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Evaluation of Tracheal Imaging by Optical Coherence Tomography

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Abstract

Background: Optical coherence tomography (OCT) is a new technology capable of generating high resolution cross-sectional images of complex tissue in real time. Analogous to ultrasound, OCT measures backscattered light intensity using coherence interferometery to construct topographical images of complex tissue. Since OCT uses infrared light rather than acoustic waves, its spatial resolution is exceptionally high (2–10 μm). Recent advances in data acquisition, analysis, and processing enable real-time imaging, and make OCT a potentially valuable tool for pulmonary airway diagnostic applications, including assisting directed airway biopsies. ***Objective:*** This study evaluates feasibility of OCT for delineating proximal airway microstructures in various animal as well as human tracheas. ***Methods:*** Excised trachea samples from New Zealand white rabbits, Duroc pigs, and human trachea were imaged using a compact, 1,300-nm broad-band superluminescent-diode-based prototype fiber OCT device we constructed. The resulting structural OCT images were compared to conventional hematoxilin and eosin (HE) stained histological sections from the same samples. ***Results:*** OCT was able to delineate microstructures such as the epithelium, mucosa, cartilage, and glands in all samples. ***Conclusion:*** These findings suggest that integration of OCT with flexible fiberoptic bronchoscopy could enhance pulmonary diagnostic medicine and detection of pathologic tissue changes in various respiratory diseases.

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Introduction

Optical coherence tomography (OCT) is a new technology capable of generating high resolution cross-sectional images of complex tissues in real time. OCT is analogous to ultrasound in that it measures backscattering intensity of infrared light in order to construct a topographical image of the tissue. Compared to ultrasound, OCT has the potential for much higher resolution (2–10 μm vs. 40–50 μm) imaging and higher sensitivity than other currently available imaging modalities [1]. However, there is an inverse relationship between resolution and depth of imaging. As resolution increases, the depth of penetration of the images decreases. Depth of OCT penetration is currently at approximately 3–5 mm. The initial clinical applications of OCT were described for retinal scanning and imaging of other ocular structures in ophthalmology. Past studies have examined the ability of OCT to evaluate a wide range of ophthalmic diseases, such as macular degeneration, retinopathies, and glaucoma [2, 3]. Due to its

Fig. 1. Schematic of OCT imaging system. The light source of a 1,310-nm broadband superluminescent diode with 50 nm bandwidth (FWHM), and the theoretical resolution of 10–15 μm. The light source was coupled with He-Ne laser guidance beam.
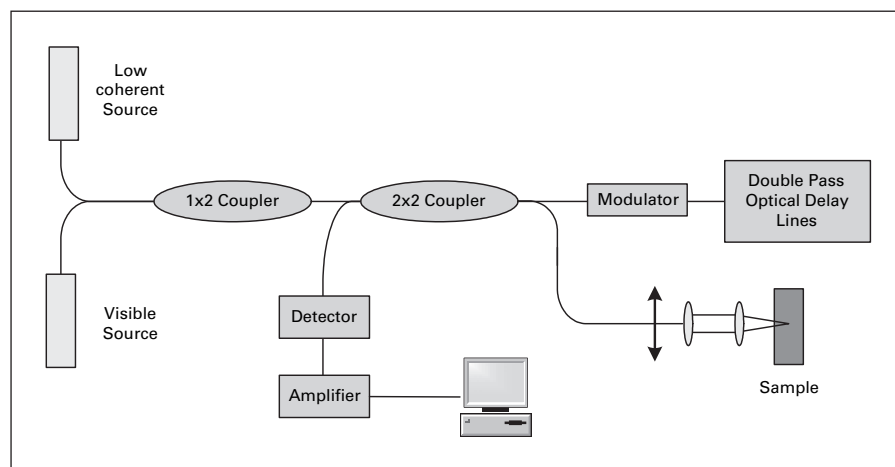
transparent nature with minimal scattering and maximal penetration, the retina provides a uniquely suitable medium for OCT imaging. However, in other more opaque tissues, attenuation due to scattering and absorption becomes more significant. More recently, OCT has been evaluated for imaging complex tissues such as the skin [4], vasculature [5], gastrointestinal tract [6], urinary tract [7], and pancreatobiliary tract [8].

There are relatively few studies focusing on OCT imaging of the respiratory tract [9]. Certain characteristics of OCT, including high resolution rapid imaging adaptable to flexible fiberoptic administration, suggest that it may be a uniquely suitable modality for imaging and detecting many pulmonary diseases. Recent advances in data acquisition, analysis and processing have enabled near real-time OCT imaging. One limitation of OCT is its shallow depth of penetration, caused by scattering, reflection, and absorption of light in tissues. This difficulty can be partially overcome by careful selection of near infrared wavelengths of the light source for the tissues being examined. High resolution at depths of 2–3 mm can be achieved by using wavelengths in the 1,300-nm range, a reasonably well optimized range for airway tissue. This depth of penetration is adequate for many important diagnostic situations in airway diseases and other pulmonary medicine applications. Potential applications include evaluation of airway inhalation injury, lung transplant airway assessment, evaluating the extent of superficial malignancies and improving the accuracy of endobronchial biopsies. For analogous reasons, pleural application of OCT technology can be envisioned as well.

This purpose of this study is to examine the feasibility of upper airway imaging in multiple species through the use of OCT. In a study conducted by Pitris et al. [9], samples from human upper respiratory tract were imaged using a short pulse chromium-forsterite laser (λ 1,280 nm, and $_\Delta\lambda$ 130 nm). This current study seeks to further advance this field of investigation beyond that initial report. Several advances have been made in the OCT system design since the original report [9]. The OCT data acquisition rate and processing time have been greatly shortened from 10–30 s to less than 1 s per image; so the display can virtually be achieved in real time. A superluminescent diode with a center wavelength of 1,310 nm and a bandwidth of 70 nm was used for tracheal tissue imaging. The computer-reconstructed images have a pixel size of 10 × 10 μm. Evaluating multiple species enables us to examine airways comparable in scale not only with adult patients, but also with neonatal/pediatric patients and assess the OCT applicability of potential animal models for future studies.

Materials and Methods

A simplified diagram of the OCT system design is shown in figure 1. A low temporal coherence laser light source, near the infrared wavelength, is connected to a Michelson interferometer. The light passed into the interferometer is split into sample and reference beams. The split beams are then reflected back from the sample surface and a rapidly translating reference mirror, respectively. These reflected beams are then recombined at the partially reflecting beamsplitter in the interferometer, producing a detectable interference pattern whenever the reference arm distance coincides with the coherence path distance of the reflected sample beam. The generated interference signal is detected by a photodiode, followed by signal processing and data acquisition by a computer. Finally, a cross-sectional image can be constructed by repeating the measurements of axial profiles of adjacent points along a sampling line.

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The transverse resolution of the OCT image is an optical property of the lens used in the system [1], where f is the focal length, d is the spot size, and λ is the wavelength.

$$Dx \text{ (transverse resolution)} = \frac{4\lambda}{\pi}\frac{(f)}{(d)}$$

In other words, if the lens aperture increases, the transverse resolution decreases. On the other hand, transverse resolution is directly proportional to the focal length. The axial resolution is determined by the bandwidth of the light source:

$$Dz \text{ (axial resolution)} = \frac{2\ln(2)\lambda^2}{\pi(_\Delta\lambda)}$$

where λ is the wavelength, and $_\Delta\lambda$ is the source bandwidth. It, therefore follows from equation [2] that increasing bandwidth of the light source can lead to proportional improvement in axial resolution at a given wavelength. The relatively inexpensive SLD selected for this prototype is capable of generating 70 nm wide bandwidths at full width half maximum (FWHM) [10]. FWHM denotes that the bandwidth is the range covered between the two points where the transmission percent is half of its maximum.

This OCT system can perform cross-sectional imaging of complex airway tissues with an axial and transverse resolution of 10–15 μm. The 14 mm × 1.3 mm airway images were acquired and displayed in 'real time' on a computer screen. An aiming guide beam (He-Ne laser, λ = 633 nm) was coupled to the system, since the OCT light source is not visible.

Tracheas were harvested from healthy New Zealand White (NZW) rabbits (n = 8), Duroc pigs (n = 4), and a human sample. A sagittal cut was made on the posterior surface of the tracheal tissues along the trachealis muscle. The tissues were sectioned into 1.5 × 1.5 cm flat samples. The samples were mounted on corkboards of the appropriate size with the lumen of the trachea exposed. The samples were gently rinsed with saline to clean the mucous and debris, and maintained in isotonic saline solution. Immediately before the OCT scan, a thin layer of K-Y Lubricating Gel (Johnson & Johnson Products Inc, New Jersey, N.J., USA) was applied on the surface to prevent dehydration. Small notches were cut on the sample edges to mark the location to be scanned. A sagittal scan was performed between the notches with guidance from the He-Ne laser source. The OCT scans were performed within hours of the animals' sacrifice. The human autopsy specimen was stored in a cold room before sampling.

Following the scan, the tissues were fixed in 10% formalin for 24 h and the scanned regions of the samples were stained with routine hematoxylin and eosin (HE) dyes, processed into standard paraffin blocks, and sectioned into 5-μm slices for comparative histological examination.

Results

The initial screening images were scanned covering a 14-mm by 1.3-mm area, and the areas of interest were rescanned with the highest resolution at 2 mm by 1.3 mm. The range of depth of penetration was between 1–3 mm deep. The images were rendered in logarithmic intensity scale with the least backscattering areas presented as black. An OCT image of a NZW rabbit trachea is shown in figure 2 with the associated histology. The corresponding layers of the epithelium, mucosa, and cartilage are clearly differentiated as well as a number of glandular tissues. The images of Duroc pig (fig. 3) and human (fig. 4) further demonstrate the ability of OCT to delineate epithelial, mucosal, and cartilaginous layers in different sizes of the tissues.

Discussion

High-resolution OCT imaging can be performed through small diameter flexible fiberoptics (with a fiber-optic diameter of 9 μm and imaging lenses <1 mm diameter). Unlike ultrasound imaging, contact between the probe and imaging tissue is not needed. The ability of OCT to delineate different airway layers such as the epithelium, mucosa, and cartilage was verified in all samples. Figures 2–4 show the high degree of similarity in images of cartilage and mucosal glands between OCT and histological sections.

It must be noted that capability of OCT has inherent limitations. There is a trade-off between the four fundamental design parameters (optical power, acquisition speed, axial resolution, and sensitivity), expressed by the following relationship:

$$\frac{\text{SNR } Vs}{Ps\,Dz} = \text{constant}$$

where Dz is axial resolution, and Ps optical power [10]. Vs is the velocity of the reference mirror oscillation, thus speed of data acquisition. SNR is signal to noise ratio, representing sensitivity. Consequently, the optimal balance between speed of image acquisition against resolution must be considered for individual clinical application needs (since optical power must be limited).

Generally, penetration depth of OCT is attenuated by absorption and scattering. Both of these phenomena are wavelength dependent. The red end of the spectrum has minimum absorption of water and blood; the major constituents of normal tissue, while scattering increases with increasing frequency [11]. Thus, at frequencies in the 1,100- to 1,300-nm range, a balance between increased light transmittance, scattering, and resolution appears to be an optimal region for depth of penetration of OCT for imaging of airway tissues, though additional studies would be important for confirmation. Future technical research development and stable, affordable broader band Gaussian laser sources will improve resolution capabilities.
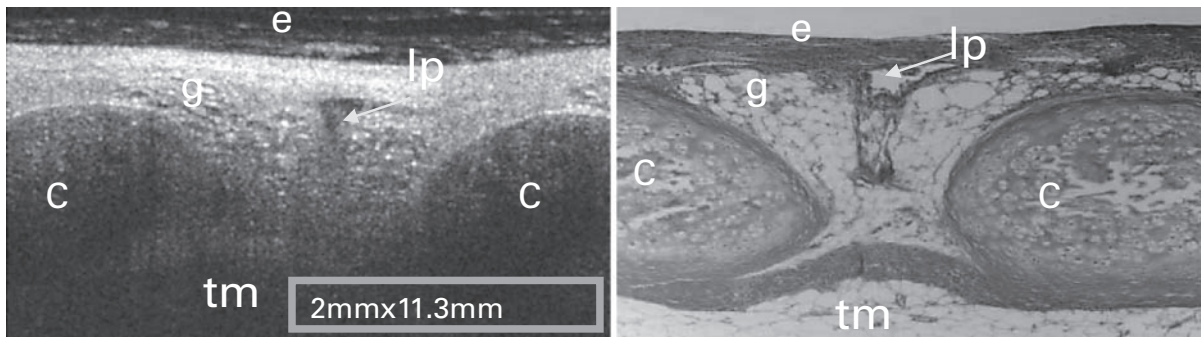
Fig. 2. Comparison between OCT and HE section of a rabbit trachea. Epithelium (e), mucosa (m), and cartilage (c) are clearly differentiated as well as a number of glandular tissues (g) and an artificial tear (arrow).
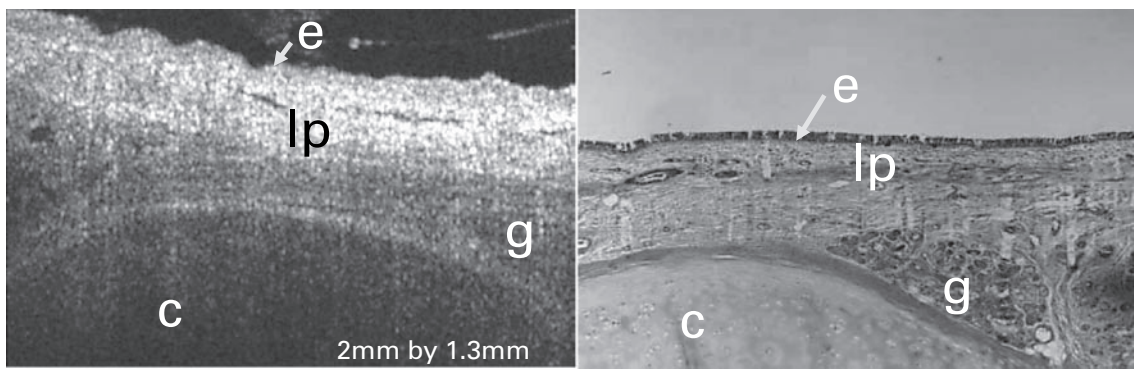

Fig. 3. Comparison between OCT and HE section of a pig trachea. OCT image corresponds to the area outlined in the HE section.
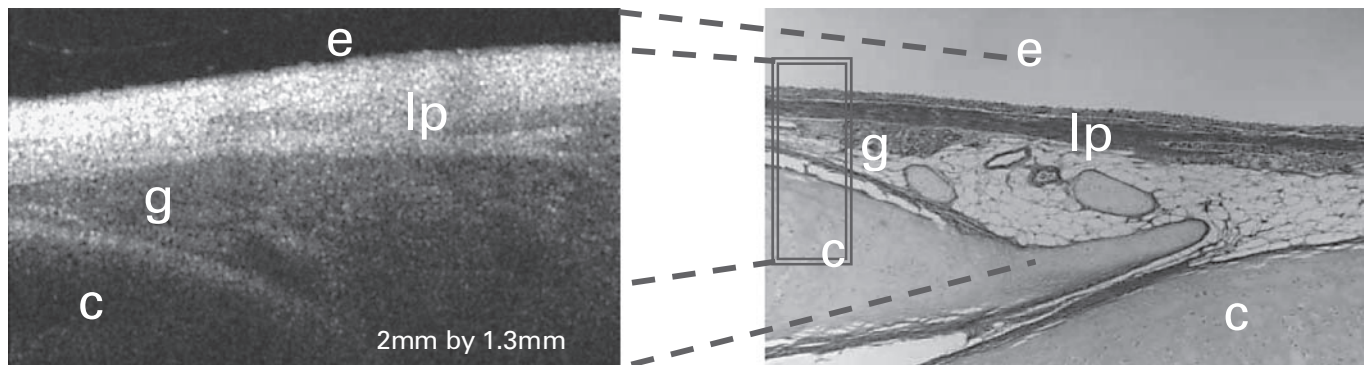

Fig. 4. Comparison between OCT and HE section of a human trachea.

Identification of substructures such as mucosal, glandular tissues and submucosal structures could become a basis for assessing different pathological changes. Our results demonstrate that OCT images of these structures are comparable to histology images in different animal models, and support the concept that, with further development, OCT could become a powerful technology in pulmonary diagnostic medicine, by providing a means to evaluate these microstructures and monitor structural changes and disease progression over time.

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Future research is needed in areas of integration of OCT with flexible fiberoptic bronchoscopic probes and detection of pathologic tissue changes in various respiratory diseases. Pulmonary diseases that result in subsurface airway morphology changes could be studied with OCT. OCT would be a particular asset in pulmonary diseases where invasive biopsy would be impractical or infeasible. Furthermore, 'structural OCT' can be combined with polarization optics for tissue birefringence analysis, and spatially localized high resolution OCT Doppler flow analysis, collectively referred to as 'functional OCT,' [12, 13]. As we move to very high resolution optical diagnostics at any site, including airways, one is looking at progressively smaller regions. Using autofluorescence bronchoscopy is now being examined in our lab to localize areas of interest in the airway. The areas of suspicion highlighted by autofluorescence are then examined using high resolution OCT. In this manner, the field of interest is narrowed using autofluorescence [14]. Autofluorescence is sensitive but non-specific. Therefore, OCT will hopefully increase the specificity in suspicious regions.

The micron scale resolution of OCT produces images approaching that of conventional 'gold standard' histology. Near real-time image acquisition, enabled by recent technical advances, makes OCT more suitable for in vivo usages. OCT is capable of almost real-time imaging of rather small sections in vivo since the respiratory cycle is relatively slow and motion artifact is not a significant issue at the capture rate of about one frame per second. We are currently imaging trachea and lung in vivo and find that it is still possible to image at this rate without any major issues. Moreover, newer broader bandwidth laser systems are being developed now that can deliver 1-μm axial resolution. At this resolution, nuclei and cell walls can be easily distinguished. It remains uncertain whether it will be possible to definitely differentiate dysplasia from malignancy with OCT, but it is not unlikely that this will happen in the near future.

Because of its compact fiberoptic design, OCT can be integrated to a wide variety of instruments, such as endoscopes, laparoscopes, and catheters. The initial pulmonary endoscopic application of OCT may be for guidance to improve safety and yield during conventional endobronchial biopsy. With further technical advances and translational studies, OCT may become useful as an endoscopic pulmonary screening and diagnostic tool. The potential for structural and functional OCT in pulmonary medicine is encouraging.

Acknowledgements

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