New technologies for *in vivo* ultrastructural and functional imaging using optical coherence tomography

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Optical coherence tomography (OCT) is a noninvasive imaging technique that provides microscopic tomographic sectioning of biological samples. OCT fills a valuable niche in imaging of tissue ultrastructure, providing subsurface imaging with high spatial resolution (~10 μm) in three dimensions and high sensitivity (>110 dB) *in vivo* with no contact needed between the probe and the tissue. With single-mode fiber optic implementation, OCT has been adapted to minimally invasive diagnostic imaging technologies such as endoscopy and laparoscopy. In this application OCT provides the physician with near-histological resolution imaging of sub-surface tissue morphology, potentially aiding in biopsy site selection or even approaching the goal of "optical biopsy." In order to be appealing for *in situ* diagnostics, however, OCT must provide the clinician with near real-time imaging. We have developed a high speed OCT system and have demonstrated, for the first time, *in vivo* imaging at various frame rates up to video rate. Real time imaging has allowed visualization of dynamic events without motion artifacts as well as visualization of features and structures in physiological samples, which may be overlooked or misinterpreted in still images.

We report on the design and initial clinical experience with a real-time endoscopic optical coherence tomography (EOCT) imaging system. Several technological innovations are introduced which improve EOCT efficiency and performance. Recent studies using the EOCT prototype in gastrointestinal (GI) endoscopy show that EOCT can clearly differentiate mucosal layers and reveal mucosal and submucosal structures in several GI organs. These initial data indicate a positive potential for EOCT as a screening tool for pre-cancerous metaplastic and dysplastic mucosal morphologies, complimenting, or perhaps replacing the practice of random biopsy. EOCT may also prove a useful tool for staging of early mucosal cancers, and monitoring and guidance of endoscopic therapies and surgeries.

Color Doppler optical coherence tomography (CDOCT) is a functional extension of OCT that can image flow in turbid media such as biological tissue, with spatial resolution similar to OCT. In CDOCT, phase-sensitive detection is used to detect localized Doppler shifts of the probe light induced by moving scatterers in the sample. We report the first demonstration of *in vivo* imaging of human blood flow using CDOCT. Images of bi-directional blood flow in the human retina were acquired with an OCT system using a modified slit lamp device in the sample arm. This technology holds the potential to aid in the diagnosis of several important ocular diseases, including diabetic retinopathy, glaucoma, and age-related macular degeneration.

We have also developed a CDOCT system capable of imaging flow in real time. Time-domain Doppler processing of the interferometric signal is accomplished in hardware using a novel autocorrelation technique. We demonstrate, for the first time, real time imaging of bi-directional flow with CDOCT in a phantom consisting of intralipid solution flowing in glass capillaries. This technology may potentially allow *in vivo* flow imaging for medical applications such as perfusion monitoring, and endoscopic evaluation of bleeding peptic ulcers.