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REVIEW ARTICLE

Diagnosis and evaluation of pulmonary diseases with endobronchial optical coherence tomography

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Abstract:

Optical coherence tomography (OCT) is a novel optical imaging technology with high resolution, the ultra fine probe makes it feasible to advance into medium and small airways for measuring luminal caliber and airway thickness. It was reported that endobronchial OCT might be of help for diagnosis and evaluation of pulmonary diseases. OCT could be performed to detect early lung cancer and precisely positioning for lesion biopsy, evaluate the severity of COPD and asthma, assess the airway injury, as well as explore the mechanism of pulmonary vascular and airway diseases.

Introduction

Optical coherence tomography (OCT) is a novel imaging technique which has ultra-high resolution at micrometer level and generates 2D or 3D real-time images by a minimally invasive probe (Gora, Suter, Tearney, & Li, 2017). OCT system was firstly applied in [ophthalmic](#) (Jia et al., 2015; Spaide, Klancnik, & Cooney, 2015) and cardiovascular diseases (Ali et al., 2016; Hoang et al., 2016; Jia et al., 2015). Subsequently, bronchoscopic guidance made it possible to detect lung and airway disorders due to its essential characteristics (Majkut, Sadr, Shimada, Sumi, & Tagami, 2015; Ozaki et al., 2016; Ramamoorthy et al., 2015): 1) ultrafine catheters (0.9mm in diameter) could be advanced into small airways for detection; 2) real-time and minimally invasive imaging modalities; 3) the entire airway wall can be displayed (scanning depth of 3-5mm) with resolution at the micron scale. Compared with other diagnostic methods for respiratory diseases (such as computed tomography, endobronchial ultrasound, transbronchial biopsy, etc. (Dincer, Gliksberg, & Andrade, 2015; Facciolongo et al., 2016; Mahesh, 2016), OCT might be a supplement in the diagnosis of small airway diseases and pulmonary nodules. In the present work, we reviewed the principles of OCT, its application and prospects for the evaluation of respiratory diseases.

Principle and procedure of OCT

OCT is mainly composed of an interferometer that produces low coherent light (near-infrared light with the wave length of 780-2500 nm) (Burgess & Hammond, 2007). Two reflecting light emitted by coupler is integrated and collected by a detector to produce an OCT image. Different components of tissues has variable optical reflectance and present with different OCT imaging density and grey values (Majkut et al., 2015; Ozaki et al., 2016; Ramamoorthy et al., 2015).

The OCT probe, ranged from 0.9 to 2.4 mm in diameter, scans with automated rotating and rotary auto-pullback, which makes it feasible to advance into medium and small airways for detection. Under the guidance of flexible bronchoscope, the probe could be inserted into the target bronchus through the working channel. Following the patients are asked to hold their breath at the end of a full inspiration, the OCT catheter is pulled back to the target bronchus for automatic scanning, obtaining cross sectional and longitudinal images of the airway structure.

Application of OCT in lung and airway diseases

Feasibility study

In 1997, Tearney et al. (Tearney et al., 1997) firstly used OCT to detect the tracheas of rabbits *in vivo*, and found that airway epithelium and cartilage could be detected by OCT imaging. Yang et al. (Yang et al., 2004) performed OCT and histological analysis on excised swine airways, and concluded that OCT could clearly demonstrate the airway epithelium, lamina propria, submucosal glands, cartilage and perichondrium. In 2015, Chen et al. (Chen et al., 2015)

examined 3rd-9th generation of bronchi by using OCT, computed tomography (CT) and histological analysis, indicating that airway structures imaged with OCT had a good correlation with those shown by CT scans and histological examination.

OCT in bronchogenic carcinoma

Current diagnostic modalities for early bronchogenic carcinoma are limited by low imaging resolution and difficult in sampling minor lesions (Hariri, Applegate, et al., 2013). In 2005, Tsuboi et al. (Tsuboi et al., 2005) reported that airway tumors exhibited an inhomogeneous distribution and loss of layer structures in OCT images. Whiteman et al. (Lam et al., 2008; Whiteman et al., 2006) and Lam et al. (Lam et al., 2008) suggested that OCT imaging visualized squamous metaplasia of airway epithelial tumors, and indicated that the airway epithelium of invasive carcinoma was thicker than that of pre-invasive carcinoma, while atypical hyperplasia was thicker than that of metaplastic tissue. Hariri et al. (Hariri et al., 2015) studied adenocarcinoma, squamous carcinoma and poorly differentiated carcinoma using OCT and histological examination, and found OCT detection had a positive diagnostic rate of 80%. Moreover, Hariri et al. (Hariri, Mino-Kenudson, et al., 2013) and Shostak et al. (Shostak, Hariri, Cheng, Adams, & Suter, 2018) introduced OCT to guide transbronchial needle aspiration (TBNA), indicating that OCT guidance might improve the positive diagnostic rate of pulmonary lesions.

OCT in chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterized by a decrease or loss of pulmonary elastic recoil and airflow limitation caused by emphysema and airway remodeling (Rabe & Watz, 2017), particularly in small airways. The changes of pulmonary function often lag behind small airway disorders, hence, routine lung function test is limited in the diagnosis and evaluation of early COPD (Liao et al., 2015). Coxson et al. (Coxson et al., 2008) examined smokers by using OCT, lung function test and high resolution CT (HRCT), and found a good correlation between OCT and HRCT measurements. Moreover, OCT was more sensitive in reflecting FEV₁ changes caused by obstructive airway diseases, and more accurate for measuring airway wall thickness. The results suggested that OCT could better reflect COPD small airway disorders compared with CT scanning. Ding et al. (Ding et al., 2016) explicated the structural change of small airway in heavy smokers with normal lung function was similar to that of COPD patients, both showing small airway luminal stenosis and airway wall thickening. The results indicated that OCT could identify small airway disorder of early COPD, especially in the high-risk population of heavy smokers with normal lung function. Overall, endobronchial OCT could sensitively reflect airway remodeling and small airway disorders in COPD, and thus be of importance for the early diagnosis and evaluation of COPD.

OCT in asthma

Asthma is mainly characterized by chronic airway inflammation and airway remodeling. Asthmatic airway remodeling induced by airway smooth muscle thickening, glandu-

lar hyperplasia and fibroplastic proliferation (Papi, Brightling, Pedersen, & Reddel, 2017). Suter et al. (Suter et al., 2017) conducted OCT imaging in patients with allergic asthma (AA) and allergic non-asthma (ANA), and observed significant increase of airway remodeling in AA compared with that of ANA, suggesting that OCT could help assess asthmatic airway remodeling *in vivo* and improve determination of disease phenotype. Kirby et al. (Kirby et al., 2015) introduced OCT for evaluation of the effect of bronchial thermoplasty (BT) on severe asthma, and found that OCT could demonstrate changes of airway structure components including secretion, airway glands and smooth muscles, inflammatory infiltration and airway wall thickness, suggesting that OCT could be help for the assessment of BT on severe asthma and patients selection. Adams et al. (David C. Adams et al., 2016) combined OCT and birefringence microscopy to observe the thickness of airway smooth muscle *in vitro*, evaluate the contractility of smooth muscle, and compare airway structures between healthy controls and patients with asthma. The results suggested that OCT could clearly exhibit the structural morphology of airway smooth muscle and airway components changes in patients with asthma.

OCT in benign tracheal stenosis

Endotracheal intubation is the most common cause of benign airway stenosis (Gelbard et al., 2015; Jefferson, Cohen, & Rutter, 2016; Plojoux et al., 2015; Rahman, Fruchter, Shitrit, Fox, & Kramer, 2010). Karamzadeh et al. (Karamzadeh et al., 2005) and Ridgway et al. (Ridgway et al., 2008) reported that OCT detection clearly detected the structural changes of airway injury after endotracheal intubation, suggesting that OCT could be used to monitor airway structural changes during endotracheal intubation. Some studies combined endobronchial ultrasound with OCT to observe airway structures before and after laser ablation for airway stenosis caused by endotracheal intubation (Murgu & Colt, 2013; Murgu, Colt, Mukai, & Brenner, 2010). The results indicated that OCT combined with other modalities could help guide interventional pulmonary physicians to identify appropriate therapeutic strategies, and to avoid stenosis recurrence and correlated complications caused by repeated laser treatment on stenotic airway segments.

OCT in inhalation airway injury

Smoke inhalation injury refers to lung injury and acute respiratory distress syndrome as a result of injury of the respiratory tracts and lung parenchyma caused by heat and smoke (Walker et al., 2015). Brenner et al. (Brenner et al., 2007) used animal models of inhalation injury and reported that OCT could show early thickening of the airway wall after smoke inhalation, suggesting that OCT was helpful for early diagnosis of smoke inhalation injury. A subsequent study conducted OCT imaging to measure the changes of upper trachea, lower trachea and proximal bronchus after smoke inhalation injury, indicating that the wall thickness of the lower trachea progressively increased, and was positively correlated with the arterial carboxyhemoglobin level. The findings suggested that the extent of thickening of the lower trachea measured by OCT was valuable for the evaluation of smoke inhalation airway injury (Brenner et al., 2008).

OCT in cystic fibrosis

The pathological changes of cystic fibrosis (CF) are characterized by mucus retention and airway obstruction due to mucociliary clearing dysfunction. In 2013, Liu et al. (Liu et al., 2013; Liu et al., 2014) reported that OCT could detect the thickness of airway surface liquid and ciliary function, including ciliary beat frequency and mucociliary transport rate. In 2016 Chu et al. (Chu et al., 2016) firstly confirmed the feasibility of OCT to measure the thickness of airway surface mucus and ciliary beating *in vivo*. Birket et al. (Birket et al., 2018) used OCT to study CF in transmembrane conductance regulator (CFTR) gene knock-out mice, and concluded that airway submucosal glands played an important role in the onset of CF, the injured airway epithelium did not increased mucus viscosity and mucociliary transport obstruction with the absence of glands. Furthermore, the effect of ivacaftor (a regulator of CFTR) on airway mucosal cilia of CF could be evaluated by OCT measurement (Birket et al., 2016; Raju et al., 2017).

OCT in pulmonary vascular diseases

The deterioration of pulmonary hypertension (PAH) would increase the right ventricle pressure and lead to dyspnea (Chia, Wong, Faux, McLachlan, & Kotlyar, 2017). Hou et al. (Hou et al., 2010) used OCT to scan the pulmonary arteries of patients with PAH, and found that OCT was superior to intravascular ultrasound for accurately measuring the arterial intima thickness. Tatebe et al. (Tatebe et al., 2010) performed OCT to study PAH and found that the pulmonary artery intima of PAH patients was significantly thicker than that of healthy subjects. Subsequently, they further confirmed that OCT was more effective in the diagnosis of chronic thromboembolic pulmonary hypertension compared with intravascular ultrasound (Tatebe et al., 2013). In addition, OCT had been used to distinguish red pulmonary artery blood clots from the white ones (Hong, Wang, Zhong, Zeng, & Zhang, 2013; Hong, Wang, Zhong, Zeng, & Wu, 2012), and to evaluate the effect of pulmonary angioplasty in patients with PAH (Dai, Fukumoto, et al., 2014; Dai, Sugimura, et al., 2014; Sugimura et al., 2012).

OCT in obstructive sleep apnea

Obstructive Sleep Apnea (OSA) is a sleep-related respiratory abnormality characterized by reduced or stopped respiratory airflow during sleep. Pharyngeal abnormality is considered to be the major pathological change in OSA. Isono et al. (Isono et al., 1997) found that the pharynx of OSA patients closed more easily as compared to healthy subjects. Thus, subsequent studies used OCT to measure the diameter, length, and morphology of the upper airway in patients with OSA, and found that OSA patients have a smaller palatopharyngeal cross-sectional area than individuals without OSA (Armstrong et al., 2006; Leigh et al., 2008; Walsh, Leigh, Paduch, Maddison, Philippe, et al., 2008). Walsh et al. (Walsh, Leigh, Paduch, Maddison, Armstrong, et al., 2008) found that the cross section of upper airway tended to be circular when OSA patients were in a lateral position, suggesting that airway collapse could be avoided by refraining from being in a supine position.

Future prospects

Some limitations should be taken into consideration although OCT could clearly detect the airway structures: 1) OCT imaging could not completely substitute for histopathological analysis; 2) secretion and respiratory movement might affect the OCT imaging; 3) automatic image processing requires further optimization and improvement; 4) detection depth limits OCT to the evaluation of the entire tracheal wall and lung parenchymal diseases; 5) the OCT probe could not be used to explore the whole lung or more distal small airway. Therefore, future studies could perform OCT in combination with other diagnostic modalities (Gora et al., 2017). OCT combined with electromagnetic navigation bronchoscope (ENB) can help accurate positioning the target airway, and improve the reproducibility of OCT imaging, which might be of importance for the comparison of airway disease status before and after treatment, as well as the long-term follow-up and diseases evaluation. OCT combined with respiratory gating technique could reduce the measurement error caused by respiratory motion artifacts, and thus more accurately measure airway diameter and guide the design and selection of airway stents (McLaughlin et al., 2009). Researchers have developed an OCT derivative technology to segment the airway and secretion layer during image processing, which could help reduce the effect of airway secretion on OCT imaging (David C Adams et al., 2017).

In conclusion, OCT imaging might be valuable for detection and early diagnosis of airway disorders (particularly in identifying small airway disorders and accurate positioning early tumor), as well as evaluating the therapeutic efficacy for lung diseases.

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