NEW METHODS

Endoscopic Doppler optical coherence tomography in the human GI tract: initial experience

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Background: Expanding the current endoscopic optical coherence tomography (OCT) system with Doppler capability may augment this novel high-resolution cross-sectional imaging technique with functional blood flow information. The aim of this feasibility study was to assess the clinical feasibility of an endoscopic Doppler OCT (EDOCT) system in the human GI tract.

Methods: During routine endoscopy, 22 patients were imaged by using a prototype EDOCT system, which provided color-Doppler and velocity-variance images of mucosal and submucosal blood flow at one frame per second, simultaneously with high-spatial-resolution (10-25 μ m) images of tissue microstructure. The images were acquired from normal GI tract and pathologic tissues.

Observations: Subsurface microstructure and microcirculation images of normal and pathologic GI tissues, including Barrett's esophagus, esophageal varices, portal hypertensive gastropathy, gastric antral vascular ectasia, gastric lymphoma, and duodenal adenocarcinoma, were obtained from 72 individual sites in vivo. Differences in vessel diameter, distribution, density, and blood-flow velocity were observed among the GI tissue pathologies imaged.

Conclusions: To our knowledge, this is the first study to demonstrate the feasibility of EDOCT imaging in the human GI tract during routine endoscopy procedures. EDOCT may detect the different microcirculation patterns exhibited by normal and diseased tissues, which may be useful for diagnostic imaging and treatment monitoring.

Optical coherence tomography (OCT)¹ is an emerging endoscopic imaging technique that can visualize mucosal and submucosal microstructure at the micrometer scale.²⁻⁸ Analogous to pulse-echo sonography, OCT performs cross-sectional imaging by sending near-infrared light into tissue and by detecting reflected light from tissue structures at different depths. A low-coherence light source and an optical interferometer permit highresolution (~10 μm) depth discrimination. By using optical fibers, endoscopic OCT systems perform imaging via a catheter through the accessory channel of endoscopes, similar to miniprobe EUS. Currently, the axial resolution (~10 μm) of endoscopic OCT is approximately 10-fold better than high-frequency (12 MHz) EUS. 9 Initial clinical studies of OCT in the GI tract have been promising; for example, OCT has been shown to be highly sensitive and specific for the detection of specialized intestinal meta-

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plasia.⁸ Functional OCT imaging was developed with the addition of Doppler measurements^{10,11} and has been demonstrated in human retina¹² and skin¹³ in vivo. Doppler OCT can serve as an important diagnostic adjunct, enabling the detection and the monitoring of changes in microvasculature after therapeutic intervention¹³⁻¹⁵ and may be useful for assessment of vascular disease progression.

The aim of the present study was to evaluate the clinical feasibility of in vivo imaging of mucosal and submucosal blood flow by using the endoscopic Doppler OCT (EDOCT) system in both normal and diseased conditions of the GI tract. Here we present our first clinical experience with this new technology, used during 22 endoscopic procedures.

PATIENTS AND METHODS

Patients

Twenty-two patients (10 women, 12 men), with a mean age of 63 years (range 36-88), undergoing routine EGD or

flexible sigmoidoscopy at St. Michael's Hospital (Toronto, Canada) were enrolled in this study and were imaged with EDOCT. Informed consent was obtained from each patient. The study was approved by the Research Ethics Review Board of St. Michael's Hospital. Indications for endoscopy included surveillance of Barrett's esophagus (BE), gastric antral vascular ectasia (GAVE), gastroesophageal reflux, esophageal varices, portal hypertensive gastropathy (PHG), esophageal/gastric/duodenal tumors, and radiation proctitis. The patients were prepared per standard clinical endoscopy procedures. As the endoscope was advanced, pathologic lesions were identified, first, based on the white-light endoscopic appearance. For both normal and pathologic sites, the EDOCT imaging and routine biopsies then were performed from distal to proximal as the endoscope was withdrawn. Because this was a feasibility study, not all normal sites were imaged to avoid unduly lengthening the procedure time.

EDOCT imaging

We previously reported an EDOCT system suitable for simultaneous subsurface imaging of microstructure and microcirculation in the GI tract. $^{16\text{-}18}$ Our EDOCT system can detect bidirectional blood flow with a velocity sensitivity better than 100 $\mu m/s$ when operating in color-Doppler mode, which conventional Doppler US techniques cannot achieve. Our system also displayed the variance of blood-flow speed, which can potentially quantify flow as fast as 10 cm/s, yet maintains sensitivity to capillary microcirculation. For easy clinical interpretation, the structural images are displayed in logarithmic gray scale, identical to EUS and another OCT system.⁵ Color-Doppler OCT information is displayed with the same color map used in color-Doppler EUS, and the velocity variance image is displayed in a "hot" color scale as in power-Doppler US. The technical details of the EDOCT system have been described previously. 17,18 Briefly, a custommade motorized scanner (Fig. 1A) was mounted below the hand controls of the endoscope (Model GIF-IT140; Olympus Optical Co, Ltd, Tokyo, Japan) and a catheter (2-mm outer diameter) was passed through the accessory channel of the endoscope (Fig. 1B). At the distal end, the plastic catheter had a transparent cover of 0.3-mm thickness. An optical fiber, terminated with a side-viewing imaging tip, was translated back and forth within the catheter (Fig. 1C) by the scanning motor. The catheter was placed in gentle contact with internal mucosal surfaces under videoendoscope guidance (Fig. 1D). The imaging probe provided cross-sectional images of the luminal wall, with fields of view approximately 2 mm (lateral) by 1.5 mm (depth). The spatial resolution of the EDOCT images was about 25 µm (lateral) by 10 µm (depth), and the minimum detectable velocity was ~100 μm/s when acquiring EDOCT images at 1 to 2 frames per second. The blood flow velocity was calculated by using the Doppler equation,

Capsule Summary

What is already known on this topic

- Optical coherence tomography (OCT) can cross-sectionally image mucosal and submucosal structures at the micrometer level.
- As a mini-probe through the accessory channel of the endoscope, OCT has about 10-fold better resolution than high-frequency EUS.
- Endoscopic Doppler OCT (EDOCT) allows for functional OCT imaging and monitoring of changes in microvasculature.

What this study adds to our knowledge

- In a single-center, pilot and feasibility study on 72 subjects, EDOCT was used to assess differences in vessel diameter, distribution, and blood flow patterns in normal and abnormal upper gastrointestinal epithelia.
- EDOCT is a promising modality for functional imaging and disease monitoring.

 $V = \frac{\lambda}{2n\cos\theta} f_D$, where $\lambda = 1.3~\mu m$ is the EDOCT wavelength, $n \approx 1.4$ is the tissue average index of refraction, θ is the angle between the blood flow and the optical beam, and f_D is the Doppler frequency detected by the EDOCT system. If a particular image did not allow flowangle determination, we assumed it to be $\pm 60^{\circ}$ and labeled it as V^* .

Histologic correlation

When clinically indicated, mucosal biopsy specimens of the imaged areas were obtained. Because the OCT field of view (FOV) was only 2 × 1.5 mm, care was taken to colocalize the FOV with the biopsy as closely as possible. After OCT imaging, the EDOCT catheter was withdrawn from the accessory channel, and biopsy forceps were introduced. The EDOCT catheter was designed with a quick release mechanism to minimize the change over time. The probe-exchange process was constantly monitored through the endoscopy video, and the probe location was verified against visual landmarks. Biopsy specimens underwent routine H&E stain processing and immunologic CD34 staining for vascular endothelium, and pathologic evaluation was performed by a GI pathologist (G.G.) blinded to the EDOCT images. Biopsy specimens were not obtained when contraindicated, such as in patients with esophageal varices or portal hypertension.

RESULTS

No procedural or medical complication occurred during EDOCT imaging in this pilot study. In vivo EDOCT imaging of the human GI tract was compatible with standard clinical endoscopic equipment, and clinical endoscopists

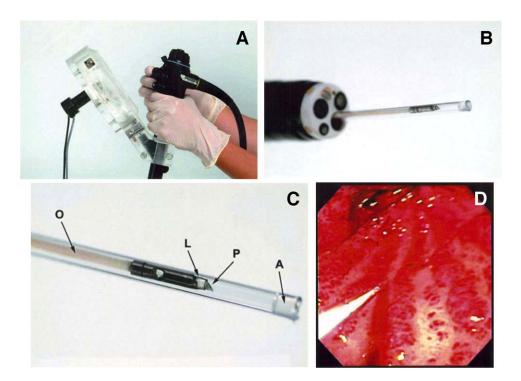


Figure 1. A, EDOCT scanner attached over the accessory port of the endoscope. **B,** Endoscope tip with catheter passed through the accessory channel. **C,** Fiber-optic probe within the transparent plastic catheter (outer diameter 2 mm). The imaging tip consists of an optical fiber *(O)* terminated with a focusing lens *(L)* and a 90° prism *(P)* to divert the light beam sideways. The catheter was sealed with adhesive *(A)*. **D,** Videogastroscope image of the catheter in contact with the stomach wall of a GAVE patient.

Diagnosis	Sites imaged	OCT structural appearance	EDOCT microvascular features*
Normal esophagus	31	Distinct layers	Small vessels in lamina propria
			Medium vessels in submucosa
BE	7	Distinct layers absent	Diffuse, small vessels in superficial mucosa
		Prominent glands	
Esophageal adenocarcinoma	1	Distinct layers absent	Diffuse, small vessels in superficial mucosa
Esophageal varices	5	Layers distorted by large vessels in lamina propria	Large vessels in lamina propria with high-velocity blood flow
Normal stomach	11	Pits and crypts at surface	Rarely, diffuse, small vessels in superficial mucosal
		Decreased signal at depth	
GAVE	7	Pits or crypts absent	Diffuse, small vessels in superficial mucosa
PHG	5	Pits or crypts absent	Diffuse, medium vessels in superficial mucosa
		Increased signal at depth	
Gastric lymphoma	1	Pits or crypts absent	Diffuse, small vessels in superficial mucosa
Normal duodenum	2	Villi	Medium vessels at villi roots when probe flattened villi
Duodenal adenocarcinoma	1	Villi disrupted	Diffuse, small vessels in superficial mucosa
Proctitis	1	Mucous glands	Medium vessels close to glands

EDOCT, Endoscopic Doppler optical coherence tomography; OCT, optical coherence tomography; BE, Barrett's esophagus; GAVE, gastric antral vascular ectasia;

PHG, portal hypertensive gastropathy.

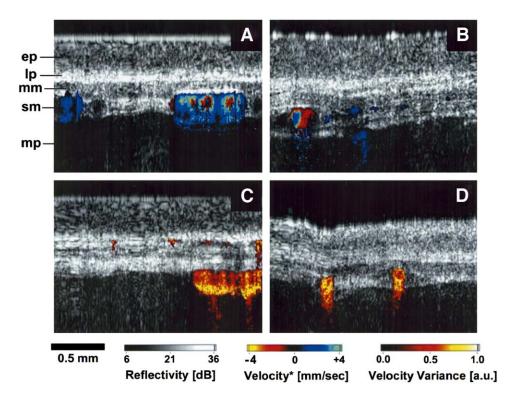


Figure 2. EDOCT images of normal esophagus with the 5 layers indicated: epithelium (*ep*), lamina propria (*lp*), muscularis mucosa (*mm*), submucosa (*sm*), and muscularis propria (*mp*). **A** and **B**, Color-Doppler images showing vessels of microcirculation in the muscularis mucosa, submucosa, and muscularis propria. The color rings in the larger vessels were caused by aliasing, because of the flow velocity exceeding the maximum detection range (about ± 4 mm/s). **C** and **D**, Velocity-variance images of microcirculation; the probe was in contact with the epithelial surface and the compression flattened the epithelium in **A** and **C**.

incorporated EDOCT imaging into routine endoscopy sessions without difficulty. Images were collected from normal esophagus (n=6), normal stomach (n=8), BE (n=5), esophageal varices (n=4), GAVE (n=7), PHG (n=5), neoplastic lesions (n=3), and radiation proctitis (n=1); n=1; n=1

Thirty-one histologically confirmed normal esophageal sites were imaged with EDOCT, including the middle (12) and distal (19) segments of the esophagus. As seen in Figure 2, 5 anatomical layers were identified from the structural EDOCT images, in agreement with previous non-Doppler OCT studies. With the blood flow information overlaid on the structural image, numerous subsurface blood vessels were observed (Fig. 2).

The images in Figure 2 were typical of the normal structural and microcirculation patterns in the middle and distal segments of the esophagus. The blood vessels located in the submucosa and muscularis propria ranged from about 100 to 400 μm in diameter. These vessels were presumed to supply the lamina propria with its superficial

network of small vessels with diameters less than 50 μ m, including capillaries (Fig. 2C). We found that certain subsurface features in the esophagus varied with different probe contact pressure. In particular, the reflectivity of the muscularis mucosa changed with contact pressure, as reported previously.⁵ EDOCT was able to image deeper vessels when the pressure was increased (Fig. 3), because the thickness of both the muscularis mucosa and the submucosa decreased while applying more pressure.

Striking differences were observed in both the microarchitectural and microcirculatory patterns when imaging 7 histologically confirmed BE sites in 5 patients. In the structural EDOCT images of BE, the distinct tissue layers were absent, and abnormal glands were observed below the epithelium (Fig. 4), consistent with previous structural OCT studies.^{6,8} Diffuse patterns of small blood vessels were observed in the metaplastic epithelium, unlike the EDOCT images of normal esophagus, which typically showed no epithelial blood vessels. In addition, the larger blood vessels situated in the submucosa and deeper layers observed in normal esophagus, were absent. These observations were in agreement with CD34-stained histology. In one patient, a histologic diagnosis of poorly differentiated adenocarcinoma was made prospectively. The layered architecture seen in normal esophagus was absent in the EDOCT images of this neoplasm (Fig. 5). Diffuse mucosal

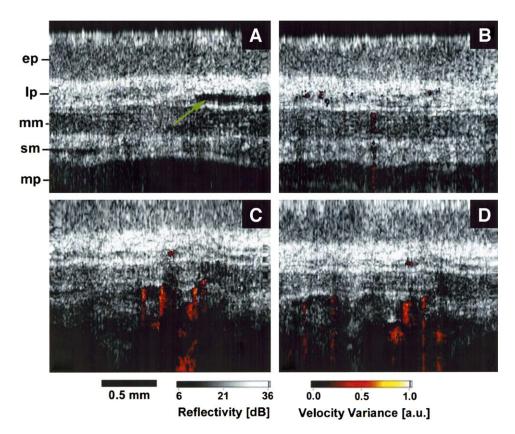


Figure 3. EDOCT images of normal mid segment esophagus at the same site with different probe contact pressures. **A** and **B**, Mild pressure: the mucus ducts *(green arrow)* remained open, and the muscularis mucosa was clearly delineated from the lamina propria and submucosa; few blood vessels were detected in the tissue under mild contact pressure. **C** and **D**, With increased pressure, the lamina propria became brighter, the contrast between muscularis mucosa and submucosa was reduced, and more blood vessels were detected.

microcirculation also was observed, which was different from normal or variceal esophagus. In patients with esophageal varices, biopsies were contraindicated, so the diagnosis was confirmed by clinical history and videogastroscope appearance. Consistent with the underlying pathology, the EDOCT images revealed vessels that were significantly dilated (Fig. 6) compared with the vessels seen in the normal esophagus. These dilated vessels were seen within the lamina propria, which normally contains only small capillaries.

Eleven sites of histologically confirmed normal gastric mucosa in 8 patients were imaged. As seen in Figure 7, the typical gastric pits and crypts were observed in the structural EDOCT images, similar to previous OCT studies. The Compared with the esophagus, there was very little light reflected from the normal stomach tissue deeper than $\sim 300~\mu m$. As a result, vessels in the lamina propria and the submucosa were not detected. The only vessels that were detected were found in the superficial mucosa, and even these vessels were marginally observable. In patients with GAVE, there was some flattening of the pits and crypts compared with normal stomach (Fig. 8). Increased microvasculature was observed in the superficial gastric mucosa, consistent with the histologic and clinical features of GAVE. Five patients with histories

of PHG were imaged (Fig. 9). The EDOCT images showed flattening of the mucosal surface morphology. Superficial microvasculature was more prominent compared with normal stomach. The depth of imaging also was greater than in normal stomach, which suggested possible changes in the tissue optical property. Subtle differences, e.g., edema secondary to vascular congestion, may be responsible for this effect. An ulcerating gastric lesion, which was later histologically identified as high-grade B-cell lymphoma, was imaged in one patient. Structurally, the gastric mucosal surface lacked the "pit and crypt" appearance of normal stomach. Functionally, there was increased superficial vascularity, consistent with the ulcerating nature of the lesion. The ability to measure the absolute blood-flow velocity in subsurface vessels by using the Doppler equation is illustrated in Figure 10.

In this pilot study, emphasis was placed on demonstrating the technical feasibility of EDOCT, and relatively fewer patients were recruited to image the small and the large bowel. Little microcirculation was detected in normal duodenum, despite visualization of the duodenal villi (Fig. 11), the structural EDOCT images of which were consistent with a previous OCT study.⁵ The villi structure was disrupted in a patient with histologically confirmed duodenal adenoma, and multiple small blood vessels

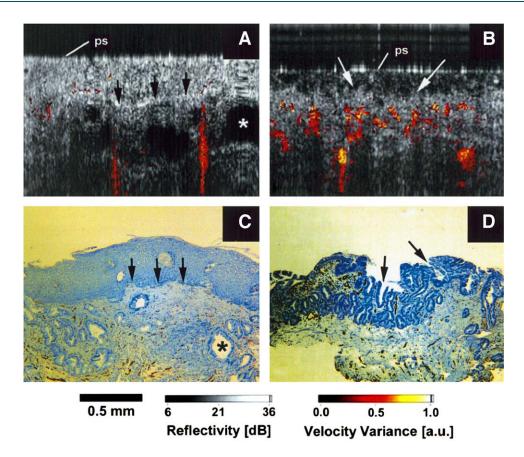


Figure 4. EDOCT images of Barrett's esophagus (BE) from two different patients with CD34 (dark brown) histologic comparison. **A** and **C**, Subsquamous BE with mucosal glands (asterisks) underneath the clearly delineated epithelial-lamina propria interface (arrows). **B** and **D**, BE with superficial glandular structure (arrows) and microvasculature close to the surface. (**C** and **D**, Orig. mag. ×10.) PS, External surface of the imaging tip.

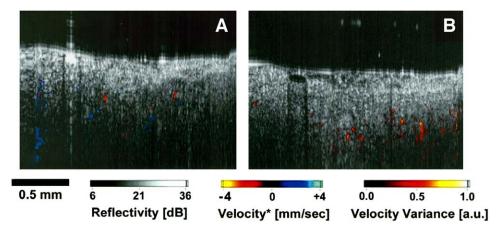


Figure 5. A, Color EDOCT images of esophageal adenocarcinoma. B, Velocity variance EDOCT images of esophageal adenocarcinoma.

could be identified in the lesion (Fig. 12). One patient with proctitis, had histologically confirmed active inflammation imaged (Fig. 13). Glandular structures with surrounding microcirculation were observed.

DISCUSSION

We believe this is the first study to demonstrate the clinical feasibility of EDOCT imaging to characterize both the microstructure and the microcirculation in a variety of GI tissues in vivo. The spatial resolution achieved in both structural and Doppler modes is comparable with current non-Doppler OCT systems.³ In Doppler mode, the apparatus achieved the highest velocity resolution reported endoscopically to date, 10- to 100-fold better than that of Doppler EUS.¹⁹ The combined high spatial and velocity resolution provided a unique opportunity to image subsurface microcirculation in the GI wall during endos-

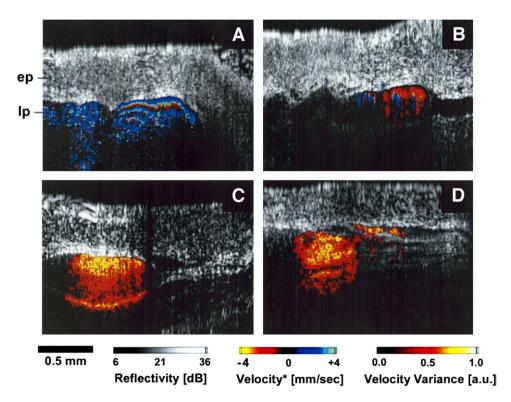


Figure 6. EDOCT images of esophageal varices. **A** and **B**, Doppler images of blood flow in the dilated variceal vessels. The blood flow velocity in (**A**) is more than 3 times greater than that seen in normal esophagus. **C** and **D**, Velocity-variance images of microcirculation in dilated variceal vessels.

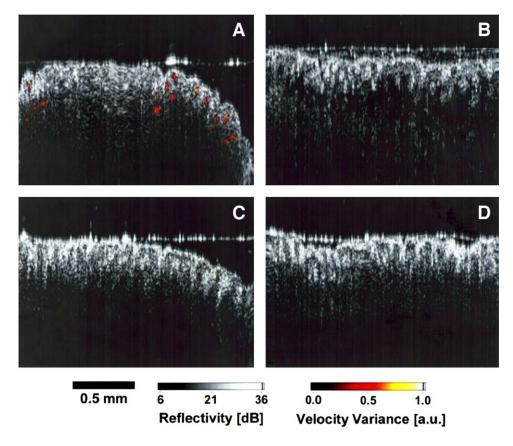


Figure 7. EDOCT images of normal stomach mucosa from 4 different patients. A and B, Proximal stomach. C and D, Distal stomach.

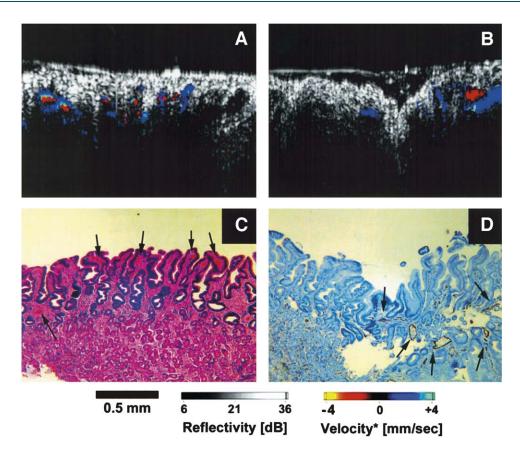


Figure 8. A and **B,** Color EDOCT images of GAVE in two patients. **C,** Consistent with the H&E staining, dilated microvasculature (*arrows*) is present immediately beneath the tissue surface. **D,** Consistent with the CD34 staining, dilated microvasculature (*arrows*) is present immediately beneath the tissue surface. (**C** and **D,** Orig. mag. ×10.)

copy. This represents a significant technical advance in endoscopic OCT, where functional information via blood flow detection complements microstructural data.

The addition of blood-flow information to OCT structural information helped to identify subsurface features. While both blood vessels and mucus glands were hyporeflective in structural EDOCT images, they were clearly distinguishable when blood-flow information was included. Blood vessels displayed strong flow signals, while mucus glands had no color-Doppler or velocity variance signals (for example, Fig. 13). Care had to be taken when interpreting the Doppler images of some blood vessels where vertical "streaks" appeared directly underneath the vessels, which could interfere with the vessel-diameter assessment. These "streaks" were previously reported as "Doppler shadows," 13 likely caused by forward scattering of light through the blood vessels. In these cases, the upper contour of the vessel should be used to estimate the vessel diameter.

This clinical experience suggested that EDOCT imaging was only as demanding as miniprobe EUS imaging, extending the clinical endoscopy session by about 10 to 20 minutes. It was important for the endoscopist to place the catheter in steady and gentle contact with the lumen wall to obtain high-quality images. Collapsing the lumen

around the EDOCT catheter, as previously suggested,⁵ provided additional stabilization, but the endoscopic view of the catheter was obstructed. Hence, lumen collapse was only used as a last resort when motion artifacts were particularly severe. Excessive pressure between the probe and the imaged tissue was avoided to prevent microcirculation collapse. However, some pressure was useful to increase depth of imaging in some cases. Currently, no miniaturized pressure sensors have been integrated with OCT catheters, and, thus, reproducible and controlled contact pressure is currently not possible. In the future, micromachined electromechanical sensors may be available to standardize the probe contact pressure.

Images obtained by the EDOCT system suggest that the muscularis mucosa may be distinguished from the adjacent layers under the right conditions. However, increased contact pressure may reduce the contrast between the layers. The blood-flow information, such as a small capillary network in the lamina propria and larger vessels in the submucosa, could provide additional clues for layer identification and confidence in the assessment of muscularis mucosa. EDOCT may be useful in detecting whether neovascular invasion beyond the muscularis mucosa and to provide information for clinical management.

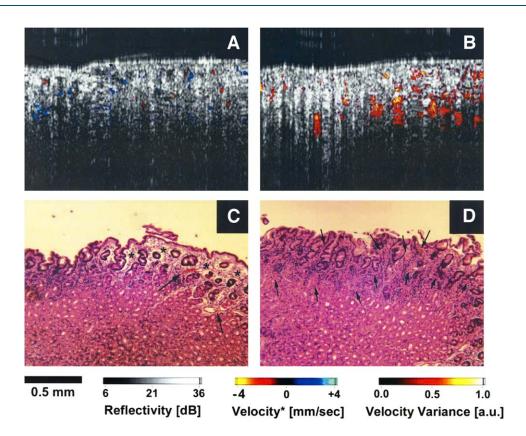


Figure 9. A, Color EDOCT images of portal hypertensive gastropathy (PHG) showing superficial vessels, consistent with the H&E histology in $\bf C$ and $\bf D$ marked by arrows. $\bf B$, velocity variance EDOCT images of PHG, showing superficial vessels, consistent with the H&E histology in $\bf C$ and $\bf D$ marked by arrows. ($\bf C$ and $\bf D$, Orig. mag. $\times 10$.) *Edematous areas.

We were unable to compare the EDOCT images of GI microcirculation with a criterion standard because no such standard for in vivo microcirculation visualization exists. In previous non-Doppler OCT studies, standard histology was the appropriate criterion standard for microstructure. Yet, for microcirculation imaging, comparison with histology is not optimal. Pathologists routinely quote microvessel density (MVD) as a measure of vascularization; however, this is quantified ex vivo and does not necessarily reflect the in vivo state of microcirculation, which varies with physiologic changes, including capillary recruitment and pathologic processes, e.g., vascular congestion. A previous in vivo study of gastric adenocarcinomas that used laser Doppler flowmetry²⁰ suggested that tumor blood flow did not correlate with MVD observed in ex vivo histologic samples. Doppler EUS, CT angiography, and other in vivo blood-flow imaging techniques lack the necessary spatial and velocity resolutions to be comparable with EDOCT. Significant challenges lie ahead for validating the EDOCT findings, because no existing technologies can provide microcirculatory information at a scale that is comparable with the EDOCT images.

These difficulties aside, this study showed that EDOCT could visualize subsurface microvasculature. This has been the first reported endoscopic technology that allowed visualization of subsurface microscopic blood flow at the

individual vessel level. With further technologic improvements and additional clinical experience, EDOCT may enable in vivo measurement of microvascular vessel density during endoscopy, a capability that would help quantitatively assess tumor vascularization. Previous GI studies showed that, while OCT structural images were highly sensitive and specific for specialized intestinal metaplasia,8 no conclusive data were available for detecting dysplasia, which is critical in the management of BE. It is possible that the addition of in vivo blood-flow information could provide a useful quantitative index for identifying dysplasia. As illustrated in Figure 4, EDOCT can detect Barrett's tissue beneath neosquamous epithelium. This capability could potentially be used in follow up of patients after endoscopic ablation of high-grade dysplasia. When imaging GI varices, the distance between the epithelial surface and these blood vessels could be measured with micron accuracy, which might be of diagnostic value when assessing the bleeding risks of the vessels. A number of endoscopic therapeutic procedures, such as sclerosant injection and heat probe, target the mucosal and submucosal blood vessels to treat bleeding lesions. EDOCT potentially can evaluate treatment efficacy in vivo and can provide real-time treatment monitoring during endoscopy.

This was a clinical feasibility study, and the main objective was to demonstrate that EDOCT could be performed

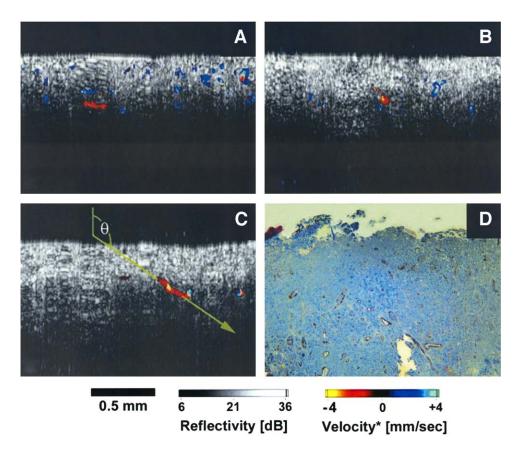


Figure 10. A, B, and **C,** Consecutive color EDOCT images of the ulcerating surface of a gastric lymphoma with an abundance of subsurface microvasculature indicated by the bidirectional blood-flow patterns. The direction of blood flow in a vessel is indicated *(arrow)* in **C**; the flow velocity estimated as 4 mm/s in this 50- μ m-diameter vessel. **D,** Corresponding CD34 stained section, illustrating the superficial microvasculature (orig. mag. \times 10).

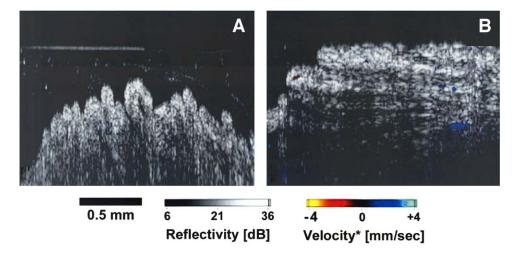


Figure 11. A, EDOCT images of normal duodenum, showing clearly resolved villi (\sim 200 μ m across) when the catheter was not in contact with the mucosal surface. B, When the catheter came into contact with the duodenum wall, the villi were flattened and blood flow could be observed at the roots of the villi.

without complications in the GI tract in patients with a variety of conditions. Unlike CT angiography and Doppler US, which reveal only relatively large blood vessels, EDOCT visualized smaller blood vessels in normal esophagus, stomach, and duodenum, and in patients with esophageal varices, GAVE, and PHG. A limited number of patients with several different pathologies were studied, so the EDOCT observations made here should be consid-

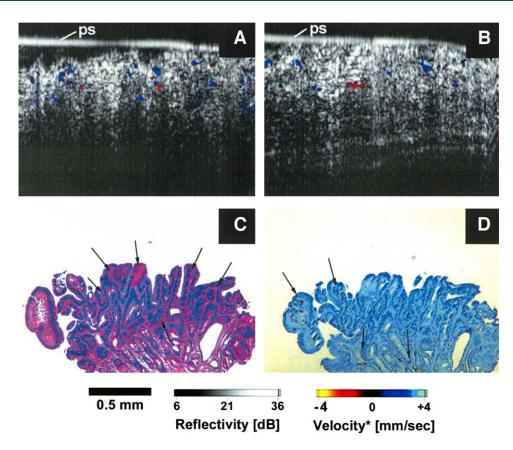


Figure 12. A and B, Color-Doppler EDOCT images of duodenal adenoma, with increased microvascularity in the villi, consistent with the H&E (\mathbf{C}) and CD34 (\mathbf{D}) stained sections as marked by arrows. (\mathbf{C} and \mathbf{D} , Orig. mag. $\times 10$.)

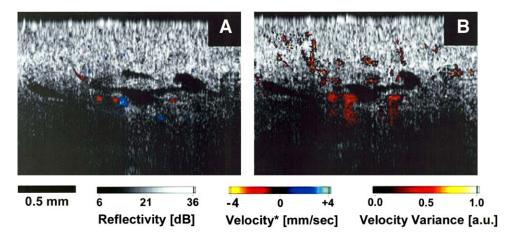


Figure 13. A, Color-Doppler EDOCT images of rectal mucosa in a patient with proctitis. B, Velocity variance EDOCT images of rectal mucosa in a patient with proctitis.

ered preliminary but with substantial differences noted between normal and diseased tissues. Future EDOCT studies are required to establish definitively the normal microcirculation patterns in different parts of the GI tract and the ability of EDOCT to detect microvascular changes during disease progression. Rigorous trials will be needed to determine whether EDOCT can distinguish not only

between healthy and diseased tissues but also between different pathologies.

CONCLUSIONS

The results of this study demonstrated that Doppler OCT imaging is feasible in the GI tract during endoscopy

for detection of mucosal and submucosal microcirculation. The spatial and velocity resolutions allowed visualization of small subsurface blood vessels that were previously unavailable to GI endoscopists by using currently available imaging techniques. The different microcirculation patterns observed in normal and in pathologic GI tissues prompt further EDOCT studies with larger sample sizes and more clinical focus to elucidate the ability of EDOCT to provide diagnostic information. The images presented here are the first tomographic images of the normal and the pathologic tissues in the GI tract to include Doppler flow maps of subsurface microcirculation.

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