Bronchial Thermoplasty in severe asthma

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CHAPTER 7

Optical Coherence Tomography and confocal laser endomicroscopy in pulmonary diseases

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ABSTRACT

Purpose of review

Current imaging techniques (X-ray, computed tomography scan, ultrasound) have limitations in the identification and quantification of pulmonary diseases, in particular, on highly detailed level. The purpose of this review is to provide an overview of the current knowledge of innovative light- and laser-based imaging techniques that might fill this gap.

Recent findings

Optical Coherence Tomography (OCT) and confocal laser endomicroscopy (CLE) are high-resolution imaging techniques, which, combined with bronchoscopy, provide ‘near histology’ detailed imaging of the airway wall, lung parenchyma, mediastinal lymph nodes, and pulmonary vasculature. This article reviews the technical background of OCT and CLE, summarizes study results, and discusses its potential clinical applications for various pulmonary diseases.

Summary

Although investigational at the moment, OCT and CLE are promising innovative high-resolution optical imaging techniques for the airway wall, lung parenchyma, mediastinal lymph nodes, and pulmonary vasculature. Clinical applications might contribute to improved disease identification and quantification, guidance for interventions/biopsies, and patient selection for treatments. Development of validated identification and quantification image-analysis systems is key for the future application of these imaging techniques in pulmonary medicine.
INTRODUCTION

Current imaging techniques, such as X-ray, computed tomography (CT) scan and (endobronchial) ultrasound, are important for the diagnosis of various lung diseases. However, they do not provide detailed anatomical information on a cellular or histology level. Optical Coherence Tomography (OCT) and confocal laser endomicroscopy (CLE) are innovative light and laser-based imaging techniques with much higher resolutions, but decreased penetration depth in comparison to CT and ultrasound [Figure 1].

OCT and CLE – combined with bronchoscopy – provide complementary information to CT and ultrasound imaging in the assessment of the airway wall, alveoli, mediastinal nodes and pulmonary vasculature. This review describes the technological background of OCT and CLE, summarizes study data in obstructive lung disease, lung cancer, interstitial lung disease (ILD) and pulmonary hypertension and discuss its potential diagnostic applications in pulmonary medicine [Table 1].

Figure 1. Different imaging techniques of human airways with their resolution (arrow on top) and depth of imaging (arrow on bottom). From left to right: High resolution CT-scan image of the chest; Radial EBUS image of right lower lobe bronchus; Optical Coherence Tomography image of a right lower lobe basal bronchus; Confocal laser endomicroscopy image of the airway mucosa.
(Source: J.N.S. d’Hooghe MD, L. Wijmans MD, P.I. Bonta MD PhD, dr. J.T. Annema MD PhD, Academic Medical Center Amsterdam, The Netherlands)
Table 1. Pulmonary diseases assessed by optical coherence tomography (OCT) and confocal laser endomicroscopy (CLE) in human clinical trials

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<td>Metastatic lymph nodes</td>
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<td>Sarcoidosis (24)</td>
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BPA, balloon pulmonary angioplasty; COPD, chronic obstructive pulmonary disease; CTEPH, chronic thromboembolic pulmonary hypertension; ILD, interstitial lung disease.

OPTICAL COHERENCE TOMOGRAPHY: TECHNICAL BACKGROUND

OCT is able to provide real-time high-resolution cross-sectional images of superficial tissue using near-infrared light (wave length 890-1300 nm) at 10-15 μm resolution with a maximum penetration depth of 2-3 mm (26). OCT was invented in 1991 and initial research focused on imaging the transparent retina (25). Since then, the OCT technique has evolved and improved to miniaturised OCT probes, able to image non-transparent tissue and intravascular structures. Currently, OCT is used in clinical practice in ophthalmology (retina assessment (27)) and interventional cardiology (e.g. stent apposition and restenosis (28-31)). The clinical application of OCT in pulmonary medicine is currently under investigation.
For the airway wall and lung parenchyma, OCT images are generated during bronchoscopy by insertion of a ~1mm OCT probe through the bronchoscope. Subsequently, by an (automated) pullback cross-sectional images of airway or alveolar segments are generated [Figure 2] (32). The pulmonary vasculature can be imaged by OCT during right heart catheterization similar to coronary OCT imaging (11, 30). OCT imaging studies in lung parenchyma and pulmonary nodules are limited to animal or human ex-vivo studies (1, 33-37). OCT imaging of the airway wall and the pulmonary artery is reviewed below.

Figure 2. 3D OCT reconstruction of a right lower lobe bronchus. 3D reconstruction of 540 cross-sectional OCT images obtained during an automated pullback in the right lower lobe bronchus (St Jude system), demonstrating an airway segment of 5.4 cm with branches (arrowheads) and the transition from the larger more central right lower lobe bronchus (left) to a smaller distal basal bronchus (right).
(Source: J.N.S. d’Hooghe MD, P.I. Bonta MD PhD, J.T. Annema MD PhD, Academic Medical Center Amsterdam, The Netherlands)

OCT OF THE AIRWAY WALL

First, in animal and human ex-vivo studies the feasibility of OCT to visualize different airway layers and structures, including the epithelial layer, lamina propria, glandular tissue, and cartilage was demonstrated [Figure 3] (1, 38-40). The use of OCT for the identification of bronchial lesions in humans in vivo has been evaluated, demonstrating that OCT can distinguish invasive carcinoma from carcinoma in situ and dysplasia from metaplasia, hyperplasia and normal (2).

In addition to the identification of airway wall structures and lesions, OCT has been investigated for its ability to quantify airway dimensions and related airway
remodelling. This is of great interest since obstructive lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are characterized by remodeling of the airway wall (41-43). The current available imaging technique to quantify airway wall remodeling is a high-resolution CT (HRCT), which is hampered by its limited resolution and has the drawback of radiation exposure.

Figure 3. Identification of airway wall layers by OCT. Cross-sectional OCT image of an in-vivo basal bronchus of the right lower lobe visualizing; the OCT probe (1mm diameter), airway lumen, epithelium, lamina propria, submucosa, and cartilage. OCT, Optical Coherence Tomography.
(Source: J.N.S. d’Hooghe MD, P.I. Bonta MD PhD, J.T. Annema MD PhD, Academic Medical Center Amsterdam, The Netherlands)

In porcine airways it was shown that OCT was able to quantify, separate airway wall layers including mucosal, submucosal and cartilage layers which correlated
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well with histology measurements (44). Coxson et al found a strong correlation between CT and OCT measurements of the lumen and wall area in 44 current and former smokers. Notably, the correlation between predicted FEV₁ and measured wall area for smaller airways was stronger for OCT than for CT (45). Likewise, in COPD smokers and non-smokers (4 per group) OCT measurements for the luminal- and total airway wall area, obtained using bronchoscopic navigation software for accurate matching, correlated well with both histology and CT (46). Furthermore, in COPD patients with different levels of airway obstruction there was strong correlation with OCT airway dimension parameters (4).

![Figure 4. OCT imaging of the pulmonary artery. Left panel: Right heart catheterization showing the catheter (black arrow) in the pulmonary artery with OCT probe in situ (white arrow), C=cor, L=lung. Middle panel: OCT cross section of a normal part of the pulmonary artery. Right panel: OCT cross section visualizing webs/bands (white arrow) of a pulmonary artery from a CTEPH patient. (Images kindly provided by prof. dr. N. van Royen and dr. H.J. Bogaard, Free University of Amsterdam, the Netherlands)](image)

Since these results were obtained by manually tracing the perimeters, it is comforting that Kirby et al found a high inter/intra-observer reproducibility of OCT measurements of airway wall parameters (32). However, automated software for airway wall measurements is highly needed. Recently, Suter et al, developed and validated a novel birefringence microscopy platform which is able to visualize and quantify airway smooth muscle (ASM) fibers (5). Since new therapies are developed targeting airway remodeling in general and ASM in particular, such as bronchial thermoplasty (BT) for severe asthma patients, airway wall dimension/ASM content quantification by OCT could play an promising role in patient selection for treatments that target airway remodeling (6)
OCT OF THE PULMONARY VASCULATURE

Pulmonary hypertension (PH) can be classified in 5 major categories. Pulmonary artery hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) share elevated pulmonary artery pressures but are characterized by different pathological vascular features (47). OCT is potentially useful in differentiating between PAH and CTEPH and possibly also other categories of PH (12, 13, 48). As such OCT might fulfil the promise of minimally invasive, optical biopsy. Tatebe et al showed that OCT in PAH demonstrated thickening of the media of the pulmonary artery wall as compared to healthy controls. In CTEPH, pulmonary arteries showed specific features compatible with either thrombotic occlusion and/or luminal bands/webs (12, 49) [Figure 4]. Furthermore, OCT can be used to evaluate the effectiveness of balloon pulmonary angioplasty (BPA) in 12 distal-type CTEPH patients (14).

In addition to the identification PH-specific pathologic features of the pulmonary artery by OCT, quantification of changes in pulmonary artery assessed by OCT was predictive for an unfavourable clinical outcome in patients with PAH (11). Dai et al quantified pulmonary artery remodelling by assessing 3 morphometric parameters (wall-area ratio, thickness-diameter ratio and thickness) of 2-6 OCT cross sections in 79 PH patients, 10 borderline PH patients and 35 non-PH subjects. Results showed a significantly increase of the 3 morphometric parameters in borderline PH and PH when compared with non-PH which significantly correlated with the mean pulmonary artery pressure and pulmonary vascular resistance (48). Moreover, when following 14 PAH patients after pharmacologic treatment a reverse remodeling (improvement of >2 of the 3 morphometric parameters) response was observed in 8 of the 14 PAH patients (48).

In the largest study of 64 PAH patients, 23 CTEPH patients and 17 controls, the intimal morphological changes were predominant in PAH patients as compared to CTEPH patients and controls. In 14 (60.9%) of the 23 CTEPH patients, OCT images could be obtained distal from the stenotic or occluded pulmonary arteries all showing features of intravascular bands/webs (13).

In conclusion, OCT may qualify as the technique to differentiate different types of PH, such as PAH and CTEPH. Furthermore, OCT might play a future role in guidance and monitoring of treatment in PH e.g. balloon pulmonary angioplasty in CTEPH.

OCT FUTURE PERSPECTIVES

OCT has potential to become a valuable imaging technique for assessing the airway wall (remodeling) in obstructive lung disease. Additionally, OCT might be
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of value for assessing pulmonary artery pathology (e.g. bands/webs in CTEPH) and remodeling (e.g. intimal thickening in PAH) in PH. With the use of quantified parameters, OCT might play a future role in patient selection and monitoring treatment response for specific treatments targeting airway/artery remodeling (e.g. bronchial thermoplasty/BPA). Technological advancements such as the birefringence microscopy platform for ASM detection will result in improved and more specific OCT imaging.

CONFOCAL LASER ENDOMICROSCOPY: TECHNIQUE

Confocal laser endomicroscopy (CLE) uses low power laser bundles (488nm or 600nm) in a fiber optic probe, that can be inserted into the working channel of a bronchoscope or even in the lumen of an EBUS/EUS needle to obtain real-time microscopic images of the tissue that is investigated. The backscattered light, from one specific tissue plane, is focused through a pin-hole, while the backscattered light from surrounding tissue is eliminated. This leads to high resolution imaging of one specific plane of tissue in focus.

The CLE technique visualizes tissue with resolutions up to 3.5 micrometer (µm), with a maximum depth of 240 µm and field of view of 600 µm, which enables real-time imaging of the elastin network of the alveolar space [Figure 5] and individual cells in a pulmonary tumor [Figure 6]. Based on the imaging target of choice, autofluorescence (for example for visualizing the elastin network of the lungparenchym) or a fluorescent dye, such as fluorescein or acriflavine hydrochloride (to visualize airway epithelium, pulmonary tumors and metastatic lymph nodes at a cellular level) can be used (7, 17, 19, 20, 50, 51).

In pulmonary medicine, 2 different CLE-techniques, probe and needle based are currently used. Probe-based CLE (pCLE) is most commonly used and involves a 1.8 mm diameter probe that fits through the working channel of a bronchoscope. By approximation of the tip of the probe to the lung tissue images are generated based on autofluorescence properties of elastic fibers in the alveolar septa and airways.(50, 51).

The second technique is needle-based CLE (nCLE), that can be combined with endosonography or CT guided biopsy by fitting a confocal miniprobe (diameter 0.91 mm) through the lumen of a 19 Gauge needle. By positioning the needle under ultrasound guidance in the tumor, a real-time “optical biopsy” can be performed [Figure 6]. Following CLE imaging the probe is retracted and a FNA is obtained. The technique is currently limited to transthoracic and esophageal approach because the probe does not fit through the commercially available EBUS needles. For this purpose, in most cases fluorescein is administered intravenously as a fluorescent dye.
Figure 5. Example of CLE imaging of lung parenchyma. Upper panel: HRCT-scan image of a patient diagnosed with desquamative interstitial pneumonia (DIP) a distinct form of interstitial lung disease (ILD), with abnormalities in the RLL (lower circle) and with normal appearance of the RML (upper circle). Left lower panel: increased image-density and filling of alveolar spaces in abnormal CLE image of corresponding diseased area on HRCT imaging. Left lower panel: CLE image corresponding to normal alveolar area on HRCT imaging.

(Source: L. Wijmans MD, P.I. Bonta MD PhD, J.T. Annema MD PhD, Academic Medical Center Amsterdam, The Netherlands)
Figure 6. Needle based CLE imaging of a lung tumor. Left panel: EUS image of a centrally located lung tumor, ES=lumen of the esophagus, T=Tip of the nCLE probe, N=19G biopsy needle. Middle panel: nCLE images from the inside of the pulmonary tumor; the dark aggregates represent tumor cells. Right panel: Corresponding cytological image of the fine needle aspirate showing aggregates of enlarged atypical cells with large nuclei, marked atypia and hyperchromasia, characteristic for an adenocarcinoma (May-Grünwald Giemsa stain, 200x).
(Source: L. Wijmans MD, J.T. Annema MD PhD, Academic Medical Center Amsterdam, The Netherlands)

pCLE OF THE LUNGPARENCHYMA

HRCT imaging provides excellent overview of the lung parenchyma but has limitations in detailed imaging. Current HRCT imaging has frequently difficulties distinguishing different ILD subsets resulting in the need for lung tissue biopsy by either VATS or cryobiopsy - procedures with a substantial morbidity in an already vulnerable population. As such, pCLE could potentially serve as a minimally invasive diagnostic technique in ILD. Alveolar proteinosis is a form of ILD that was shown to be characterized with pCLE-imaging by fluorescent floating amorphous substances in the alveoli lumen sticking to conglomerates along with alveolar macrophages. These features were reduced after a whole-lung lavage and were found in areas with and without abnormalities on HR-CT scan (15).

To examine the characteristics of lung cancer on pCLE imaging, a comparison with histology was performed by examination of 18 lobectomy specimens containing non-small-cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Three primary features for pCLE were found: alveolar dysesthetics with thickening of alveolar walls, alveolar edema and a large amount of macrophages. The stromal component for adenocarcinoma specimens had a highly fluorescent field penetrated by dark hollows, while squamous cell carcinoma specimens had stromal components that appeared as ‘biparously’ branching, highly fluorescent fibers. No stromal component was observed in any small-cell lung carcinoma specimen (18). Another difficulty with imaging malignant lesions is the actual localization and endobronchial detection of the lesion. The first case-reports where bronchial
navigation combined with CLE have recently appeared and showed that it was feasible to image a subcentimeter solitary pulmonary nodule (SPN) with pCLE in vivo and real-time (17).

nCLE OF MEDIASTINAL COMPARTMENT

Fine needle aspirations and biopsies are important diagnostic approaches for cancer diagnostics and analysis of mediastinal lesions. Although generally successful, these approaches have significant false negative rate, due to inappropriate needle placement. A (smart) needle such as nCLE might further increase the diagnostic yield.

The nCLE technique was first introduced in gastroenterology. nCLE criteria were described for different pancreatic masses, e.g. adenocarcinoma (dark cell aggregates, irregular vessels with leakages of fluorescein), chronic pancreatitis (residual regular glandular pancreatic structures), and neuroendocrine tumors (NET, black cell aggregates surrounded by vessels and fibrotic areas). These criteria correlated with the histological features of the corresponding lesions (52). Considering the low negative predictive value of EUS-FNA in pancreatic masses, nCLE findings can be helpful to rule out malignancy in case of an inconclusive EUS-FNA (52).

nCLE trial results in the diagnosis and staging of lung cancer showed the diagnostic feasibility in peripheral and centrally located pulmonary tumors using a transthoracic (19) and EUS approach (20). Furthermore, the feasibility of the EUS guided nCLE technique for imaging of metastatic mediastinal lymph nodes was shown (19). This report describes two distinct imaging characteristics of normal lymph node structure. The collagen-rich capsule of the lymph node is visualized as thin bright fibers on a dark background and the cortex of the lymph node has a bubbly appearance from loosely aggregated lymphoid-cells. Adenocarcinoma was characterized by dark clumps and in malignant lymphoma enlarged lymphoid centers were described (24). However due to the heterogeneity of the group studied, low numbers of each disease entity were available. The advantage of nCLE technique is that it allows a wider assessments across the organ of interest, which is more likely to reveal pathologic changes. Optical needle biopsy techniques, like nCLE may also help to reduce sampling error because it provides real-time microscopic details. In addition, optical biopsies may assist the endoscopist in confirming adequate tissue acquisition in centers where on-site cytopathologists are not available.
CLE: FUTURE PERSPECTIVES

The diagnostic scope of the CLE technique can be remarkably widened by the introduction of specific fluorescent markers capable of detecting specific respiratory-disease modulating entities (e.g., lung cancer-markers, microbial agents, signaling pathway proteins, medication). Currently there are no in-human reports in pulmonary medicine, however the first results of in human use of a labeled peptide in gastrointestinal lymph nodes are promising. A peptide specific for adenocarcinoma was administered and confocal endomicroscopy imaging found 3.8-fold greater fluorescence intensity for esophageal neoplasia compared with Barrett’s esophagus and squamous epithelium with 75% sensitivity and 97% specificity (53). No toxicity was attributed to the peptide in either animal or patient studies. Therefore CLE- recognition of fluorescent labeled entities could in the future potentially become helpful in guiding biopsies, monitoring of therapeutics and tumor detection.

Both nCLE and pCLE are currently investigational techniques in pulmonary medicine, that require further validation before the step into the clinic can be made. A recent official statement of the European Society of Gastrointestinal Endoscopy (ESGE) regarding the utilization of advanced endoscopic imaging in gastrointestinal endoscopy was recently published, stating that the development of validated classification systems is advocated to support the use of optical diagnosis in combination with advanced endoscopic imaging(54).

CONCLUSION

OCT and CLE are complementary, microscopic imaging techniques, that might provide important added value to current imaging modalities including HRCT and endosonography. Advantages are the ‘near histology’ resolution and the ‘real-time’ component of the imaging. CLE is promising for lung cancer detection, analysis of mediastinal lesions, with on the horizon the detection of pulmonary nodules by labeling of specific markers. The OCT technique has the potential to qualify as an airway wall/pulmonary artery remodeling biomarker, useful for patient selection and monitoring of treatment response. Validated, identification and quantification image analysis strategies for OCT and CLE imaging are needed to assess the added value in pulmonary clinical practice.
KEY POINTS

1. OCT generates real-time, highly detailed images on a resolution at ‘histology’ level of the airways and pulmonary vasculature; as such, OCT is able to identify and quantify airway- and vascular wall layers.
2. CLE provides real-time, high resolution images on a ‘cellular’ level of mediastinal nodes, intrapulmonary masses and alveoli.
3. OCT and CLE are innovative imaging techniques, that combined with bronchoscopy might be of added value for airway wall, mediastinal nodal, lung tumor, alveolar and vascular assessment.
4. Validated identification and quantification image analysis strategies are needed in dedicated clinical trials to assess the added value of OCT and CLE to existing imaging technologies

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Conflict of interest

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