology that measures sound echoes reflected by tissues. Even the collected images are similar to ultrasound pictures. OCT generates tissue images with a resolution of < 10 μm and a penetration depth of 2–3 mm.

A number of catheter-based OCT systems are commercially available, including some compatible with the working channel of a standard bronchoscope. OCT imaging of the tracheobronchial wall enables visualization of the epithelium, basement membrane, lamina propria, bronchial glands and ducts, vessels and cartilage [10]. Recently, needle-based OCT catheters were built to facilitate imaging beyond the bronchial wall [11]. These probes may assess placement before tissue collection by aspiration or biopsy. Polarization-sensitive OCT and optical frequency domain imaging are the second-generation OCT imaging modalities and are currently being evaluated [12].

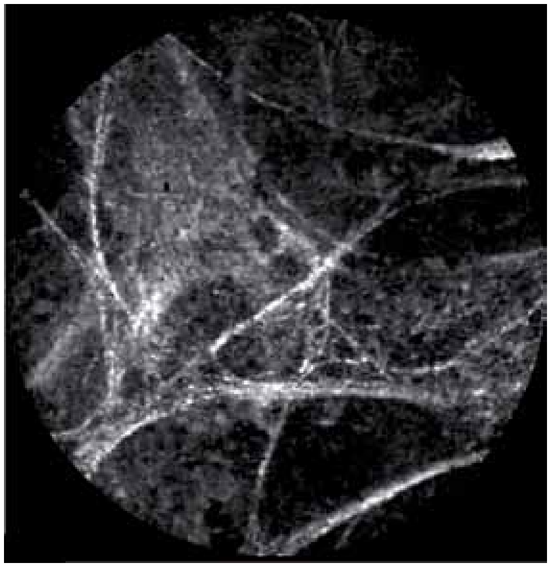
IP requires rigorous training and credentials assessment

• Confocal laser (endo)microscopy

This fascinating technology is based on the autofluorescence properties of elastin fibers present in the walls of the airways, from the trachea through the alveolar septae. It is the only technology at this time that allows real-time (in vivo) alveoscopy (bronchoalveoscopy in addition to bronchoscopy) [13].

Scanning confocal microscopy is a well-established technique that was developed in 1955 by Minsky. It has the ability of "optical" sectioning of tissues in depth by rejecting out-of-focus light by means of a confocal pinhole. For in vivo clinical imaging the use of a single-mode fiber instead of a confocal pinhole was the next technical step. Together with the capability of optical fibers to deliver and collect light confocally from tissues, the scanning capacities also improved. These scanning systems may act distally or proximally to the light guide (usually a laser beam). Without further detailing the engineering concept, there are two commercially available confocal laser microscopy systems: the Pentax-Optiscan® system that uses distal scanning and the Cellvizio® system that uses proximal scanning.

Figure 3. Alveoscopy at pCLE (probe confocal laser endomicroscopy)



Cellvizio® (Mauna Kea Technologies, France) is composed of a laser unit, a range of fibered objectives, and dedicated software that allows the capture of images at a rate of 12 frames per second. Two types of lasers are used: a 488 nm "blue" laser and a 660 nm "red" laser for reflectance imaging. Probes were designed for use in different medical specialties. The pulmonary probe, called "Alveoflex," has a diameter of 1.4 mm and can pass through the channel of a standard bronchoscope. Thus, this technique is named probe confocal laser endomicroscopy [Figure 3]. The depth of resolution is fixed at 50 μm and the field of view is limited at 600 μm. This "touch-and-see" procedure is the only one that enables in vivo alveoscopy. Conceptually, it may distinguish between normal alveoli and alveolitis due to various inflammatory processes or tumors. Various indications have been described but the specificity is still under debate [14,15]. This is due to the lack of specific dyes for pulmonary tissues that may distinguish various cell populations. The future development of dyes based on immunochemistry or nanotechnology may further improve the pCLE yield, especially for oncologic indications [16].

PLEURAL CAVITY EXAMINATION

Reaching the pleural cavity for diagnostic or therapeutic reasons is common practice. Pleural aspiration (thoracentesis) and chest drain insertion may be required in various clinical situations. Image guidance is not always necessary (especially in large pleural

OCT = optical coherence tomography

pCLE = probe confocal laser endomicroscopy effusions or tension pneumothorax). However, advances in ultrasound technology, especially the probe design, have significantly improved the yield and lowered the complication rates of these procedures even in experienced hands [17]. The role of pleural manometry in routine thoracentesis is debatable. In my opinion, this measurement provides valuable information on the cause of the effusion and, more importantly, regarding the lungs' ability to expand as fluid is withdrawn. This may be done at bedside with a syringe-pump system as part of a standard thoracentesis kit [18]. Pleuroscopy ("medical" thoracoscopy) is an invasive procedure for diagnosing pleural effusions or pleural thickening. This is a surgical procedure that differs from video-assisted thoracoscopy which uses different access ports for viewing and working instruments. "Medical" thoracoscopy requires one-lung ventilation for creating a working space in the hemithorax. Depending on the particular facility (i.e., availability of chest surgeons) this is a surgical procedure with a potentially serious complication rate [19].

THERAPEUTIC INTERVENTIONAL PULMONOLOGY

Treating lung disorders through the bronchoscope is a well-established method, whether the intent is curative or palliative. Most techniques address the need for reestablishing patency of airways affected by malignant or benign disorders. The general trend is a combination of techniques for this purpose instead of a single procedure.

BRONCHOSCOPIC DEBULKING AND/OR BALLOON DILATATION

This is a technique based on the use of a rigid bronchoscope with a beveled tip. This element allows coring through large tumors or dilating airway strictures. Balloon dilatation is used in situations of obstructed airways mainly due to disorders partially affecting their wall. When all the layers of the airway wall are distorted (as in tracheomalacia) its beneficial effect is less evident. Combined with other methods (like stenting) it may have a beneficial effect on disease management [20].

LASER THERAPY

Interaction between laser and tissue results in vaporization, coagulation, hemostasis and necrosis. These effects were used by both Laforet et al. [21] and Dumon et al. [22] in their pioneering approach to restore patency of the tracheobronchial tree. Whereas ear, nose and throat surgeons used the CO_2 laser, IP physicians use the Nd:YAG laser (neodymium-ytrium-aluminium garnet). Its advantages include the ability to reach more distal airways, deep penetration of tissues (3–5 mm), photocoagulation and hemostasis. It is less precise than the CO_2 laser, but the probe may pass the channel of a standard flexible bronchoscope.

ARGON PLASMA COAGULATION

Argon plasma coagulation involves the jet of ionized argon gas (plasma) that is directed through a dedicated probe passed through the bronchoscope channel. Its main indication is the treatment of bleeding airway mucosa by ignition of the gas by high frequency electric current. This coagulation effect may also be beneficial for treating endobronchial lesions [23].

ELECTROCAUTERY AND CRYOTHERAPY

These are valuable alternatives to laser procedures. Electrocautery has immediate effects on tissue, while cryotherapy induces necrosis through hypothermic cellular crystallization and microthrombosis with late effects. The main advantage of cryotherapy is the ability to reach the lung periphery without risking airway wall perforation. Both flexible and rigid probes are available [24]. The use of cryo-probes for large biopsies of lung tissue was recently described; it was found effective in the follow-up of lung-transplanted patients and bleeding complications were minimal [25].

ENDOBRONCHIAL BRACHYTHERAPY

Inserting wires through the bronchoscope channel may generate radiation through an obstructive airway tumor. As described by Yankauerin [26], iridium 192 may have a significant debulking effect on airway tumors. This technique may also be used for treating benign disorders such as post-transplant stenosis or airways amyloidosis [27].

TRACHEOBRONCHIAL STENTING

Since the British dentist Charles Stent used a device to support the healing of gingival grafts, the term "stent" was used for any device able to support the anatomy of any hollow structure (blood vessels, esophagus, urinary tract). Stents are made from stiff materials, either metal or silicone. The first reliable airway stent was the T-tube built by Montgomery in the 1960s. Later the silicone stent developed by Dumon became popular in the early 1990s, but it requires rigid bronchoscopy for placement or removal. Metal stents covered with silicone became the most useful as they are easily positioned with flexible bronchoscope guidance and there is no need for general anesthesia [28]. Stents are used in the palliative therapy of malignant and less common benign disorders. Stent placement usually follows other therapeutic interventions such as laser or electrocautery to maintain patency of airways. With its immediate relief of dyspnea, stents have a valuable impact on the quality of life of cancer patients. However, their potential for migration, granulation formation and secretion adherence reduces their feasibility in the management of benign disorders (like strictures) where surgery is preferred, when possible [29].

EMERGING THERAPEUTIC TECHNIQUES

Since bronchoscopy aids airway visualization, in the last decade a considerable amount of research addressed novel approaches to treat bronchial asthma and emphysema. The most-investigated procedures are described here.

• Bronchoscopic therapy of emphysema by lung volume reduction

Emphysema is a destructive irreversible lung disease caused primarily by smoking. The destruction of the pulmonary architecture makes therapeutic targeting by drugs very difficult. The results of surgical techniques for treating emphysema were first published more than 10 years ago [30]. In that well-designed study 1218 patients were randomized to receive the best available medical treatment versus lung volume reduction surgery. Patients with heterogenous emphysema who were treated with lung volume reduction surgery showed improvement in exercise capacity in the 2 years following the surgery. The mortality rate at 90 days was significantly higher than in the control medically treated patients, although the subgroup with predominant upper lobe emphysema showed better results. The two messages that this important study sent to the pulmonary medical community were that surgery to treat upper lobe predominant emphysema and low exercise capacity has a good outcome, but the mortality rate and hospitalization time are remarkably high. These conclusions prompted the search for alternative non-surgical ways to reduce the lung volume in diseased areas. Many techniques were developed for this purpose. They may be classified as having a proximal effect: bypassing and blocking of the airways (stents, unidirectional valves, spigots, coils), or a distal effect: acting on alveolated lung parenchyma (polymeric sealants, thermal vapor ablation). All of these procedures are currently in the phase of clinical trials and their outcome is not known [31,32].

• Bronchial thermoplasty

This is another non-pharmacological procedure used to treat refractory bronchial asthma. Asthma is an inflammatory disease characterized by diminished airway diameter (bronchoconstriction). To be effective, any asthma therapy must reduce both the symptoms and the likelihood of exacerbations, and improve quality of life (NAEPP 2007) [33]. Bronchial thermoplasty affects all of these by using the properties of radiofrequency ablation on the smooth muscle of the airway. High temperatures are able to disrupt the actin-myosin interaction and produce loss of muscle cell function. This effect was added to the gradual reduction of bronchial hyper-responsiveness observed with bronchial thermoplasty (dose-dependent result) [34]. By affecting the muscular tone of the bronchial wall, bronchial thermoplasty may be considered a disease-modifying therapy. Fibrosis of the muscular layer generates a favorable remodeling of the bronchial wall and reduces the constriction that characterizes the asthmatic attack. The long-term results of this modality in patients with severe persistent asthma were recently published [35]. A 5 year follow-up of more than 150 patients who were treated with bronchial thermoplasty showed the benefits of this procedure in terms of safety and asthma control.

Figure 4. PleurX Drainage System (CareFusion USA)

PLEURAL THERAPEUTIC CATHETERS

The pleural cavity contains a small amount of lubricating fluid. Air or a significant amount of fluid accumulation is the result of diseases that impair lung movement and generate shortness of breath. Thorax drainage is an invasive procedure used mainly in acute situations. Chronic pleural effusions occur mainly in malignancies (malignant pleural effusion). These malignant pleural effusions are responsible for most respiratory symptoms in cancer patients, affecting their quality of life. Tunneled indwelling pleural catheters are increasingly used worldwide for palliation of malignant pleural effusions. This is an effective alternative to pleurodesis; it ameliorates symptoms and reduces hospital stay [36] [Figure 4]. Indwelling pleural catheters may be placed in the pleural cavity in an outpatient procedure with local anesthesia and drainage can be done at home. Patients are able to control their symptoms by themselves and even pleurodesis may be achieved in almost 50% of cases. Complications include displacement, catheter tract metastases or infection (empyema), but they occur in a minority of cases [37].

CONCLUSIONS

Interventional pulmonology has become an active and dynamic chapter in pulmonary medicine. New therapeutic opportunities were applied to the old diagnostic indications, particularly asthma, COPD, pleural diseases and lung cancer. Although most of these new technologies are still at the research level, their potential use in routine medical care is impressive. As a new medical specialty, IP warrants intensive training in a well-designed syllabus [38]. The complexity of the new technologies requires simulator use for manual skill development and the eventual award of credentials. As in the case of interventional cardiology, radiology and gastroenterology, IP represents a reliable alternative to surgery in selected cases [39]. The impressive development of molecular imaging and nanotechnology will further advance IP to the level of cell diagnosis and therapy [40].

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